Tuberculosis in England, a high-income Western European setting with low incidence: Recent trends, Social determinants and Prevention through BCG vaccination

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Declaration

I, Patrick Nguipdop Djomo, declare that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

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Abstract

While the tuberculosis (TB) burden in England is low compared to some parts of the word, annual incidence rates have not declined in over two decades, and remain among the highest in developed countries.

In the first part of my thesis, I examined trends in TB notifications rates in England with emphasis on the UK-born population, which because of its relatively lower incidence, has received less attention than foreign-born groups. This analysis showed that for nearly two decades, rates have remained mostly stagnant in White UK-born populations, except in the elderly in which rates continue to decline, whereas TB rates have been declining in foreign-born subjects and UK-born ethnic minority groups in the past decade. Given the strong link between poverty and TB, I also investigated the association between socio-economic deprivation and the risk of TB in England. An ecological analysis suggested that the association between small-area level deprivation and TB rates in a recent 5-year period was much stronger in the UK-born population than in the foreign-born population. To investigate the role of deprivation in the UK-born White population further, I used data from a case-control study of UK-born White young adults in which information was collected on individual-level socio-economic determinants of health. The analysis showed a four times higher risk of TB in subjects with an education level below O-levels compared to those with a degree, as well as an association between increased TB risk and area-level deprivation, tobacco smoking, drug use, and homelessness.

In the second part of the thesis, I focused on BCG vaccination, a longstanding part of the TB prevention toolkit, and which has been somewhat overlooked compared to case finding and treatment. I reported a survey of the implementation at the local level of the 2005 change to England's BCG policy replacing the universal vaccination of schoolchildren by targeted vaccination of higher-risk infants. Heterogeneity in the healthcare service pathways for BCG vaccination was noted, as well as challenges to the identification of, and service delivery to, the targeted groups. I also conducted an ecological study estimating the vaccine uptake in a 3-year period (2006-2008) following the policy change and its association to some area-level factors, with results suggesting that about one third of eligible infants may have missed vaccination. Finally, I conducted a historical cohort study measuring the long-term duration of BCG-derived protection against tuberculosis using data from Norway, a low-incidence setting comparable to England. I found that BCG effectiveness lasts for at least 20 years, longer than previously estimated.

Overall, my thesis highlights the existence of stagnant TB rates in UK-born White young adults, and particular social determinants such as tobacco smoking, drug use and homelessness, that are amenable to specific interventions to reduce the risk of TB in a currently neglected population group. It also presents evidence to improve BCG policies targeted at high-risk groups in low-incidence settings and vaccination uptake. The new information on the duration of BCG protection can also help inform any review of the cost-effectiveness of BCG vaccination in the general population.

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List of Abbreviations

aOR	adjusted Odds Ratio
APC	Annualised Percent Change
AUDIT-C	Alcohol Use Disorder Identification Test - Consumption
BCG	Bacillus Calmette Guerin
BTS	British Thoracic Society
CDSH	Commission on Social Determinants of Health
CI	Confidence Interval
COVER	Cover of Vaccination Evaluated Rapidly
DAG	Directed Acyclic Graph
DALY	Disability-Adjusted Life Years
DPT	Diphtheria Pertussis Tetanus vaccine
EPTB	Extra-Pulmonary Tuberculosis
ESRC	Economic and Social Research Council
ETS	Enhanced Tuberculosis Surveillance System
EU	European Union
EW	England and Wales
GP	General Practitioner
GBP	Great Britain Pound Sterling
GCE	General Certificate of Education
HIC	High Income Countries
HIV	Human Immunodeficiency Virus
HPA	Health Protection Agency
IGRA	Interferon Gamma Release Assay
IMD	Index of Multiple Deprivation
IRR	Incidence Rate Ratio
ISC	Indian Subcontinent ethnic background (Indian, Pakistani, Bangladeshi)
LFS	Labour Force Surveys
LMIC	Low and Middle Income Countries
LSOA	Lower-layer Super Output Area
LTBI	Latent Tuberculosis Infection
MDR-TB	Multi-Drug Resistant Tuberculosis
MICE	Multiple Imputation by Chained Equations
MRC	Medical Research Council

MSOA	Middle-layer Super Output Area
Mtb	*Mycobacterium tuberculosis*
NatCen	National Centre for Social Research
NHS	National Health Service
NIGB	National Information Governance Board
NOIDS	Notification of Infectious Diseases System
OA	Output Area
ONS	Office for National Statistics
OPCS	Office of Population Census and Surveys
OR	Odds Ratio
pa	per annum
PAF	Population Attributable Fraction
PCD	Postcode unit
PHE	Public Health England
PHLS	Public Health Laboratory Services
PPD	Pure Protein Derivative
PPS	Probability Proportional to Size
PSE	Poverty and Social Exclusion in the UK survey
PTB	Pulmonary Tuberculosis
RCT	Randomised Controlled Trial
SDH	Social Determinant of Health inequality
SES	Socio-Economic Status
Sm+	Smear positive
SRS	Simple Random Sample
SSA	Sub-Saharan Africa
TB	Tuberculosis
TBPT	Tuberculosis Prevention Trial
TST	Tuberculin Skin Test
UK	United Kingdom
USD	United States Dollar
VE	Vaccine Efficacy / Effectiveness
WHO	World Health Organization
WWII	Second World Ward
XDR-TB	Extensively-Drug Resistant Tuberculosis

1.   <u>**Introduction**</u>

Tuberculosis remains a major cause of morbidity and mortality in many parts of the world. It is estimated that about 1.7 to 2 billion people across the world are infected by *Mycobacterium tuberculosis* (*Mtb*) (1, 2); approximately 10% are expected to progress to clinical disease, of which nearly half develop lung disease and become potentially infectious, sustaining the transmission cycle (3). Since the 1980s, TB has been resurging as a public health problem in several high-income countries (HIC) with low TB incidence, including in England where the disease was once considered to be on a steady elimination course (4). Nowadays in England, the highest TB incidences are reported in large metropolitan areas, with the heaviest burden on those subjects born abroad in high TB incidence countries, as well as in older people (5). A great proportion of disease in these two groups appears to be caused by the reactivation of latent *Mtb* infection (LTBI) most likely acquired in their country of origin in the case of foreign-born subjects, or in the past when the risk of infection was slightly higher for older native individuals (6).

By contrast, the TB incidence and risk of infection in the general native population (those born in the UK) are relatively low, and the TB-associated morbidity appears to mostly concentrate in the more vulnerable and socio-economically deprived segments of the population, in which there is evidence of sustained transmission (5). These deprived populations include groups at high risk of TB, like people with current or past history of homelessness and prison stay, in which high prevalence of *Mtb* infection have consistently been reported (7). Socio-economic deprivation and the resulting social stratification have also been associated with unequal distribution of health-related behaviours and other determinants of health, including some presumed or known TB risk factors (e.g. tobacco smoking, alcohol abuse, and use of controlled drugs), as well as limited access to, and/or contact with, the health system (8). In addition to the direct disease burden on the affected population subgroups, the continued local TB transmission - albeit concentrated in these groups - also represents a risk for the wider community, and outbreaks have been reported (9, 10). The risk is further compounded by the spread of multi-drug resistant TB (MDR-TB), which by defeating the arsenal of available antibiotics, paradoxically renders casual encounters with a prehistoric pathogen like *Mtb* potentially lethal even in the richest countries (11).

The localised pockets of TB transmission in the native population have proven challenging to control, compromising the progress towards eliminating TB as a public health problem. Projections based on recent modelling work have suggested that in spite of the current range of control tools and measures, the current average rates of decline in TB rates in most countries, including in the majority of low TB incidence countries (i.e. those with annual TB notifications <10 per 100,000 people) would most likely be insufficient to meet the targets sets by the World Health Organization's (WHO) global TB strategy beyond 2015 to reach pre-elimination levels (defined as annual notifications <1 per 100,000) by 2035 and elimination levels (defined as annual notifications < 1 per million) by 2050 (12). In light of these projections, among other recommendations to strengthen and boost TB control efforts, the latest global TB strategy recommends increasing efforts and actions to reduce the effect of the underlying social determinants of tuberculosis (12-14). This includes mapping and targeting TB high-risk groups, as well as gaining a better understanding of the social determinants underlying the risk of TB and appropriately addressing these. Tuberculosis has been known as a disease of poverty for almost as long as population-wide records exist, with the disease burden greater in the least affluent segments of the population (15). However, our understanding of some of the causal pathways through which poverty affects the risk of tuberculosis remains limited. Furthermore, these pathways are likely to be setting and context specific, and probably change as societies evolve. While reducing social injustice and related health inequalities must remain the long-term goal, a better understanding of some of the pathways through which poverty affects the risk of tuberculosis may help inform and/or improve more targeted interventions directed at relevant pathways and within the grasp of public health.

The WHO global TB strategy (13, 14) and several mathematical models (16) also concur that amongst other tools, effective vaccination against tuberculosis has a major role to play in order to achieve TB elimination. The Bacillus Calmette-Guerin vaccine (BCG) remains the sole TB vaccine licensed for use in humans to date, with good efficacy against severe childhood tuberculosis reported consistently throughout the world (17, 18), and variable, but up to 80% protection against pulmonary TB reported in several countries (19), including in the United Kingdom. Since its introduction in the 1920s, BCG has grown to become one of the most used vaccines in the world; more than 4 billion doses have been administered in humans and universal vaccination is currently recommended in over 157 countries (20, 21). The limitations of BCG have been

recognised, including the variations in the vaccine efficacy between settings and populations (19), and major efforts are underway to develop new and more effective TB vaccines. At least twelve vaccine candidates are currently at various stages of development, although only one is undergoing human testing (22, 23). However, vaccine development efforts have so far been hampered by the complexities and limitations of the current understanding of human's immune response to *Mtb* infection and TB disease, as well as the mechanism of BCG-derived immune protection against tuberculosis (22). Therefore, additional insights gained into BCG-derived protection against tuberculosis, including the duration of protection, can potentially be useful to vaccine development efforts. Furthermore, the implications of prior BCG vaccination and any potential interaction with newly developed TB vaccines will most likely have to be considered, in light of the widespread use of BCG vaccination throughout the world. This includes for example the duration and changes in levels of BCG effectiveness against tuberculosis, which may be relevant to the timing and effect of TB booster vaccines (24), a major family of current TB vaccine candidates designed to improve immunity elicited by BCG.

Until new and more effective TB vaccines become available, the WHO global TB strategy recommends continuing BCG vaccination (13, 14). While universal vaccination of all neonates soon after birth is still advised in high TB incidence areas, many low TB incidence countries have changed or are in the process of revising their BCG vaccination policies to discontinue or move from universal to more targeted approaches, based on changes in the epidemiology of TB and BCG vaccination's cost-benefit and cost-effectiveness (21). Updated information on BCG, including on the duration of protection, could also assist in the revision of the cost-effectiveness of various BCG vaccination strategies that currently assume waning in the vaccine's efficacy 10-years after vaccination.

2. **Objectives and Overview of Thesis**

The stated long-term aim of the WHO strategy against TB is to eliminate the disease as a public health problem, which is often defined as reducing the annual incidence below one case per million. Achieving this vision would require countries where TB incidence is currently low to make swift progress towards pre-elimination by 2035, i.e. annual incidence of less than 1 per 100,000 persons. The overall aim of this research project was to explore aspects of the epidemiology and control of tuberculosis in England, a high-income country with low TB incidence in Western Europe where technical measures to reach pre-elimination stage might be more feasibly implemented. Although the greatest proportion of TB cases in England are now reported in people born abroad, the emphasis in this project was on tuberculosis in the UK-born population, in which it can be reasonably argued that most of the disease is associated with local infection, and to some extent re-activation in later life, and where the effect of measures to prevent TB at the local level should be demonstrated for progress towards elimination. My expectation is that the findings may inform control strategies, as well as some research priorities targeting this specific population group.

My thesis is two-pronged, as follows:

In the first part,

(1) I revisited trends in TB notification rates in England over the past three decades, from 1983 to 2014, while noting the similarities and differences in trajectories between the UK-born and foreign-born populations.

(2) I then explored the association at the ecological level between small-area level of deprivation and population composition, and tuberculosis notification rates over a recent 5-year period (2008-2012), again contrasting the UK-born and foreign-born populations.

(3) Finally, I used a nationwide TB case-control study to further investigate how socio-economic status and some related social determinants of health inequality are associated with the risk of tuberculosis at the individual level in UK-born adults from White ethnic background. I used a formal causal framework to explore possible behavioural and lifestyle determinants of health through which poverty may contribute to perpetuating TB in the study population.

The second part of this project concentrated on BCG vaccination, one of the longstanding TB prevention tools that has been less well examined than case finding and treating recently.

(4) First, I reported a 2010-2011 survey of the implementation at local-level of a major change in BCG vaccination policy recommendations in England in 2005, when universal vaccination of schoolchildren was discontinued, and replaced by targeted vaccination of high-risk infants.

(5) I also estimated the BCG uptake in a 3-year period (2006-2008) after the policy change, and I explored the association of local vaccine uptake to some area-level factors.

(6) Lastly, I used linked-registers data from Norway, a low-incidence European setting comparable to England in its level of development, to measure the long-term duration of, and changes to BCG levels of effectiveness against TB with time since vaccination.

The last chapter summarises the key results and the relationship between these findings, a brief discussion of some of the shared strengths and frailty of the work presented, as well as some reflections on the findings' relevance to policy and potential future research.

3. <u>Background</u>

3.1 Overview of the Natural History of Tuberculosis

Tuberculosis (TB) is one of humanity's oldest scourges, with evidence of skeletal tuberculosis found in prehistoric human remains dated as old as 5000BC (25, 26). The disease is caused by species of mycobacteria, a ubiquitous family of rod-shaped bacteria (bacilli) that are readily found in the environment, including in water, soil, various animals, and even some plants (27). The main aetiological agent of TB in humans is *Mycobacterium tuberculosis* (*Mtb*), although disease caused by other closely related mycobacterial species has been reported, notably from *M. africanum*, and *M. bovis* (28).

Tuberculosis causative agents' main route of transmission is airborne (29). In respiratory TB patients who have sufficient mycobacteria in their respiratory tract, coughing, sneezing, shouting or even singing can aerosolise the infectious sputum, producing droplet nuclei; these are tiny airborne particles of 1-5 microns in diameter that can remain suspended in the air for up to several hours. Inhaling droplet nuclei containing *Mtb* can lead to infection in susceptible individuals exposed to this air. The effectiveness of transmission is affected by a number of factors, including the infectiousness of the source TB patient, the susceptibility of the individuals exposed, the proximity, duration and frequency of exposure, as well as the infectious dose / concentration of *Mtb* particles in the air. The infectiousness is greater in patients in whom *Mtb* can be found in the sputum under microscopy (Smear Positive patients [Sm+]), as well as those expelling more bacilli in the air for other reasons (e.g. lung cavitation, chronic and frequent cough) (30, 31). Individual susceptibility to infection when exposed can be increased by various factors, including a compromised immune system. Various environmental factors may affect the concentration of *Mtb* infected air particles, including for example poor ventilation or enclosed spaces, high humidity and dampness (32); whereas closer, prolonged and/or frequent exposure increases the likelihood of transmission (3). In practical terms, this means that the risk of transmission is higher among household contacts of patients with respiratory tuberculosis, especially those with Sm+ TB (30, 31). It has been estimated that about 30% to 50% household contacts and one in six casual contacts of patients with smear positive active respiratory tuberculosis get infected (30, 33).

Upon effective transmission, most subjects develop a chronic latent infection with *Mtb* (Latent TB infection or LTBI); although it is now thought that some individuals are able to successfully clear the pathogen (34, 35). Only a minority, about 5-15% infected subjects will progress to TB disease in their lifetime (3, 36). The risk of progression to disease is

highest 1-2 years after infection, with an estimated risk of disease in the 1st year of 1.5%; the cumulative risk of disease in the first 5 years after infection is between 5-10%, compared to ~5% for the rest of the lifetime. This is likely the result of a selection process through which those with the least natural immunity to *Mtb* develop the disease shortly after infection, whereas others may 'resist' the infection until a later time (3). For this latter group, the development of disease is usually considered to be caused by the 're-activation' of their latent infection. This is common in the elderly, consistent with old age-related immuno-senescence. However, frequent and prolonged exposure, as well as higher infectious doses may increase the likelihood of progression to disease (3). Similarly, increased susceptibility in the host increase the risk of progression to disease, with for example about 30% lifetime risk of disease in people with untreated diabetes (37) and up to 10% risk per year in those with untreated HIV infection (38). There is also evidence that re-infection may occur (39, 40), which is an important risk factor for disease, considering that progression to disease is 10 times more likely following recent infection than if an older infection (3).

3.2 Summary of Tuberculosis Epidemiology with emphasis on low burden countries

Tuberculosis remains a disease of great burden across the world, both in terms of mortality and morbidity. It was the global leading cause of death by any single infectious disease in 2014, responsible for about 1.5 million deaths, of which 1.1 million were HIV negative subjects, and 140000 were children (1). The World Health Organisation (WHO) also estimated that there was 9 to 10 million incident cases worldwide in the same year, for a global incidence of about 133 per 100000, and including nearly half-a-million cases of Multi-Drug Resistant TB (MDR-TB) (1). The burden of disease is unequally distributed between countries along gradients of economic output, with over 80% of TB cases occurring in 22 high-TB burden low-income developing countries that account for only 60% of the world population. The worst affected area is sub-Saharan Africa, a region with the poorest countries in the world, and where the average incidence was estimated at 281 cases per 100,000 in 2014, more than twice the global incidence (1).

While TB is truly a disease of poverty and low-income countries, it still poses significant concerns to public health in most developed countries. The annual number of cases in many high-income countries is not negligible, considering that TB is a prehistoric disease for which relatively affordable advanced diagnostic tools and effective treatment regimens

have been available for 70-80 years. It is notable that nearly 50000 new TB cases were notified in the seven most advanced economies in the world in 2014 (G7 i.e., France, Germany, Italy, United Kingdom, Japan, Canada and the United States of America) (1, 41). It was also estimated that approximately 340000 new TB cases occurred in Europe in 2014, including over 40000 in subjects born and living in the European Union or European Economic Area (EU/EEA) (41). The threat that TB represents in Europe is further compounded by the fact that approximately one quarter of all MDR-TB cases in the world occurred in this region which only account for about 10% of the world population (1).

Table 3.1: Annual TB notifications and rates in G7 countries in 2014
(Source Global TB report 2015 (1))

Country name	Population	Number of new TB cases	Rate per 100000
Canada	36000000	1568	4.4
France	64000000	4845	7.4
Germany	81000000	4488	5.6
Italy*	60000000	3153	5.3
Japan	127000000	19615	15
United Kingdom	64000000	7077	11
United States	319000000	8949	2.8

*Note: Italy did not report to WHO and ECDC in 2014 so numbers were extrapolated from 2013

One major change in the global epidemiology of TB was the advent and global spread of HIV in the 1980s, which provided TB with the opportunity to thrive in immunologically weaker hosts; TB in turn became one of the principal causes of death in HIV-infected subjects (42, 43). Although HIV-TB co-infection is less common in HIC than in low and middle-income countries (LMIC), it remains a challenge, not least because it mainly affects vulnerable subgroups like migrants, homeless people and injecting drug users (44). Also, the impact of HIV on TB epidemiology in high-burden settings has worldwide repercussions, because of increased population mobility and migration fluxes. Another development is the emergence of multi- and extensively- drug-resistant TB (respectively MDR-TB [i.e. *Mtb* strains resistant to both isoniazid and rifampicin, the core components of the first line anti-tuberculosis treatment], and XDR-TB [i.e. MDR-TB also resistant to fluoroquinolone drugs and at least one of the three injectable second line drugs]), whose genetic selection was probably helped by suboptimal treatments and patients' poor adherence to therapy. Outbreaks of MDR-TB were reported from the late 1980s in the USA,

with MDR strains subsequently found almost everywhere in the world where drug resistance testing is available (45). These resistant strains not only represent a major global threat to the arsenal of antibiotics available to combat this old disease, further compounded by the substantial lag in discovery and development of novel effective therapies (11, 46), but they are also more virulent and severe, more difficult and costlier to treat (11); the gruelling treatment regimen often requires patients to take nearly 20 pills per day for 24 months (over 14000 tablets in total) and has more adverse side effects than standard therapy, and a lower cure rate and higher case-fatality rate than drug sensitive TB (11).

The trends in TB incidence in many developed countries changed from around the mid-1980s, with a slowing in the pace of decline in annual notification rates, or even a reversal with increasing rates (4, 47). While the change was partly attributed to the degradation of TB control services in some settings (48), another major contributing factor was the increasing number of TB cases reported in people who have migrated from developing countries with higher TB incidence towards developed countries where TB incidence was lower (4). Nowadays, the burden of TB in most developed countries is greater in people with ties to high-TB incidence parts of the world. In the past 5 years in the UK, two-third of TB cases have been reported among people born abroad, with a TB notification rate estimated at 83/100,000 in this group (5). Large metropolitan areas are more affected; 40% of TB cases in the UK occurred in London in 2011, with the TB annual rate nearly three-times higher than the national average (49). A similar pattern is reported in most Western European countries (41, 50). It is thought that most TB in the foreign-born population in developed countries is caused by *Mtb* infection prior to arrival in the country of residence, although there is also evidence that re-infection may also contribute to the lifelong risk of disease (51). TB rates in the native-born population of these developed countries are not negligible, and while a proportion occurs in the elderly population in which the reactivation of older LTBI is common, other age groups are also affected. Over the past 10 years in the UK, nearly 60% of UK-born TB cases were reported in subjects aged 15-64 years old; this age-group also accounted for three-quarters of MDR-TB among the UK-born (5). Strain-typing studies from low-incidence developed countries additionally suggest that substantial proportions of TB in locally-born adults in such settings are caused by recent infection (52, 53). Transmission chains have been shown to be concentrated in high-risk population groups including homeless, drug users and prisoners (53), and probably sustained by these groups relative social marginalization, deprivation, overcrowding and often limited access/contact with the health system. Overall, the re-

emergence of TB presents a complex and challenging epidemiologic picture in high-income countries.

3.3. *Tuberculosis control strategies in low burden countries*

The main objective of tuberculosis control is to interrupt *Mtb* transmission cycle, which can be achieved through a number of interventions, including the reduction of the source of infection in the community through case finding and effective treatment, with priority given to infectious individuals (those with respiratory TB), depleting the reservoir of those latently infected using screening and preventive chemotherapy, and prevention of new infections through BCG vaccination and infection control measures (54-56).

In most developed countries, especially in the Western hemisphere, tuberculosis rates declined steadily during the 20th century, at an estimated annual rate of 4% in the post-industrial period, due to a combination of improvement in hygiene and in living standards, with some contribution from the sanatorium movement (26, 57-60), then accelerating to over 10% per year when medical interventions were added to control measures from around the mid-20th century (54, 61). The latter included antibiotic therapy, mass BCG vaccination, nationwide mass tuberculin skin testing (TST) and chest X-ray screenings in several countries in the 1960s-70s (55). Preventive treatment of latent TB was not widely used for various reasons, including the fact that relative to the general population, it was a burdensome treatment (antibiotics for up to 9-12 months, with non-negligible risk of toxicity in otherwise healthy subjects) with a relatively low impact (very large number of individuals need to be treated to avert a single TB case), and there were challenges to the diagnosis of LTBI (low specificity of TST and interaction with BCG) (56). Nonetheless, the other interventions contributed to bringing down TB incidence in many developed countries to such low levels that by the late 1970s, TB control in these countries mainly centred around passive case finding and treatment though routine care, and BCG vaccination.

Unfortunately, as noted in the previous section, a global resurgence in TB was observed from around the mid-1980s, which also affected trends in low-incidence countries (4). The upswing in TB incidence in Western countries was initially thought to be mostly due to the emergence and spread of HIV; but the contribution of disinvestment in TB control programmes and degradation of services was also noted, as well as the role of socio-economic factors like the rise in homelessness (48). The change in trends was unfortunate because TB incidence had declined to such low levels in some countries that the prospect

of elimination (defined by WHO as TB incidence <1 per million population) was not unreasonable (62). It is considered that TB elimination is possible with the interventions currently available, because *Mtb* is a relatively inefficient pathogen with a slow replication rate and low transmissibility; there are effective diagnostic tools to identify infectious individuals, and these subjects can rapidly be rendered non-infectious with existing treatments, therefore interrupting transmission.

In several high-income settings, the resurgence of TB in the context of low incidence has been accompanied by changes to the epidemiological paradigm that have challenged the established control strategies and services. Some of the emerging challenges have included adapting the TB control strategy to a context in which a substantial proportion of reported cases are in foreign-born subjects and results from transmission that occurred out of the country, and the concentration of disease in the native population to specific groups with high levels of socio-economic deprivation and often social marginalisation, with limited interaction with the health system (often identified as 'hard-to-reach' or 'under-served' population groups) (4). These epidemiological changes have contributed to creating localised pockets of transmission that have proven difficult to eliminate. For example, protracted TB outbreaks limited to specific groups (e.g. UK-born young adults from White ethnic background, drug dealers and drug users, sex workers, prisoners etc.) have been reported in England (9, 10, 63), and a recent examination of universal strain typing data in London has suggested that clustering was more frequent in the UK-born population (53).

Most affected developed countries have gradually re-invested in their TB control programmes and services, and revised their TB control strategies in response to the resurgence of TB, including increasingly moving from mostly passive to active case finding, through interventions like screening of migrants at higher risk of TB, outreach screening activities to high risk populations, and active screening of TB cases' contacts. For example, in England, the recently adopted Collaborative TB Strategy 2015-2020 has called for substantial investment in the nationwide expansion of an outreach TB screening service targeted at under-served population (including homeless shelters), based on an existing model that has been implemented in London since 2005, as well as funding to establish new services for testing and treating LTBI in people recently arriving from high TB incidence countries; the infrastructure and coordination of TB control services was also revised (64, 65). In addition, the development of new medical technologies has contributed to improved TB control, including for instance the development of a more specific diagnostic test for LTBI, the Interferon Gamma Release Assay (IGRA) (66, 67), and shorter chemoprophylaxis regimens (3 to 6 months) (68-70). The IGRA is a blood assay

that measures the cell-mediated immune response to selected antigens specific to *Mtb*, including the early secreted antigenic target 6 (ESAT-6) and the culture filtrate protein 10 (CFP-10), two proteins not produced by all strains of the BCG *M. bovis* as well as most non-tuberculosis mycobacteria; this makes the assay more specific than the TST which uses a non-specific Pure Protein Derivative (PPD) that contain over 200 mycobacterial antigens that causes cross-reactions with mycobacteria other than *Mtb* (67, 71). The availability of a more specific diagnostic test for LTBI and shorter treatment regimens have permitted some countries to expand the prevention of new cases through targeted screening and treatment of high risk individuals (including TB cases contacts) (72-74). While these improvements to TB control efforts are commendable, recent modelling work has suggested that in spite of the contribution of all current medical technologies, the current pace of decline in TB incidence even in low incidence countries in which steady decline is observed is still not enough to reach the 2015 End-TB global strategy target of TB elimination (12). A review of trends in 33 countries and territories with notified TB incidence <100 notified cases per million estimated that the average annual decline in the 27 countries in which steady decline was reported between 2000 and 2012 was about 3% per year, and that only 4 countries were likely to meet the pre-elimination target (<10 notified cases per million) by 2035 (12). The review also noted that the current decline rates were far below the 18% or 11% average annual decline required to reach TB elimination (<1 notified case per million) by 2035 or 2050 respectively (12). The WHO 2015 End-TB global strategy recognises that additional actions will be required to make substantial progress towards the goal of TB elimination, including for example addressing health inequalities in the society and the underlying social determinants of TB, and the development of innovative tools like a more effective preventive vaccine (12-14). Poverty reduction can be a longer term, complex endeavour requiring political will to be achieved. However, some poverty-related social determinants of health inequalities (SDH) may be modified more easily, and could represent useful targets for intervention in the short to medium term (e.g. good nutrition, better accommodation with adequate ventilation and UV lights etc.). The design of such targeted interventions can be informed by a better understanding of the pathways through which socio-economic deprivation affects the risk of tuberculosis.
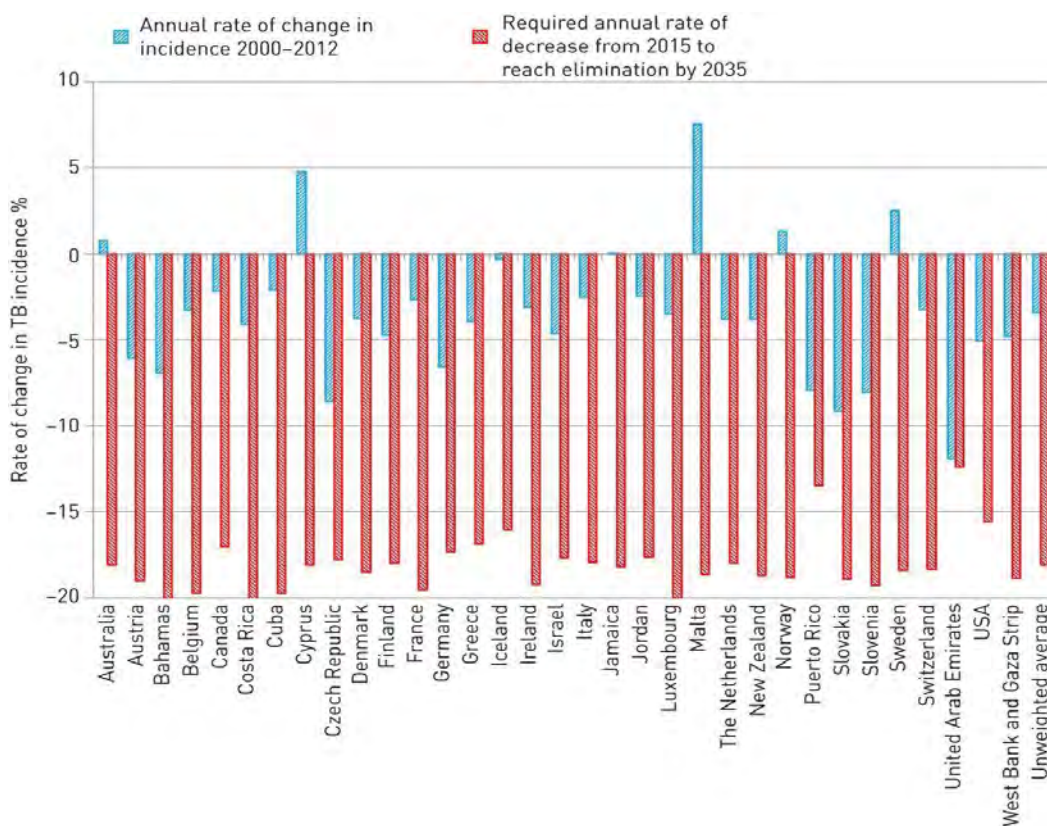
Figure 3.1: Observed versus required annual rate of change in tuberculosis (TB) incidence to reach TB elimination (less than one case per million) by 2035 in 33 low-incidence countries *(reproduced from Lonnroth et al 2015 (12), Creative Common Licence).*

3.4. BCG vaccination against tuberculosis

The Bacillus Calmette-Guerin (BCG) is an attenuated vaccine developed by the eponymous French scientists between 1908 and 1920 through over 230 successive in vitro subcultures of a strain of *Mycobacterium bovis* every 3 weeks (75, 76). The vaccine was first administered to humans orally in 1921, and has since being given mainly via the subcutaneous or intradermal route. The use of BCG vaccination as part of TB control programmes rapidly expanded after its introduction, especially in response to TB resurgence in Europe following the Second World War; it has been estimated that between 1948 and 1974, more than 1.5 billion infants and children were vaccinated with BCG, including through large vaccination campaigns by UNICEF, WHO and the Scandinavian Red Cross (76, 77). Nowadays, BCG remains one of the most widely used vaccines in the

world; it is part of the routine immunisation programme in more than 165/194 (85%) independent countries and territories, including at least 157 where universal vaccination of neonates is recommended (21), and the WHO estimates that the vaccine is given to about 100 million children every year (20). The BCG vaccine currently used is derived from various cultures of the initial BCG strain by various laboratories under different conditions, therefore with some genetic diversity between various strains; this has led some authors to argue that BCG should not be considered as a single vaccine, but as a family of closely related vaccines (75).

Efficacy of BCG vaccination against tuberculosis

The efficacy of BCG against tuberculosis has been controversial since the initial evaluations of the vaccine, with direct effect on national policies and recommendations. Most published studies around the world have reported good protection of BCG vaccinated infants and children against tuberculous meningitis and miliary, two severe forms of the disease commonly reported in young children. The results from these studies have been synthesised and discussed in at least four systematic reviews and meta-analyses (17-19, 78), with pooled average vaccine effectiveness (VE) against miliary and meningitis estimated at about 75% in case-control studies and over 80% in randomised control trials (RCT) (17, 19). The most recent systematic review of the six BCG trials in which these outcomes have been reported has estimated that on average the vaccine is associated with 85% (95%CI 69% to 92%) reduction in the risk of meningeal and/or miliary tuberculosis compared to placebo, with greater efficacy (90% to 92%) measured in the trials in which participants were less likely to have been sensitised to tuberculin prior to vaccination (neonatal vaccination or stringent tuberculin skin testing prior to vaccination) (19). However, the estimates of BCG's protection against pulmonary tuberculosis have been much more variable between study settings, ranging from no evidence of efficacy, for example in India's Tuberculosis Prevention Trial (TBPT) (VE = -5%, 95%CI -25% to 12%) (79), to strong protective effect, including in the British MRC trial (VE = 78%, 95%CI 69% to 84%) (80). Overall, eighteen RCTs of BCG efficacy against tuberculosis have been published, of which ten did not report any significant protection in the vaccinated group, whereas eight trials found significant protection ranging from 28% to 90% (19, 81). The possible reasons for this heterogeneity in efficacy have been widely debated, and are extensively reviewed by Fine (75, 82). It has been speculated based on the available evidence that one of the most important factors is prior infection with *Mtb* or sensitisation

by environmental mycobacteria (both detectable by positive reaction to the tuberculin skin test (TST)), which might interfere with BCG. Among other evidence, one argument advanced in support of this hypothesis is the geographical gradient in BCG efficacy noted in several reviews (17, 19, 75), with greater vaccine efficacy observed in studies at latitudes further away from the equator, which is consistent with greater exposure to the ubiquitous environmental mycobacteria in the warm and wet climates nearer the equator (27). Furthermore, Mangtani *et al* in their meta-regression analyses of BCG trials found that the pooled BCG efficacy was greater in trials in which participants were vaccinated in the neonatal period, or after stringent TST, thus less likely to have been sensitised to tuberculin prior to vaccination (19). Overall, the meta-analysis of all 18 BCG trials estimated BCG average efficacy against pulmonary tuberculosis of respectively 73% (95%CI 68% to 77%) at latitudes of ≥40°, 33% (95%CI 9%;50%) at latitudes of 20-40°, and 13% (95%CI 1% to 23%) at latitudes of 0-20°. The pooled BCG efficacy against pulmonary tuberculosis was estimated at 60% (95%CI 44% to 72%) when administered to neonates, and 75% (95%CI 69% to 79%) when given to children negative after stringent TST (19, 81). In summary, in spite of the variability in the observed levels of protection, the available evidence strongly suggests that BCG provides moderate protection against pulmonary tuberculosis when administered to uninfected and unsensitised (TST-negative) subjects.

The current understanding of BCG's mechanism of action remains limited, and it is plausible that the vaccine-derived immune memory wanes with time, leading to a gradual decline in BCG efficacy. This is important because while neonatal vaccination as recommended by most countries can help prevent severe TB in childhood, the wider impact of BCG on transmission depends on preventing pulmonary TB (the infectious form of disease), which is more common in later life. Data on BCG duration of protection also has implications for cost-effectiveness modelling of vaccination strategies (24). Unfortunately, there is little empirical data on the long-term efficacy of BCG against tuberculosis and factors that may affect it (24).

Only a few BCG studies followed-up participants beyond 15-20 years after vaccination, and the small number of events beyond 15 years of observation has limited the power of studies with longer follow-up. In a previous systematic review of the literature, Sterne *et al* reviewed data from ten RCTs with information on BCG efficacy in tuberculin-negative subjects in successive periods of time since vaccination (83). Seven trials reported efficacy beyond 10 years of follow-up, but only two trials provided data up to 20-years post-vaccination. The efficacy of BCG in seven of the ten trials reviewed appear to wane with time since vaccination at annual rates varying from 5% to 14%, although this decline was

only significant in the British MRC trial, with BCG VE dropping from about 84% 0-5 years after vaccination to 69%, then 59% respectively 5-10 and 10-15 years later (84), corresponding to an average annual decline of 8% (95%CI 3% to 13%) (83). The systematic review of studies on the duration of BCG efficacy was updated in 2013, with the addition of 22 non-experimental studies (including nine case-control and five cohort studies) to the ten trials in the previous review (81). The conclusions of this latter review were similar to the previous, with good evidence of BCG protection against tuberculosis for up to 10-15 years after vaccination, with effectiveness estimates of between 20% and 50% protection after 15 years (81). Only one study with a 60-year follow-up of participants of the US American Indians and Alaska Natives BCG trial reported an average VE over 50-years of 55% (95%CI 31% to 77%), with estimated VE = 48% 40 to 49 years after vaccination (85). Overall, the current evidence suggests that BCG-derived protection against tuberculosis may decline in time after vaccination, but also that the vaccine efficacy may last beyond 15 years, which would be longer than previously assumed. Given the variation in VE observed across settings, it is also possible that the rate at which the VE decline vary between settings.

Population impact of BCG vaccination against tuberculosis

The overall population impact of BCG vaccination on the TB epidemic has not been formally evaluated. There is good evidence of the direct impact of BCG on severe TB in children, consistent with the vaccine-derived protection that it affords against miliary and meningitis TB (78). For example, the analyses of routine surveillance data from Sweden revealed a seven-fold increase in the cumulative incidence of TB in children <5 years old in the 5 years following the discontinuation of universal infant BCG in 1975, compared to the cumulative incidence in the 5-years prior to discontinuation (86), although the overall increase in case number cases was assessed too small to warrant the reintroduction of universal vaccination in that country at the time. Similarly, in West Germany, a 2-year interruption of infant BCG in the birth cohort 1975-77 was associated with a ten-fold increase in the cumulative TB rates, with a re-introduction of routine vaccination due to the high TB rates (60 per 100000) in children under 5 years (87). More broadly, Trunz *et al* have estimated through modelling that the 100 million BCG doses administered to children throughout the world in 2002 may have prevented between 24000 to 36000 TB meningitis and 7300 to 26000 miliary cases in their first 5 years of life, making BCG a very cost-effective health intervention with a cost of only about 206USD (95%CI 150USD to

272USD) per Disability Adjusted Life Year (DALY) gained (78). By comparison, note that England's National Health Service (NHS) general threshold for public health interventions to be considered cost-effective is between 20000GBP (~25000USD) and 30000GBP (37500USD) per quality-adjusted life years.

On the other hand, there is little consensus on the magnitude BCG's contribution to interrupting TB transmission and the broader reduction of TB burden. The variations in measured levels of efficacy in different parts of the world, and the fact that the burden of TB remains very high in many developing countries in spite of high BCG coverage have often been used to support the argument that the vaccine has contributed little to TB control (75). Besides, the formal evaluation of the population impact of vaccination has been complicated by the fact that even in European countries where high levels of vaccine efficacy have consistently been reported, large scale vaccination was introduced at a time when several other TB control interventions were concurrently implemented (e.g. introduction of antibiotic therapy and chemoprophylaxis, mass TB screening with chest X-ray and TST), all of these in the context of rapid recovery in living standards following WWII (26, 88). However, there is some evidence in the literature in support of BCG's role in TB Control efforts. For instance, Bjarveit & Waaler (89) compared trends in TB notifications in the 1950-60s between three Scandinavian countries in which routine mass BCG vaccination was implemented (Norway Sweden and Denmark) to two US states where no mass BCG was employed (Upstate New-York and Ohio), but with otherwise comparable TB control programmes and surveillance systems. Although TB had declined in all five settings over the study period, the average annual rates of decline in TB and pulmonary TB (PTB) incidence in the birth cohorts that had received BCG 5-10 years earlier were 2-3 times faster than the same birth cohorts in the US states with no routine BCG, whereas the pace of decline were similar in all five settings in the older birth cohorts which did not benefit from BCG, therefore supporting the hypothesis that BCG may have been responsible for some acceleration in the pace of TB decline (89). Similar findings were reported by Styblo & Meijer when comparing TB rates in Norway and Denmark to The Netherlands where BCG was not used routinely, although it was more difficult to disentangle the indirect effect of BCG from that of other interventions (90). Using model-based data, Brewer *et al* (91) suggested that in the USA, the annual BCG vaccination of 10% TST negative non-HIV infected children <15 years and 1% TST negative adults ≥15 years could help prevent about 17% TB cases over 10 years, assuming a vaccine effectiveness of 50% (between 16% cases if VE = 34% and 22% cases if VE = 70%). The importance and potential contribution of TB prevention through vaccination to the global fight against TB

have also been explored in numerous mathematical models in recent years, including various vaccination strategies, as well as the potential impact of new vaccines that could interrupt various stages of TB natural history (e.g. prevention of infection or pre-exposure vaccination, prevention of progression to disease in infected individual or post-exposure vaccination) (16). Most models concur that TB vaccines with better and more consistent efficacy than BCG would greatly contribute to reducing the global burden of TB (16), and there are ongoing efforts to develop more effective TB vaccines (22, 23).

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SECTION A – Student Details

Student	Patrick Nguipdop Djomo
Principal Supervisor	Punam Mangtani and Laura Rodrigues
Thesis Title	Tuberculosis in England, a high-income Western European setting with low incidence: Recent trends, Social determinants and Prevention through BCG vaccination

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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Where is the work intended to be published?	Thorax
Please list the paper's authors in the intended authorship order:	Patrick Nguipdop-Djomo, Laura C. Rodrigues, Ibrahim Abubakar, Punam Mangtani
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the reseach idea, obtained and prepared the various datasets. I conducted the statistical analyses and interpretation of results with advice from my supervisors and co-authors, and I lead the manuscript preparation, including writing the initial draft and implementing revisions following

	discussions and comments from my supervisors and co-authors.

Student Signature: _____   Date: _27/2/2017_

Supervisor Signature: _____   Date: _27/2/2017_

4. <u>Manuscript 1:</u> Trends in tuberculosis notification rates in England between 1983 and 2014, a 30-year retrospective analysis

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Abstract

Background: Tuberculosis (TB) notification rates in England and Wales (EW) have ceased to decline from the 1980s, due to increased incidence in foreign-born residents and plateauing of rates in the UK-born population. Long-term trends in the UK-born population and their potential determinants have received relatively less scrutiny than the foreign-born population because of the greater burden of disease in the latter group.

Objectives: To investigate trends in TB notifications rates in England and Wales between 1983 and 2014 in relation to place of birth, age-group and ethnicity, and assess the interplay between these factors and the long-term trends in the UK-born population.

Methods: Annual notification rates were calculated using numerator data from the 5-yearly National Tuberculosis Surveys of 1983, 1988, 1993 and 1998 (with information on age, sex, place of birth, ethnicity, and clinical data of notified TB cases) and routine notifications from the Enhanced Tuberculosis Surveillance system (ETS) from 1999 to 2014. Adjustment for changes in age-and-sex population composition with time was done by direct standardisation using the 2013 population estimates as the standard population.

Results: The overall TB rates declined at an average annualised rate of 6.5% between 1983 and 1988 (from 13.2 per 100000 to 9.4 per 100000), with similar trends in the UK-born and foreign-born populations. However, the rates ceased to decline from 1988, and had increased to 11.1 per 100000 by 1998, and 15 per 100000 by 2005, plateauing thereafter until 2012. The reversal of trends from 1988 to 2005 appeared to be driven by increased foreign-born rates and plateauing of rates in the UK-born population. However, since 2006, rates have been declining in foreign-born residents, at an average annual pace of 7% (from 121 per 100000 in 2005 to 63 per 100000 in 2014), whereas TB rates in UK-born have continued to be stagnant. The analysis by age-groups shows that in the UK-born population, rates have continued to decline in the elderly (≥75 years old) age groups since 1983, whereas rates in younger adults have gradually increased, and those in children and older adults have plateaued. A stratification by ethnicity also suggested that between 2000 and 2014, TB rates have been declining in UK-born ethnic minority groups, whereas they have been stagnant in the White ethnic groups.

Conclusions: The failure of TB rates to decline in the UK-born population of England and Wales for over a quarter of a century, especially in young adults and in the White ethnic group, suggest the persistence of local pockets of ongoing transmission that challenge TB elimination efforts, and underscore the fact that current TB control efforts have not had the success expected in these groups, in spite of the availability of effective treatments and accessible services.

Introduction

The tuberculosis (TB) notification rate in England and Wales (EW) in 2014 was estimated at 12 per 100,000 subjects (1), the same level reported over 30 years ago in 1983 (2). It is well documented that from the mid-1980s, trends in TB rates in several developed Western countries deviated from the rapid and steady decline observed since the early 20th century, to either stagnate or increase (3, 4). The failure of annual TB rates to decline was first noted in the United States (US) in 1985 (4), with similar observations following from several other developed low TB-incidence countries shortly after, including England (3). The resurgence of TB in several developed countries was due to a combination of TB rates ceasing to decline in native populations, and to a greater extent, a steep rise in the number of TB cases among foreign-born migrants from high TB incidence parts of the world (3). The latter was a direct consequence of increased global population mobility, and reflected migration patterns from low-income developing countries where the TB burden is greater, towards high-income developed countries with low-TB incidence. In most developed Western countries, more than 50% of all TB cases are now reported among foreign-born subjects (5, 6). Since the resurgence of TB, the epidemiology of tuberculosis in foreign-born migrants in developed countries has received much attention, including in the UK (7-9), and trends in these groups are closely monitored by surveillance systems. Understandably, more resources have been allocated to fighting TB in these groups, and the TB control strategy and measures have been intensified and adapted to the changing face of TB epidemiology in these developed low-incidence countries.

However, while comparable countries (e.g. USA, Germany, the Netherlands) have been able to bring their TB rates under control and return to a sustained decline in annual incidence over the past 10-20 years (5, 6), TB notifications in EW have steadily increased since the mid-1980s, from under 10 per 100,000 subjects in the mid-1980s to a peak of 15.6 per 100,000 subjects in 2011 (10). The number of TB cases has dropped slightly since 2012 (1), but the decline appears to be mostly among foreign-born cases, with very little change to TB rates in the UK-born population (1). It is also unclear to which extent the recent decline among foreign-born populations in EW is attributable to specific TB control measures or other factors, for example migration patterns or global TB trends, and whether this decline will be sustained in the medium to long term.

The stagnant TB incidence among UK-born population in EW have received relatively less scrutiny than trends in the foreign-born population. The initial analyses of increased notifications from the mid-1980s suggested a possible contribution from the increase in

life expectancy and shift in the population age distribution towards older age groups, in whom immune-senescence increases the risk of disease due to reactivation of Latent TB Infection (LTBI) (11, 12). Other investigations have also noted increasing rates among UK-born subjects from ethnic minorities, who are at greater risk of Mycobacterium tuberculosis (*Mtb*) exposure and infection. However, the 2015 TB surveillance report in England notes a decrease in the number of UK-born cases aged ≥65 years old over the past 10 years, notably those from the White ethnic group, which contrast with the lack of decline in other age groups (1). In contrast to foreign-born TB cases, for whom a substantial proportion of cases is thought to result from *Mtb* infection prior to entry into the UK, thus affected by the global TB epidemiology, it is likely that a non-negligible amount of TB in the UK native population is caused by recent local transmission. The corollary would be that national policies can be tailored to interrupt such transmission, and in doing so, progress further towards TB elimination within the country. A better understanding of the dynamics and factors that affect TB trends in the UK born population can help inform those policies.

In this study, I investigated trends in the epidemiology of tuberculosis in England and Wales between 1983 and 2014 in relation to age-groups, place of birth and ethnicity. My main objectives were to gain further insight into the interplay between place of birth and ethnicity, and to assess if those three factors affect the trends in the UK-born population.

Methods

Tuberculosis Notifications (Numerators) Data Sources

1983-1998: Before the establishment of a central TB surveillance system in EW in 1999, the statutory TB notifications reported at the central level through the Notification of Infectious Diseases system (NOIDS) did not record information on patient characteristics such as the ethnicity, country of birth, time since entry in the UK, and clinical details (date of diagnosis, site of disease, previous treatment, bacteriology and histology results, drug sensitivity), making it difficult to examine the effect of such parameters on TB trends. These variables were examined periodically through special national surveys organised starting in 1965, then done in 1978-79, and approximately every 4-5 years thereafter until 1998 (13). For this study, I used data from the 1983, 1988, 1993 and 1998 national TB surveys, respectively conducted by the British Medical Research Council (MRC – 1983 and 1988 surveys), and the Public Health Laboratory Service (PHLS)/British Thoracic Society (BTS)/Department of Health Collaborative Group (1993 and 1998 surveys). The detailed

methods for these surveys are published (2, 14-16). Briefly, in the survey year, a copy of all TB notification forms received from all 403 local authorities in England and Wales were sent to the survey team, which in turn obtained from the notifying clinicians further information for each notified case using a clinical form. The detailed demographic and clinical information required for the analyses was extracted from the clinical form, with additional information on drug-sensibility obtained from the regional centres for tuberculosis bacteriology and the Mycobacterium Reference Unit of the PHLS. The notifications copies were also checked by the survey team against the weekly returns routinely made by local authorities to the Office of Population Censuses and Surveys (OPCS), to ensure that all notifications were captured.

In line with previous national TB surveys, the 1983, 1988 and 1993 surveys collected data for the first 6 months of the year from 02nd January to 02nd July, and the number of TB cases reported over the survey period was then multiplied by an appropriate scaling coefficient that account for the survey period as well as seasonal differences in the notifications, to obtain estimates for the whole year. I obtained each survey's scaling factor from the official reports (2, 14, 15) (respectively 1.953 for 1983, 1.9348 for 1988, and 1.886 for 1993) and applied the same methodology to calculate numerators for these three survey years.

1999-2014: For this time-period, I used TB notifications to the central continuous TB surveillance system (also known as the Enhanced Tuberculosis Surveillance system or ETS). This system was piloted in EW in 1998 alongside the last national TB survey (16), and was formally introduced in 1999. The notification of all TB cases by clinicians to the surveillance system is compulsory, with each case report including detailed demographic and clinical information. Details on the surveillance system is available from the annual surveillance reports (1). Anonymised TB notification data were kindly provided by Public Health England (PHE).

Population Estimates (Denominators) Data Sources

For each notification year, I obtained population estimates by age, sex, ethnicity and place of birth from the Office for National Statistics (ONS) Labour Force Surveys (LFS). The LFS is a continuous large national survey of household living at private addresses, whose chief purpose is to provide information on the residential labour market (17). The survey data are primarily used by the UK government for planning and monitoring various social and economic policies, but they also routinely used for various health statistics and they have

been used to monitor TB notification rates since the 1970s (17). The LFS were done between March and May every two years from 1973 to 1983, then annually from 1984 to 1991 (including quarterly data collection throughout the year and a boost survey between March and May), and they have been quarterly since 1992, with various enhancements (18). For the analysis period 1993 onwards, I used LFS data from the 'Spring' quarter, which correspond to the "March to May" period used in previous LFS surveys. Briefly, the survey includes the selection and interview of around 150,000 individuals from about 60,000 households every quarter, using a complex sampling design (17, 18); the reported response rates vary between waves from 55 to 80%, and the ONS carry out various adjustment and weighting after data collection to account for non-response, as well as reweighting using exact population census estimates (17, 18). The details on the surveys' methodology and changes in time are described in details in the LFS documentation (18).

LFS data are subject to sampling variability given the survey design and sample size. However, an advantage of the survey data over ONS mid-year population estimates is that whereas the latter are aggregated by age-and-sex, the LFS also provide detailed concurrent information by place of birth, ethnicity and time since entry in the UK for those subjects born abroad, useful denominators to examine various trends in TB rates. Using this population denominator also allows the comparison of our estimates to those in the literature, and existing surveillance reports on TB by ethnicity and place of birth, given that routine statistics and previous national TB surveys used LFS data as denominators.

Statistical analysis

Overall and subgroup specific crude annual TB notification rates were obtained by dividing the number of TB cases by the corresponding denominator, and the data were plotted in graphs. I also calculated age and sex standardised rates to investigate any effect of change in the population structure on trends, using direct standardisation by 5-year age-sex groups with the 2013 LFS population estimates as the standard population. Average trends in TB rates between time periods t_o and t_a were examined by calculating the annualised percent change (APC) using the formula **APC(%) = 100*([TB rate at t_a / TB rate at t_0]$^{(1/[t_a-t_0])}$ - 1)**. The APC were based on standardised rates, thus accounting for changes in the population age structure. All rates are based on full population data, including the very large population denominators (hundred thousand to millions person per year), which combined with relatively low TB rates, lead to extremely small standard errors and very narrow 95% confidence intervals.

I examined trends by place of birth, contrasting the UK born to the non-UK born population (called here foreign born), then by broad ethnic group. Self-defined ethnicity in the national TB surveys and the ETS are based on the standard categories used by the ONS for censuses and LFS. The information on ethnicity was merged into four groups, respectively White, Indian Subcontinent (including Indians, Pakistani and Bangladeshi), Black (including Black Africans, Black British, Black Caribbean, and Black Other[1]), and Mixed/Others (including Mixed White/Other and Other Ethnicity). I also examined the distribution of type of disease by comparing cases with pulmonary involvement (Pulmonary TB or PTB) to those with no pulmonary involvement (Extra-pulmonary TB or EPTB).

The information on whether some subjects were born in the UK and the ethnicity was missing for a small proportion of notifications since the introduction of the continuous surveillance system. Besides the analysis of the subset with complete data, the association between missingness and other notifications' characteristics was first investigated by logistic regression. Variables associated with missingness were then used as predictors in multiple imputation by chained equations (MICE) models to impute ten datasets. As a sensitivity analysis for place of birth and ethnicity subgroups, rates were computed for each imputed dataset and then averaged across all ten datasets.

All analyses were performed in Stata 14® and graphs were produced using Microsoft Excel®.

Results

The estimated numbers of TB notifications for the 5-yearly survey years 1983, 1988, 1993, and 1998 were respectively 6449, 4659, 5102 and 5653. There were 117655 TB cases notified to the Enhanced Tuberculosis Surveillance system (ETS) from its inception in 1999 till 2014, increasing gradually from 5692 cases in 1999 to a peak of about 8300 notifications in 2011 - 2012, then dropping to 6635 cases in 2014 (figure 1). Over the study period, the population of EW increased from about 49 million in 1983 to over 57 million in 2014; this included more than a doubling in the estimated population of foreign-born subjects from about 3.5 million in 1983 to over 7.5 million in 2014.

The information on whether patients were born in the UK or abroad was available for 96% (21089/21863) of notifications in survey years, and 92% (108512/117655) cases in the ETS

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[1] Number of TB cases and population for Black British, Black Caribbean (formerly named West Indians) and Other Blacks were very small, therefore grouped with the larger Black African group.

(supplementary table 4.1). The proportion with missing data on place of birth in the ETS steadily declined over time from 13% in 1999 to only 2% in 2014. The information on the self-reported ethnicity was missing in about 4% cases notified between 1999 and 2014, and less than 1% in the surveys data. Missing data on place of birth was strongly associated with the year of case report, age, type of TB, ethnic group and sex; and missing data on ethnicity was strongly associated with the year of case report, age, type of TB, and whether UK-born or not. The detailed results are presented in supplementary tables 4.2 and 4.3. All analyses reported below were repeated using the imputed datasets as a sensitivity analysis, and the results were identical, including all trends. Therefore, only the complete case analyses are reported here.

Overall Tuberculosis Notification Rates in UK-born and Foreign-born populations

The detailed trends in TB notifications and TB rates overall and by place of birth are presented in figure 4.1. Between 1983 and 1988, overall TB notification rates (per 100000 population ($/10^5$) in EW declined from 13.2 to 9.4, equivalent to an average annualised percent change (APC) of -6.5% per annum (pa). The TB rates were nearly 10 times higher in foreign-born than in UK-born subjects, but the decline was observed in both UK-born (APC $\approx$ -7% pa) and foreign-born subjects (APC $\approx$ -6% pa). The overall rates ceased to decline from 1988, with a slight increase to $11.1/10^5$ by the 1998 survey, an average APC of about +2% pa During that period, there was an average increase of about +3% pa among foreign-born subjects (from $60/10^5$ in 1988 to $80/10^5$ in 1998). TB rates in the UK-born population went from about -7% pa decline in the 1983-1988 period to become stagnant at about $5/10^5$ from around 1988 onwards. The steady increase in the overall TB rate continued after the introduction of the ETS in 1999, until 2005 when rates peaked at about $15/10^5$ and remained unchanged until 2012. The overall TB rates seem to be declining since 2013, with a lower notification rate of $12/10^5$ reported in 2014 (see figure 4.1).

Between 1999 and 2005, TB rates in foreign-born population rose by an average 6% per annum (average $APC_{1999-2005} \approx$ +6% pa), while TB rates in UK-born subjects remained stagnant. During that period, the proportion of foreign-born cases who had developed TB within 5 years of entry to the UK also increased, from 45% in 1999 to 60% in 2005. The foreign-born population TB rates started to decline consistently from 2006, with an average annual percent decline of 7% pa between 2005 and 2014 (including ~14% decline between 2013 and 2014 from $72/10^5$ to $63/10^5$). The proportion of foreign-born TB cases who were recent migrants also reduced over that period, dropping back to 40% by 2014. The

notifications in the UK-born population did not significantly decline over this 2006-2014 period. The direct standardisation by age and sex did not change any of the observed trends (see figure 1). All subsequent results presented are based on age-and-sex standardised analyses.

Type of disease

When looking at the trends in the numbers and distribution of type of TB (figure 4.2), the rapid increase in TB rates among foreign-born until 2005 was due to a near 10% average annual increase in the number of both pulmonary (PTB) and extra-pulmonary (EPTB) cases, going from about 1500 cases each in 1999 to respectively 2700 and 2600 cases by 2005. The number of foreign-born PTB cases ceased to rise between 2005 and 2012, and the yearly increase in EPTB cases slowed from 10% over the same period to about 3% per year. From 2013 and 2014, the numbers of foreign-born cases for both type of disease appear to be declining in recent years (about 10% and 17% decline between 2013 and 2014 respectively for PTB and EPTB). In the UK-born population, the numbers and distribution of type of TB seem to have been relatively stagnant since 1988 onwards.

Trends in Tuberculosis Notification Rates by Age Groups

The examination of notification rates by age groups (figure 4.3) show that overall, the steady decline in TB rates observed in the elderly population aged ≥75 years in the 1980s has continued at a relatively similar pace until 2014 (figure 4.3a). Meanwhile, rates in young adults aged 15-34 years rapidly increased from 1988, progressively overtaking TB rates in all other age groups to move from being the age group with the 2nd lowest rates in 1988 (after children aged 0-14 years) in 1988 to become the one with the highest TB rates by 2001.

Focusing on the foreign-born population (figure 4.3b), the increase in TB rates from 1988 was observed in nearly all age groups, although the rates in the elderly population ceased to increase from 1993. By 2005, TB rates in all age groups except the elderly were approximately double those observed in 1988, with for example a steep increase among young adults aged 15-34 years from TB rate of about $83/10^5$ in 1998 to peak at $166/10^5$ in 2005, and among children aged 0-14 years from $15/10^5$ in 1988 to $39/10^5$ in 2005. Since 2005, TB rates appear to be declining steadily in all age-groups in foreign-born populations, with the fastest decline observed in the group with the highest rate, young adults aged 15-34 years (APC ≈ -9% pa between 2005 and 2014).

In the UK-born population (figure 4.3c), the decrease in TB rates observed in the early 1980s appears to have continued at relatively similar pace in the older age-group (≥75 years old). A similar decline in TB rates was observed among subjects aged 55-74 years, until around 2005 when rates ceased to decline. In contrast to the older age-groups, the TB rates in young adults (15-34 years) gradually increased to move from the age-group with the 2nd lowest rates after children aged 0-14 years in 1988 to being the group with the 2nd highest rates after the elderly by 2005, and they have relatively been stable since then. The notification rates in the other age groups (0-14 and 35-54 years) ceased to decline around 1988 and they have remained relatively stagnant until recently.

Ethnicity and Tuberculosis Notification Rates

The trends in TB rates by ethnicity are presented in figure 4.4. It appears the rapid increase in TB rates since the 1980s was mostly driven by a steep increase in TB rates among the foreign-born Black ethnic group (figure 4.4b), as well as the failure of TB rates to decline among foreign-born from the Indian sub-continent (ISC; Indian, Pakistani and Bangladeshi). Among foreign-born subjects with Black ethnicity, TB rates increased from $48/10^5$ in the 1988 survey to $169/10^5$ in the 1998 survey, and from $190/10^5$ in 1999 to peak at $356/10^5$ in 2005, overtaking the ISC as the group with the highest TB rates in EW among foreign-born subjects by 2001; this corresponded to 18 years of over 10% pa year-on-year increase in rates. Since 2005, TB rates in Black foreign-born subjects have been falling at a steep and steady pace of about 12% per year, dropping below rates in the ISC ethnic group in 2009. The TB rates in the foreign-born ISC ethnic group have also been declining since 2009, by an annual average of 8% pa, although they remain higher than in all other ethnic groups in 2014.

On average, TB rates in the UK-born ISC and Black minority ethnic groups have been declining between 2000 and 2014, with the trends since 2008 mirroring those in the same ethnic groups in the foreign-born population (figure 4.4c). On the other hand, although TB rates in the White majority ethnic group and Mixed and other ethnic groups are much lower than among ethnic minorities, they have mainly stagnated over the past 15 years.

Discussion

Summary of main findings

This long-term retrospective analysis reveals a relatively complex dynamic in the TB epidemiology between various population subgroups that underpins trends in TB notification rates in EW over the more than 30-year study period. In agreement with existing literature, I found that a major contributor to the failure of TB rates to decline from the mid-1980s was the rapid rise in TB rates in the foreign-born population. However, our analysis further highlighted the fact that this steep increase in rates was disproportionately in the Black ethnic group and among young adults since 1993, while rates in foreign-born population from the Indian subcontinent (ISC) remain relatively stable. I also found that after peaking in 2005, TB rates in the foreign-born population groups appear to have been declining at a steady pace in the past 10 years, with the steepest drop observed in young adults and the Black ethnic group.

On the other hand, TB rates in the UK-born population ceased to decline in the mid-1980s and have since been stagnating. I found that TB rates in the elderly have been declining consistently over the analysis period, whereas TB rates in other age groups, including young adults have increased then plateaued. In general in the UK-born population, TB rates appear to have been declining consistently in the ethnic minority groups since 2008, whereas they have remained relatively stable in the White ethnic group.

Tuberculosis in the foreign-born population

The rapid increase in number of cases and TB rates in the foreign-born population in the mid-1980s, especially the Black ethnic group, is not surprising and reflected migration patterns at that time. During that period, the UK experienced large new immigration currents from sub-Saharan Africa (SSA), a part of the world in which TB incidence rates are among the highest in the world. This population movement was a combination of migration from low-income countries in SSA towards higher income countries like the UK, in search of better life opportunities in the context of the global economic recession of the 1980s, and refugees and asylum seekers fleeing hardships from their home countries (19, 20). This is further evidenced by the fact that the steepest increase in TB rates was observed among working-age adults, which represent the largest demographic group of migrants (20). The number of asylum applicants to the UK also increased steeply over that period, for example from about 5000 in 1987 to over 73000 by 1991 (21). The more stable rates in foreign-born subjects from the Indian subcontinent (ISC) are likely explained by older and

relatively stabilised migration patterns, dating from the 1950-60s, which were restricted by the 1970s following the passage of the UK *Immigration Act 1971*.

It is likely that the emergence and spread of HIV in the 1980s and the associated resurgence of TB in sub-Saharan Africa (22) have also contributed to increasing TB rates in foreign-born young adults in EW, especially in those from Black African ethnic background. The linkage of data from the 1993 and 1998 national TB surveys to HIV surveillance databases showed that in 1993, 8.5% TB cases in Black Africans aged ≥15 years were HIV positive, increasing to 10% in 1998 (23). Furthermore, an audit of surveillance data from 1999 to 2003 suggested that about 20% of TB cases reported in non-UK born Black Africans aged ≥15 years were co-infected with HIV (24). However, the impact of HIV on overall TB trends in foreign-born subjects was slightly mitigated by the fact that HIV/TB coinfection rates were much lower in the other foreign-born ethnic groups. For example, the HIV/TB co-infection rates in foreign-born TB cases aged ≥15 years from Indian, Pakistani or Bangladeshi ethnic background remained stable at 0.4% in 1993, 1998, and between 1999 and 2003 (at a time when they constituted between 40% and 50% of foreign-born TB cases aged ≥15 years, compared to 11% to 25% for Black Africans) (23, 24), with an overall rate of HIV/TB co-infection among all foreign-born TB cases aged ≥15 years between 1999 and 2003 of 7.2% (24).

The reasons behind the decline in TB rates among foreign-born subjects observed since 2006 are less clear. The close monitoring of TB epidemiology in foreign-born populations in most low-incidence countries since the disease resurgence from the mid-1980s to early 1990s may have played a role in disease control. In several countries, including in the UK, the TB prevention and control strategies have been adapted to account for changes to TB epidemiology, and substantial investment were made in control efforts targeting TB in foreign-born subjects. Such efforts included for example the introduction or scaling up of various combinations of pre-entry, upon-entry and post-entry screenings for active pulmonary tuberculosis and treatment, and treatment of LTBI (25). However, there is little evidence of the effect of these specific measures on the TB trends in England. Interventions like chest X-ray screening of travellers for tuberculosis at ports of entry have been shown to have a very low yield and not to be cost-effective (26, 27). The implementation of global system for the systematic pre-entry screening of prospective travellers from 101 high TB burden countries towards the UK only completed recently between 2012 and in 2014 (28, 29). Before that, the pre-entry system was piloted between October 2005 and September 2012 in only 15 countries (Bangladesh, Burkina Faso, Cambodia, Cote D'Ivoire, Eritrea, Ghana, Kenya, Laos, Niger, Pakistan, Somalia, Sudan, Tanzania, Thailand and Togo), with

the analysis showing an annual screening yield during the pilot period ranging from about 10 cases in 2006 to a maximum of just over 100 cases in 2009 (29). Overall, while the now expanded pre-screening programme may have an impact on future TB epidemiology in foreign-born subjects, it is unlikely to explain the decline in rates in the foreign-born populations, observed since 2006. Overall, while investments in TB control have gradually improved, and public health control efforts have been scaled up, there is no obvious public health interventions to which the steady decline in TB notifications observed in the foreign-born population since 2006 can be attributed.

Meanwhile, prior publications have highlighted the strong correlation between immigration policies and migration patterns, and tuberculosis rates in low-incidence high-income countries (30). Our analysis also noted the positive correlation between the trends in TB rates in foreign-born subjects and the proportion of foreign-born cases who were recent migrants. It is interesting that the 2005 peak in TB incidence among foreign-born observed in EW and subsequent decline in rates coincided with a similar pattern in the number of asylum applications to the UK three years earlier and changes to migration laws. In 2002, the UK passed the *National, Immigration and Asylum Act 2002*, a major policy change aimed at discouraging asylum seekers and some migrants from coming to the UK, including a range of measures such as curtailing support and rights for asylum seekers. The changes to the immigration laws that lead to a drastic reduction in the number of asylum applications in the UK, from a peak of 103081 applications in 2002 to 60047 in 2003, and 22644 by 2010 (31). Although asylum seekers may only constitute a small proportion of net migration to the UK, this population group tend to include more vulnerable and relatively poorer subjects, compared to other migrants from the same country of origin, thus likely to have higher risk of disease. Several authors have reported the high prevalence of TB and LTBI among asylum seekers (32, 33), and given that the risk of active disease is highest in the 2-5 years following infection, it would not be surprising if recent trends in TB rates among foreign-born subjects were significantly influenced by the number and country of origin of refugees and asylum seekers. The trends in number and provenance of asylum seekers to the UK may have contributed to the decline in TB rates observed in the foreign-born population since 2006, especially in the Black African groups in which the number of asylum application dropped almost exponentially from over 36000 in 2002 to approximately 8500 by 2010 (31), while TB rates fell from about 350/10^5 in 2005 to 125/10^5 by 2013. There was no major change in TB public health policy or public health interventions around 2004-2005 or earlier, to which the sudden and complete reversal in TB trends in foreign-born population may be solely attributed. As the

number of asylum applications to the UK has been increasing since 2011, health policy makers may need to be aware of its potential influences on future TB trends, which would be important for planning. Finally, TB trends in the foreign-born population are likely also influenced by the trends in their respective country of origin. Substantial gains have been registered in the past 10 years in the global fight against TB, with significant reduction in incidence and disease burden in many countries (34, 35). It is therefore possible that part of the recent decline in TB rates in the foreign-born population of EW may be ripples from the shift in the global epidemiology of TB, although this would difficultly by itself explain the near 10% average annual decline in foreign-born TB rates registered in recent years.

Tuberculosis in the UK-born population

In contrast to the foreign-born population in which TB rates have been dropping in recent years, TB rates in the UK-born population of EW appear largely unchanged in over two decades. It is not surprising that in the UK-born population, the rates are higher in British Asians and Black ethnic minority groups compared to the White ethnic majority. These groups have a higher risk of TB due to their links to high-TB incidence regions the world, including through relatives and community contacts, as well as possible travels to these areas (36, 37). Note that the TB trends in the UK-born ethnic minority groups in recent years have largely mirrored those in their respective foreign-born counterparts, including a similar steady decline in rates observed since 2005. One hypothesis is that the greater proportion of TB among UK-born subjects from ethnic minority groups results from transmission within the UK rather than during travels abroad in the high-TB incidence regions to which they have links. It also highlights the importance that TB control efforts in the foreign-born population may play in reducing transmission locally. But note that the White ethnic group still account for more than 60% of UK-born TB cases, and the rates in this group have mostly been stagnant.

The trends by age groups in the UK-born population also suggest that the status quo is not a mere consequence of an aging population and a shift in the age distribution of disease towards the elderly. Overall in the UK-born population, TB notification rates in the older population groups have continued to decline at fairly steady pace over the past three decades, whereas the incidence in younger adults have increased in the mid-1980s, then stabilised. Disease in the adult population is more likely to be a consequence of recent infection rather than reactivation of an older infection, especially given the very low risk of infection in the UK (e.g. average annual risk of infection estimated to <4 per 1000 in

1971-73 and rapidly declining) (38). This suggest that ongoing *Mtb* transmission within the UK may substantially contribute to the failure of TB rates to decline in the UK-born population.

It has been noted that in countries with low TB incidence, including the UK, the disease tends to be concentrated in specific groups with higher risk, and often limited access or contacts with the health system (5). Tuberculosis has long been known as a disease of poverty, with high prevalence reported in groups like the socio-economically deprived, homeless people and ex-prisoners. There have been consistent reports of rising levels of poverty in EW over the past three decades, which may have contributed to sustaining low levels of TB transmission in some segments of the population. For example, the Economic and Social Research Council (ESRC)-funded Poverty and Social Exclusion in the UK surveys (PSE) have estimated that in 2012, household overcrowding was back to levels found in 1983, with nearly 10% household affected, and also that number of people living in inadequate housing conditions had increased from 9.5 million in 1999 to nearly 13 million (39). A rise in the number of homeless subjects and rough sleepers has also been noted across the country (40). However, poverty does not directly cause TB, and it would be helpful to better understand the pathways through which poverty and deprivation increase the risk of TB in the adult UK-born population. The insight that such an analysis will provide can help inform the TB control efforts directed at this specific population group.

Strengths and Limitations

My interpretation of TB trends in EW is dependent on the results being accurate, unbiased, and not substantially affected by artefacts. The population denominators used to calculate the rates were derived from the Labour Force Survey (LFS) data. These surveys are designed to be representative of the resident population, and the datasets offer readily available estimates for different population subgroups that are otherwise not routinely available, for example estimated numbers by place of birth, ethnicity and age groups; this is the reason the data is commonly used for various official health statistics and for policy planning (17). A limitation of the LFS data is that some smaller segments of the population may be underrepresented (e.g. older subjects from non UK-born minority ethnic groups) (18), which in turn may lead to unstable and/or inaccurate estimates. While this limitation may affect the accuracy of TB notification rates estimates in smaller population groups, it is unlikely to have had great effect on the trends over the more than 30-year study period,

especially given that the same denominator source was used throughout. Another challenge with the denominator was accounting for changes in the population structure over the long study period, as well as the doubling of the foreign-born population. I explored this through direct standardisation or age and sex, and there was very little effect on the TB rates trends.

The TB notifications on the other hand depend on the completeness of reporting. The data I used to examine trends from 1983 to 1998 were collected as part of an extensive national survey that included an audit of routine notifications (2, 14-16), and therefore unlikely to be affected by under-notification. An audit of the ETS using capture-recapture methods in the four years 1999-2002 following its implementation suggested about 15% under-notification overall, but improving in time (41). A triangulation exercise that compared TB reports from routine notifications, the national surveys (and the surveillance system from 1999) as well as laboratory data between 1988 and 2000, also found that trends in notifications over that period were not greatly affected by completeness (42).

While I acknowledge that the results presented here are purely descriptive, no obvious events in the study timelines could be found that may have caused an artefact that affected or explained the observed trends. A pan-London surveillance system – the London TB Register - was introduced in 2002 to improve TB surveillance across the capital city, given that London accounts for over one-third TB cases in EW (43). However, it did not have any visible effect in the trend, as there was no sudden change in the number of TB cases reported following the implementation of the register. Another significant change to TB control was the introduction of a mobile screening unit in London in April 2005, for active case finding in hard-to-reach groups like the homeless (44, 45). But this outreach service only report about 100 cases per year (44), so it cannot explain the peak in TB notification rates in 2005, nor the subsequent steady decline observed in foreign-born and UK-born ethnic minorities since 2006. Overall, in spite of the data limitations, the estimates presented here are likely to be a robust reflection of the underlying trends in TB rates in England and Wales over the study period.

I also note that TB surveillance data published since the present analyses were conducted have shown a steady year-on-year decline in TB rates in the UK-born population in recent years, including across all ethnic groups (46). Although the relative distribution of cases by ethnic group has remained stable, the number of UK-born TB cases has dropped by 22.7% between 2012 and 2015, including a 21.5% decline in White UK-born subjects (46). This correspond to an average 8% annual decline in the overall number of UK-born TB cases over this 4-year period. However, the reason for the recent decline after decades of

stagnation are not clear. It has been speculated that this might be linked to a combination of a reduction in the number of foreign-born cases (via the pre-entry screening programme and also lower number of migrants from high TB burden countries), and better TB control measures in the UK (including improvement in TB control and early impact of the new programme of testing and treating latently infected (LTBI) subjects) (46). Investigations are required to understand factors that underlines these recent trends and whether they are likely to be sustained; but these are beyond the scope of this thesis.

Conclusions and recommendations

In summary, my analyses of trends in TB notification rates in various population subgroups in EW reveals a relatively complex epidemiology. It appears that TB rates have been declining at steady pace in the foreign-born populations as well as the UK-born ethnic minorities in recent 8-10 years. The trends in the foreign-born population may have been affected by immigration policies to a greater extent than public health interventions. This deserves further investigation, because if likely, this link would be important for forecasting future trends as well as policy planning, including, for instance, designing targeted and acceptable cost-effective interventions or strategies. At the same time, the close correlation between rates in the foreign-born population and UK-born ethnic minority groups highlights the importance of close monitoring and sustaining TB control efforts in foreign-born population within EW. It appears that TB control efforts targeted at the UK-born population did not have the expected success over the study period, as rates have been stagnating in this population over nearly a quarter of a century, in spite of the availability of services and effective treatments. Furthermore, this lack of progress in control mainly affect younger age groups, underscoring the fact that there remain pockets of sustained transmission in the country that may be difficult to interrupt. If there is any chance of progressing towards elimination of TB as a public health problem in EW in the near future, such pockets of transmission need to be identified, and the factors that have prevented the current control strategy to be effective should be better understood and dealt with.

4.1a. Annual number of TB notifications in England and Wales 1983-2014, and distribution by place of birth
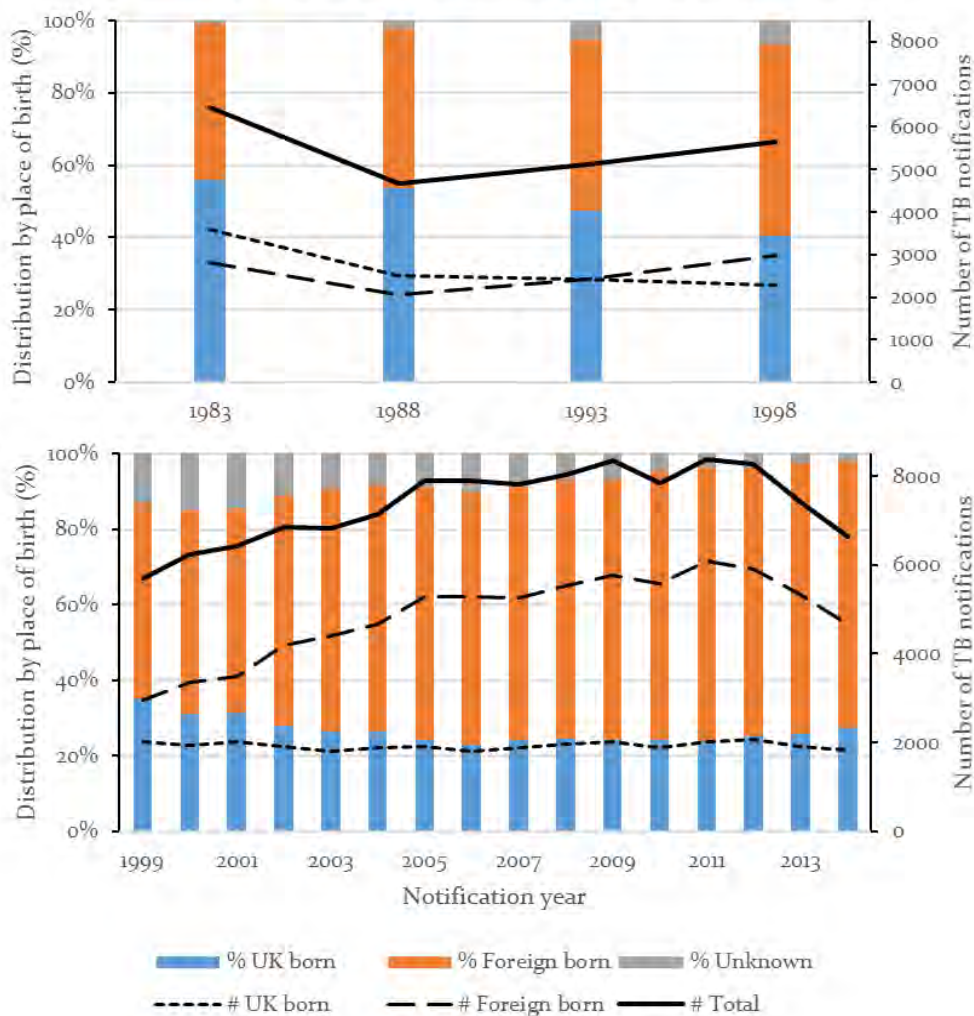
4.1b: Crude and age-sex standardised TB notification rates in England and Wales 1983-2014 overall and by place of birth
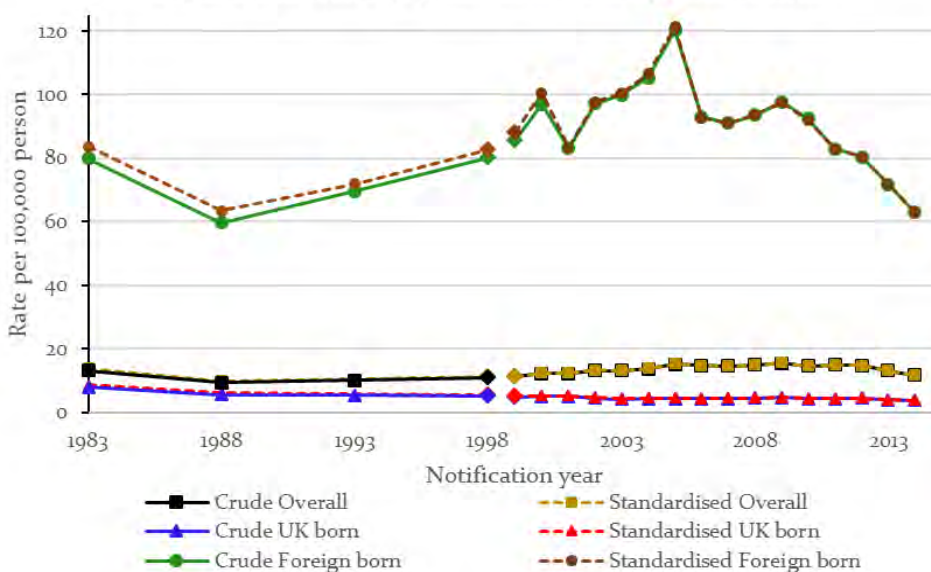
Figure 4.1: Distribution of notified TB cases and TB rates in England and Wales in 1983, 1988, 1993, 1998 and 1999-2014
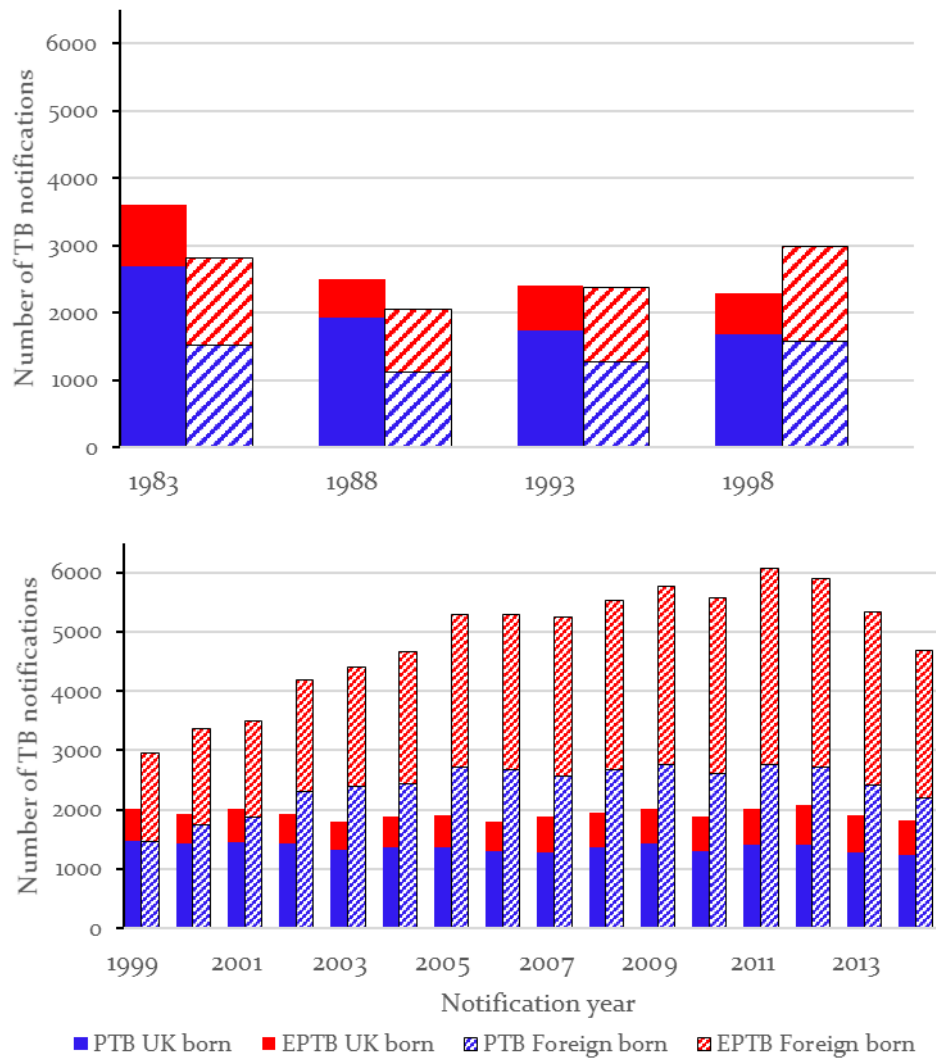
Figure 4.2: Number of TB notifications by place of birth and type of TB (Pulmonary TB (PTB) and Extra-Pulmonary TB (EPTB)) in England and Wales 1983-2014

4.3a: Age and sex standardised overall TB notification rates by age group in England and Wales 1983-2014

4.3b: Age and sex standardised TB notification rates in Foreign born subjects by age group in England and Wales 1983-2014

4.3c: Age and sex standardised TB notification rates in UK born subjects by age group in England and Wales 1983-2014

Notification year

0-14yrs   15-34yrs   35-54yrs   55-74yrs   75+yrs

Figure 4.3: Age and sex standardised TB notification rates in England and Wales 1983-2014 by age group, overall, and in UK born and Foreign born populations
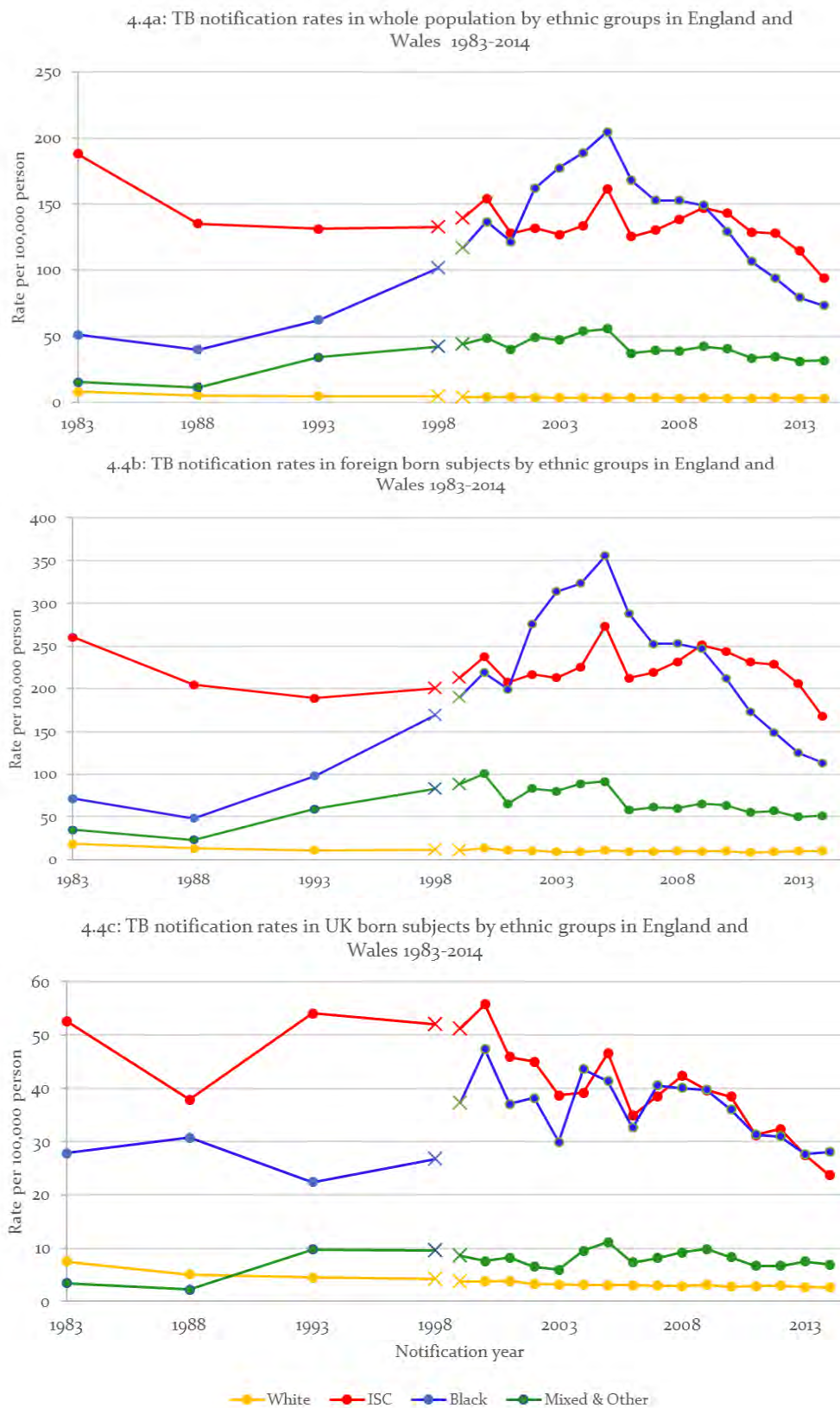
Figure 4.4: Trends in TB notification rates by ethnic groups in England and Wales 1983-2014

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Supplementary tables

Supplementary table 4.1: Missing data on place of birth and ethnicity in TB notifications by reporting years

Notification year		UK born or foreign-born (%)	Self-reported ethnicity (%)
All notifications	131723	9727 (7.4%)	4639 (3.5%)
1983*	3302	21 (0.6%)	0 (0.0%)
1988*	2408	51 (2.1%)	4 (0.2%)
1993*	2705	137 (5.1%)	0 (0.0%)
1998*	5653	375 (6.6%)	77 (1.4%)
1999	5692	736 (12.9%)	348 (6.1%)
2000	6224	921 (14.8%)	388 (6.2%)
2001	6421	914 (14.2%)	564 (8.8%)
2002	6858	753 (11.0%)	342 (5.0%)
2003	6819	627 (9.2%)	295 (4.3%)
2004	7144	600 (8.4%)	171 (2.4%)
2005	7891	706 (8.9%)	277 (3.5%)
2006	7893	809 (10.3%)	286 (3.6%)
2007	7817	677 (8.7%)	338 (4.3%)
2008	8023	545 (6.8%)	249 (3.1%)
2009	8356	570 (6.8%)	348 (4.2%)
2010	7828	371 (4.7%)	296 (3.8%)
2011	8389	307 (3.7%)	271 (3.2%)
2012	8266	298 (3.6%)	186 (2.3%)
2013	7399	167 (2.3%)	111 (1.5%)
2014	6635	142 (2.1%)	88 (1.3%)

*1983, 1988, and 1993 notifications based on national TB surveys, thus only half-year data

Supplementary table 4.2: Association between missingness of place of birth and notification's characteristics

(All notifications included except 3.5% with missing data on ethnicity; N= 127084)

	# with missing data (prevalence in %)	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio* (95% CI)	p-value
Sex					
Female	4159 (7.1%)				
Male	5568 (7.6%)	1.12 (1.06; 1.18)	<0.001	1.07 (1.02; 1.13)	0.005
Age group					
0-14 years	470 (6.9%)				
15-29 years	2244 (6.1%)	0.91 (0.80; 1.03)		0.93 (0.81; 1.06)	
30-49 years	3137 (6.6%)	0.97 (0.86; 1.10)		0.95 (0.84; 1.08)	
50-59 years	1142 (8.5%)	1.35 (1.18;1.55)	<0.001	1.18 (1.03; 1.35)	<0.001
60-79 years	2062 (9.8%)	1.65 (1.45; 1.87)		1.33 (1.17; 1.52)	
≥80 years	672 (11.7%)	2.08 (1.79;2.41)		1.61 (1.38; 1.87)	
TB type					
Pulmonary	4864 (8.0%)				
Extra-pulmonary	4049 (7.1%)	0.81 (0.77; 0.85)	<0.001	0.94 (0.89; 1.00)	0.011
Both	780 (6.0%)	0.78 (0.71; 0.85)		0.88 (0.81; 0.97)	
Ethnic group					
White	2458 (7.6%)				
Indian	1623 (5.6%)	0.72 (0.68; 0.77)		0.86 (0.82; 0.94)	
Pakistani	774 (3.9%)	0.49 (0.45; 0.53)		0.59 (0.54; 0.64)	
Bangladeshi	173 (3.4%)	0.50 (0.43; 0.59)	<0.001	0.63 (0.53; 0.74)	<0.001
Black African	791 (3.3%)	0.41 (0.75; 0.98)		0.54 (0.49; 0.59)	
Black Caribbean	271 (6.6%)	0.86 (0.75; 0.98)		1.04 (0.91; 1.18)	
Other and Mixed White/Other	550 (4.1%)	0.51 (0.47; 0.57)		0.65 (0.59; 0.72)	

*Adjusted for all variables in the table and notification year

Supplementary table 4.3: Association between missingness of ethnicity and notification's characteristics

(All notifications included except 7.4% with missing data on ethnicity; N= 121996)

	# with missing data (%)	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio* (95% CI)	p-value
Sex					
Female	2098 (3.6%)				
Male	2541 (3.5%)	0.96 (0.86; 1.06)	0.403	0.96 (0.87; 1.06)	0.394
Age group					
0-14 years	262 (3.8%)				
15-29 years	1252 (3.4%)	0.97 (0.78; 1.21)		0.77 (0.62; 0.97)	
30-49 years	1664 (3.5%)	0.89 (0.71; 1.10)	<0.001	0.70 (0.56; 0.88)	<0.001
50-59 years	477 (3.6%)	0.70 (0.53; 0.91)		0.58 (0.44; 0.76)	
60-79 years	759 (3.6%)	0.64 (0.50; 0.83)		0.58 (0.45; 0.74)	
≥80 years	225 (3.9%)	0.75 (0.54;1.04)		0.70 (0.50; 0.98)	
TB type					
Pulmonary	2195 (3.6%)				
Extra-pulmonary	2097 (3.7%)	0.95 (0.85; 1.05)	0.402	0.83 (0.75; 0.93)	<0.001
Both	347 (2.7%)	0.90 (0.75; 1.08)		0.79 (0.66; 0.95)	
Place of birth					
UK-born	349 (0.9%)				
Foreign-born	1230 (1.4%)	1.54 (1.36; 1.73)	<0.001	1.49 (1.31; 1.89)	<0.001

*Adjusted for all variables in the table and notification year

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Patrick Nguipdop Djomo
Principal Supervisor	Punam Mangtani and Laura Rodrigues
Thesis Title	Tuberculosis in England, a high-income Western European setting with low incidence: Recent trends, Social determinants and Prevention through BCG vaccination

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The Journal of Epidemiology and Community Health (JECH)
Please list the paper's authors in the intended authorship order:	Patrick Nguipdop-Djomo, Laura C. Rodrigues, Ibrahim Abubakar, Punam Mangtani
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the reseach idea, obtained and prepared the various datasets. I conducted the statistical analyses and interpretation of results with advice from my supervisors and co-authors, and I lead the manuscript preparation, including writing the initial draft and implementing revisions following

| | discussions and comments from my supervisors and co-authors. |
| | |

Student Signature: _____   **Date:** _23/2/2017_

Supervisor Signature: _____   **Date:** _27/2/2017_

5. <u>Manuscript 2:</u> An ecological analysis of the association between tuberculosis notification rates in England between 2008 and 2012 and small area-level deprivation

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Abstract

Background: Tuberculosis (TB) rates in England are among the highest in developed countries and have not declined in over a decade. Poverty has long been known as a driver of tuberculosis, although in England, the greatest burden of disease is reported in foreign-born residents from high TB incidence parts of the world. Little has been done in recent years to examine socio-economic trends in TB rates in England, and to disentangle the role of deprivation from that of place of birth in the current TB epidemiology.

Objectives: To measure the overall association between England's 2008-2012 TB notification rates and small area-level deprivation, as well as separately in the UK-born and foreign-born populations.

Methods: Ecological analysis of the association between quintiles of England's 2010 Index of Multiple Deprivation (IMD) rank and TB rates at the Lower-layer Super Output Area (LSOA; average population ~1500) level, measured with negative binomial and zero-inflated negative binomial regression models, adjusting for age, sex, urban/rural area classification, and area-level percentage of non-White residents.

Results: There was a log-linear gradient between area-deprivation levels and TB rates, with overall TB rates in the most deprived quintile areas three times higher than the least deprived quintile after adjustment for age and sex (IRR=3.35; 95%CI: 3.16 to 3.55), and 80% higher (IRR=1.81; 95%CI: 1.71 to 1.91) after further controlling for the urban/rural classification and percentage of non-White residents. The association and gradient appear stronger in the UK-born than the foreign-born population, with UK-born TB rates in the most deprived quintiles about two-and-a-half times higher than the least deprived quintile (IRR=2.39; 95%CI: 2.19 to 2.61) after full adjustment, whereas the comparable figure for foreign-born subjects was 80% higher (IRR=1.78; 95%CI: 1.66 to 1.91).

Conclusions: The results suggest that socio-economic deprivation continues to play a substantial role in sustaining the TB epidemic in England, especially in the UK-born population, and support the case for further investigations into the underlying social-determinants of TB.

Background

The tuberculosis (TB) annual notification rates in England remain among the highest in high-income countries. Annual rates in England during the past decade have stagnated between 12 and 15 per 100,000 persons (1), over four times higher than in the USA (2), and two to three times higher than in France, Germany and the Netherlands (3) for example. The greatest burden of disease - for instance nearly three-quarters of notified TB cases in 2015 - is observed among people born out of the United Kingdom, especially in population groups originating from parts of the world with high TB incidence and prevalence (1). The disproportionate distribution of disease in these population groups is well established, and it has received wide attention in terms of both investigations and public health policies and actions (4-6). A steady decline in the number of foreign-born TB cases in England has been reported in the past five years (1), possibly due to a combination of lower immigration from high burden countries and public health measures (e.g. 2012-2013 introduction of pre-entry TB screening for 101 countries with high TB incidence (7, 8)).

Whilst the heightened attention to TB in high-risk foreign-born subjects is justified and commendable in light of the greater disease burden in this group, it may have overshadowed the fact that TB rates in UK-born subjects have ceased to decline nearly 30 years ago, with rates increasing from the mid-1980s and plateauing in the past 20 years (see manuscript 1). In the UK-born population, TB seems to concentrate mainly in the most vulnerable and socio-economically deprived segments of the population, in which there is some evidence of ongoing local transmission (1, 9). These stagnant rates in the UK-born population of England occur in spite of the country being among the wealthiest in the world, and therefore capable of affording and implementing the most effective TB control interventions and tools available to eliminate the disease as a public health problem. The World Health Organisation (WHO) projections, based on mathematical models, further suggest that even in countries with low TB incidence (i.e. annual TB notifications <10 per 100,000 people), the implementation of the current array of TB control interventions may need to be supplemented by additional measures in order to meet the post-2015 global TB strategy goal of reaching pre-elimination levels (defined as annual notifications <1 per 100,000) by 2035 and elimination levels (defined as annual notifications <1 per million) by 2050 (10). The recommended additional measures include, among others, increased efforts and actions to address and reduce the underlying social determinants of tuberculosis (10).

Social deprivation and poverty are among the oldest known drivers of TB, highlighted in part by the correlation between improvements in the standard of living and nutrition, and the steady and rapid decline in TB rates and mortality in Western Europe during the first-half of the 20th century (11), before the large-scale introduction of medical technologies like chest X-Ray screening, antibiotic therapy and vaccination (12). Because of the resurgence of TB in England in the mid-1980s to early 1990s, several studies attempted to examine the potential contribution of social deprivation to reversing the disease trends. Using available routine data, several ecological analyses measured the association between TB notification rates and area-level deprivation, with most reporting higher TB rates in the most deprived areas of the country, and in doing so, helping to draw the attention to the disproportionate burden of disease in the most deprived communities, and to prioritise and allocate resources; a summary of these studies is presented in Table 5.1. However, these previous studies faced the challenge of disentangling the role of deprivation to that of place of birth in explaining higher TB rates in deprived areas (13, 14), because of the conflation of these two determinants of disease at the area-level (see table 5.1). The population density of foreign-born subjects, especially from high-TB burden and low-income countries, is higher in metropolitan areas where there are more employment opportunities, with the greater proportion often residing in deprived areas where accommodation may be more affordable, among other reasons.

Unfortunately, until the introduction of a central TB surveillance system in England in 1999, the information on the place of birth of notified TB cases was not routinely reported, with the data collected systematically only during the 5-yearly national TB surveys (15). This limited the ability to separately investigate the association of area-level deprivation to TB rates in UK-born and foreign-born subjects. The coalescence between these determinants of TB risk may have obfuscated the relationship between deprivation and tuberculosis in the UK-born population, raising the question of whether the previously reported relationship between TB notification rates and area-level deprivation merely reflects the fact that there are more foreign-born subjects at higher risk of TB (thus more foreign-born TB cases) residing in the deprived area, with weaker or no real gradient in UK-born TB rates across area deprivation levels. It is also notable that the most recent study examining this question used data nearly 20 years old (16), predating the introduction of the new TB surveillance system and therefore not accounting for changes to the TB epidemiology in England in the past two decades. Prior studies may have also been limited to some extent by the relatively large geographical area and heterogeneity in the population size of the analyses study units. The smallest study unit used by previous

research was the electoral wards, with population size varying from under 5000 to over 26000 persons per ward (17, 18); whereas some studies using units as large as local authorities (14) (population estimates in 2001 varying from 35165 in West Somerset to 990384 in Birmingham). In 2001 the UK Office for National Statistics (ONS) introduced a more homogeneous geographical statistical unit for data collection and area-level statistics outputs in England, the Output Area (OA), which allows populations to be grouped in smaller and more socially-homogenous geographical units of similar size (19).

As little has been done in recent years to examine socio-economic trends in TB rates in England in an era of rapid population movements and travel, and in view of the availability of more information than in previous years, this study was designed to investigate the current relationship between tuberculosis notification rates between 2008 and 2012 in England and area-level deprivation, as well as to attempt to disentangle the potential role of place of birth and deprivation by examining this association separately in UK-born and foreign-born populations. I also explored the relationship between TB in children aged 0 to 14 years (a proxy-measure for local TB transmission given most cases likely result from recent infection) and area-level deprivation.

Table 5.1: Overview of previous ecological studies of the association between TB notification rates and area-level deprivation in England

First Author	Year	Setting & Study Unit	Years of TB notifications	Deprivation Measure	Other measures	Analysis	Results	Limitations
Spence (20)	1993	33 Electoral Wards of Liverpool	Notifications 1985-1990	Townsend[†] & Jarman[‡]	% free school meals & % council housing	Correlation coefficient	Strong correlation between deprivation and overall TB rates (association remain when ethnic minorities excluded)	No distinction UK born vs Non UK born
Bhatti (14)	1995	Local Authorities in England and Wales (403 in total in England & Wales) (and Hackney)	Notifications 1980-1992	Jarman Census 1991	None	Indirect age-sex standardisation using national rates	Proportion increase by ethnic groups. Increase in 30% poorest but not in remainder. Strong association with overcrowding	No distinction UK born vs Non UK born
Mangtani (21)	1995	32 London Borough of London	Notifications 1982-1991	Townsend and Carstairs[¥]	Unemployment overcrowding social class and proportion migrants	Indirect standardisation and Poisson regression	Proportion migrants and overcrowding associated with TB rates, but not associated with trends in TB rates	No distinction UK born vs Non UK born
Tocque (22)	1998	33 London boroughs and 36 metropolitan districts in England	Notifications 1991	Jarman		Correlation coefficient and Poisson regression	Positive correlation Jarman and TB rates, but less strong correlation when immigration component removed from Jarman index	No distinction UK born vs Non UK born
Hawker (18)	1999	39 Electoral Wards of Birmingham	Notifications 1989-1993	Townsend score	Ethnicity	Linear regression	Association overcrowding in White population but not Asians	No distinction UK born vs Non UK born
Tocque (23)	1999	Council wards in Liverpool	Average Annual TB rate 1981-85 and 1991-95	Jarman	Ethnicity	Multivariable regression	Positive association TB rates and unemployment in 1981, but in 1991, overcrowding, elderly living alone and proportion household with head from new commonwealth	No distinction UK born vs Non UK born
Bennett (17)	2001	Electoral Wards of Manchester, Liverpool,	Hospital admissions 1991-1995	Jarman, Townsend and Carstairs	% born in India and Pakistan	Multilevel Poisson	Main explanatory is percentage born in India and Pakistan	No distinction UK born vs Non-UK born

		Birmingham and Cardiff			% residences overcrowded % residence / not owner occupied			
Parslow (16)	2001	Electoral Wards of Leeds	Cases aged 0-18 years in Leeds Chest clinic register 1982-1997	Carstairs	Proportion non-White children <19yrs and population density	Negative binomial regression of age sex standardised rates	TB rates associated with ethnicity but not deprivation; TB in non-ethnic minority associated with deprivation	No distinction UK born vs Non UK born

†Townsend index (24) is an overall deprivation index of material deprivation based on 4 census indicators (% economically active residents aged>16 years, % households with no car, % owner occupied houses and % houses with >1 persons-per-room)

¥Carstairs index (25) is an indicator of material deprivation based on 4 census indicators (unemployment among men, car ownership, low social class and overcrowding)

‡Jarman index (26) is a composite measure of deprivation designed to identify underprivileged areas where social factors may be associated with higher General Practitioners workload, based on 8 census-derived variables (% old-age pensioners living alone, number of children <5 yeas, % single parent families, number of unemployed residents, number of unskilled workers, poor housing, overcrowding [% households with >1 person-per-room], population mobility [households who moved residence at least once a year], and % households headed by a person from ethnic minority or born in the new commonwealth)

Methods:

Study design and setting:

Ecological study investigating the association between TB notification rates in England from 2008 to 2012 and small-area measures of deprivation in UK-born and foreign-born populations (the term 'foreign-born' in this study refer to subjects born out of the UK).

Study unit:

The unit of analysis was the Lower-layer Super Output Area (LSOA), which consist of the aggregation of several neighbouring Output Areas (OAs). The OAs were introduced by the Office for National Statistics (ONS) following the UK 2001 census with the aim to improve the data collection and reporting of small-area statistics used by local and central governments for policy and planning (e.g. data on education, health, employment, crime etc.), by providing small geographical units of fairly similar population size that contains socially-homogenous households. By comparison, data collection and reporting was previously based on enumeration districts of various superficies and population size, whose shape and size were determined by data collection requirements rather than social homogeneity (19).

Briefly, OAs contain between 40 and 250 residential households (average ~125), with estimated 100 to 625 residents, based on the aggregation of adjacent postcode units selected to be socially homogenous. My study units, the LSOAs, are obtained by the ONS grouping OAs in order to generate areas roughly similar in population size and socially homogeneous (in terms of tenure of household, type of dwelling, and rural urban status). LSOAs are designed to have a minimum population of 1000 and a maximum of 3000 residents, and between 400 and 1200 households (target ~600). They constitute the lowest level at which the data used by the ONS to generate area-level deprivation indices are aggregated (27). England is currently thus divided by the ONS into 171372 OAs, which are grouped into 32844 LSOAs; all LSOAs were included in the analysis.

Data sources:

TB Notifications for 2008-12 were obtained from the Enhanced Tuberculosis Surveillance System (ETS) at Public Health England (PHE). I obtained anonymised information on the age, sex, self-reported ethnicity, and UK-born status for each case. Individual residential

address postcodes at the time of diagnosis were georeferenced to the corresponding LSOA using the ONS geographic codes database. The total number of cases by 5-year age groups, sex and place of birth was aggregated for each LSOA.

Population Data: The ONS census data from 2011 was used to obtain population statistics at the LSOA level, including:

- The *resident population by place of birth* (overall and disaggregated in UK-born and foreign-born); these were used as denominator to obtain LSOA-level rates.
- The total *resident population by sex and 5-year age groups*;
- The total population by ethnic group (in ONS standard classification of self-reported ethnicity, then dichotomised into *White* (including White British, English, Irish, Scottish, Welsh, and any Other White) versus *non-White ethnicity* (ethnic group other than White, irrespective of country of birth);
- The sub-total of *foreign-born subjects born out of the European Union* (EU) (henceforth labelled *'non-EU foreign-born'*). This variable was readily available from published small-area census statistics; given that England's resident population born in EU countries other than the UK represents about a 33% of the foreign-born population, this variable (non-EU foreign-born) was considered potentially useful to distinguish and adjust for the foreign-born population originating from any of the 27 other EU countries, most of which have relatively lower TB burdens compared to other parts of the world.

Area-level Deprivation Measures: I also obtained from the ONS the most recent (2010) version of England's LSOA-level index of multiple deprivation (IMD) as well as the domain specific deprivation indices. The IMD is a multi-dimensional measure that uses 38 distinct indicators collected by the ONS at the LSOA-level to assess unmet needs due to the lack of resources along seven domains, respectively [1] income deprivation, [2] employment deprivation, [3] health deprivation and disability, [4] education, skills and training deprivation, [5] barriers to housing and services, [6] crime, and [7] living environment deprivation (27). These seven domains represent distinct but strongly correlated forms of deprivation that may be experienced by residents of an area. Respective domain-specific deprivation scored are constructed using model-based combinations of mutually exclusive sets of specific indicators from the total pool 38 indicators. The overall index of multiple deprivation (IMD) is obtained by combining the domains scores using specific weight, therefore providing a balanced composite deprivation index that account for the various aspects of deprivation in the area. The IMD is used to rank LSOA across the country based

on their relative deprivation levels, from most deprived (highest scores) to the least deprived (lowest scores) (27).

Other Area-level characteristics: I also obtained for each LSOA its urban/rural classification from the ONS 2011 Rural-Urban Definition for Small Area Geographies. LSOAs are classified into broad categories taking into account population sparsity, respectively Urban (defined as connected built-up areas with 10,000 people or more, with sub-groups including [1] major conurbation, [2] minor conurbation, and [3] city and town), and Rural (less than 10,000 residents, including [4] town and fringe, [5] village, and [6] hamlets and dispersed/isolated dwellings). Documents on the methods and detailed classification are available from the ONS (28). For this study, the information was further regrouped into three levels, respectively (i) major conurbation, (ii) minor conurbation, cities and towns, and (iii) rural areas.

Outcome and Exposure definitions

Outcome: The main outcomes for this study were the LSOA-level 5-year average annual TB notification rates respectively in all resident population, and separately in UK-born and foreign-born (non-UK born) subjects. For a subgroup analysis, I also computed TB rates in children aged 0 to 14 years, as a proximate for local transmission within England (given that TB cases in children are more likely to be a consequence of recent transmission (29), and over two-third of under 14-years old TB cases occur in UK-born children (1).

Exposures: The main exposure of interest was quintile of small- (LSOA-) level index of multiple deprivation (IMD) rank.

Confounders: The statistical analyses were controlled for confounding by age and sex, as well as LSOA urban/rural classification. I also adjusted for the area-level proportion of non-White, and the proportion of foreign-born residents.

Statistical analysis

Area-level TB notification rates:

After cleaning and standard consistency checks, the annual TB notifications over the study period were aggregated to obtain the respective numerators for each LSOA (respectively overall, UK-born and foreign-born TB cases, and children aged 0-14 years TB cases). Age was available for all cases, but about 5% had missing information on whether they were

UK-born or not, and they were not included in the analyses stratified by place of birth. The denominators to compute area-level TB notification rates were obtained from the ONS population data as detailed in the previous section. Robust standard errors were used to compute the 95% confidence intervals (95%CI) while accounting for area-level clustering.

Covariates:

The distribution of the area-level percentage of (i) non-White residents, and (ii) foreign-born residents born out of the European Union (EU) was examined and used to choose cut-offs to transform these variables into categorical variables. I also examined the correlation between non-White residents and non-EU foreign-born residents to inform adjustment in the multivariable analyses.

Association between area-level TB notification rates and deprivation level:

The association between exposure variables and LSOA-level TB rates was measured using count data regression models (30), with the log-transformed 5-year population denominator as the offset.

Before investigating the association between the exposures of interest and TB notification rates, I first explored which count data regression model was more appropriate to the data. A potential problem when modelling area-level rates of a rare disease like TB is the overdispersion due to extra-variation in rates between LSOAs. This may lead to a violation of the Poisson regression model assumption that the conditional variance of the dependent variable is equal to the conditional mean (30, 31). An approach commonly used in analyses to deal with overdispersion is to use a Negative Binomial regression model instead of a Poisson model (30). For each outcome, I computed the mean number of events per analysis unit (LSOA) and the variance to assess deviation from this assumption. I also fitted both the Poisson and Negative Binomial regressions to the data and compared the models fitness using the log-likelihood based Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). The model with the best fit to the data (smaller AIC and BIC) was used for the analysis (30, 31).

Another potential issue specific to the analysis of foreign-born TB rates is the fact that many areas have small to no foreign-born population, and therefore no expected foreign-born TB cases. This leads to 'excess' analysis units with zero counts and further variation between clusters; it may also affect the analysis for overall TB rates given that nearly 70% of TB cases in England are in foreign born (1). To address this, I used the Vuong Test (32) to further compare the Poisson and Negative Binomial models against their respective

zero-inflated counterpart with the non-EU foreign-born population used as the predictor for 'excess' zero counts (consistent with the fact the majority of foreign-born cases are in subjects born out of the EU).

Eventually, the analyses for overall and foreign-born TB rates were done using zero-inflated negative binomial regression models, with non-EU foreign-born population used as the excess zero counts' predictor, and the UK-born TB rates were analysed using a standard negative binomial regression model. All 95% confidence intervals (95%CI) were obtained using robust standard errors.

To measure the association between quintiles of area-level deprivation and LSOA-level TB notification rates, I computed crude incidence rate-ratios (IRR) first, then the age-and-sex adjusted RRs. I adjusted for confounding by age and sex by including in the model parameters their joint distribution within each LSOA (i.e. male-aged 0-14 years, female-aged 0-14 years, male-aged 15-64 years, female-aged 15-64 years, and male aged over 64 years), as suggested by Morgenstern for ecologic studies, to minimise the risk of ecological bias due to misspecification of confounders (33). Finally, I fitted a final multivariable model that measured the effect of area-level deprivation while further adjusting for non-White residents in the LSOA, as well as the LSOA's urban/rural classification. A sub-analysis of the association between area-level quintiles of deprivation and TB rates in children aged 0-14 years was also performed.

The statistical analyses were done using Stata 14$^{®}$ (StataCorp); the significance testing was done using the Wald test.

Results

Nearly 40,000 TB cases were notified in England between 2008 and 2012, for an annual average of about 8,000 cases. This corresponded to a 5-year average annual notification rate of 15 per 100000 persons, and there was no apparent trend in overall yearly rates over that period. The average annual notification rate in UK-born subjects was 4.5 per 100000, while the average rate in the foreign-born population was 80 per 100000 persons. The distribution of cases and corresponding average annual rates by LSOA characteristics is presented in table 5.2. Overall, 71% of TB cases in England over the study period were reported from the most deprived two-fifth areas, with this trend similar in UK-born and foreign-born populations. However, there were differences between these two groups regarding other LSOA characteristics. Major conurbations accounted for 56% of UK-born TB cases compared to 70% for foreign-born cases. Nearly half UK-born TB cases were reported from areas with <20% non-White population, whereas 60% of foreign-born TB cases occurred in areas with ≥40% non-White residents. This distribution of cases was similar in relation to the LSOA percentage of non-EU foreign-born residents. There was a strong correlation between LSOAs' percentages of non-White and percentage of non-EU foreign-born residents (Pearson's correlation coefficient = 0.94; $p<0.001$), so I only used the percentage of non-White subjects (irrespective of country of birth) as covariate in all subsequent analyses.

Before fitting regression models to measure the association between area-level TB rates and deprivation, I checked for deviations from the standard Poisson regression assumption that variance and mean are not too different. The variance of LSOA-level overall and foreign-born TB cases count was nearly 5 times higher than the mean, thus consistent with large over-dispersion and excess zero counts. The comparison of regression models for the association between TB rates and area-level deprivation suggested that the zero-inflation negative binomial regression provided a better fit for these two outcomes (Vuong test comparing standard to zero-inflation models $p<0.001$, and both AIC and BIC for negative binomial model much lower than for Poisson model) table 5.3). For UK-born cases, the variance was only slightly higher than the mean, and the results from the Poisson and Negative Binomial regression models were similar; however, the AIC and BIC for the Negative Binomial model suggested that the Negative Binomial model was marginally better than the Poisson model, thus the former was used for

subsequent analyses for UK-born TB rates. The results comparing the regression models are reported in table 5.3.

The Overall TB notification rates increased with area-level deprivation, with crude rates in the most deprived fifth areas of the country over 5 times higher than the least deprived quintile. However, part of this association appeared to be due to variation in the age-and-sex composition of LSOA, with the association reducing to 3 times higher TB rates in the most deprived quintile after adjustment for age-and-sex (table 5.4). The log-linear gradient in overall TB rates by deprivation quintile was still present, albeit much weaker once controlling additionally for rural/urban area classification and the percentage of non-White resident in the area. The fully adjusted TB rates varied from 14% increase in the 2nd least deprived to 81% higher in the most deprived quintile areas, when compared to the least deprived fifth of the country. The same multivariable model, controlling simultaneously for age, sex, deprivation, urban/rural classification and percentage of White/non-White residents, suggested that the overall notification rates were on average about twice as high in urban than rural areas, and nearly 6 times higher in areas with ≥40% non-White residents compared to areas with <20% non-White residents (IRR = 5.78, 95%CI: 5.49 to 6.09).

There were, however, differences in the association between area-level deprivation and TB rates in UK-born versus foreign-born populations (see table 5.4). The magnitude and gradient of association between deprivation and TB rates was much steeper in the UK-born population, in which the crude TB rates in the most deprived quintile areas were over five times higher than the least deprived quintiles (IRR = 5.19, 95%CI: 4.78 to 5.63), versus only about three times higher in the foreign-born population (IRR = 2.78, 95%CI: 2.61 to 2.96). The difference in the relationship between area-level deprivation and TB rates in these two population strata persisted after adjusting for age, sex, rural/urban classification and percentage of White/non-White residents. Compared to the least deprived quintile areas, the fully adjusted rate-ratios of association between area-level deprivation and TB rates in UK-born subjects varied from 2.40 (95%CI: 2.19 to 2.61) in the most deprived quintile to 1.21 (95%CI: 1.11 to 1.33) in the 2nd least deprived quintile areas; whereas the equivalent figures in the foreign-born population were respectively 1.78 (95%CI: 1.66 to 1.91) and 1.13 (95%CI: 1.05 to 1.23). The full results are presented in table 5.4.

Table 5.2: Tuberculosis cases distribution and 5-year average annual notification rates by LSOA characteristics in England 2008-12

	UK born			Foreign-born			All TB cases		
	Number of TB cases (column %; n= 10184)	population at risk	5-year average annual rate per 100,000 (95%CI)	Number of TB cases (column %; n=29524)	population at risk	5-year average annual rate per 100,000 (95%CI)	Number of TB cases (column %; n=39708)	population at risk	5-year average annual rate per 100,000 (95%CI)
LSOA Quintiles of Index of Multiple Deprivation									
Most deprived	4055 (40)	8574432	9.5 (9.1;9.9)	13053 (44)	2199206	119 (116.0;122.0)	17108 (43)	10773638	31.8 (30.7;32.8)
2	2431 (24)	8818466	5.5 (5.3;5.8)	8602 (29)	1861055	92.4 (88.9;96.1)	11033 (28)	10679521	20.7 (19.8;21.6)
3	1617 (16)	9255810	3.5 (3.3;3.7)	4271 (14)	1349267	63.3 (60.5;66.3)	5888 (15)	10605077	11.1 (10.6;11.6)
4	1173 (12)	9488578	2.5 (2.3;2.6)	2142 (7)	1018227	42.1 (39.4;44.9)	3315 (8)	10506805	6.3 (6.0;6. 7)
Least deprived	908 (9)	9538031	1.9 (1.8;2.0)	1456 (5)	909384	32.0 (30.2;33.9)	2364 (6)	10447415	4.5 (4.3;4.8)
Rural / Urban classification of LSOA									
Rural	781 (8)	8642493	1.8 (1.7;1.9)	447 (2)	472892	18.9 (17.0;21.0)	1228 (3)	9115385	2.7 (2.6;2.9)
Cities/minor conurbations	3707 (36)	22467460	3.3 (3.2;3.4)	8359 (28)	2580276	64.8 (62.7;67.0)	12066 (30)	25047736	9.6 (9.3;10.0)
Major conurbations	5696 (56)	14565364	7.8 (7.6;8.1)	20718 (70)	4283971	96.7 (94.4;99.1)	26414 (67)	18849335	28.0 (27.3;28.8)
Percentage of non-White residents in LSOA									
0-19.9%	4985 (49)	37612660	2.7 (2.6;2.7)	5815 (20)	3036658	38.4 (37.2;39.4)	10800 (27)	40649318	5.31 (5.29;5.4)
20-39.9%	1894 (19)	4480422	8.5 (8.0;8.9)	5851 (20)	1653640	70.8 (68.5;73.1)	7745 (20)	6134062	25.3 (24.5;26.0)
≥40%	3305 (32)	3582235	18.5 (17.7;19.3)	17858 (60)	2646841	135 (132.0;138.0)	21163 (53)	6229076	67.9 (66.2;69.7)

Table 5.3: Comparison of four count-data regression models of the association between area-level deprivation and TB notification rates

	Poisson	Zero-inflated Poisson	Negative Binomial	Zero-inflated Negative Binomial
All England population (Mean number TB case by LSOA = 1.21; Variance = 6.51)				
Least Deprived	1	1	1	1
2	1.39 (1.30;1.50)	1.40 (1.30;1.51)	1.39 (1.29;1.49)	1.39 (1.30;1.49)
3	2.45 (2.29;2.63)	2.29 (2.14;2.44)	2.41 (2.26;2.58)	2.29 (2.15;2.44)
4	4.57 (4.28;4.87)	3.60 (3.39;3.83)	4.39 (4.12;4.68)	3.74 (3.52;3.98)
Most Deprived	7.02 (6.62;7.44)	4.82 (4.56;5.09)	6.66 (6.28;7.05)	5.22 (4.94;5.51)
p-value	<0.001	<0.001	<0.001	<0.001
AIC	113707.5	92882.9	88446.2	83753.0
BIC	113749.5	92941.7	88496.6	83820.2
Vuong test	<0.001		<0.001	
Foreign-Born population (Mean number TB case by LSOA = 0.9; Variance = 4.98)				
Least Deprived	1	1	1	1
2	1.31 (1.20;1.43)	1.20 (1.10;1.31)	1.27 (1.17;1.37)	1.19 (1.10;1.29)
3	1.98 (1.84;2.13)	1.64 (1.52;1.76)	1.83 (1.71;1.96)	1.62 (1.51;1.74)
4	2.89 (2.69;3.10)	2.19 (2.04;2.35)	2.58 (2.41;2.75)	2.15 (2.02;2.30)
Most Deprived	3.71 (3.48;3.95)	2.65 (2.48;2.84)	3.41 (3.20;3.62)	2.78 (2.61;2.96)
p-value	<0.001	<0.001	<0.001	<0.001
AIC	62010.2	59288.4	58147.3	56986.8
BIC	62052.2	59347.2	58197.7	57054.1
Vuong test	<0.001		<0.001	
UK-Born population (Mean number TB case by LSOA = 0.31; Variance = 0.49)				
Least Deprived	1		1	
2	1.30 (1.19;1.42)		1.30 (1.20;1.43)	
3	1.84 (1.68;2.01)		1.86 (1.84;2.13)	
4	2.90 (2.66;3.15)		3.01 (2.69;3.10)	
Most Deprived	4.97 (4.58;5.38)		5.19 (3.48;3.95)	
p-value	<0.001		<0.001	
AIC	47865.4		45865.0	
BIC	47907.4		45915.4	

Table 5.4: Association between LSOA-level deprivation and non-White population and TB notification rates in England in 2008-12

	Crude			Age and Sex adjusted			Fully Adjusted[†]		
	IRR	95%CI	p-value	IRR	95%CI	p-value	IRR	95%CI	p-value
Overall population									
Quintiles of LSOA Index of Multiple Deprivation rank									
Least Deprived	1			1			1		
2	1.39	(1.30;1.49)		1.31	(1.22;1.41)		1.14	(1.07;1.21)	
3	2.29	(2.15;2.44)	<0.001[‡]	1.84	(1.73;1.96)	<0.001[‡]	1.35	(1.27;1.43)	<0.001[‡]
4	3.74	(3.52;3.98)		2.58	(2.43;2.74)		1.58	(1.50;1.67)	
Most Deprived	5.22	(4.94;5.51)		3.35	(3.16;3.55)		1.81	(1.71;1.91)	
Percentage of non-White residents in LSOA									
0-19.9%	1			1			1		
20-39.9%	3.31	(3.16;3.47)	<0.001	2.89	(2.75;3.04)	<0.001	2.60	(2.47;2.73)	<0.001
≥40%	8.7	(8.30;9.12)		6.96	(6.63;7.31)		5.78	(5.49;6.09)	
Rural / Urban classification of LSOA									
Rural	1			1			1		
Cities/minor conurbations	3.15	(2.95;3.37)	<0.001	2.01	(1.88;2.16)	<0.001	1.79	(1.67;1.91)	<0.001
Major conurbations	6.86	(6.43;7.32)		3.76	(3.50;4.03)		1.92	(1.78;2.06)	
Foreign-born population									
Quintiles of LSOA Index of Multiple Deprivation rank									
Least Deprived	1			1			1		
2	1.19	(1.10;1.29)		1.21	(1.12;1.31)		1.13	(1.05;1.23)	
3	1.62	(1.51;1.74)	<0.001[‡]	1.57	(1.47;1.69)	<0.001[‡]	1.34	(1.25;1.44)	<0.001[‡]
4	2.15	(2.02;2.30)		1.98	(1.85;2.12)		1.57	(1.47;1.68)	
Most Deprived	2.78	(2.61;2.96)		2.38	(2.22;2.54)		1.78	(1.66;1.91)	
Percentage of non-White residents in LSOA									
0-19.9%	1			1			1		
20-39.9%	1.72	(1.62;1.82)	<0.001	1.63	(1.54;1.73)	<0.001	1.49	(1.41;1.58)	<0.001

≥40%	3.10	(2.94;3.28)		2.64	(2.49;2.79)		2.28	(2.15;2.42)	
Rural / Urban classification of LSOA									
Rural	1			1			1		
Cities/minor conurbations	2.56	(2.29;2.85)	<0.001	2.17	(1.94;2.43)	<0.001	1.96	(1.75;2.19)	<0.001
Major conurbations	3.13	(2.79;3.50)		2.56	(2.28;2.87)		1.83	(1.63;2.05)	
UK-born population									
Quintiles of LSOA Index of Multiple Deprivation rank									
Least Deprived	1			1			1		
2	1.30	(1.19;1.43)		1.30	(1.18;1.42)		1.21	(1.11;1.33)	
3	1.86	(1.70;2.04)	<0.001‡	1.72	(1.58;1.89)	<0.001‡	1.45	(1.33;1.58)	<0.001 ‡
4	3.01	(2.76;3.28)		2.48	(2.27;2.70)		1.77	(1.63;1.93)	
Most Deprived	5.19	(4.78;5.63)		3.90	(3.59;4.24)		2.39	(2.19;2.61)	
Percentage of non-White residents in LSOA									
0-19.9%	1			1			1		
20-39.9%	3.20	(3.01;3.40)	<0.001	2.9	(2.71;3.10)	<0.001	2.39	(2.24;2.56)	<0.001
≥40%	6.99	(6.62;7.38)		5.96	(5.60;6.34)		4.25	(3.96;4.55)	
Rural / Urban classification of LSOA									
Rural	1			1			1		
Cities/minor conurbations	1.85	(1.70;2.01)	<0.001	1.44	(1.32;1.57)	<0.001	1.31	(1.20;1.42)	<0.001
Major conurbations	4.52	(4.17;4.91)		3.12	(2.86;3.4)		1.63	(1.49;1.79)	

[†] *Fully adjusted regression models include quintiles of area-level deprivation rank, and further adjusted for age, sex, urban/rural area classification, percentage of White/non-White residents*

[‡] *Test for trend*

The findings from the sub-group analysis of the association between area-level deprivation and TB rates in children aged 0-14 years (used as a proxy-measure for local TB transmission) are presented in table 5.5. Overall, the pattern of association was similar to that among UK-born subjects. There was a strong gradient of higher TB rates with increasing deprivation levels, with the crude TB rates in children ≤14 years old living in the most deprived quintile areas of the country about 10 times higher compared to those in the least deprived areas (IRR=10.07, 95%CI: 7.76 to 13.06). After adjusting for the urban/rural area classification and the percentage of White/non-White residents, there was still good evidence of association, albeit weaker, between area-level deprivation and TB rates in children ≤14 years old; fully adjusted TB rates in the two most deprived quintile areas were between 2 and 3 times higher than the least deprived quintile areas.

Table 5.5: Association between area-level deprivation and TB notification rates in children aged 0-14 years in England in 2008-12

	TB notifications			Crude			Fully Adjusted†		
	TB cases	Population aged 0-14 years	Annual TB rate (per 100,000)	IRR	95%CI	p-value	IRR	95%CI	p-value
Quintiles of LSOA Index of Multiple Deprivation rank									
Least Deprived	77	1793732	0.86						
2	94	1698737	1.11	1.29	(0.92;1.80)		1.06	(0.76;1.49)	
3	220	1752179	2.51	2.89	(2.15;3.88)	<0.001‡	1.60	(1.19;2.16)	<0.001‡
4	520	1931600	5.38	6.14	(4.69;8.05)		2.23	(1.68;2.95)	
Most Deprived	1053	2308561	9.12	10.07	(7.76;13.06)		2.84	(2.14;3.78)	
Percentage of non-White residents in LSOA									
0-19.9%	443	6986089	1.27						
20-39.9%	372	1117089	6.66	5.27	(4.45;6.25)	<0.001	3.53	(2.95;4.23)	<0.001
≥40%	1149	1381631	16.60	13.05	(11.35;14.99)		7.10	(6.00;8.39)	
Rural / Urban classification of LSOA									
Rural	28	1470602	0.38						
Cities/minor conurbations	524	4437751	2.36	6.04	(3.96;9.20)	<0.001	2.85	(1.85;4.39)	<0.001
Major conurbations	1412	3576456	7.90	19.49	(12.9;29.44)		3.50	(2.27;5.41)	

†*Adjusted for quintiles of LSOA IMD rank, percentage of non-White resident population and urban/rural area classification*

‡*Test for trend*

Discussion

These analyses suggest that over the 5-year study period (2008-2012), TB notification rates in England were positively associated with small-area level deprivation even after controlling for age, sex, urban/rural differences and the area-level proportion of non-White residents. However, this relationship appeared stronger in the UK-born population compared to foreign-born, with TB notification rates in UK-born subjects living in the most deprived quintile areas of the country nearly two-and-a-half times higher than the least deprived quintile areas after adjustment for confounding. By comparison, TB rates in foreign-born subjects from the most deprived quintile areas were just about 80% higher than the least deprived quintile areas. Area-level deprivation was also strongly associated with higher TB rates in children aged 0-14 years old.

An advantage of the current study over previous ecological analyses of the relation of deprivation to TB rates in England was the availability and use of LSOAs as study unit. The smaller and similar population size (average 1500 residents) of these statistical units, combined to the fact that the ONS designed LSOAs specifically to be more socially homogenous, allowed individuals within study units to be less dissimilar with respect to their deprivation status (my key exposure of interest), hence less misclassification. This has probably helped minimise the risk of ecological bias in measuring the association between area-level deprivation and the risk of TB (30, 34). By comparison, previous ecological studies have used larger and more heterogeneous aggregation levels, ranging from electoral wards (population varying from 5000 to 26000 per wards) (16, 17, 20) to local authorities (35,000 to nearly 1,000,000 residents per unit) (14), hence more vulnerable to misclassification of exposure. Another strength of this analysis was the use of exact population count as denominators to calculate rates, with numbers obtained from a recent population census. This may have helped to avoid some pitfalls of population estimates, which typically tend to underestimate small groups like foreign-born populations, hence overestimating rates in those groups. A possible limitation of this study could be the under-notification of TB cases, which could have led to slight underestimation of TB rates. An audit of the TB surveillance system between 1999-2002 using the capture-recapture method estimated about 15% under-reporting, but improving with time (35). The audit did not explore potential difference in under-reporting between UK-born and foreign-born populations, making it difficult to predict the likely impact of any under-notification on my findings. It is plausible that under-notification is more frequent in UK-born

population, helped by the under-notification of post-mortem cases in the elderly, and differential clinical suspicion index (36). However, under-notification of TB cases would lead to an underestimation rather than overestimation of the association of area-level deprivation and TB rates, which means that the estimates presented here are likely conservative.

The measure of deprivation used here, the Index of Multiple Deprivation (IMD), was designed to measure how the lack of resources along seven domains, income, employment, health and disability, education skills and training, barriers to housing and other services, crime, and living environment, experienced by individuals, may affect wide ranging aspects of their living conditions, including health outcomes (27). Several studies have shown that the IMD correlate well with various health inequalities, including all-cause mortality (37) and several hazardous health habits (e.g. smoking, alcohol drinking) (38). Prior to the introduction of the IMD, the most commonly used area-level measures of deprivation used in studies assessing the relationship to TB rates included the Jarman index (26), the Townsend score (24) and the Cartstair score (25). The Jarman Index was developed from a set of eight census-derived variables identified by a survey of a random sample of GPs as part of an exercise aimed at identifying under-privileged areas where social factors may lead to increase GP workloads (26). The Townsend and Carstairs scores on the other hand, were composite measures of area-level deprivation based on combining 4 census-derived indicators (24, 25). One improvement of IMD in measuring area-level deprivation compared to previous measures is that it is based on smaller geographic areas of similar population size and specifically selected to include socially homogenous households (27); whereas the census-based indicators used for former measures of deprivation were based on either enumeration districts or census wards, which had larger population and wider variation in size (for example England was formerly divided by the ONS in 9265 census wards versus about 32000 LSOAs currently). Another advantage of the IMD is the collection at the small-area (LSOA) level of 32 separate census-based indicators to capture different aspects of deprivation, providing better resolution than previous measures (27). A study found that the IMD maintained a stronger and more consistent correlation to health inequality compared to the Townsend score both in urban and rural areas (39).

The respective roles of social deprivation and immigration from high TB parts of the world in explaining the resurgence of TB in England have been the object of much debate (13). Most authors have argued that most of the disease resurgence is related to immigration from high-TB parts of the world, but some are also of the opinion that similar to comparable low-TB incidence settings, poverty and social deprivation have played an additional role in the failure of TB rates to decline since the mid-1980s (40) . Whilst it is true that the greater burden of disease in England nowadays rests with foreign-born populations, my results suggest that deprivation plays a greater role in differential TB rates in UK-born populations compared to foreign-born populations. These results contrast with the findings of Bennet *et al* who reported that in their analyses of TB rates in electoral wards in Manchester, Liverpool, Birmingham and Cardiff, variations in rates were explained by the proportion of residents born in India and Pakistan, and not by area-level deprivation (17). I contend that the difference to my results is explained by the fact that their analyses did not separately examine the association of deprivation and TB rates in UK-born and foreign-born subjects, especially in light of the fact their study was set in major conurbations with high proportion of foreign-born subjects. The weaker association between deprivation and TB rates in foreign-born populations in my study is most likely due to the fact the risk of disease is mostly associated with the higher TB burden in place of origin of many foreign-born subjects in England, and their ties to these areas, with deprivation only playing a smaller role. On the other hand, the stronger association between deprivation and TB in UK born populations is consistent with the historical link between TB and poverty, with greater prevalence of deprivation-related TB risk factors in poorer areas. These may include living in overcrowded (and possibly poorly ventilated) dwellings, as well as poorer nutritional status for example, both associated with higher risk of TB infection as well as progression to disease (29). These results are consistent with findings from the previous studies by Mangtani *et al* who reported an association between higher TB rates and overcrowding in London boroughs (21), as well as Hawker *et al* who found that overcrowding was associated with TB rates in the White population in Birmingham, but not the Asian population (18). Tocque *et al* also reported a positive association between TB rates in Liverpool council wards and unemployment, a known predictor of financial status and related circumstances (housing, nutritional status etc.) (23). Furthermore, it was found in surveys that other health determinants associated with higher risk of TB, including for instance tobacco smoking, history of prison stay, and history of homelessness, are more prevalent in socially deprived population subgroups (38). The strong association between area-level deprivation and TB rates in children aged

0-14 years also found in my study provides some support to the hypothesis that deprivation remains an important determinant of TB risk in UK-born populations. Most TB cases in children result from recent *Mycobacterium tuberculosis* (*Mtb*) infection, thus suggesting that there is perhaps more recent transmission in the most deprived areas. However, part of this association is also probably explained by the fact that a proportion of children born in the UK to foreign-born parents have an increased risk of TB due to their family ties to high TB-burden parts of the world.

In summary, the results presented here are the first in over 15 years examining variations in TB rates across gradients of area-level deprivation, and the first since the introduction of the centralised TB surveillance system, as well as the current high-resolution measure of area-level deprivation. Despite their limitations, the findings suggest that deprivation continues to play a role in sustaining the TB epidemic in the UK-born population in England, and deserve further attention. Further studies are warranted at the individual-level to investigate which deprivation-related determinants of health are related to the risk of TB, and how they may affect this risk. Such studies may be helpful in designing and planning interventions that may address such social determinants of TB, and help progress towards the aim of TB elimination in the near future. The results should also contribute to raising the awareness of the disproportionate burden of TB in the UK-born populations residing in the most deprived areas.

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SECTION A – Student Details

Student	Patrick Nguipdop Djomo
Principal Supervisor	Punam Mangtani and Laura Rodrigues
Thesis Title	Tuberculosis in England, a high-income Western European setting with low incidence: Recent trends, Social determinants and Prevention through BCG vaccination

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLoS Medicine
Please list the paper's authors in the intended authorship order:	Patrick Nguipdop-Djomo, Laura C. Rodrigues, Peter G. Smith, Ibrahim Abubakar, Punam Mangtani
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I contributed to conceptual aspects of the study design, including the sample size calculations, the design of the control sampling scheme, the revision and testing of data collection tools, and the design and delivery of training materials for interviewers. I supervised the field data

	collection, and I designed and managed the study databases. For the analyses presented here, I performed the the data cleaning and conducted all statistical analyses and interpretation of results with advice from my supervisors and co-authors, and I lead the manuscript preparation, including writing the initial draft and implementing revisions following discussions and comments from my supervisors and co-authors.

Student Signature: _____   Date: _27/2/2017_

Supervisor Signature: _____   Date: _27/2/2017_

6. <u>Manuscript 3:</u> Underlying social determinants of tuberculosis risk in UK-born adults from White ethnic background in England: a nationwide community-based case-control study

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Abstract

Background: England tuberculosis (TB) rates have been stagnant in the UK-born population for over a quarter of a century, especially among young adults. There is evidence from ecological studies that deprivation remains a risk factor. However, in this setting, few studies have recently investigated the association between poverty-related social determinants of health inequality (SDH) at the individual-level and tuberculosis disease, as opposed to infection.

Objectives: To measure the association between individual socio-economic status and some social determinants of health, and TB, while taking into account the clustering of social risk factors in subjects, and to estimate the potential population impact.

Methods: Secondary analyses of a nationwide case-control study targeted at UK-born White adults aged 23 to 38 years at diagnosis of their first TB episode, and randomly selected age-and-sex frequency-matched community-based controls. Data on some SDH (education level, household overcrowding, tobacco smoking, alcohol use, drugs use, and history of homelessness and prison) were collected during face-to-face interviews using a Computer-Assisted Personal Interview. Statistical analyses using logistic regression models was informed by a theoretical formal causal framework (Directed Acyclic Graph) of plausible inter-relation between the measured social determinants.

Results: Overall, 681 TB cases and 1183 controls were recruited. A strong association between education level and TB was noted, with risk of TB about four times higher in subjects with GCSE O-levels or below compared to those with degree or higher (OR=3.94; 95%CI: 2.74; 5.67) after controlling for age, sex, BCG vaccination and long ($\geq$3 months) stays in Africa or Asia. After simultaneously adjusting for all measured social determinants, as well as BCG vaccination and long stays in Africa or Asia, higher TB risk was also associated with tobacco smoking, use of drugs, especially injectable drugs (OR=5.67; 95%CI: 2.68; 11.98), history of homelessness, and deprivation in the area of residence. Population Attributable Fraction (PAF) estimates suggest that tobacco cessation and class-A drug use prevention could respectively help prevent 18% and 15% TB cases in the target population.

Conclusions: The results provide insight into some mechanisms through which deprivation affects the risk of TB in the study population, and support the argument for improved approaches to TB control efforts, such as integrated health and social services in high-risk young adult populations.

Background

Tuberculosis largely remains a disease of social exclusion and inequality, affecting disproportionately on the poor and most vulnerable segments of the population with an estimated 90% of cases worldwide reported from low and lower-middle income countries (1). In several low-burden settings, although the majority of cases are currently reported among migrants from high incidence countries, a substantial proportion of TB due to transmission within the native population appears to be concentrated in the more deprived and marginalised groups (2-4). Such deprivation includes income poverty, as well as multiple social disadvantages such as lower education, reduced access opportunities to good health care, and lower accommodation and living standards. Some behaviours harmful to health may also be more common in deprived populations (5), including for example alcohol abuse (6, 7), tobacco smoking (8), and use of controlled drugs (9).

Until recently, TB control strategies emphasised medical technologies (including preventive treatment and vaccination, early and better diagnosis, effective treatment, and management of co-morbidities), with less focus on addressing the underlying social determinants (10). However, the newly adopted WHO strategy to eliminate TB as a public health problem by 2035 recognises that the pace of decline required to reach this target cannot be achieved without also addressing the social determinants of TB, a priority area now embedded within the three pillars of the 2015 global end-TB strategy (11, 12). This strategy is also relevant to low-TB incidence countries, which are closer to TB elimination, and where additional efforts are required to interrupt transmission, notably among the vulnerable and hard-to-reach populations in whom it is highest. An initial step to addressing these social determinants in these countries is the proper mapping and understanding of the associated risk (3). Although TB is a classic disease of poverty, the pathways (underlying social determinants) through which poverty affects the risk of TB have not received much attention in recent times.

TB rates in the native UK-born population have not declined in more than two decades, especially among young adults (see manuscript 1), and in 2014, 60% of notified TB cases in England who had at least one of the social risk factors homelessness, drug use, alcohol abuse, or history of prison stay were aged 15-44 years (13). Pulmonary TB, the infectious form of the disease, was the most common form reported among those with at least one of these risk factors, and nearly one in ten had prior history of TB. This group was also more likely to have drug-resistant TB than those with no social risk factors, and to have negative treatment outcome. Also, 75% of UK-born cases with any of those social risk

factors were from White ethnic background, even though only 62% of all UK-born cases were from White ethnicity (13). These statistics underline the importance of understanding and addressing social determinants of TB in the UK-born population to TB control efforts.

Few studies have measured the potential increase in risk of TB associated with specific social determinants in low-incidence settings. For some potential risk factors like homelessness and prison stay, many studies are limited to documenting their prevalence among TB patients, or alternatively, the prevalence of TB disease or latent infection in these risk groups. The majority of studies of the association between poverty/deprivation and TB in low-incidence countries are ecological in nature, comparing notification rates across socio-economic levels of geography (14) (see also manuscript 2). Most comparative studies at the individual level have focused on either contrasting patients' characteristics by groups (e.g. native vs foreign born, age groups, and drug sensitive vs drug resistant), or comparing the association between these social risk factors and treatment outcome. Furthermore, the fact that such social risk factors tend to cluster in individuals provides an additional challenge, which needs to be properly accounted for when measuring their respective effect. This has been a limitation to several available studies examining this question. For example, it is known that the proportion of smokers is higher among alcohol drinkers; however, of the eight studies in which the association of alcohol drinking to risk of TB was measured in the past 40 years, only two adjusted for tobacco smoking, an established factor increasing the risk of TB (15).

This paper reports the results of a case-control study in which the association between individual socio-economic status and a range of social determinants of health, and the risk of tuberculosis were measured among UK-born young adults from White ethnic background. A causal Directed Acyclic Graph (DAG) is posited as the formal framework within which the respective potential effect of risk factors is estimated while accounting for the presence of others.

Methods

Study design and setting:

This was a community-based case-control study conducted between 2012 and 2014 across England, with controls frequency-matched to cases on birth cohort and sex. The data collected and used for the present analyses were secondary to the primary aim of the main study, which was to estimate the duration of BCG effectiveness against tuberculosis between 10 and 30 years after vaccination (16).,

Participants

<u>Cases</u> were individuals born in the United Kingdom (UK) and diagnosed with their first episode of active tuberculosis at age 23 to 38 years old between years 2003 and 2012 (hence born between 1965 and 1989), and notified to the national enhanced tuberculosis surveillance system (ETS) (13). This age-group inclusion criteria was determined by the primary objective of the study, notably estimating BCG effectiveness 10 to 25 years after vaccination in a population in which the median age at vaccination was 13 years old. The study was restricted to the White ethnic group in which the overall risk of tuberculosis is comparable to that of the general population, while the risk of TB in subjects from several minority ethnic groups in England is known to be higher and are likely to have different socio-economic drivers.

<u>Controls</u> were subjects from the same (White) ethnic background as cases and born in the UK between the years 1965 and 1989, and never diagnosed with, or treated for tuberculosis up to the time of inclusion in the study. Controls were frequency-matched to cases on sex and birth cohort ±2 years) and sampled from the same communities where cases had been reported.

<u>*Exclusion criteria:*</u>

❖ Cases with known HIV infection were excluded, as their risk of TB is higher than the general population. The same criterion was not applied to controls as it was impractical to exclude in the field. However, the HIV prevalence in the general population in England is very low (overall population prevalence 1.5 per 1,000), and much lower among UK born subjects and in the White ethnic group (17).

❖ Cases living in state institutions at the time of data collection, notably in prisons were also excluded, because of practical difficulties to arrange access to these persons at the time of the data collection.

Cases: All eligible TB cases across England notified to the Enhanced Tuberculosis Surveillance System (ETS) between 2003 and 2012 were identified and invited to take part to the study. Tuberculosis is a notifiable disease by law in the UK, and the ETS is the national TB surveillance system run by Public Health England (PHE), formally known as the Health Protection Agency (HPA).

Controls: Approximately 1200 controls were required to achieve the primary objective for which the data was initially collected. They were selected at random from the community using a three-stage self-weighted sampling scheme, thus allowing wide geographic coverage while optimising logistical efficiency. The sampling frame included the UK Office for National Statistics (ONS) Super Output Area (SOA) hierarchical geographies and the small-user Postal Address File for England. This file contains the list of all residential addresses within each postcode unit (PCD) in England. PCDs are grouped by the ONS into Output Areas (OA) using an automated process that allow for social homogeneity between resident households. The OAs are aggregated in SOAs, a level suitable for statistical reporting while preserving the anonymity of residents (SOAs count on average 125 households, with an average population of 300). Clusters of SOAs form Lower layer SOAs (LSOA - average 600 households and 1500 residents), and LSOAs are grouped into Middle layer SOAs (MSOA – average 3000 households and 7500 residents) (18). Taking into account the methods and response rate from the Health Survey for England 2004 (19) and ONS LSOA mid-2010 population estimates (20), it was estimated that approximately 9400 addresses needed to be screened in order to recruit enough controls (based the assumption that overall about 1 in 7-8 residential addresses would be yield an eligible control that accepted an invitation to participate), with a maximum of one eligible person invited to take part to the study if any in the household. To achieve wide geographic coverage, but at the same time maintain travel distances reasonable for cost-efficient screening, the sampling scheme was designed to include a single residential address from each sampled postcode unit, and a total of seven addresses per LSOA. The sampling steps were as follows:

(i)   The first stage was the selection of 449 of Middle layer Super-Output areas (MSOA) from the 6781 total across England, with probability proportional to the size (PPS) of their 2010 mid-year 25-49 years population estimates.

(ii)   The second stage was the selection of three Lower layer LSOAs in each MSOA sampled in the first stage, by simple random sampling (SRS).

MSOAs each contain on average five LSOAs of roughly similar population size.

(iii)   The third stage was the selection of seven residential addresses from each LSOA by simple random sample (SRS) using the small-user Postal Address File. To ensure an equal geographical spread of selected addresses within each LSOA, seven distinct postcode units were randomly sampled in each LSOA, then one address per postcode unit. LSOAs have on average of 30 postcode units (PCD), with each PCD containing about 15 residential addresses.

Permissions

The study obtained ethics clearance from the NHS Research Ethics Service (REC 11/H1102/11) and LSHTM Research Ethics Committee (Approval 5996), and was also granted NHS Research and Development authorisation through Public Health England (PHE, formerly HPA). Contact details of eligible study participants with history of TB episode notified to the ETS were obtained from PHE, in line with its National Information Governance Board (NIGB) health and social care approval to retain and analyse national surveillance data for public health purposes under Section 251 NHS Act 2006.

Field procedures and data collection

Cases and controls' individual interviews were conducted in their home by trained and experienced interviewers from the National Centre for Social Research (NatCen), a not-for-profit independent organisation with over 40-year experience in social survey and research in the UK.

The contact details from all eligible cases were obtained from the HPA and they were sent postal invitations to take part to the study, with the ability to opt-out (by prepaid postal return slip or Freephone hotline). NatCen's interviewers subsequently visited cases at their addresses, a signed informed consent was obtained and data was collected using a personal face-to-face interview.

An advance invitation was also mailed to the residential addresses selected to be screened for controls, with similar opt-out options as cases. The addresses were then visited by field workers and screened for eligible controls. In households with one or more eligible

subjects, one person was offered participation to the study, and data was collected by face-to-face interview after a signed informed consent was obtained.

NatCen's interviewers conducted the face-to-face interviews using the same computer assisted questionnaire and standard-operating procedures for both cases and controls. All questions used a standard script and were close-ended, and the questionnaire was tested prior to the fieldwork.

After the field data collection, participants' demographic information was used to obtain additional information from the ETS and area-level statistics from the ONS public databases.

Variables and data sources

The outcome of interest was the first episode of any form (pulmonary or non-pulmonary) of active tuberculosis diagnosed between age 23 and 38 years old. The information was retrieved from the ETS. In addition to checks in the ETS, controls were also asked during the interview if they were ever treated for tuberculosis and excluded.

Independent variables: During the face-to-face interview, interviewers collected information on a range of known and potential determinants of risk of tuberculosis, which are called in this report 'independent variables'. These included:

(a)   Socio-demographic information, including the date of birth, sex, residential postcode and highest educational level achieved. The residential postcode was linked to ONS public database to obtain the LSOA-level index of multiple deprivation. LSOAs represent the lowest level in the hierarchy of ONS statistical geographies for which the information on deprivation is available in England (21).

(b)   Lifestyle variables, notably duration, frequency and quantity of tobacco smoking, alcohol drinking, as well as Class B/C drugs (e.g. Cannabis, Benzodiazepines, Qat, Glue, Solvents, Speed or other amphetamines etc.) and Class A drugs (e.g. Ecstasy, Cocaine, crack, Heroin, LSD, Psychedelic (e.g. "magic" mushrooms).

(c)   Other determinants of the risk of TB, including BCG vaccination status, history of homelessness and prison stay (including in the UK or abroad), household overcrowding and history of long stays in parts of the world with high TB incidence.

Measures to deal with bias

All eligible TB cases notified to the ETS between 2003 and 2012 across England were invited to participate. Likewise, the sampling design for control recruitment used a multi-stage self-weighted scheme to select eligible controls across England at random, while ensuring a wide and fairly distributed geographical coverage.

Study participants were not told that the study was directly related to TB to minimise self-selection; the study title and information materials used the general term "Lung health", and several questions were introduced to discuss other common lung diseases, notably asthma and pneumonia.

Efforts were also made to ensure cases and controls had the same opportunities to take part in the study. Field workers used the same contact pattern for cases and control addresses, with several contact attempts, including at least one visit at different times of the day (morning, afternoon and evening) as well as days of the week (week-days and week-end).

Information bias:

The interviewers were aware of the case versus control status of participants because of the design of the fieldwork. However, they were trained to administer the interview in a similar fashion. Furthermore, all questions had a standard script that interviewers had to read, with no personal interpretation possible, and responses were close-ended. Interviewers also had a mix of cases and controls in their respective fieldwork package.

The study participants were blinded to the study hypotheses as discussed in the section above. To minimise social-desirability bias when collecting information on lifestyle variables and other sensitive matters, this specific data was collected in a separate section of the computer-assisted questionnaire directly completed by the participant, and then electronically locked in a way that the information was neither visible nor accessible to the interviewer.

Study size

A total of 681 cases and 1183 controls contributed data for this study. The sample size was based on the main objective of the study for which the data were initially collected (16). Assuming that 10% of the sample was an inflation to allow control for confounding, I computed that I would have over 80% power to detect odd ratios (OR) ≥1.5 for exposures with 15% or higher prevalence in the control group, and OR ≥ 1.8 for exposures with

prevalence of 5% or higher in the control group (figure 6.1). The power calculations are based on a double-sided likelihood ratio test (LRT), with 5% type-1 error threshold.
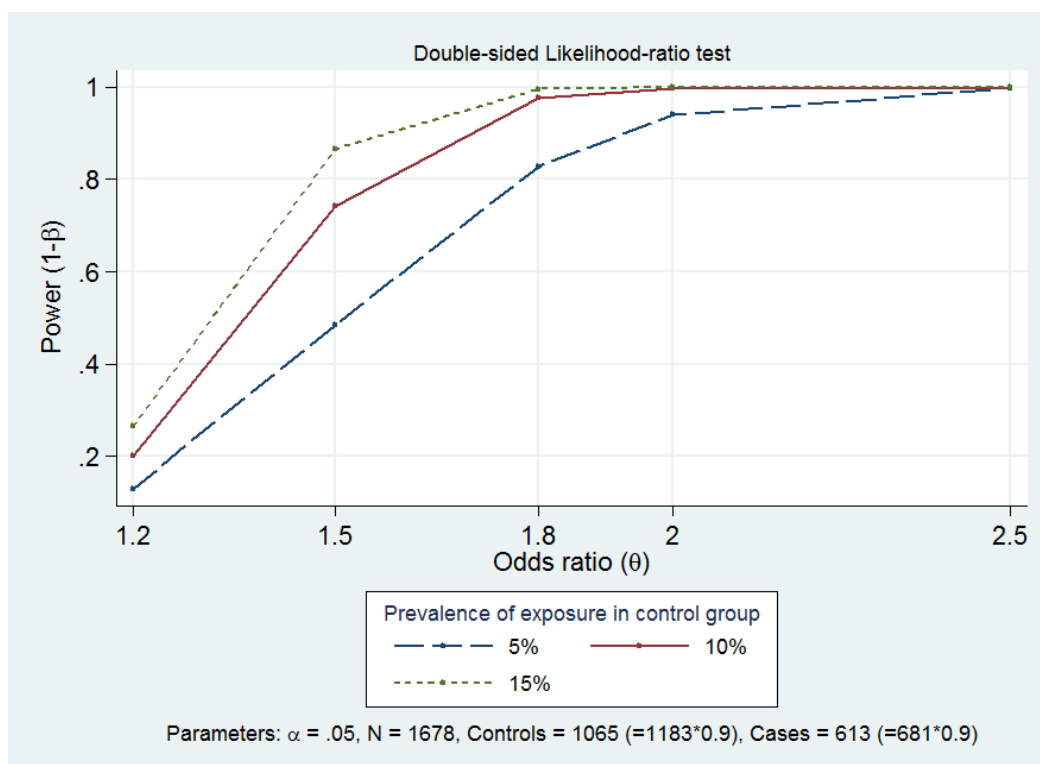
Figure 6.1: Expected study power as a function of the OR to detect possible the association between a risk factor and TB, given the available sample size

Statistical Analysis

Variables and data management

Distal determinants of socio-economic status

❖ *Educational level*: participants' highest educational attainment was grouped respectively by (1) Degree level, teaching qualification or other higher education equivalent [~17 years of formal education starting about age 5 year], (2) General Certificate of Education (GCE) A levels or equivalent level [~14-17 years of education], (3) GCE O levels or equivalent [~12-13 years of education], and (4) Lower than O levels [<12 years of education].

❖ *Small-area level deprivation:* participants' residential postcode addresses were linked to the ONS public data to obtain information on the LSOA-level index of multiple

deprivation (IMD), including the deprivation score and ranking. The IMD ranks were grouped in quintiles of deprivation based on the nation-wide ranking of LSOAs.

❖ *Household overcrowding:* Information on the number of residents in the participant's household was obtained and the number of bedroom or rooms used for sleeping purposes. The information was used to calculate the average number of persons per bedroom (ppb); this is one of the common indicators of household overcrowding used for health and policy planning (22, 23). The ppb was then transformed this into a binary variable (i) < 2 ppb, or (ii) ≥2 persons per bedroom.

Lifestyle variables:

❖ *Alcohol history: P*articipants' typical drinking pattern was captured using the frequency-quantity approach. They were asked if they consumed any alcohol whether currently or in the past (in which case they were asked when they stopped). The self-assessed information on the frequency and typical quantity of alcohol consumption was also collected using the first 2 questions of the standard 3-items AUDIT-C score (24) ([never, less than monthly, monthly, 2-4 times a month, 1-2 times a week and >=4 times a week] for frequency, and [none, 1-2, 3-4, 5-6,7-9, >=10 UK standard drink units] for quantity). This information was then combined as follows to derive an estimated maximum typical alcohol intake per week:

    ✓ The highest boundary of the reported frequency was used as an estimate of frequency of alcohol consumption per week (e.g. the category on average 2-4 times a month was considered as 4 times a month; and 1-2 times a week considered as 2 times a week).

    ✓ The midpoint of the reported quantity of alcohol consumed in a typical occasion was converted into grams of alcohol (in England, one standard drink unit corresponds on average to 8 grams/10ml of pure alcohol). Thus if a subject reported drinking for example 3-4 units in a typical occasion, this was converted to 3.5 * 8 = 28g of pure alcohol on a typical occasion.

    ✓ The information on frequency and quantity was subsequently combined into average consumption in grams of alcohol per week, and then grouped into categories (never drinker, 1-40g/week [>0 to 5 units per week] g/week, 41-112g/week [>5 to 14 units/week], and ≥112g/week [>14 units per week]).

People who had stopped drinking 5 years or more ago represented a very small group (2.8%) and were classified according to their typical consumption when there were

drinking. Only 4.5% of the study sample reported never drinking alcohol, and they were merged with the lowest consumption group.

The choice of a 5 units (40 grams) per week cut-off for the lower risk category was informed by the Health Survey for England 2011 findings that most people in England who drink only do so one or two days a week (25). The cut-off of 14 units (112 grams) per week for the higher risk category reflects the current UK guidelines that drinking above that level may have deleterious effects on health, irrespective of gender (26).

The literature on measurement of alcohol consumption suggests that quantity-frequency methods tend to underestimate alcohol consumption, as they are less likely to capture occasions or periods of excessive drinking (27, 28). There is further evidence from England that people tends to underestimate the content of self-poured drinks, thus home drinking (29). However, for the purpose of my analysis, this was a convenient and conservative estimate of levels of drinking in study participants.

❖ *Tobacco smoking:* The current and past tobacco smoking habits were ascertained in all participants. Questions were asked about the fact, as well as the duration of smoking and typical number of cigarettes per day. About 20% (213/1154) of current and past smokers reported starting to smoke before age 16 years, the age at which it was legal to purchase cigarettes in the UK between 1908 and 2007. The annual survey of smoking, drinking and drugs in young people in England revealed that between 1982 and 2005, the proportion of schoolchildren who regularly smoke at least one cigarette per week was very low in 11 and 12 years old (0 to 2%) whereas this was much higher in children aged 13,14 and 15 years (respectively 5 to 10%, 12 to 19% and 20 to 30%) (30). Furthermore, the 2014 survey reports that 46% of children who smoke at least one cigarette per week reported purchasing cigarettes themselves in shops in spite of it being illegal (30). Therefore, for those who reported starting to smoke before age 13 years, only the duration of smoking from age 13 years onwards was included in the analyses.

To estimate the lifetime tobacco consumption for each participant, the duration and frequency-quantity of tobacco smoking was combined into cigarette pack-years. This is a standard unit where 1 pack-year correspond to smoking an average of 20 cigarettes per day for 1 year, 10 cigarettes per day for 2 years, or alternatively 40 cigarettes per day for 6 months. Subjects were classified into (1) Never smoker, (2) Past smokers, (3) Occasional and daily smokers <10 packs-year, (4) daily 10-19 and (5) >=20 pack-years.

The past smoker category only included subjects who reported stopping to smoke for more than a year.

❖ *Drug use:* Participants were asked about past and current usage of class A, B and C controlled substances. Subjects were classified according to whether they (1) currently used, or had last used them (2) 1-10 years or (3) more than 10 years ago, or (4) never, respectively for class A, and class B and/or C drugs; injectable class A drugs were a separate category.

❖ *History of homelessness:* Participants were asked if they had ever been homeless, and the longest duration they spent homeless. They were grouped in (1) never been homeless, (2) homeless for ≤12 weeks, and (3) homeless for >12 weeks.

❖ *History of prison stay:* The questionnaire also enquired if they had ever been in prison in the UK or abroad, and were categorised in a binary variable respectively (1) any history of prison stay (either in the UK or abroad) or (2) never been in prison.

Other determinants of TB risk

❖ *Age/Birth cohort*: Participants were grouped in 5-year birth cohorts. The use of birth cohorts allows to simultaneously account for any effect on the risk of TB of two temporal dimensions, notably calendar time and age.

❖ *BCG vaccination*: BCG status was established by inspection of participants' upper arms for the characteristic BCG vaccination scar, and a consistent history of BCG vaccination.

❖ *Long stays in high TB incidence areas*: Participants were asked about visits with durations ≥3 months abroad. For simplicity and consistent with the global epidemiology of TB, stays in Africa and Asia were classified as higher risk for TB infection compared to stays in The Caribbean, Central or South America, Eastern Europe and other regions.

Conceptual framework

In order to inform the statistical analyses strategy, a conceptual causal framework of the hypothesised relation of the variables of interest to the risk of tuberculosis as well as to each other, was posited based on background knowledge. Following the social model of health proposed by Dahlgren and Whitehead in 1991 (31) (figure 6.2), the variables were grouped into:

(1)   Distal social determinants of health: including educational level, area-level deprivation in place of residence and household overcrowding.

(2)   Intermediate social determinants of health, notably tobacco smoking, alcohol drinking and drug misuse, as well as history of homelessness and prison stay;

(3)   Matching variables (age/birth cohort, sex) as well as a priori determinants of TB risk, including BCG vaccination and long stays (≥3 months) in high TB-incidence parts of the world (Africa and Asia).

Figure 6.2: Dahlgren and Whitehead social model of health
(Source Dahlgren and Whitehead, 1991)(31)

The relation between variables and tuberculosis was represented in a causal directed acyclic graph (DAG) in figure 6.3. This is a graph in which the observed (measured) variables are represented as '**nodes**', and the hypothesised causal relation between these variables is conceptualised in the form of directed arrows, with the graph being acyclic i.e. arrows always going in the same direction, from a presumed cause (also called '**ancestor**' variable) towards a presumed effect (also called '**descendant**' variable), thus no effect is causing itself (no feedback cycle). Within the framework, the direct association between a variable and TB is represented in the graph by a direct arrow (or '**directed path**') from that variable to TB; under the assumptions underlying the DAG, this direct arrow represents an estimate of the presumed direct 'causal' effect of that variable on the risk of TB, i.e. the effect that is not mediated through any of the other observed variables in the framework. Therefore, DAGs require explicit assumptions regarding the presumed causal relation between any pair of variables (nodes); these assumptions are very simplistic and can be limited by contemporary knowledge. However, the DAGs are conceptually useful

to identify and control for mechanisms through which spurious associations between a variable and tuberculosis may arise in the multivariable analyses, including backdoor paths (defined as '**non-causal open**' **paths** that go from a 'descendent' variable (or an effect) towards an 'ancestor' variable (a cause), and may therefore give rise to a non-causal '**spurious**' association) (32). For example, assume there was no real cause-to-effect association between drug use and TB in my study, but that there were separate causal associations between education level and drug use, and between education level and TB; a model measuring the association between drug use and TB in such study sample without adjusting for education level would show an association, albeit non-causal, because of the 'backdoor' path from *drug use* to *education level*, then from *education level* to *tuberculosis* (figure 6.3). However, if the backdoor path was 'blocked', by adjusting for education level in the statistical model, there would be no association between drug use and TB.

In the DAG, it was hypothesised that the highest educational level attained could affect employment and income in later life, hence the individual socio-economic status, and through this, influence the choice of area of residence (area-level deprivation) and type of accommodation (including overcrowding). The educational level and socio-economic status may also affect the risk of tuberculosis in part through their (indirect) effect on intermediate social determinants of health (including lifestyle risk factors), and via other pathways for which no measurements were made in this study (direct effect). It was also assumed that all associations between TB and the variables represented in the DAGs may be confounded by BCG vaccination status and long stays in high TB incidence parts of the word, two known risk factors for TB. These two variables were not represented in the DAG for visual convenience, but were treated as a priori confounders in the analyses.
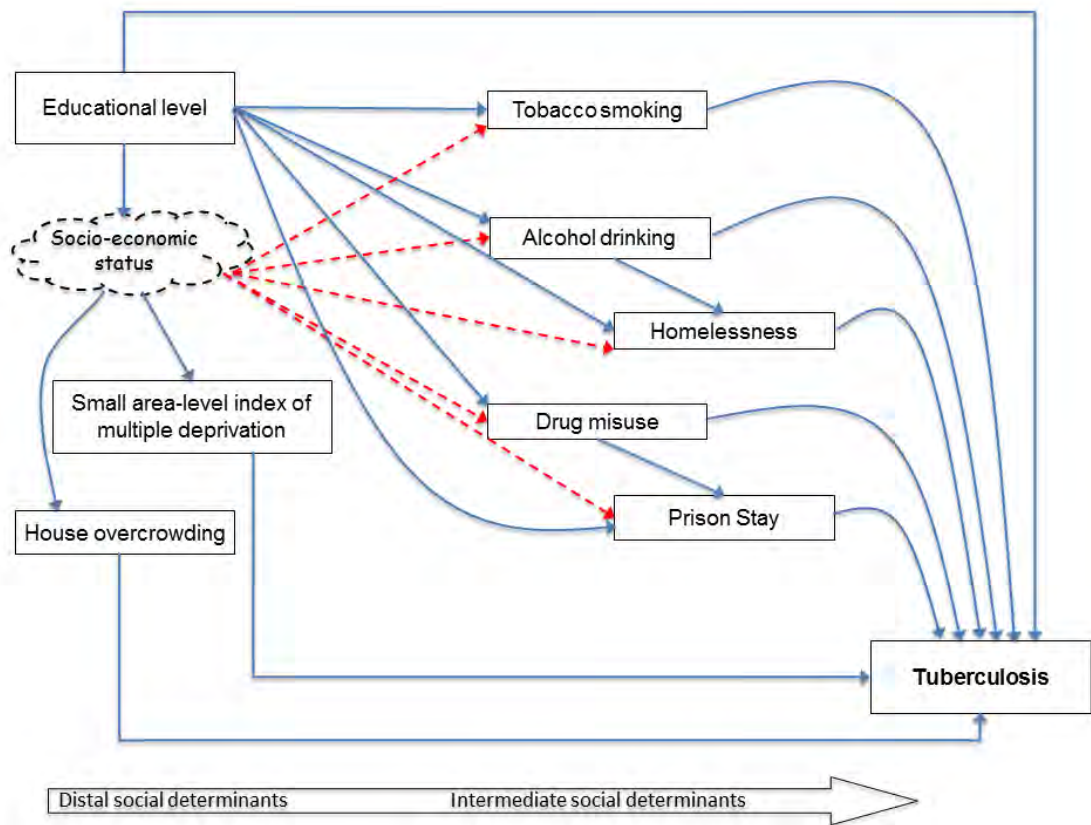
Figure 6.3: Directed Acyclic Graph (DAG) of hypothesised relation between social determinants and tuberculosis.

Note: The socio-economic status (SES) is depicted in a dash-lined cloud to indicate that this variable is not directly observed, but is assumed to be one effect of the educational level. Thus, the dash red arrows indicate that the association between SES and the intermediate social determinants of health is not directly measured in this framework. The relationship between education level and SES is represented in the DAG to explicitly assume that education level has a dual effect on the intermediate social determinants, by itself and via its effect on the socio-economic status. The assumption allows one to see back-door paths between these intermediate variables and TB that do not include education level, thus could otherwise have been missed. The variables BCG and 'long stay in high-TB parts of the world' are known independent risk factors for TB and considered a priori confounders for these analyses. They are included in all adjusted analyses and not represented in this DAG.

Descriptive analyses

The distribution of all independent variables by case and control status was tabulated and examined, including missing data. The characteristics of study participants with data missing for at least one variable were described and compared to those with complete data. To inform the multivariable model building, the correlation between related variables was also examined, especially between lifestyle variables (use of tobacco, alcohol and controlled drug), as well as history of prison and homelessness.

Associations of socio-economic and lifestyle indicators and tuberculosis

Two groups of logistic regression models were built. The first group of models was designed to measure the overall association ('total effect') of education level – the most distal indicator of socio-economic level in my conceptual framework - and tuberculosis. The second group of models measured the respective associations between tuberculosis and the more proximal (intermediate) social determinants of health inequality in the conceptual framework – some of which are assumed to mediate part of the overall effect of socio-economic deprivation on TB risk.

For each group of models, a baseline and adjusted regression models were fitted, respectively to estimate the 'crude' and adjusted odds ratios. The 'crude' estimates were obtained using regression models in which the frequency-matching variables (sex and birth cohort [in 5-year bands]) were forced (the 'baseline models). Therefore, the phrase 'crude estimates' in this chapter indicates age and sex-adjusted measures. The models in which birth cohort was fitted as a categorical variable were compared to linear; the former provided a better fit and there was strong evidence of departure from linearity, therefore birth cohort was fitted as a categorical variable in all regression models. The adjusted models for each group of variables were based on the DAG as described below:

❖ In the first model measuring the overall adjusted effect of educational level (including that possibly mediated through the intermediate social determinants), a logistic regression model was fitted, in which in addition to age and sex, there was further adjustment for the a-priori confounders (BCG status and long stays in high TB areas).

❖ The second model measured the '*direct*' fully adjusted respective association between TB and more proximal risk factors in the DAG, including area-level deprivation, household overcrowding, and the other intermediate social determinants. This model was adjusted for the matching variables age and sex, the a-priori confounders, as well as all '*nodes*' (variables) from the DAG that needed to be blocked (i.e. controlled for) to adjust for confounding to only measure the 'direct' association between each determinant and TB (i.e. non-spurious and not 'mediated' through any other observed variable in the DAG). The appropriate fully adjusted model based on the DAG eventually included all the variables, as well as educational level. When building the model, multi-collinearity was checked when simultaneously including correlated variables, by looking at changes in the standard errors and confidence intervals. Two variables (use of class B/C drugs vs use of class A drugs) with strong correlation and

evidence of multi-collinearity were fitted in turn in the model to measure their association to TB.

One caveat with DAGs is the simplistic assumption on the direction of cause-to-effect sequence between some variables. For example, alcohol abuse can contribute to causing homelessness in some subjects, but homelessness can also increase the risk of alcohol abuse. The assumptions on temporal sequence in my DAG and the resulting regression model were informed by the literature as much as possible. For example, while many ex-prisoners initiated drug use in prison, drug use also increases the risk of incarceration; however, a survey of substance abuse among prisoners in England and Wales has shown that the rates of drug use and dependence is high prior to incarceration (33, 34), with 75% heroin users and nearly 9 in 10 users of other class A drugs users reporting initiating drug use prior to incarceration (35). This explains my DAG's assumption regarding the most common direction of association between drug use and prison in my study sample. The same applies to alcohol abuse and homelessness; the directed path in the DAG is consistent with a survey of substance use in homeless people in England, in which substance use, including alcohol, was among the most common reasons contributing to becoming homeless (36).

The main analyses were restricted to observations with complete data for all variables in the DAG (complete case-analysis). All significance testing in regression models were done using likelihood ratio test (LRT). A test for trend was also conducted for ordered categorical variables in which the level-specific estimates suggested a trend. The statistical analyses were done using Stata 14.0.

Missing data

As a sensitivity analysis, the multiple imputation by chained equation (MICE) procedure was used to impute values to missing data and the analyses above repeated. The multiple imputation model included all putative variables included in the fully adjusted model, as well as the case/control status. The predictive models used were respectively logistic regression for binary variables (BCG status, person-per-bedroom, history of prison stay), ordered logistic regression for ordered categorical variables (smoking status, alcohol drinking and educational level), and multinomial logistic regression model for other non-ordered categorical variables (history of homelessness, class A and class B/C drug use). Twenty datasets were imputed, on which the same regression models as for the complete-

case analyses were repeated. Rubin's rules were used to combine estimates across imputed datasets, and obtain the 'imputed' ORs and 95% confidence intervals (95%CI).

Population attributable fractions (PAF):

For the important modifiable risk factors, the information on their frequency in the study population was combined with the magnitude of association to TB to approximate the PAF. This was used to explore the theoretical impact that various interventions on specific risk factors may have in my target population.

The PAFs were estimated by using the proportion of cases exposed and the adjusted ORs (aORs) using the formula $\textbf{PAF} = \sum \textbf{p}_i\text{'}(\textbf{aOR}_i - \textbf{1})/\textbf{aOR}_i$, where $p_i\text{'}$ is the proportion of cases with exposure level i for a specific risk factor, and aOR_i is the adjusted odds ratio for level i of that risk factor (37). This formula assumes that my aORs approximate risk ratios (rare disease assumption) and that they provide reasonable estimates of each risk factor's causal effect on tuberculosis. There is a further assumption that the respective prevalence of exposure in the sampled cases are comparable to that in all cases. Finally, an implicit assumption of the logistic regression (used to obtain risk factors' aORs) is that their effects are multiplicative, not additive. Therefore, the individual PAFs cannot be combined to obtain a 'joint PAF' of any combination of risk factors.

Results

Characteristics of study participants

The characteristics and distribution of various risk factors in cases and controls is presented in table 6.1. There was 9% more female control participants than cases, but the distributions by birth cohorts were comparable in cases and controls. Eighty-eight percent (1618/1864) of participants had complete data for all key variables; the most missing data were found in alcohol drinking (3%), tobacco smoking (3%) and educational level (3%).

Over 40% cases lived in the most deprived fifth of the country, and one in five also reported no education at O-level equivalent or above, compared to one in twenty controls. Lifestyle risk factors were fairly common among cases, with over a quarter smoking daily with lifetime consumption greater than 10 pack-years versus one in eight controls, 18% cases reporting drinking above the recommended limit of 14 units per week compared to 11% controls, and one in ten cases had a history of using injectable class A drugs versus 1% controls. A very strong correlation was also found between using class B and C drugs, and using class A drugs (Spearman correlation coefficient = 0.76). The clustering of social risk factors was also more common in cases than in controls; for example, 7% cases reported both using class A drug, and history of homelessness and prison stay, compared to only 1% controls (figure 6.4)
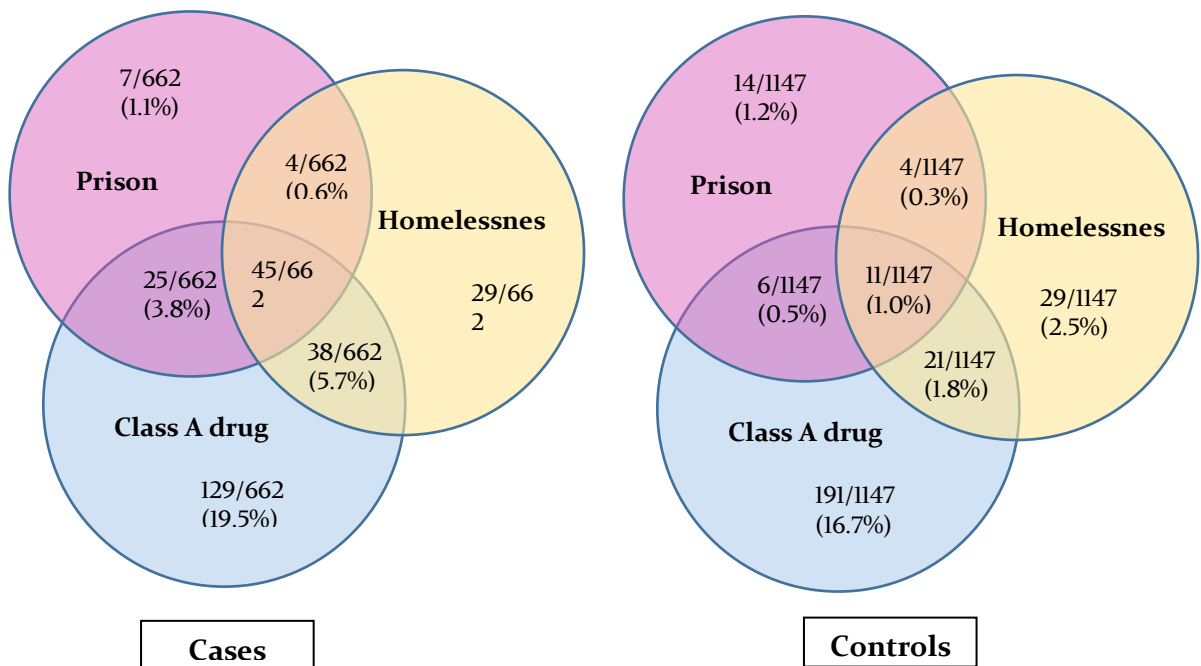
Figure 6.4: Venn diagram of the prevalence of history of class A drug use, homelessness and prison stay in cases and controls

Table 6.1: Characteristics study participants

Variable	Cases (%) (n=681)	Controls (%) (n=1183)
Sex		
Female	345 (51%)	710 (60%)
Male	336 (49%)	473 (40%)
Birth cohort		
1965-1969	65 (10%)	175 (15%)
1970-1974	179 (26%)	318 (27%)
1975-1979	216 (32%)	263 (22%)
1980-1984	152 (22%)	264 (22%)
1985-1989	69 (10%)	163 (14%)
Education level		
None	132 (19%)	75 (6%)
O level, GCE or GCSE	208 (31%)	366 (31%)
A level, SCE Higher	91 (13%)	250 (21%)
Degree or Teaching degree	218 (32%)	461 (39%)
missing	31 (5%)	31 (3%)
BCG vaccination status		
BCG vaccinated	509 (75%)	1024 (87%)
Unvaccinated	164 (24%)	154 (13%)
missing	8 (1%)	5 (0.4%)
Stay of 3 months or more in High TB-incidence areas (Africa or Asia)		
No	610 (90%)	1126 (95%)
Yes	71 (10%)	57 (5%)
Small area-level deprivation		
Least deprived quintile	64 (9%)	238 (20%)
2nd quintile	101 (15%)	236 (20%)
3rd quintile	107 (16%)	237 (20%)
4th quintile	131 (19%)	236 (20%)
Most deprived quintile	278 (41%)	236 (20%)
Persons per bedroom		
<2 person per bedroom	587 (86%)	1104 (93%)
≥2 persons per bedroom	77 (11%)	77 (7%)
missing	17 (3%)	2 (0.2%)
Tobacco smoking		
Never smoked	191 (28%)	508 (43%)
Past smoker	94 (14%)	215 (18%)
Occasional/Daily <10 pack-years	202 (30%)	277 (23%)
Daily 10-19.9 pack-years	119 (17%)	106 (9%)
Daily ≥20 pack-years	57 (8%)	47 (4%)
missing	18 (3%)	30 (3%)
Typical Alcohol consumption		
Do not drink alcohol	36 (5%)	49 (4%)
Drink up to 40g (5 units)/week	324 (48%)	658 (56%)
Drink 41-112g (5-14 units)/week	172 (25%)	300 (25%)
Drink >112g (>14 units)/week	120 (18%)	130 (11%)
missing	29 (4%)	46 (4%)

Class B and C drugs misuse		
Never used any	378 (56%)	818 (69%)
Last used >10 years ago	63 (9%)	135 (11%)
Last used 1-10 years ago	95 (14%)	106 (9%)
Used <1 year ago	130 (19%)	93 (8%)
missing	15 (2%)	31 (3%)
Class A drugs misuse		
Never used any	426 (63%)	921 (78%)
Last used >10 years ago	44 (6%)	88 (7%)
Last used ≤10 years ago	128 (19%)	131 (11%)
Used injectable class A drugs	66 (10%)	12 (1%)
missing	17 (2%)	31 (3%)
History of homelessness and sleeping rough		
Never	556 (82%)	1104 (93%)
≤12 weeks	61 (9%)	43 (4%)
>12 weeks	57 (8%)	25 (2%)
missing	7 (1%)	11 (1%)
History of prison in UK and/or abroad[†]		
Never been in prison	593 (87%)	1132 (96%)
Stayed in prison[†]	83 (12%)	35 (3%)
missing	5 (1%)	16 (1%)

[†]*including 10 (1.5%) cases and 2 (0.2%) controls with history of prison stay abroad*

Association between distal social determinants (education level, area-level deprivation in place of residence, and household overcrowding) and tuberculosis

In the baseline model, the 'crude' odds of TB in subjects with none or lower than O-level and equivalent educational level was nearly four times higher than in those with degree-level education (OR=3.84; 95%CI=2.70 to 5.47), whereas the risk seemed comparable to baseline in subjects with education at GCE O and A-level equivalent. This pattern of association remained unchanged after adjusting for age, sex, BCG vaccination status and long stays in high TB areas (table 6.2).

There was also a strong association between area-level index of multiple deprivation (IMD) and TB, with a risk of TB nearly twice and four times higher in subjects respectively from the most deprived fourth and fifth quintiles compared to those in the least deprived fifth areas. These associations remained strong, albeit slightly attenuated after adjustment for confounding by other variables (respectively [aOR=1.74; 95%CI=1.16 to 2.59] for the 2nd most deprived quintile and [aOR=3.30; 95%CI=2.23 to 4.88] for the most deprived quintile). The risk of TB was nearly doubled in those living in overcrowded housing when controlling for age and sex; but the OR was smaller after further adjustment for

confounding (aOR=1.42; 95%CI=0.95 to 2.12) (detailed results in table 6.3). Most of the confounding in these analysis was due to the a priori confounders BCG vaccination and stays of 3 months or more in high TB incidence parts of the world, and the 'backdoor paths' through education level (see supplementary table 6.1).

Table 6.2: Overall association between Education level and tuberculosis

Variable	Baseline model*			Adjusted model**		
Complete Case analysis (n = 1638; 578 cases and 1060 controls)						
	OR	95%CI	p-value	aOR	95%CI	p-value
Degree or Teaching degree	1			1		
A level, SCE Higher	0.78	(0.58;1.06)		0.79	(0.58;1.08)	
O level, GCE or GCSE	1.19	(0.93;1.53)	<0.001	1.28	(0.99;1.66)	<0.001
None	3.84	(2.70;5.47)		3.94	(2.74;5.67)	
MICE* Imputed datasets (n = 1864; 681 cases and 1183 controls)**						
Degree or Teaching degree	1			1		
A level, SCE Higher	0.82	(0.61;1.10)		0.85	(0.63;1.15)	
O level, GCE or GCSE	1.30	(1.02;1.65)	<0.001	1.41	(1.10;1.81)	<0.001
None	4.21	(2.92;5.65)		4.21	(2.99;5.92)	

Baseline model adjusted for age (birth cohort) and sex
**Adjusted model: Educational level adjusted for age, sex, BCG vaccination status and stays ≥3 months in high TB incidence areas (Africa or Asia). Other variables not included in model because assumed to be mediators in causal framework.
***MICE = Multiple Imputation using Chained Equations

Association between tuberculosis and intermediate social determinants and other risk factors

Focusing on the intermediate social determinants of health (table 6.3), the strongest association after adjusting for confounding was found between TB and misuse of class A injectable drugs, with over five times increase in the risk of TB (aOR=5.67; 95%CI=2.68 to 11.98) as compared to people who never misused class A drugs. The risk of TB was also about 50% higher in those who reported using either non-injectable class A or class B and C drugs within the past 10 years. After controlling for confounding, there was also strong evidence (p=0.008) of a mild dose-effect association between tobacco smoking and TB, including 17%, 25%, 61% and 72% higher risk of TB respectively in past smokers, and subjects smoking occasionally or less than 10 pack-years daily, 10-19.9 pack-years, and 20

or more pack-years, compared to non-smokers. The typical weekly levels of alcohol consumption reported in this study sample were not associated with TB.

The risk of TB in subjects reporting a history of homelessness of up to 12 weeks and over 12 weeks were respectively 66% (aOR=1.66; 95%CI=0.99 to 2.79) and double that of those with no such history (aOR=2.01; 95%CI=1.11 to 3.63); meanwhile the association observed between history of prison stay and TB in the baseline model (OR=3.88; 95%CI=2.49 to 6.04) disappeared once all variables were controlled for (aOR=1.34;95%CI=0.79 to 2.28). There was no single variable explaining most of the confounding by itself, with most of the associations disappearing only after the simultaneous inclusion in the multivariable model of tobacco smoking, drug use, alcohol use, history of homelessness, and education level.

For the other risk factors investigated, subjects who reported stays with duration of 3 months or more in Africa or Asia were nearly three times as likely to have TB (aOR=2.67; 95%CI=1.74 to 4.08), whereas the risk of TB was halved in those who had received BCG.

Finally, consistent with the causal diagram hypotheses that part of the association between education level and tuberculosis is mediated by some intermediate variables, the four-fold higher odds in subjects with none or lower than O-level compared to those with degree-level education (OR=3.94; 95%CI=2.74 to 5.67) was attenuated to an OR=1.76 (95%CI=1.16 to 2.68) after controlling for all intermediate social determinants.

Missing data

The characteristics of the 226 (12%) subjects with data missing for at least one variable were compared to those 1638 (88%) with complete data for all variables. Fifteen percent (103/681) of cases had missing data compared to 10% (123/1060) in controls (p=0.003). The distribution and association of missingness to other variables is reported in the supplementary table 6.2. Broadly, those with missing data were slightly less educated, more deprived, heavier tobacco smokers and alcohol drinkers; they were also more likely to have a history of homelessness. However, they were comparable to those with no missing data with regards to other characteristics (including age, sex, BCG status, long stays abroad, drug use and history of prison).

The findings did not appear to be affected by the missing data, with the results from statistical analyses after multiple imputation of missing data similar to those of the complete case analyses, but with narrower confidence intervals (see table 2 for education level and supplementary table 6.3 for other variables).

Table 6.3: Association between intermediate social determinants and tuberculosis[∞]

Variable	Baseline model[†]			Fully adjusted Model[‡]		
n = 1638; 578 cases and 1060 controls	OR	95%CI	p-value	OR	95%CI	p-value
Quintiles of Index of multiple deprivation						
Least deprived quintile	1	-		1	-	
2nd quintile	1.70	(1.16;2.51)		1.76	(1.18;2.64)	
3rd quintile	1.60	(1.09;2.35)	<0.001	1.51	(1.01;2.27)	<0.001
4th quintile	1.95	(1.34;2.85)		1.74	(1.16;2.59)	
Most deprived quintile	4.38	(3.07;6.24)		3.30	(2.23;4.88)	
Persons per bedroom (ppb)						
<2 ppb	1			1		
≥2 ppb	2.01	(1.40;2.88)	<0.001	1.42	(0.95;2.12)	0.091
Tobacco smoking						
Never smoked	1	-		1	-	
Past smoker	1.33	(0.98;1.82)		1.17	(0.83;1.65)	
Occasional / <10pk-yr	1.89	(1.45;2.46)	<0.001	1.25	(0.92;1.69)	0.008*
Daily 10 to 19.9 pk-yr	2.67	(1.90;3.75)		1.61	(1.09;2.38)	
Daily ≥20 pk-yr	3.49	(2.18;5.59)		1.72	(0.98;3.01)	
Typical Alcohol drinking						
Non-drinker/ ≤40g/wk	1	-		1	-	
41-111g/wk	0.98	(0.77;1.25)	0.015	1.00	(0.76;1.3)	
≥112g/wk	1.54	(1.13;2.10)		1.06	(0.75;1.51)	0.936
Class B/C drug misuse						
Never	1	-		1	-	
>10 years ago	0.88	(0.62;1.25)		0.73	(0.49;1.08)	0.004
1-10 years ago	1.94	(1.40;2.7)	<0.001	1.55	(1.07;2.23)	
<1 year ago	2.78	(2.00;3.85)		1.49	(1.00;2.20)	
Class A drug misuse						
Never	1	-		1	-	
>10 years ago	0.91	(0.6;1.38)		0.72	(0.45;1.14)	
≤10 years ago	1.91	(1.42;2.57)	<0.001	1.51	(1.07;2.12)	<0.001
Injectable	10.57	(5.44;20.53)		5.67	(2.68;11.98)	
BCG vaccination status						
No	1	-		1	-	
Yes	0.45	(0.35;0.57)	<0.001	0.51	(0.38;0.68)	<0.001
Stay of 3 months or more in High TB-incidence areas (Africa or Asia)						
No	1	-		1	-	
Yes	2.27	(1.54;3.34)	<0.001	2.67	(1.74;4.08)	<0.001
History of homelessness						
Never	1	-		1	-	
≤12 weeks	2.92	(1.86;4.59)	<0.001	1.66	(0.99;2.79)	0.005*
>12 weeks	4.35	(2.56;7.40)		2.01	(1.11;3.63)	
History of prison stay						
No	1	-		1	-	
Yes	3.88	(2.49;6.04)	<0.001	1.34	(0.79;2.28)	0.273

[∞]*The associations between TB and the a priori confounders BCG vaccination and long stays in high TB incidence parts of the world are also reported in the table*

[†]*Baseline model is controlling for frequency-matching variables birth cohort and sex*

[‡]*Fully adjusted model further controls for education level and all the variables presented in the table*

*p-value of test for trend

Potential population impact of TB risk factors

The information on the likely frequency of modifiable risk factors in the target population and their 'net' adjusted association to TB was combined to approximate risk-factors-specific population attributable fractions (PAFs) as described in the statistical analyses section; the results are presented in table 6.4. While the association of TB to tobacco smoking was relatively weak, the high prevalence suggested that preventing this habit could help avoid about 18% TB cases in my target population. Similarly, interventions to prevent misuse of class A drugs could help avoid 15% TB cases, with about 8% by reducing injectable drug A abuse. The calculations also suggest that school BCG vaccination may have helped prevent about 12% cases in this population, and reducing homelessness could reduce 7.6% TB notifications. The respective effect of these risk factors is not assumed to be additive; therefore, the joint PAF for any combination of risk factors is not the sum of their respective PAFs, and the results presented should not be interpreted as such.

Table 6.4: Estimates of Tuberculosis Population Attributable Fraction for specific risk factors

Risk Factor/Levels at risk	# Exposed Cases	% Exposed Cases (N=578)	aOR	Level specific PAF	Total Risk Factor PAF*
Tobacco smoking					
Past smoker	91	16%	1.17	2.3%	
Occasional / <10pk-yr	173	30%	1.25	6.0%	18%
Daily 10 to 19.9 pk-yr	96	17%	1.61	6.4%	
Daily ≥20 pk-yr	47	8%	1.72	3.3%	
Class A drug misuse					
<10 yrs	110	19%	1.51	6.4%	14.7%
Injectable	57	10%	5.67	8.2%	
Class B/C drug misuse					
1-10 years ago	84	15%	1.55	5.3%	11.6%
<1 year ago	109	19%	1.49	6.2%	
BCG					
Unvaccinated	140	24%	1.96	11.8%	11.8%
Stay of 3 months or more in High TB-incidence areas (Africa or Asia)					
Yes	62	11%	2.67	6.9%	6.9%
History of homelessness					
≤12 weeks	50	9%	1.66	3.6%	7.6%
>12 weeks	46	8%	2.01	4.0%	

$PAF = \sum p_i'(aOR_i - 1)/aOR_i$, where p_i' is the proportion of cases with exposure level i for a specific risk factor, and aOR_i is the adjusted odds ratio for level i of that risk factor

Discussion

Summary main findings

This study represents to my knowledge the first attempt at using a formal causal framework to examine how the association between individual socio-economic status (SES) and tuberculosis (TB) in the native population from a high-income and low-TB burden setting may be explained by some aspects of the social determinants of health. This causal framework allowed us to make explicit assumptions on the inter-relation between these determinants, and therefore to control for mutual confounding when measuring their respective association to TB. Using the educational level as an indicator for individual SES, I found that amongst UK-born White adults in England, the risk of TB is higher in lower SES groups, with four times greater odds of TB among those with none or education level below O-level, compared to those with A-level and above. My analyses also suggested that in the target population, some of this association between socio-economic status and TB could be explained through the place of residence (based on small-area level of deprivation), tobacco smoking, misuse/abuse of controlled drugs, as well as homelessness. The other social determinants of health inequalities measured in the study (household overcrowding, alcohol drinking and history of prison stay) were only weakly associated with TB after adjusting for these risk factors. The analysis also showed that BCG vaccination halved the risk of TB in those vaccinated, whereas travels for 3 months or more in high-TB burden parts of the world was associated with more than a doubling in the risk of disease. The estimates of population impact suggested that interventions targeting tobacco smoking and drug misuse (especially class A drugs) may contribute to substantially reducing the burden of tuberculosis in the target population.

Overall SES (using Educational level as an indicator) and risk of tuberculosis

There are studies supporting the idea that in low-incidence settings, poverty and lower SES remain associated with greater risk of *Mtb* infection (14), as well as delay to diagnosis and treatment (38), and poorer treatment outcome and mortality (39). However, there is less data on the association between individual SES and the risk of TB disease. Most studies addressing this specific question have been ecological by design, thus focusing on variations in the distribution of disease across gradients of deprivation or poverty at area-level (40). These studies have been helpful to highlight areas of greater burden and where more resources are needed for control efforts, but they have only provided limited insight

on how individuals SES relates to their risk of disease, including within poor areas where the burden of disease is higher. My results that the risk of TB is nearly four-fold higher in individuals with none or lower education level, irrespective of intermediate determinants such as tobacco smoking and drug use, is consistent with the few published studies that have measured the association between an individual-level indicator of SES and TB disease, even though the direct comparison between my results and those studies is complicated by the variation in the indicators used to measure individual SES. In their case-control study of risk factors of TB in Adults in Washington in 1988-90, Buskin et al. used family income, years of education and housing conditions to create a composite binary SES variable; they found that the risk of TB in lowest SES category was about four times higher than that of the highest SES group (41). Another case-control study in Greenland in 2004-06 using occupation as the proxy-measure for SES, also observed that TB was four times more likely in unemployed subjects compared to those in work or studies (42). The similarity of these results to ours despite the use of different indicators confirms the hypothesis that lower SES is an important risk factor for active TB in this study population.

It also reflects the close correlation between educational level and SES in developed countries. It has been argued that education level is a good indicator of SES, because it is greatly determined by parental SES, as well as a strong predictor of future employment and earnings, therefore taking into account both early life influences and adulthood SES (43); it is also relatively easy to measure accurately, therefore minimising measurement error. The higher risk of disease in subjects from lower SES status is probably a composite consequence of an increased risk of exposure to and infection by *Mtb*, and a higher probability of progression to disease once infected. However, it is unlikely that lower SES directly causes these, but instead, SES determines the distribution of more proximal risk factors, including social determinants, which in turn can affect the risk of infection and disease. The suggestion fits with the WHO Commission on Social Determinants of Health (CSDH) framework which postulates that the pathways through which socio-economic stratification result in health inequalities is by causing unequal distribution of social determinants of health in the society (44, 45).

Risk factors associated with increased risk of TB

The extent to which selected social determinants of health inequality (SDH) explain the association between individual's SES and the risk of TB in my study population was

investigated within a causal framework that allowed simultaneous exploration of their respective potential effects. After taking into account all other variables and potential pathways between SES and TB in my framework, there was evidence that the higher risk of TB related to lower SES was explained in part by tobacco smoking, drug misuse, history of homelessness, and area-level deprivation, whereas the evidence of association between TB and respectively alcohol drinking, history of prison stay, and household overcrowding was no longer apparent once controlling for the other pathways in this dataset.

The association found between tobacco and tuberculosis is consistent with results from four of five previous studies in the UK in which this was measured, including two case-control studies in which current smokers were found to be on average 60% more likely to develop TB than non-smokers (46, 47); A similar result was recently reported from a US study (48). Two previous systematic reviews of the association between tobacco smoking and tuberculosis found overall nine studies in developed countries (8 case-control and 1 cross-sectional studies), of which six reported evidence of association with odds ratios between 1.6 and 3.9 for current smokers compared to non-smokers (49, 50). The fact that the effect of lower SES on the risk of TB is mediated through tobacco smoking is not surprising; studies have consistently found that the prevalence of tobacco smoking is higher among subjects from lower SES background, and that the age at initiation of smoking is much younger (8, 30). The various harmful effects of tobacco smoking on health are well documented, including on the immune system (51, 52). It is biologically plausible that the tobacco-related loss of mucosal immunity in the respiratory tract increases the risk of *Mtb* infection in smokers, even at lower exposure doses; and the impairment of both innate and adaptive immune responses by tobacco can lead to higher risk of disease in infected individuals. The plausibility of a direct effect of tobacco smoking on the risk of TB is supported further by the dose-effect observed in my study, with the risk in daily smokers higher than in occasional and past smokers.

Regarding drug use, although a number of studies in recent times have reported a greater prevalence of *Mtb* infection (TST positive tests) among drug users than the general population, there is scant evidence on the association between drug use and TB disease (53, 54). In my study, subjects who admitted to using either of class C, B or non-injectable class A drugs in the past 10 years were about 50% more likely to develop TB, and the risk in those admitting to using injectable class A drugs was much higher, nearly 5 times that of non-drug users after controlling for other proximal risk factors. In 1971, well before the HIV pandemic, Reichman *et al.* reported that the prevalence and incidence of TB among drug users in Harlem, New York were respectively 9 and 10 times higher than that of its

general population (55), which is consistent to the unadjusted estimates obtained for the association between use of injectable drugs and TB in my study. In the same analyses, these authors found that the TST rates in the drug-user population were similar to the general population of Harlem, which supports the hypothesis that drug use may be independently associated with increased risk of developing TB disease after infection (55).

In the context of low TB incidence in most developed countries in contemporary times, the higher prevalence of *Mtb* infection reported among drug users could also still be due to higher probability of exposure and transmission among drug users, for example as a result of frequenting or congregating in spaces with inadequate ventilation. Two studies respectively in the USA (56) and the UK (57) have found that smear positive TB is nearly twice more frequent among drug users than other forms of TB, and delays to diagnosis are more frequent, which may both contribute to more transmission in this population group. However, the biological mechanisms through which drug use may increase the risk of TB are not clear. There are studies suggesting drug use may impair the immune system (58), and it has been speculated that pulmonary damage is related to some forms of drug abuse, for example frequent smoking of crack-cocaine and other inhaled drugs, may affect alveolar macrophages (59) (58). It is also possible that co-infection with HIV and under-nutrition may contribute to the much higher risk in those using injectable drugs. Recent *Mtb* infection, which is likely in these risk groups given frequent exposure, is also in itself a strong risk factor of disease, with nearly 5-10% risk of TB in the 2-5 years following infection, as compared to much lower risk over the rest of a lifetime (60).

The higher prevalence of a number of lifestyle behaviours hazardous to health among homeless people, especially those sleeping rough, is well documented; such behaviours include tobacco smoking, drug use and harmful alcohol drinking (36, 61). This is evident in my study, because the association between homelessness and TB is nearly halved after controlling for these other risk factors; for instance, the 4 times higher risk of TB in those reporting being homeless for more than 12 weeks compared to those who have never been homeless dropped to twice the risk after additional controlling for the other factors. However, even after taking into account the other social determinants, there was still good evidence that history of homelessness was independently associated to a higher risk of TB. This is likely explained by the role of other factors frequent in homeless subjects that were not accounted for in my study, for example poorer nutritional status, which contributes to weakening the immune system, as well as greater likelihood of exposure to subjects with infectious TB.

In my analysis, the risk of TB was also higher in those in general living in deprived areas, even after controlling for other risk factors and social determinants (up to three times increase in those living in the most deprived quintile areas). The IMD-based measure of deprivation most likely captures aspects of poverty that affects the risk of TB through pathways other than the social determinants measured in my study. Two of the seven domains that are included in the composite IMD, barriers to housing and services, and living environment deprivations, capture aspects of the living environment that may affect the risk of infection, including for instance quality of housing and household overcrowding (21). The IMD also measures income and employment deprivation (21), which are associated with nutritional status and health frailty, and through that may affect the risk of disease.

Risk factors with weak evidence of an association with TB

The association between alcohol drinking and TB in this study population was consistent with the results of the sole previous UK study in which this was measured (62), but was weaker than reported in several other studies. Subjects who reported regularly drinking on average 14 units or more per week, were only about 50% more likely to have TB than non-drinkers, and alcohol was no longer associated with TB after adjusting for other social determinants, whereas a previous systematic review of the literature reported a pooled relative risk of nearly three times more TB among drinkers (15). Although the comparison of various studies is complicated by variation in the definitions and classification of alcohol abuse, the difference probably reflects the duration of exposure, as my study population was mainly relatively younger adults (23 to 38 years), hence less likely to have been exposed to chronic harmful drinking long enough to affect their immunity, while several of the studies reporting stronger association included older adults, and/or on subjects with recorded diagnosis of alcohol abuse (15). Also, the fact that several prior studies did not always control for some confounders may have contributed to overestimating the alcohol-related relative risk of TB; for example, a cohort study in Canada reported an adjusted relative risk of 3.12 (95%CI 1.26-7.72), but did not control for tobacco smoking (63), whereas another cohort in Finland in which the analysis were adjusted for tobacco smoking found no association (64).

Household overcrowding and history of prison stay were both strongly associated with TB in my baseline model, but these associations were weaker after adjusting for other variables. It is documented that overcrowding may increase the risk of *Mtb* exposure and

infection (65, 66), and the higher prevalence of LTBI among prisoners has been noted in several surveys (67); the strong association with TB after controlling for age and sex, is consistent with the fact that recent infection is in itself a strong risk factor for disease (60). The weaker association between overcrowding and TB after additional adjustment for other determinants in my study sample may reflect the fact that subjects living in overcrowded households are more likely to be from lower SES, and could therefore also be at higher risk of exposure to other TB risk factors, for example tobacco smoking. A similar reasoning could be held regarding the association between TB and history of prison stay. For example the prevalence of tobacco smoking, drug use and homelessness among ex-prisoners is higher than the general population (33, 34); and as discussed in the previous section, both drug use and homelessness can increase the risk of TB e.g. via poor nutritional status, including in infected ex-prisoners. Alternative explanations for the weak evidence of association between TB and history of prison stay after adjustment could include the underreporting of other risk factors like drug use and history of homelessness in the control group, which may have caused overestimation of their association with TB, and in turn an underestimation of the association between history of prison and TB. It is also possible that the overall association between history of prison stay and TB was underestimated in my study sample due to under-reporting of prison stay among cases, and the analysis not taking into account parameters like the duration of prison stay and time since last prison stay.

Study strengths and limitations

One caveat of using a formal causal framework in my study is that it requires relatively simplistic causal assumptions for the complex relationship between the various social determinants. For example, while drug users are at higher risk of prison stay, many ex-prisoners develop their addiction during their prison stay (34, 35). However, in my analyses, the assumptions were made to obtain conservative estimates for all associations investigated. Another frailty that my study share with many observational designs based on recall of exposure, was the difficulty in ascertaining the precise temporal sequence between participants' exposure to some of the risk factors and *Mtb* infection and TB. This is mitigated to some extent by the fact that some of the risk factors investigated tend to be correlated in time, in that recent exposure status is a relatively good predictor of past exposure status. Furthermore, reverse causality is not a major concern for the relationship of TB to the determinants of health measured in this study.

A difficulty inherent to investigating social determinants of a disease like tuberculosis that disproportionately affects socially marginalised and deprived segments of the population is that cases with the highest levels of exposure (at highest risk) can be difficult to trace and enrol in the study. Reasonable efforts were made to find and include such individuals; for example, attempts were made (including some successful) to contact eligible notified cases who are still homeless, but with known contact details at shelters or temporary accommodations. Likewise, the sections of the questionnaire collecting data on socially-sensitive habits and history, including tobacco, alcohol and drug use, history of homelessness and prison stay were collected confidentially using a self-administered computer assisted software which allowed the participants to enter the information themselves in confidence and electronically locked it so it was not accessible to the interviewer; this was not only to minimise bias in reporting of the information, but also to ensure equal chance of participation to the study of people with higher exposure levels. However, overall the proportion of cases that could successfully be contacted was lower in the most deprived area than in the least deprived areas. The study was also restricted to people who had their first ever notified episode of TB, thus not including those with relapse who may have higher prevalence of some of the risk factors of interest. Another issue related to the retrospective ascertainment of exposures is the measurement accuracy; the misclassification of some variables may have contributed to underestimate some associations. It is therefore possible overall that the associations between TB and of some of the social determinants of health investigated here may have been underestimated, and my results are relatively conservative.

Conclusions and recommendations

Despite of their limitations, the results presented here provide some insights into some of the mechanisms through which social deprivation affects the risk of TB in the adult native population of a low-incidence developed country. As noted in introduction, the TB rates have been stagnating in the native adult UK population for nearly a quarter of a century, in spite of the scaling up of control efforts in recent years, and new threats have emerged, not least the spread of multi-drug resistant TB strains. The new global TB strategy adopted by the WHO in 2015 recognises that additional actions are needed to complement the current TB control and prevention tools to progress towards elimination, including addressing the underlying social determinants of TB (3). Although further studies are needed to build a stronger the body of evidence to make policy recommendations, the potential impact of interventions addressing some of the social determinants investigated

should be noted. The population attributable fraction estimates based on my conservative analyses suggest that interventions like tobacco smoking cessation in white UK born young adults may help reduce up to a fifth of TB cases in the target population, while drug addiction treatment could help avert nearly 15% disease. A recent UK-based qualitative study has highlighted the need to integrate care across a number of social and health services to address the complex needs of TB patients in order to achieve better treatment outcome (68). My results provide further arguments in support of such integrated approach, as it could also help prevent cases and reduce the burden of disease among vulnerable groups, and at the same time improve the cost-effectiveness of combined public health interventions by pooling resources.

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Supplementary table 6.1: Association between tuberculosis, and area-level deprivation in place of residence and household overcrowding

	Baseline model*			Adjusted model 1**			Adjusted model 2**		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Quintiles of Index of multiple deprivation									
Least deprived quintile	1	-		1	-		1	-	
2nd quintile	1.70	(1.16;2.51)		1.87	(1.26;2.79)		1.76	(1.18;2.64)	
3rd quintile	1.60	(1.09;2.35)	<0.001	1.60	(1.07;2.38)	<0.001	1.51	(1.01;2.27)	<0.001
4th quintile	1.95	(1.34;2.85)		1.94	(1.31;2.87)		1.74	(1.16;2.59)	
Most deprived quintile	4.38	(3.07;6.24)		3.82	(2.60;5.60)		3.30	(2.23;4.88)	
Persons per bedroom (ppb)									
<2 ppb	1	-		1	-		1	-	
≥2 ppb	2.01	(1.40;2.88)	<0.001	1.67	(1.14; 2.44)	0.009	1.42	(0.95;2.12)	0.091

Baseline model adjusted for matching variables birth cohort and sex

** Adjusted model 1 further adjusted for a priori confounders BCG status and long stay (≥3 months) in Africa or Asia, and Education level

*** Adjusted model 2 control for all variables in the table and in the adjusted model 1, as well as tobacco smoking, drug use, alcohol drinking, history of homelessness, and history of prison stay.

Note: This supplementary table illustrates that most of the confounding in measuring the association between the variables presented in the table and TB was due to education level and the a priori confounders.

Supplementary table 6.2: Characteristics of subjects with and without missing data, and association to missingness

Variable	Missing data (%) (n=226)	Complete data (%) (n=1638)	Crude OR (95%CI)	p-value
TB status				
Controls	123 (54%)	1060 (65%)	-	
Cases	103 (46%)	578 (35%)	1.53 (1.16;2.03)	0.003
Birth cohort				
1985-1989	25 (11%)	207 (13%)	-	
1980-1984	49 (22%)	367 (22%)	1.10 (0.66;1.84)	
1975-1979	52 (23%)	427 (26%)	1.01 (0.61;1.67)	0.219
1970-1974	75 (33%)	422 (26%)	1.47 (0.91;2.38)	
1965-1969	25 (11%)	215 (13%)	0.96 (0.54;1.73)	
Sex				
Female	118 (52%)	937 (57%)	-	
Male	108 (48%)	701 (43%)	1.22 (0.93;1.62)	0.157
Education level				
Degree level	51 (31%)	628 (38%)	-	
A level, SCE Higher	25 (15%)	317 (19%)	0.97 (0.59;1.60)	
O level, GCE or GCSE	59 (36%)	515 (31%)	1.41 (0.95;2.09)	0.020
None	29 (18%)	178 (11%)	2.00 (1.23;3.26)	
Small area-level deprivation				
Least deprived quintile	34 (15%)	268 (26%)	-	
2nd quintile	29 (13%)	308 (19%)	0.74 (0.44;1.25)	
3rd quintile	28 (12%)	316 (19%)	0.70 (0.41;1.18)	<0.001
4th quintile	44 (19%)	323 (20%)	1.07 (0.67;1.73)	
Most deprived quintile	91 (40%)	423 (26%)	1.69 (1.11;2.59)	
Persons per bedroom (ppb)				
<2 ppb	184 (89%)	1507 (92%)	-	
≥2 ppb	23 (11%)	131 (8%)	1.44 (0.90;2.30)	0.142
BCG vaccination status				
Unvaccinated	41 (19%)	277 (17%)	-	
BCG vaccinated	172 (81%)	1361 (83%)	0.85 (0.59;1.23)	0.401
Stay of 3 months or more in High TB-incidence areas (Africa or Asia)				
No	212 (94%)	1524 (93%)	-	
Yes	14 (6%)	114 (7%)	0.88 (0.50;1.57)	0.666
Tobacco smoking				
Never smoked	48 (27%)	651 (40%)	-	
Past smoker	24 (13%)	285 (17%)	1.14 (0.67;1.90)	
<10 pack-years	56 (31%)	423 (26%)	1.80 (1.20;2.69)	<0.001
10-19.9 pack-years	34 (19%)	191 (12%)	2.41 (1.51;3.86)	
≥20 pack-years	16 (9%)	88 (5%)	2.46 (1.34;4.53)	
Typical Alcohol consumption				
≤ 40g (5 units)/week	76 (50%)	991 (61%)	-	
41-112g (5-14 units)/week	43 (28%)	429 (26%)	1.31 (0.88;1.93)	
>112g (14 units)/week	32 (21%)	218 (13%)	1.91 (1.23;2.97)	0.017
Class B and C drugs misuse				
Never used any	104 (58%)	1092 (67%)	-	

Used >10 years ago	20 (11%)	178 (11%)	1.18 (0.71;1.95)	
Used 1-10 years ago	24 (13%)	177 (11%)	1.42 (0.89;2.28)	0.062
Used <1 year ago	32 (18%)	191 (12%)	1.76 (1.15;2.69)	
Class A drugs misuse				
Never used	122 (69%)	1225 (75%)	-	
used >10 years ago	15 (8%)	117 (7%)	1.29 (0.73;2.27)	
used ≤10 years ago	31 (17%)	228 (14%)	1.37 (0.90;2.07)	0.355
Used injectable class A	10 (5%)	68 (4%)	1.48 (0.74;2.94)	
History of homelessness				
Never	174 (84%)	1486 (91%)	-	
≤12 weeks	19 (9%)	85 (5%)	1.91 (1.13;3.21)	0.012
>12 weeks	15 (7%)	67 (4%)	1.91 (1.06;3.42)	
History of prison stay				
Never been in prison	187 (91%)	1538 (94%)	-	
Stayed in prison	18 (9%)	100 (6%)	1.48 (0.88;2.50)	0.158

Supplementary table 6.3: results of the sensitivity analyses of the association between distal and intermediate determinants and TB after multiple imputation for missing data (fully adjusted model[‡])

Variable	Complete case			Multiple imputation		
	OR	95%CI	p-value	OR	95%CI	p-value
Quintiles of Index of multiple deprivation						
Least deprived quintile	1	-		1	-	
2nd quintile	1.76	(1.18;2.64)		1.64	(1.12;2.41)	
3rd quintile	1.51	(1.01;2.27)	<0.001	1.54	(1.05;2.26)	<0.001
4th quintile	1.74	(1.16;2.59)		1.87	(1.29;2.73)	
Most deprived quintile	3.30	(2.23;4.88)		3.30	(2.29;4.75)	
Persons per bedroom (ppb)						
<2 ppb	1			1		
≥2 ppb	1.42	(0.95;2.12)	0.091	1.34	(0.92;1.95)	0.128
Tobacco smoking						
Never smoked	1	-		1	-	
Past smoker	1.17	(0.83;1.65)		1.01	(0.73;1.41)	
Occasional / <10pk-yr	1.25	(0.92;1.69)	0.008*	1.24	(0.93;1.65)	0.004*
Daily 10 to 19.9 pk-yr	1.61	(1.09;2.38)		1.61	(1.12;2.32)	
Daily ≥20 pk-yr	1.72	(0.98;3.01)		1.66	(0.99;2.76)	
Typical Alcohol drinking						
Non-drinker/ ≤40g/wk	1	-		1	-	
41-111g/wk	1.00	(0.76;1.3)		1.10	(0.86;1.43)	
≥112g/wk	1.06	(0.75;1.51)	0.936	1.20	(0.86;1.67)	0.494
Class B/C drug misuse						
Never	1	-		1	-	
>10 years ago	0.73	(0.49;1.08)	0.004	0.74	(0.51;1.06)	0.004
1-10 years ago	1.55	(1.07;2.23)		1.52	(1.07;2.16)	
<1 year ago	1.49	(1.00;2.20)		1.43	(0.99;2.07)	
Class A drug misuse						
Never	1	-		1	-	
>10 years ago	0.72	(0.45;1.14)		0.79	(0.51;1.22)	
≤10 years ago	1.51	(1.07;2.12)	<0.001	1.46	(1.05;2.02)	<0.001
Injectable	5.67	(2.68;11.98)		5.36	(2.63;10.90)	
BCG vaccination status						
No	1	-		1	-	
Yes	0.51	(0.38;0.68)	<0.001	0.51	(0.39;0.67)	<0.001
Stay of 3 months or more in High TB-incidence areas (Africa or Asia)						
No	1	-		1	-	
Yes	2.67	(1.74;4.08)	<0.001	2.63	(1.76;3.94)	<0.001
History of homelessness						
Never	1	-		1	-	
≤12 weeks	1.66	(0.99;2.79)	0.005*	1.51	(0.94;2.41)	0.008*
>12 weeks	2.01	(1.11;3.63)		1.88	(1.09;3.23)	
History of prison stay						
No	1	-		1	-	
Yes	1.34	(0.79;2.28)	0.273	1.45	(0.88;2.38)	0.144

[‡]*Fully adjusted model controls for sex, birth cohort, education level and all the variables presented in the table*

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Student	Patrick Nguipdop Djomo
Principal Supervisor	Punam Mangtani and Laura Rodrigues
Thesis Title	Tuberculosis in England, a high-income Western European setting with low incidence: Recent trends, Social determinants and Prevention through BCG vaccination

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	BMJ Open		
When was the work published?	July 2012		
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Student Signature: _____ Date: 20/2/2017

Supervisor Signature: _____ Date: 27/2/2017

7. <u>Manuscript 4:</u> BCG vaccination in England since 2005: a survey of policy and practice

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BCG vaccination in England since 2005: a survey of policy and practice

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ABSTRACT

Objective: Assess the current BCG vaccination policies and delivery pathways for immunisation in Primary Care Trusts (PCTs) in England since the 2005 change in recommendations.

Design: A survey of key informants across PCTs using a standardised, structured questionnaire.

Setting: 152 PCTs in England.

Results: Complete questionnaires were returned from 127 (84%) PCTs. Sixteen (27%) PCTs reported universal infant vaccination and 111 (73%) had selective infant vaccination. Selective vaccination outside infancy was also reported from 94 (74%) PCTs. PCTs with selective infant policy most frequently vaccinated on postnatal wards (51/102, 50%), whereas PCTs with universal infant vaccination most frequently vaccinated in community clinics (9/13, 69%; p=0.011). To identify and flag up eligible infants in PCTs with targeted infant immunisation, those who mostly vaccinate on postnatal wards depend on midwives and maternity records, whereas those who vaccinate primarily in the community rely more often on various healthcare professionals.

Conclusions: Targeted infant vaccination has been implemented in most PCTs across the UK. PCTs with selective infant vaccination provide BCG vaccine via a greater variety of healthcare professionals than those with universal infant vaccination policies. Data on vaccine coverage would help evaluate the effectiveness of delivery. Interruptions of delivery noted here emphasise the importance of not just an agreed, standardised, local pathway, but also a named person in charge.

INTRODUCTION

Tuberculosis (TB) remains a public health problem in England. After a century of consistent decline in the incidence and annual infection risk, the incidence of TB has been rising since the late 1980s.[1] TB is concentrated within certain groups of the population (including migrants from high-prevalence countries, prisoners, homeless persons and other marginal populations) and in urban areas.[2]

Since the 1950s, immunisation with the BCG vaccine, which has been shown to be highly effective in the UK population,[3] has

ARTICLE SUMMARY

Article focus
- An important control measure, especially in the era of multidrug-resistant tuberculosis, is BCG vaccination. In 2005 the UK moved from a school-aged universal BCG vaccination policy to a targeted policy towards children at high risk. To date, it is unknown as to how this vaccination policy is operating at the local level (via Primary Care Trusts)

Key messages
- Targeted infant vaccination has been implemented in most areas in England, but delivery pathways are complex and appear to vary between Primary Care Trusts.
- Areas with selective infant vaccination provide BCG vaccine via a larger number of healthcare providers than those with universal infant vaccination policies.
- These findings emphasise the need to standardise local pathways, to allocate clear responsibilities and to monitor vaccination coverage.

been a part of TB control efforts in England. The routine policy had been primarily to administer the BCG vaccine to all tuberculin-negative schoolchildren aged 10–14 years. In some areas BCG was given during infancy and it was recommended that it should also be given to 'children of immigrants in whose communities there is a high incidence of TB', among other high-risk groups.[4] In 2005, this policy was replaced by a targeted immunisation programme directed at children with high risk of TB exposure.

The change in policy came after several years of discussion in the independent government advisory committee, the Joint Committee of Vaccination and Immunisation (JCVI). In the 1990s, it was estimated that due to the low TB incidence, universal school-age vaccination was no longer cost-effective.[5] Universal BCG vaccination, however, remained policy largely because the incidence was rising slowly and health authorities

were unsure about the impact that the emerging HIV epidemic could have on TB epidemiology.[5] [6] In 2005, after the HIV epidemic had stabilised and the UK had already fulfilled the criteria of the International Union Against Tuberculosis and Lung Diseases (IUATLD) to stop routine immunisation (which recommends different policies for different levels of TB, based on economic appraisals and the balance between the benefits and risks of BCG vaccination),[7] the JCVI recommended stopping universal school-age vaccination and replacing it with a targeted infant vaccination programme.[5]

As part of this targeted infant programme, it is agreed that universal vaccination is the most effective way to reach all eligible children in areas of the country with TB incidence ≥40 per 100 000 person-years (pyrs). In areas with TB incidence <40 per 100 000 pyrs, a selective approach is recommended to immunise only infants at high risk, that is, if their parents or grandparents originate from a country with an incidence ≥40 per 100 000 pyrs, if travelling to a high-incidence country for 3 or more months or when in contact with a TB case. In addition, children of any age at high risk of TB should be vaccinated at suitable opportunities.[8]

In view of possible organisational changes in the NHS and given the current TB epidemiology in the country, we considered it important and timely to assess the BCG vaccine policy and the main vaccine delivery pathways across the commissioning bodies for community and hospital care (Primary Care Trusts, PCTs) in England.

METHODS

A standardised, mostly closed-ended structured questionnaire was designed (available from the authors). The questionnaire covered the vaccination policy inside and outside infancy, eligibility criteria and their documentation, delivery pathways and constraints to service delivery. The questionnaire was piloted in four London PCTs.

In November 2010, we contacted all 152 PCTs in England. Immunisation leads and other staffs involved in TB control and BCG vaccination implementation were electronically mailed a copy of the questionnaire and a web-link to an internet equivalent created using the survey engine SurveyMonkey. As delivery of BCG vaccine involves a chain of activities and responsibilities, respondents were asked to gather information from other key informants as needed. A reminder was sent after 4 weeks. After an additional 4 weeks, we contacted non-respondent PCTs by telephone to gather the information required.

At completion of the active data collection, as an additional data check, between August 2011 and September 2011, we searched PCTs' websites and related NHS sources for publicly available documents on their current BCG vaccination policy. We assessed the agreement between the information on these publicly available documents and the data collected from the survey.

We compared distribution frequencies using a χ^2 test or Fisher's exact test where appropriate. For each variable, we only included observations for which data were available.

RESULTS

Between November 2010 and March 2011, 123 questionnaires representing 129/152 PCTs (85%) were returned: 72 (59%) as electronic documents and 51 (41%) via the internet survey. No difference in TB notification rates was found between responding and non-responding PCTs (data not presented). We found publically available current BCG policy documents for 114 (88%) of the 129 PCTs. Two (2%) PCTs were excluded from subsequent analysis because their BCG policy could not be determined from the responses. Sixteen (13%) PCTs reported universal infant vaccination and 111 (87%) selective infant vaccination. The agreement with publically available BCG policy documents was high, with only three (2%) PCTs reporting a policy that was different from the information in these documents. Responses from these three PCTs to more detailed questions in the questionnaire were consistent with a selective infant vaccination at that time.

Three PCTs reported changing their policy between 2006 and 2011; one PCT followed the national recommendation and changed from targeted infant vaccination to universal infant vaccination as TB incidence exceeded 40 per 100 000 pyrs; one PCT changed to universal infant vaccination, although their TB incidence was <40 per 100 000 pyrs but justified doing so because of a borderline TB rate, high TB rates in neighbouring areas and high population mobility; one PCT had a universal infant vaccination programme prior to 2006, although their TB incidence was below the threshold, and changed to targeted infant vaccination.[9]

Some PCTs reported vaccination policies that did not reflect the JCVI recommendations. Six PCTs reported targeted infant vaccination despite having a 3-year average TB incidence ≥40 per 100 000.[9] Documents obtained from the websites, however, of three of these PCTs, state that they implement universal infant BCG vaccination. Six of the 16 PCTs reporting universal vaccination had 3-year average TB incidence ≤40 per 100 000.[9] They were all in or close to major conurbations.

Vaccination during infancy

PCTs with a selective infant BCG vaccination policy administer BCG via a wider range of healthcare providers than PCTs with universal infant BCG vaccination (table 1). PCTs with selective policy most frequently offer vaccination on postnatal wards (51/102, 50%) but also vaccinate in community (24/102, 24%) and hospital clinics (27/102, 26%); PCTs with universal policy more frequently offer vaccination in community clinics (9/13,

Table 1 Place where BCG is primarily administered and systems reported to document BCG vaccination in 127 Primary Care Trusts with infant vaccination policy

	Selective infant vaccination	Universal infant vaccination
	n (%)	n (%)
Place of primary BCG administration	N=102*	N=13**
Postnatal ward	51 (50)	4 (31)
At home	0	0
At community clinic	24 (23)	9 (69)
At chest clinic	17 (17)	0
At hospital paediatric clinic	10 (10)	0
Systems in use for BCG documentation	N=107***	N=16
Antenatal/maternity records	43 (40)	5 (31)
Birth notification records	15 (14)	2 (12)
Paper log books held by midwives	6 (6)	1 (6)
Child health information system	100 (93)	14 (88)
School health records	27 (25)	5 (31)
GP	50 (46)	3 (19)
Red Book	103 (96)	16 (100)
Discharge letters	37 (35)	2 (12)

GP, general practitioner.
*Nine, **three and ***four missing values for those variables.

69%) and less frequently on postnatal wards (4/13, 31%, p=0.011).

All PCTs that vaccinate primarily on postnatal wards do so during the infants' first month of life, whereas only 13/37 (35%) PCTs that mainly vaccinate in community clinics do so in the infants' first month of life (p<0.001).

BCG vaccination receipt in infancy is documented in various ways across PCTs, and this did not depend on the vaccination policy (table 1). It is most consistently documented in the Red Book (119/123, 97%) and in the Child Health Information Systems (114/123, 93%). It is also noted in other registers and notes (table 1), but always in combination with either or both of the former two (figure 1).

Selective infant vaccination

In the 111 PCTs with selective infant vaccination, 71% reported routinely assessing eligibility for BCG. They all offer BCG vaccination to children with parents or grand parents born in countries with TB incidence ≥40 per 100 000 pyrs (table 2). Six PCTs reported that travel to a high-incidence country for 3 or more months is not an eligibility criterion; and two PCTs reported that contact with a TB case is not a selection criterion either.

Two main BCG delivery pathways were apparent from the information on identification and primary place of immunisation, but with considerable overlap. Where
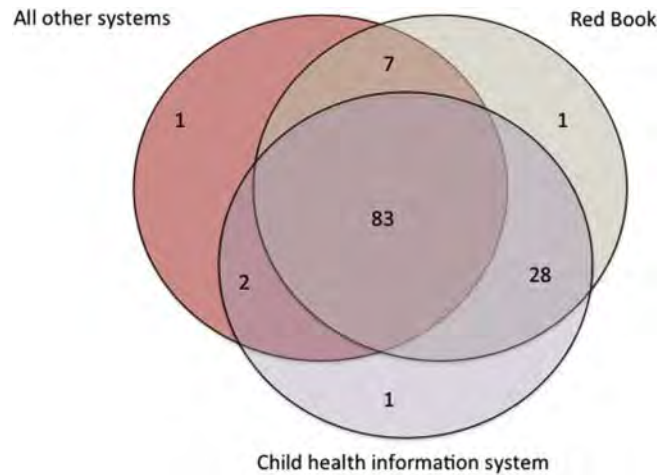
Figure 1 Principal systems used to document BCG vaccination and their combinations in Primary Care Trusts with infant vaccination policy (N=123).

midwives are primarily responsible for identifying eligible infants, they are more frequently vaccinated on postnatal wards (37/56, 66%) than when eligibility is flagged by general practitioners (GPs), health visitors (HVs) or paediatricians (12/44, 27%; p<0.001). Conversely, in PCTs in which eligible infants are primarily flagged up by GPs, HVs or paediatricians, they are more frequently vaccinated in community clinics (32/44, 73%) than when midwives identify them (19/56, 34%; p<0.001). In line with these delivery pathways, when infants are identified by midwives or vaccinated on postnatal wards, their eligibility is most frequently flagged up in maternity records, whereas when infants are identified by GPs, HVs or paediatricians or when they are vaccinated in community clinics, various systems are used with no clear preference (table 3).

Vaccination outside of infancy

Vaccination outside infancy was reported in 94/127 (74%) PCTs. In 14/94 (14%) PCTs vaccination outside of infancy is offered to preschool children only, in 9/94

Table 2 Selection criteria employed to decide eligibility for BCG vaccination in 111 Primary Care Trusts with a targeted infant vaccination policy

	n (%)*
Infant of parents born in country with incidence >40 per 100000	107 (100)
Contact with TB	93 (87)
Prolonged travel	94 (88)
Parental request	14 (13)
Insecure accommodation	13 (12)
Socially deprived	2 (2)
Asylum seeker/refugees	2 (2)

*Four observations with missing data.
TB, tuberculosis.

Table 3 Systems in use to flag up infants' eligibility for BCG vaccination stratified by main responsible for identification in 111 Primary Care Trusts with targeted infant vaccination

Systems used to flag up eligibility	Identification primarily by midwives* N=51	Identification primarily by GP, HV or paediatrician* N=38
Maternity records	43 (84%)	14 (37%)
Baby's hospital notes	28 (55%)	18 (47%)
Red Book	25 (49%)	22 (56%)
Birth notification records	10 (20%)	6 (16%)
Child health information system	10 (20%)	6 (16%)

*Twenty-two observations with missing data.
GP, general practitioner; HV, health visitor.

(9%) to schoolchildren only and in the remaining PCTs to both groups. HVs are most frequently involved in identifying eligible preschool children (51/85, 51%). GPs alone were mentioned by 3/85 (4%) PCTs but 33/85 (36%) PCTs reported that both GPs and HV identify eligible preschool children. A similar pattern was seen for the identification of school children: school nurses alone identify eligible school children in 56/80 (70%) PCTs, GPs alone in 9/80 (11%) PCTs and in 15/80 (19%) PCTs both school nurses and GPs identify school children.

All PCTs offering vaccination outside infancy reported assessing previous BCG immunisation in eligible children using at least one of the criteria recommended by the Green Book. Sixty-four of 94 (68%) PCTs use a combination of reliable parental recall, documentary evidence and presence of a scar as evidence of previous BCG vaccination. Seventy of 94 (18%) PCTs use the combination of a BCG scar and reliable recall; whereas 13/94 (14%) consider only one criterion as sufficient evidence.

Logistic constraints hindering BCG administration

Of all PCTs, 26/127 (20%) reported periods between 2005 and 2010 during which they could not administer BCG due to logistic constraints. The most frequent reasons are vaccine supply shortage and lack of trained health workers (including access to training) to administer the vaccine. One PCT reported various episodes where no BCG could be administered as a result of a pending business case over who was to carry out BCG vaccination when the previously appointed community paediatrician retired. A similar problem was reported in a different PCT reporting unclear responsibilities after the adult respiratory department stopped seeing paediatric patients. In one PCT, BCG could not be administered over a 2-year period due to the absence of funding agreements and was only reintroduced after a school outbreak.

DISCUSSION

Six years after its introduction, the 2005 recommendation for BCG vaccination has been implemented in the vast majority of England PCTs. All surveyed PCTs have an infant vaccination policy in place, but a quarter of these PCTs do not report offering vaccination outside infancy. Selective infant vaccination mostly takes place on the postnatal ward and during the first month of life whereas universal infant vaccination mainly happens in community clinics and after the first month of life. In PCTs with a selective infant vaccination policy, this survey found greater variation in the organisation of BCG vaccine delivery.

We were unable to gather information from 15% of the PCTs. However, TB notification rates between responding and non-responding PCTs were similar, suggesting results presented are not likely to be biased.

Since the JCVI issued their recommendations in 2005, there has been an ongoing discussion about how to define areas of high TB incidence in the context of the policy.[10–12] Universal infant vaccination is, for operational reasons, recommended in PCTs where the TB incidence is ≥ 40 per 100 000 pyrs, as it is agreed that this is the most efficient way to reach all infants at high risk of TB in such areas. Nevertheless, the cut-off incidence for targeted infant vaccination is debated as children in PCTs with an incidence <40 per 100 000 pyrs can still be at high risk of TB.[13]

In this survey, six PCTs in or close to urban areas reported vaccinating all infants, although their PCT-specific incidence is <40 per 100 000 pyrs. This could indicate that some PCTs in urban areas are considering regional incidence to inform their policies, rather than PCT-specific incidence. Nevertheless, it remains uncertain if this strategy ensures that the maximum number of eligible children are being immunised, and if it is more cost-effective than a PCT-specific informed targeted vaccination policy. Further analysis of the economic efficiency of regional BCG vaccination is required.

Surveys of BCG vaccination policies and practices in England and Wales in 1982 and 1992 indicated considerable variations across health districts.[14 15] In 1992, 15 of the 186 health districts in England had already stopped their routine school immunisation programme; 148 offered BCG to selected groups of neonates and five districts routinely gave BCG to all their neonates.[15] Today, variation in local BCG vaccination policies is lower but the organisation of BCG delivery remains highly variable. We find that PCTs commission a wide range of healthcare providers to deliver the vaccine. This heterogeneity across PCTs also demands a high level of organisation between PCTs if services such as maternity care straddle PCT borders. Hospitals may not be co-terminous with PCTs and hence infants from PCTs with different policies and practices can be born in the same hospital. In this light, it is of concern that many PCTs do not have service-level agreements to organise BCG administration either within the PCT or across

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boundaries.[4] This and the complexity of managing a localised service could also explain why some PCTs were unable to deliver BCG during periods where service providers changed.

The commissioning of BCG may become more complex if it becomes the responsibility of Clinical Commissioning Consortia. In its current form, the suggested changes to the NHS structure could lead to consortia responsible for overlapping geographical areas. If services are not commissioned across boundaries and responsibilities are not clearly assigned, the current heterogeneity in policies and practices could increase and seriously compromise the targeted infant vaccination. Infant hepatitis B vaccination is another selective programme, being given to infants of mothers screened antenatally and found to be positive for hepatitis B carriage. It works best when there is an identified person in each area, who is responsible for coordinating the programme.[16] This model should be considered for the BCG programme.

While the structural organisation of the NHS poses challenges for the 2005 recommendations, the implementation of a targeted vaccination policy is, in its self, demanding.[17] Hence, it is vital to monitor the implementation to assure high vaccination coverage. Good data on BCG immunisation coverage are complicated to assemble in PCTs with targeted infant vaccination where the denominator is unclear. Data from audits, however, show that vaccination coverage in areas with targeted infant vaccination can be low[18] and that even in PCTs with high coverage, it can vary greatly between maternity units[19] and ethnic groups.[20] We find that a wide range of healthcare professionals are involved in the identification of eligible children. It is therefore conceivable that infants are not identified due to unclear responsibilities. In addition, our findings suggest that some health professionals involved in the BCG vaccination programme might be unfamiliar with recommended eligibility criteria; this could contribute to low coverage rates.[21] A standardised pathway to identify eligible infants, with clear responsibilities and roles and regular training of staffs involved, could contribute to high vaccination coverage in PCTs with selective vaccination policy.[22 23]

In addition to the correct identification of infants at risk, assuring that the vaccine is administered is another challenge of a targeted vaccination policy.[17 22] Half of the PCTs vaccinate on postnatal wards—a vaccine delivery pathway associated with high vaccination coverage in local audits.[22–24] The other half, however, vaccinate in a community setting or clinics which in this survey was associated with vaccination at an older age. The different delivery pathways probably reflect local circumstances. Immunising newborns in postnatal wards may be more optimal in conditions in which the workload is manageable at that level, with either a relatively lower number of eligible newborns or a sufficient number of skilled personnel to administer BCG. Vaccinating in the community might be more effective in areas with higher numbers of eligible newborn (especially if universal

BCG vaccination) and limited number of trained staffs to administer the vaccine in postnatal wards. However, the latter could mean a higher risk of attrition as parents may not return their children to immunisation appointments, as reported in previous audits.[23 25] A study in South London found that parents would be more interested if the vaccine was accessible on a 'drop-in' basis from community clinics[18] in such areas.

Another aspect that might affect efficient delivery is that the most commonly used systems for documentation of BCG receipt are often not the systems used to flag up eligibility. Aligning the systems used to identify eligible children with the system used to document BCG vaccination could be an effective way to ensure that identified infants receive the vaccine and a means to estimate coverage.[24] Also, BCG vaccination was not delivered with other routine infant vaccinations possibly because of the need for specific training for an intradermal vaccination. The addition of BCG vaccination to offer of other routine infant vaccinations in specific regions could be another way of ensuring coverage of those at risk.

The 2005 BCG policy for the UK also recommends vaccinating previously unvaccinated children who are at high risk of TB. Despite the policy, a quarter of all PCTs do not report vaccinating outside infancy. Although the absence of vaccination outside infancy may conserve resources in areas with low levels of migration, some PCTs in urban centres with presumably high levels of migration do not report vaccinating outside infancy. This suggests that greater efforts are needed to strengthen targeted BCG vaccination outside infancy.

In conclusion, a targeted infant BCG vaccination has been implemented in most PCTs across England, either as part of postnatal hospital care or a community vaccination programme separate from other childhood vaccinations via a number of locally agreed healthcare professionals. Information to assess coverage would be useful to monitor successful provision of an effective measure to prevent childhood TB.

relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement No additional data are available.

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student	Patrick Nguipdop Djomo
Principal Supervisor	Punam Mangtani and Laura Rodrigues
Thesis Title	Tuberculosis in England, a high-income Western European setting with low incidence: Recent trends, Social determinants and Prevention through BCG vaccination

If the Research Paper has previously been published please complete Section B, if not please move to Section C

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	following discussions and comments from my supervisors and co-authors.

Student Signature: _____ Date: _27/2/2017_

Supervisor Signature: _____ Date: _27/2/ 2017_

8. <u>Manuscript 5:</u> Uptake of neonatal BCG vaccination in England: performance of the current policy recommendations

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AUDIT, RESEARCH AND GUIDELINE UPDATE

Uptake of neonatal BCG vaccination in England: performance of the current policy recommendations

Patrick Nguipdop-Djomo,[1,2] Punam Mangtani,[1] Debora Pedrazzoli,[1,2] Laura C Rodrigues,[1] Ibrahim Abubakar[2,3]

ABSTRACT
BCG uptake among infants in England has not been measured since targeted infant vaccination replaced universal schoolchildren vaccination in 2005, mainly because of the challenges in defining denominators. We estimated uptake between 2006 and 2008 by dividing number of BCG doses administered to infants by number of all live births (where BCG vaccination is universal) or ethnic minority/Eastern Europeans live births (where infant-BCG vaccination is selective). Weighted average uptake was 68% (95% CI 65% to 71%), slightly higher in primary care trusts with universal (72% (95% CI 64% to 80%)) than selective (66% (95% CI 61% to 70%)) policy; and also 13% higher in areas vaccinating in postnatal wards compared with community settings.

INTRODUCTION
England's policy since 1953 of universal BCG vaccination of schoolchildren was replaced in 2005 by targeted immunisation of infants at higher risk of disease. Selective immunisation of eligible infants in PCTs with annual tuberculosis (TB) incidence <40/100 000, notably those with family ties to high TB-incidence countries and universal vaccination of all neonates in PCTs with annual TB incidence ≥40/100 000 is recommended. It is essential that the performance of the BCG vaccination programme, like other components of TB control efforts, is continuously and rigorously monitored and evaluated. This is challenging in the current programme because appropriate denominators to measure infant-BCG uptake are not routinely available, especially in areas with selective vaccination.

METHODS
We estimated the 2006–2008, 3-year average infant-BCG uptake in each PCT by dividing the number of BCG doses in children aged ≤1 year by the number of eligible delivered live births (according to local BCG policy). The average national uptake was calculated using each PCT's eligible population as weights. Live-birth information per ethnic group and PCT of residence was obtained from the Office for National Statistics (ONS). We obtained BCG dose numbers from the National Health Service Information Centre (NHS-IC) annual reports, based on PCTs' returns of immunisation activities (KC50 forms). For PCTs with universal BCG, uptake was in all live births. For PCTs with selective BCG vaccination, the eligible population was live births to parents born in countries

joining the European Union (EU) since 2004 and non-EU European countries (mostly former Soviet Union) and to ethnic minority parents.

We also investigated how BCG uptake at PCT-level differed by current (universal or selective) vaccination policy, primary place of vaccine delivery (postnatal ward versus community setting) and provision of infant-BCG since the 1970 to the 1980 s. Multiple linear regression was used, weighted by the population eligible for BCG, adjusting for PCT-level age-standardised and sex-standardised TB incidence, and for ONS PCT-level Index of Multiple Deprivation, and proportion of ethnic minority among live births.

Using Stata V.12.0 for analyses, means were compared by t test and analysis of variance (ANOVA) as appropriate. Proportions were compared using Fisher's exact test. Significance testing in the regression models was conducted by using ANOVA.

RESULTS
Twenty-eight of 151 (19%) PCTs had data on number of infant-BCG doses that were missing for at least 1 year, between 2006 and 2008, and were excluded from analyses. Their characteristics were not different from the 123 PCTs included (see online supplementary table S1). The 3-year average BCG uptake varied from 5% to 100%, with a weighted average of 68% (95% CI 65% to 71%) across the 123 PCTs. BCG uptake was on average higher in PCTs with universal (72% (95% CI 64% to 80%)) than selective (65% (95% CI 62% to 70%)) vaccination policy (p=0.21) (see table 1). Thirty PCTs (24%) had uptake lower than 50% (respectively 3/17 (18%) with universal and 27/106 (25%) with selective policy).

At univariable analysis, uptake was roughly 11% (95% CI 4% to 18%) higher in areas that offered infant-BCG vaccination since 1980 (p=0.004) and 9% higher (95% CI 2% to 16%; p=0.01) in PCTs that vaccinate primarily on postnatal wards compared with those doing so in community settings. There was also evidence of higher uptake in the most deprived areas (p=0.008) and those with high TB incidence (p=0.001). After controlling for PCT-level TB incidence, deprivation rank and proportion of ethnic minority live births, uptake was 10% (95% CI 2% to 18%; p=0.01) higher in PCTs that provided infant-BCG since the 1970s–1980s than those that did not and 13% (95% CI 6% to 20%; p<0.001) higher in areas immunising primarily in postnatal wards compared with community settings. Results were similar when analyses

Table 1 Three-year average BCG uptake* (2006–2008) and association with Primary Care Trust (PCT)-level characteristics

Variables	Average BCG uptake (%) (95% CI)	Unadjusted β coefficient† (95% CI)	p Value	Adjusted β coefficient‡ (95% CI)	p Value
Current infant BCG policy					
Selective (n=106)	65.6 (61.6 to 69.5)	—	0.073	—	0.38
Universal (n=17)	71.6 (63.7 to 79.5)	6 (−0.6 to 12.7)		4.2 (−5.3 to 13.6)	
Past infant BCG policy					
No previous infant BCG (n=53)	60.0 (54.4 to 65.6)	—	0.004	—	0.013
Infant BCG since 1980s (n=66)	71.0 (66.7 to 75.1)	10.9 (3.6 to 18.2)		9.9 (2.1 to 17.6)	
Index of multiple deprivation					
Most deprived (n=40)	73.0 (68.1 to 77.8)	—	0.008	—	0.07
Moderately deprived (n=42)	62.5 (56.4 to 68.7)	−10.4 (−17.8 to −3.0)		−9.5 (−17.6 to −1.2)	
Least deprived (n=41)	62.7 (55.6 to 69.7)	−10.3 (−19.1 to −1.5)		−2.5 (−15.7 to 10.8)	
Age-and-sex standardised 3-year average annual TB incidence (per 100 000 person-years)					
0–19.9 (n=84)	65.2 (61.2 to 69.2)	—	0.001	—	0.015
20–39.9 (n=25)	62.5 (54.0 to 71.0)	−2.7 (−10.5 to 5.1)		−5.6 (−20.9 to 9.8)	
40+ (n=14)	76.5 (68.8 to 84.2)	11.3 (3.4 to 19.2)		7.6 (−10.2 to 25.4)	
Percentage ethnic minority among 2006–2008 live-births					
0–19.9% (n=72)	63.8 (58.2 to 68.8)	—	0.16	—	0.87
20–39.9% (n=25)	64.8 (67.6 to 77.6)	0.9 (−9.3 to 11.2)		−3.7 (−17.6 to 10.2)	
40%+ (n=26)	70.9 (64.1 to 77.7)	7.0 (−1.6 to 15.7)		−3.4 (−21.4 to 14.7)	
Primary place of infant BCG vaccination					
Community settings (n=48)	63.5 (58.2 to 68.8)	—	0.01	—	0.0005
Postnatal ward (n=54)	72.6 (67.6 to 77.6)	9.1 (1.86 to 16.3)		12.9 (5.9 to 20.0)	

*Twenty-eight PCTs excluded because they had missing data for infant-BCG doses at least 1 year over the study period.
†For categorical variables, the β coefficient represents the respective difference between average coverage in each stratum and the baseline category.
‡Adjusted for all other variables in the table.

were restricted either to PCTs with universal or selective policy, respectively. When adjusting for all factors, uptake was not different between universal and selective policy PCTs (p=0.38) (see online supplementary table S2 for details).

DISCUSSION

We present the first estimates of infant-BCG uptake in England since the 2005 change in policy from routine universal BCG vaccination of schoolchildren to infant-BCG. For the past 8 years, no denominator has been readily available for continuous monitoring of uptake.

We used numerator data (BCG doses) from the NHS-IC, which carefully assess the data for validity, including checking of unusual year-on-year variations. We only analysed PCTs that have reported BCG doses every year from 2006 to 2008; but as they are estimates the results should be treated with some caution. The denominators used to calculate uptake were only available for a limited number of years (2005–2008) to assess uptake in areas with a selective policy that included infants born to parents from ethnic minorities and to parents from European countries with annual TB rate >40/100 000 (mostly Eastern Europe and the former Soviet Union); they constitute the main population groups targeted by the infant-BCG programme. Although these data are imperfect, we believe the results provided fair approximations of infant-BCG uptake in the eligible population, especially given the current paucity of alternative data sources in England. These estimates provide a useful insight in the effectiveness of the delivery of BCG under the current BCG vaccination programme in England.

Targeted infant immunisation is challenging to implement and monitor, in areas where only selected groups are vaccinated. It requires close coordination between antenatal services, which usually identify eligible infants before birth and childhood

vaccination services that administer the vaccine after birth. Collaboration between commissioning bodies is also important; coterminous PCTs may have different local policy or delivery systems, yet share areas covered by the same maternity wards. Several European countries have reported drops in BCG vaccination uptake after switching from universal to targeted policy. In Sweden, uptake among eligible infants dropped from over 95% to 2% when universal neonatal BCG was replaced by a targeted programme in 1975.[1] Similarly, in France coverage fell from 77% to 58% in 2007.[2] This highlights the need to closely monitor BCG uptake.

It could be argued that 68% infant-BCG uptake within 3 years of the policy change reflects fairly successful implementation of the new guidance in most areas in spite of the limited data monitoring. We speculate that experience of infant-BCG pre-2005 in several PCTs contributed to the smooth transition from routine schoolchildren vaccination; this is supported by higher uptake in areas that offered infant-BCG since the 1980s. By 1991, 82% (153/186) English health districts already offered some infant-BCG services although there was much variability on targeted groups.[3] Contributing factors could also include increased awareness and allocation of more resources to TB control activities around the study period. In the 2009 national tuberculosis survey, 60% (67/112) PCTs reported an increase in the funding of their TB services and 74% (83/112) routinely carried TB health promotion and awareness raising activities.

The average uptake hides the heterogeneity between areas. Our estimate implies roughly one in three infants at high risk for tuberculosis did not receive BCG vaccine over the study period, and one in four PCTs had uptake lower than 50%, including three with universal infant-BCG policy. This does not reflect a wider problem with vaccine delivery services in some PCTs; BCG uptake was not correlated to routine infant

immunisations in PCTs during the study period (see online supplementary figure S1). PCTs with longer experience of infant-BCG pre-2005 had higher uptake. PCTs vaccinating primarily in postnatal wards also had better uptake than in community settings (mostly clinics). Immunisation of eligible newborns before they leave hospital may be easier than having parents return later on. An audit found that 40% newborns who left hospital without BCG did not attend later appointments.[4] However, the effectiveness of a postnatal strategy will depend on adequate numbers of trained staff in postnatal wards relative to the number of eligible newborns. A study in areas with high number of eligible newborns found that the high staff turnover and brief neonatal stay affected BCG uptake in postnatal wards.[5] 'Drop-in' vaccination clinics have been suggested as an alternative to circumvent the issue of low attendance in community settings, and the idea has since been used in several areas. In summary, the organisation of vaccine delivery can affect uptake, and while local circumstances should be taken into account, continuous monitoring is essential in shaping services.

The absence of denominators is the main impediment to adequately measure BCG uptake to monitor the BCG vaccination programme in England; the absence of rigorous data of number of vaccine doses given could also improve. As part of his 2004 action plan for stopping tuberculosis in England, The Chief Medical Officer recommended the effective monitoring of BCG immunisation; it is worrying that over 8 years later, this has not yet been implemented. Collection through the Cover of Vaccination Evaluated Rapidly programme of the number of BCG doses administered is under discussion. These efforts should be welcomed by policy makers and supported by commissioners and healthcare providers who have the responsibility to collect and provide accurate information. It is also essential that suitable denominators are collected as part of these efforts, notably in areas with selective infant-BCG vaccination. The monitoring system implemented for the hepatitis B vaccine, which is also only administered to selected groups of infants, could be used as a model. In such a system, for instance, it would be statutory for midwives in areas with selective vaccination policy to flag and notify pregnant women whose newborn will be eligible for BCG, with linkage of information to maternities and the local child health information system. In an era of tuberculosis re-emergence, emergence of multidrug-resistant strains, with tuberculous meningitis and miliary cases still reported among UK-born children, adequate monitoring of the BCG vaccination programme is critical to ensure its future performances, especially in the context of recent structural changes to the NHS.

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Uptake of neonatal BCG vaccination in England: performance of the current policy recommendations

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Supplementary material

Additional table 1: Characteristics of PCTs not included in final multiple regression models (because of missing information on at least one variable in the model)

Variable	PCTs not in final models (Total=21)	PCT in final models (Total=102)	p-values
Vaccination policy (%)*			
Universal (n = 17)	5%	16%	0.30
Selective (n=106)	95%	84%	
Index of Multiple Deprivation*			
Most deprived (n=40)	38%	32%	
Moderately deprived (n=42)	33%	34%	0.53*
Least deprived (n=41)	29%	34%	
Age-and-sex standardised 3-year average TB incidence (per 100,000)*			
0-19.9 (n=84)	86%	65%	
20-39.9 (n=25)	6%	22%	0.23
>=40 (n=14)	5%	13%	

Column percentages

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Supplementary material

Additional table 2: Comparison of mean infant-BCG uptake by primary place of immunisation, stratified by current vaccination policy

Current infant BCG policy / Primary place of infant BCG vaccination	Uadjusted beta coefficient (95%CI)	p-value	Adjusted beta coefficient** (95%CI)	p-value
Universal				
Community settings (n=10)	-		-	
Postnatal ward (n=6)	1.2 (-17.7 to 20.1)	0.90	14.4 (-12.4 to 41.1)	0.26
Selective				
Community settings (n=38)	-		-	
Postnatal ward (n=48)	19.5 (11.6 to 27.4)	<0.0001	18.3 (9.3 to 27.3)	<0.0005

**Adjusted for all other variables in the main model: past infant BCG policy, PCT-level index of multiple deprivation, standardised 3-year average TB incidence, and ethnic minority population in the birth cohort.

Supplementary material

Additional figure 1: Scatter plot of average DPT coverage* in infants against BCG uptake between 2006 and 2008 in PCTs included in the study

Scatter plot of DPT coverage against BCG in infants from 2006 to 2008

correlation coef = -0.05
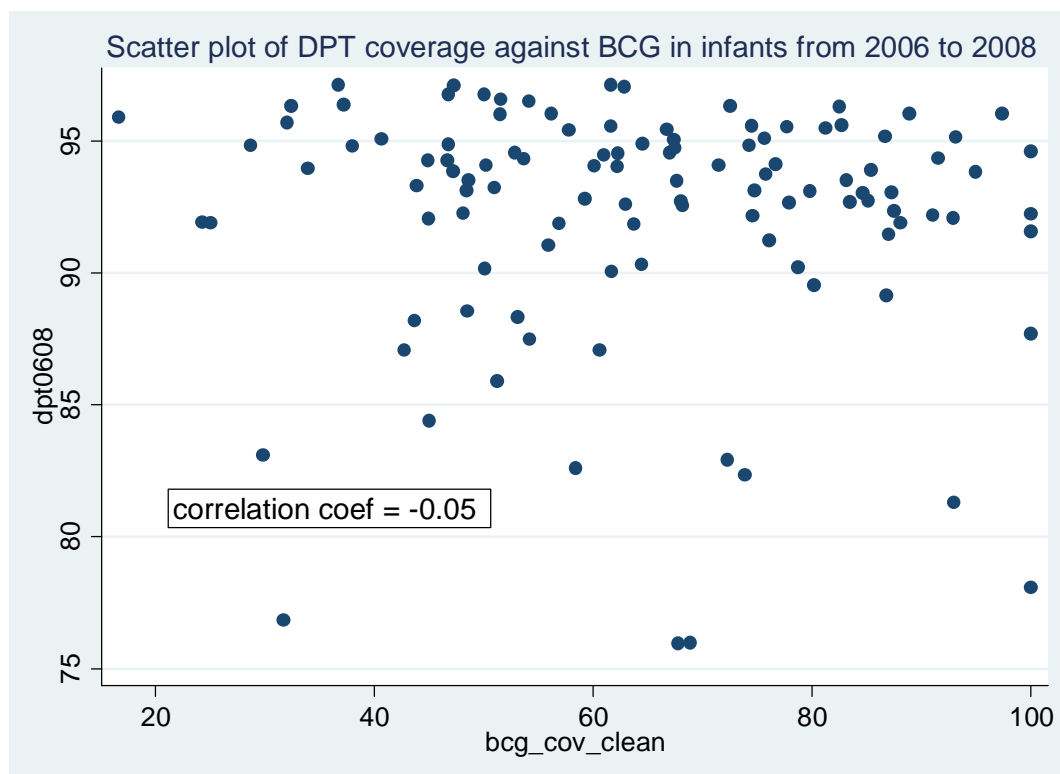
*Data from NHS Information Center Immunisation statistics annual report

This scatter plot suggests that there is no association between infant-BCG uptake and that of other routine infant vaccines within PCTs. Therefore, low BCG uptake in some PCTs is most likely not due to wider difficulties with infant-vaccines delivery services.

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9. <u>Manuscript 6:</u> Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study

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Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study

Patrick Nguipdop-Djomo, Einar Heldal, Laura Cunha Rodrigues, Ibrahim Abubakar, Punam Mangtani

Summary

Background Little is known about how long the BCG vaccine protects against tuberculosis. We assessed the long-term vaccine effectiveness (VE) in Norwegian-born individuals.

Methods In this retrospective population-based cohort study, we studied Norwegian-born individuals aged 12–50 years who were tuberculin skin test (TST) negative and eligible for BCG vaccination as part of the last round of Norway's mandatory mass tuberculosis screening and BCG vaccination programme between 1962 and 1975. We excluded individuals who had tuberculosis before or in the year of screening and those with unknown TST and BCG status. We obtained TST and BCG information and linked it to the National Tuberculosis Register, population and housing censuses, and the population register for emigrations and deaths. We followed individuals up to their first tuberculosis episode, emigration, death, or Dec 31, 2011. We used Cox regressions to estimate VE against all tuberculosis and just pulmonary tuberculosis by time since vaccination, adjusted for age, time, county-level tuberculosis rates, and demographic and socioeconomic indicators.

Findings Median follow-up was 41 years (IQR 32–49) for 83 421 BCG-unvaccinated and 44 years (41–46) for 297 905 vaccinated individuals, with 260 tuberculosis episodes. Tuberculosis rates were 3·3 per 100 000 person-years in unvaccinated and 1·3 per 100 000 person-years in vaccinated individuals. The adjusted average VE during 40 year follow-up was 49% (95% CI 26–65), although after 20 years, the VE was not significant (up to 9 years VE [excluding tuberculosis episodes in the first 2 years] 61% [95% CI 24–80]; 10–19 years 58% [27–76]; 20–29 years 38% [–32 to 71]; 30–40 years 42% [–24 to 73]). VE against pulmonary tuberculosis up to 9 years (excluding tuberculosis episodes in the first 2 years) was 67% (95% CI 27–85), 10–19 years was 63% (32–80), 20–29 years was 50% (–19 to 79), and 30–40 years was 40% (–46 to 76).

Interpretation Findings are consistent with long-lasting BCG protection, but waning of VE with time. The vaccine could be more cost effective than has been previously estimated

Funding Norwegian Institute of Public Health and London School of Hygiene & Tropical Medicine.

Introduction

BCG, the sole tuberculosis vaccine licensed for use in human beings, is an important part of tuberculosis control efforts.[1] It provides, on average, 86% protection against miliary and meningeal tuberculosis in children.[2–4] It also protects against pulmonary tuberculosis, although its effect varies geographically and seems higher further from the equator,[5–7] ranging, for instance, from no evidence of protection in the Indian Tuberculosis Prevention Trial up to an efficacy of 78% in the British Medical Research Council trial.[7] Reasons for such variability[7,8] include good efficacy if vaccination is done before infection with *Mycobacterium tuberculosis* or sensitisation by environmental mycobacteria.[7,9] BCG might also protect against tuberculosis infection itself,[10,11] suggesting a greater contribution to tuberculosis control than that previously assumed, although understanding of the immunological basis of BCG-derived protection remains low.[12]

BCG is one of the commonest vaccines, but the duration of effect against tuberculosis is unclear, even though this information could affect vaccination policies.

The substantial decrease in tuberculosis incidence in the 1980s to 1990s led several countries to move from universal vaccination of infants (most western European countries) or schoolchildren (eg the UK and Norway) to targeted vaccination of infants at high risk of tuberculosis;[13] whether BCG protection will last until young adulthood when the risk of pulmonary tuberculosis and transmission to others is high is unclear. Improved understanding of long-term changes in BCG protection might also be useful not only to develop and test new tuberculosis vaccines, but also to adapt vaccination schedules. BCG booster vaccine candidates are designed on the premise of enhancement of weak or waned preexisting BCG-derived protection.[14] Other tuberculosis vaccine candidates (recombinant BCG or other attenuated mycobacterium-based vaccines) are empirically inspired or derived from BCG,[14] and the performance of BCG can inform their potential effect.

BCG protection can last for up to 15 years.[15] Little information exists beyond that period because studies have either relatively short follow-up or few events if

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Research in context

Evidence before this study

All ten published randomised trials of BCG were reviewed for evidence for the duration of BCG efficacy against tuberculosis by Sterne and colleagues in 1998. This review was complemented by a comprehensive systematic review by Abubakar and colleagues in 2012, which also included all observational studies. Abubakar and colleagues searched for articles in electronic medical databases up to May 31, 2009 (including MEDLINE, Embase, Cochrane Central Register, and others), and in trial registers and grey literature sources. Search terms for disease were "TB", "tuberculosis", "tubercle bacill*", "*M. tuberculosis* complex", "*M. bovis*", "*M. africanum*", "*M. canetti*", "*M. microti*", and "*M. tuberculosis*", and for intervention were "BCG vaccine", "BCG", "BCG vacc*", "BCG imm*", and "Bacillus Calmette". Details of all databases searched are published in the report. We repeated the search strategy in MEDLINE, Embase, Cochrane Central, and Web of Knowledge, but identified no new additions. Authors of the most recent review suggested that BCG is, on average, effective against tuberculosis if given to individuals not already infected with *Mycobacterium tuberculosis* or sensitised by environmental mycobacteria, and the vaccine can protect for 10–15 years. Pooled VE estimates (against all forms of tuberculosis disease) from trials were 60% (95% CI 37–74) for 0 to less than 5 years, 56% (17–76) for 5 to less than 10 years, and 46% (18–64) for 10–15 years. Seven of the ten trials provided some data for follow-up beyond 15 years after vaccination, but investigators of only one noted evidence of protection, whereas the others had too few events for meaningful estimates. Abubakar and colleagues also identified 22 relevant observational studies (consisting of five cohort, five case-population, nine case-control, and three cross-sectional studies), of which only four had some data for BCG effectiveness up to 20 years after

vaccination. Authors of three of these studies suggested decreasing but persisting protection 15–20 years after vaccination. Overall, evidence is consistent with significant BCG-derived protection against tuberculosis for 10–15 years after vaccination, with waning over time; however, the vaccine effect beyond that period is uncertain.

Added value of this study

Long-term follow-up of participants in the Native American and Alaska Natives BCG trial suggested that BCG could protect against tuberculosis for up to 60 years. Our study is, to our knowledge, only the second (and the first from western European countries) in which some of these findings are replicated. Our results suggest a BCG protection of about 50% during 40 years, with some evidence of about 40% effectiveness 30–40 years after vaccination. The consistency between results from these two settings strengthens the hypothesis that BCG-derived immunity could persist for much longer than 10–15 years as previously assumed.

Implications of all the available evidence

A longer duration of protection than that currently thought would imply that BCG is potentially more cost effective and beneficial than was previously estimated. This finding could be relevant if countries revise their BCG vaccination policies in response to changing tuberculosis epidemiology, especially in low-incidence countries. The potentially long-lived effect of BCG should be investigated and taken into account in development of new tuberculosis vaccines, especially in view of our low understanding of immunity to *M tuberculosis*. The duration and changes in levels of BCG-derived protection would also be relevant to scheduling of vaccination if the new family of BCG-booster vaccines was successfully developed and introduced.

follow-up is long. Follow-up of participants in the Native American and Alaska Natives BCG trial[16] showed significant BCG protection up to 40 years after vaccination, although these findings have not yet been substantiated elsewhere. We used a retrospective population cohort from Norway from which well preserved information from the tuberculin skin test (TST) and BCG status was available, with reliable linkage to good tuberculosis surveillance from 1962 to 2011, to assess BCG effectiveness for 40 years in the general population and a European setting.

Methods

Study design and population

In this retrospective population-based cohort study, we studied Norwegian-born individuals aged 12–50 years who were TST negative to whom intradermal BCG vaccination was offered as part of the nationwide Norwegian mandatory mass tuberculosis screening and BCG vaccination programme that took place between

1948 and 1975.[17–19] We only included those screened during the last round of the programme, which took place between 1962 and 1975, when data were computerised and all tuberculosis cases were compulsorily reported to the central National Tuberculosis Register (established in 1962). We excluded individuals who had tuberculosis before or in the year of screening, and those with unknown TST and BCG status. We did not include those younger than 12 years because they were not routinely offered BCG unless they had been in contact with a person with tuberculosis. We did not specifically exclude immunocompromised individuals; immunosuppression was not a specific contraindication for BCG vaccination during the study period because HIV infection was not yet present and most immunosuppressant drugs were not yet present or widely used. Furthermore, no clear reason exists why occurrence of these factors (if any) during follow-up should affect tuberculosis rates in vaccinated and unvaccinated people differently.

We obtained ethical clearance from the Norwegian Research Ethics Committee (reference number 2012/755/REK nord).

Procedures

In the tuberculosis screening and BCG vaccination programme, participants were screened for tuberculosis in mobile units, consisting of chest radiography and a TST with use of the adrenalin von Pirquet (aP) method,[18] which was standard in Norway until 2004. Screening campaigns were repeated every 2–10 years depending on local tuberculosis incidence. Overall attendance for the tuberculosis screening and BCG vaccination programme was 80–85%; the rest did not attend because they had been screened in another programme (about 5%—eg, as a military recruit), because they were ill or temporarily absent (5–10%), or because of an unknown reason (about 5%).[17] School leavers (13–14 years of age) with a negative TST were also offered vaccination through the annual school screening programme.

Tuberculin skin testing with the aP method was done using Danish Old Tuberculin at a concentration corresponding to about 70% of the international standard from 1947 to 1953, which was subsequently doubled from 1954 to improve sensitivity.[19] A positive reaction was defined by an induration of 4 mm or larger. BCG was manufactured at the Bergen State BCG Laboratory (Bergen, Norway) using the Swedish Gothenburg strain.[20] Liquid BCG was used until 1959, progressively replaced by freeze-dried BCG between 1959 and 1973,[21] with standardisation between the two formulations done by routine comparison of postvaccination TST induration size in schoolchildren.[22] From 1973, BCG was provided from Statens Serum Institute, Copenhagen, Denmark.

Participants accrued person-years from entry until their first tuberculosis episode, emigration, death, or end of follow-up (Dec 31, 2011). We ascertained tuberculosis through linkage to the National Tuberculosis Register and checked censoring by death or emigration in the population register. Prophylactic treatment for latent tuberculosis infection was seldom used in Norway before 2002 and was therefore not a concern. We linked data sources directly using the birth number, a unique 11 digit personal identifier allocated to all Norway residents at birth or immigration and used across administrative databases.

The tuberculosis mass screening database contained information about date and results of chest radiography and TST and about BCG vaccination. BCG status was ascertained from health cards (about 87%), scar examination (about 7%), and self-reported vaccination history (about 6%). The National Tuberculosis Register provided notifications of tuberculosis since 1962[23,24] and county-level tuberculosis rates. Its completeness was estimated at 95% in 2008 on the basis of crosschecking carried out since 1975 with rifampicin prescriptions and laboratory results.[23,25] Census data (1960 and 1970) provided

information about potential confounders, which were birthdate, sex, and marital status, and proxy measures for socioeconomic position (head of household's education
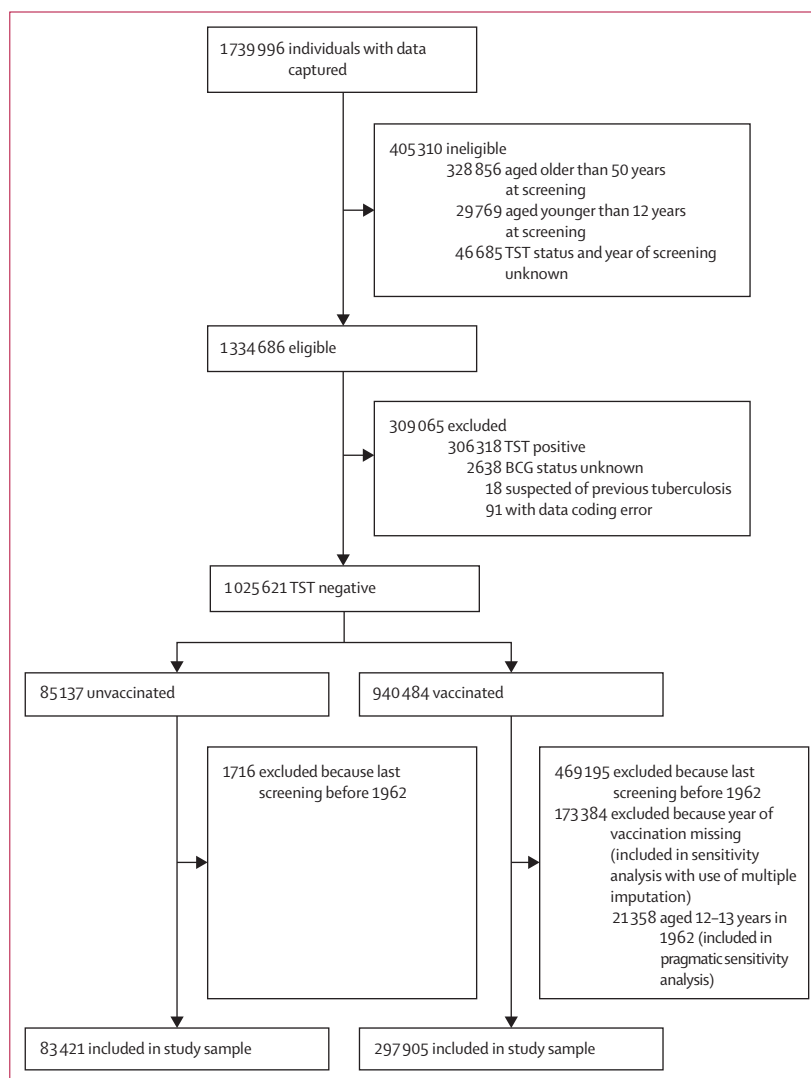
Figure 1: Flowchart from the population cohort to the study sample
TST=tuberculin skin test.

	Vaccinated (n=297 905)	Unvaccinated (n=83 421)
Sex		
Female	163 634 (55%)	54 340 (65%)
Male	134 271 (45%)	29 081 (35%)
Age at entry (years)		
12–15	145 366 (49%)	3171 (4%)
16–20	67 990 (23%)	6251 (7%)
21–30	29 989 (10%)	5943 (7%)
31–40	27 217 (9%)	21 315 (26%)
≥41	27 343 (9%)	46 741 (56%)
		(Table 1 continues on next page)

	Vaccinated (n=297 905)	Unvaccinated (n=83 421)
(Continued from previous page)		
Birth cohort (year of birth)		
1910–19	5026 (2%)	38 771 (46%)
1920–29	30 566 (10%)	26 813 (32%)
1930–39	25 371 (9%)	7272 (9%)
1940–49	67 809 (23%)	5930 (7%)
≥1950	169 133 (57%)	4635 (6%)
Marital status		
Married	78 321 (26%)	63 932 (77%)
Single or other	216 162 (73%)	18 455 (22%)
Missing	3422 (1%)	1034 (1%)
Education level of head of household		
Lower secondary or less	151 968 (51%)	52 554 (63%)
Higher secondary	120 522 (40%)	27 430 (33%)
Tertiary, vocational, or postsecondary	24 383 (8%)	2652 (3%)
Missing	1032 (<1%)	785 (1%)
Type of municipality		
Rural	125 580 (42%)	36 765 (44%)
Urban	171 916 (58%)	46 489 (56%)
Missing	409 (<1%)	167 (<1%)
Number of residents in household		
0–2	21 002 (7%)	19 504 (23%)
3–4	132 790 (45%)	41 137 (49%)
5–6	109 416 (37%)	18 292 (22%)
≥7	34 276 (12%)	4319 (5%)
Missing	421 (<1%)	169 (<1%)
Occupation of head of household		
Manufacture, construction, or mining and blasting	119 232 (40%)	34 571 (41%)
Technical, scientific, or humanities and arts	24 814 (8%)	4653 (6%)
Administration and management, sales, or services	38 234 (13%)	11 475 (14%)
Agriculture, forestry, or fishing	54 497 (18%)	17 025 (20%)
Trade, transport, or communication	49 356 (17%)	13 178 (16%)
Military, other	10 136 (3%)	1438 (2%)
Missing	1636 (1%)	1081 (1%)
5 year average annual tuberculosis notification rate for 1961–65 per 100 000 person-years		
<20	127 961 (43%)	41 976 (50%)
20–25	78 637 (26%)	17 310 (21%)
≥26	91 300 (31%)	24 135 (29%)
Missing	7 (<1%)	0
Follow-up		
Median (years)	44 (41–46)	41 (32–49)
Total (person-years)	12 425 273	3 131 918
Number of first tuberculosis episodes (rate per 100 000 person-years)		
All tuberculosis	157 (1·3)	103 (3·3)
Pulmonary tuberculosis	121 (1·0)	78 (2·5)

Data are n (%) or median (IQR), unless otherwise indicated.

Table 1: Baseline characteristics

Statistical analysis

We transformed quantitative variables into categories. We classified 5 year average annual tuberculosis rates at the county level during 1961–65[26] (proxy for local epidemiology) into three levels (less than 20, 20–25, and 26 and more per 100 000 person-years). We grouped head of household's education level into lower secondary or less (up to tenth grade), higher secondary (11th to 13th grade), and postsecondary, vocational, or tertiary. We grouped head of household's occupation by sectors related to tuberculosis infection risk in Norway[27]—namely, manufacturing, construction, mining and blasting, technical, scientific, humanities and arts, administration and management, sales and services, agriculture, forestry and fishing, trade transportation and communication, military, and other. Finally, we grouped household size into four categories (zero to two, three to four, five to six, and seven and more residents).

We computed HRs and 95% CIs comparing overall and time-specific (5 year and 10 year intervals) tuberculosis rates in BCG-vaccinated individuals with unvaccinated individuals by fitting Cox regression models to the data. We adjusted for age-specific tuberculosis risk as a time-updated variable; we also took into account demographic and socioeconomic factors and time (in 10 year bands from 1960 to account for secular changes during the long follow-up). 7093 (2%) of 381 326 individuals had data missing for at least one covariate; we excluded them from analyses. Starting with a model only including BCG status fitted on the age timescale, we added calendar time and then potential confounders in turn on the basis of descending order of magnitude of confounding at bivariable analysis. We checked their effects on overall vaccine effectiveness (VE) and any collinearity with vaccination status. We obtained time-specific HRs by fitting an interaction between split follow-up time and BCG status. We assessed statistical evidence of log-linear change in HR (thus VE) between time intervals and departure from linearity. We obtained p values using Wald or likelihood ratio tests as appropriate. We assessed the proportional hazard assumption graphically using Nelson-Aalen cumulative hazard plots. We obtained BCG VE and 95% CIs using the formula VE=$(1 - HR_{v/u}) \times 100$, where v=vaccinated and u=unvaccinated. We repeated analyses for pulmonary tuberculosis. We did statistical analyses using Stata 13.

We did two sensitivity analyses: first, of TST stringency (by excluding individuals who developed tuberculosis in the first 2 years after screening who would probably have already been infected but not yet been reactive to TST), and, second, of missing information of the year of vaccination (missing in 18% of BCG-vaccinated individuals across the database, of whom a proportion would have been vaccinated after 1962 and so be eligible for the study). We used two approaches for this second sensitivity analysis: first, we assumed that all were

level and occupation, number of residents in the household, and urban or rural category of place of residence) at enrolment.

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vaccinated as soon as they reached the eligible age (pragmatic sensitivity analysis) and, second, we used predictive mean matching (PMM) multiple imputation by chained equations[28] (appropriate for truncated quantitative data: in our case, the year of vaccination limited to 1948–75 during the mass screening). We generated ten imputed datasets using a PMM imputation model including all baseline covariates and the age-adjusted cumulative tuberculosis hazard. We repeated the Cox multivariable analysis for each imputed dataset restricted to eligible individuals (ie, enrolled during 1962–75) and obtained the imputed HRs by combining estimates across datasets using Rubin's rules.[29]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1 334 686 (77%) of 1 739 996 individuals registered in the tuberculosis screening database were eligible, of whom 1 025 621 (77%) were TST negative (figure 1). 940 484 (92%) of these individuals were vaccinated and 85 137 (8%) were unvaccinated. The final study sample included 83 421 (22%) TST-negative unvaccinated and 297 905 (78%) BCG-vaccinated individuals. Baseline characteristics are presented in table 1. BCG vaccinated individuals were

more likely to be male and younger at enrolment than were unvaccinated individuals. The head of household's education level was higher in vaccinated (144 905 [48%] of 297 905 higher secondary or better) than in unvaccinated (30 083 [36%] of 83 421) individuals, although the distribution of occupational groups was similar between groups. Finally, a higher proportion of BCG vaccinated individuals (143 692 [49%] of 297 905) lived in households with five or more residents than did unvaccinated individuals (22 611 [27%] of 83 421). The distribution of other baseline characteristics was otherwise broadly similar between groups. Median follow-up was 44 years (IQR 41–46) for vaccinated and 41 years (32–49) for unvaccinated individuals. Censoring by emigration was negligible (5627 [1%]), and age-adjusted overall survival was similar between groups (appendix).

Age-adjusted tuberculosis rates were similar across categories for most baseline characteristics (appendix), except for sex: tuberculosis rates of men were more than twice those of women (2·2 vs 5·6 per 100 000 person-years; HR 2·46 [95% CI 1·67–3·62]). We noted no interaction between baseline variables and BCG VE, except for weak evidence for education-level (lower VE for lower education levels) and county-level (lower VE in counties with an incidence of more than 25 per 100 000 person-years) tuberculosis rates (appendix). Stratified analyses were consistent with only weak confounding by individual baseline variables.

Overall, 260 first episodes of tuberculosis were reported, of which 103 cases per 3 131 917 person-years

See **Online** for appendix

	Number of tuberculosis cases/person-years	Crude rate (per 100 000 person-years)	Crude HR*	Crude VE*	p value	Adjusted HR†	Adjusted VE (%)†	p value
Overall								
Unvaccinated	103/3 131 917	3·3 (2·7 to 4·0)	..	..	..	..	..	..
Vaccinated	157/12 425 272	1·3 (1·1 to 1·5)	0·36 (0·27 to 0·48)	64% (52 to 73)	<0·0001	0·51 (0·35 to 0·74)	49% (26 to 65)	<0·0001
0–9 years (including tuberculosis events in first 2 years after screening)								
Unvaccinated	29/812 004	3·6 (2·5 to 5·1)	..	..	..	..	..	..
Vaccinated	46/2 920 797	1·6 (1·2 to 2·1)	0·45 (0·25 to 0·80)	55% (20 to 75)	0·006	0·49 (0·26 to 0·93)	51% (7 to 74)	0·03
0–9 years (excluding tuberculosis events in first 2 years after screening)								
Unvaccinated	27/812 000	3·3 (2·3 to 4·8)	..	..	..	..	..	..
Vaccinated	36/2 920 781	1·2 (0·9 to 1·7)	0·41 (0·23 to 0·76)	59% (24 to 77)	0·005	0·39 (0·20 to 0·76)	61% (24 to 80)	0·006
10–19 years								
Unvaccinated	44/784 840	5·6 (4·2 to 7·5)	..	..	..	..	..	..
Vaccinated	45/2 874 574	1·6 (1·2 to 2·1)	0·35 (0·21 to 0·58)	65% (42 to 79)	<0·0001	0·42 (0·24 to 0·73)	58% (27 to 76)	0·002
20–29 years								
Unvaccinated	15/704 774	2·1 (1·3 to 3·5)	..	..	..	..	..	..
Vaccinated	29/2 794 374	1·0 (0·7 to 1·5)	0·72 (0·36 to 1·43)	28% (–43 to 64)	0·35	0·62 (0·29 to 1·32)	38% (–32 to 71)	0·22
30–40 years								
Unvaccinated	15/830 300	1·8 (1·1 to 3·0)	..	..	..	..	..	..
Vaccinated	37/3 835 528	1·0 (0·7 to 1·3)	0·72 (0·35 to 1·46)	28% (to 46 to 65)	0·36	0·58 (0·27 to 1·24)	42% (–24 to 73)	0·16

Data in parentheses are 95% CIs. HR=hazard ratio. VE=vaccine effectiveness. *Adjusted for present age (years; Cox model fitted on age timescale). †Fully adjusted for present age, time, and baseline characteristics (test for log-linear trend in HRs by timeband p=0·015).

Table 2: BCG vaccine effectiveness against all tuberculosis
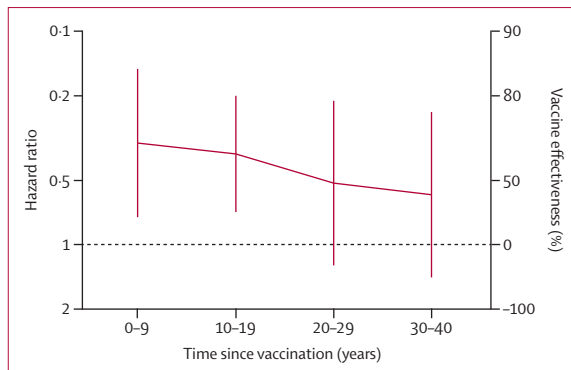
Figure 2: **BCG vaccine effectiveness against pulmonary tuberculosis by time since vaccination**
Error bars are 95% CIs. Tuberculosis cases occuring in the first 2 years after screening are excluded.

occurred in unvaccinated individuals (crude rate of 3·3 [95% CI 2·7–4·0] per 100 000 person-years) and 157 cases per 12 425 272 person-years occurred in vaccinated individuals (1·3 [1·1–1·5] per 100 000 person-years), corresponding to an age-adjusted HR of 0·36 (95% CI 0·27–0·48) and VE of 64% (95% CI 52–73; table 2). After adjustment for calendar time and baseline covariates, the HR was 0·51 (0·35–0·74), with an average adjusted VE of 49% (26–65) during 40 years. Baseline covariates had little confounding effect (appendix), with most confounding due to calendar time.

Adjusted BCG VE was 51% (95% CI 7–74) in the first 10 years after vaccination (61% [95% CI 24–80] if excluding tuberculosis episodes in the first 2 years), remaining at 58% (27–76) 10–19 years after vaccination, and then subsequently dropping to 38% (–32 to 71) at 20–29 years and 42% (–24 to 73) at 30–40 years. We noted weak evidence that change in HRs between time intervals was not log-linear (p=0·015). Detailed results are presented in table 2. A further breakdown of VE in 5 year bands for the first 20 years after vaccination is provided in the appendix. Estimates remained similar, except for the first 10 years, when VE is lower, at 21% (–102 to 69; 42% [–76 to 81] if excluding tuberculosis episodes in the first 2 years) in the first 5 years after vaccination, than in 5 years to less than 10 years after vaccination (61% [17–81]). Nelson-Aalen cumulative hazard plots did not show severe deviation from the proportionality assumption (appendix).

The adjusted VE against pulmonary tuberculosis during 40 years was 55% (95% CI 32–70). It was 57% (8–80; 67% [95% CI 27–85] if excluding tuberculosis episodes in the first 2 years) for 0–9 years and 63% (32–80) for 10–19 years, falling to 50% (–19 to 79) 20–29 years after vaccination and 40% (–46 to 76) 30–40 years afterwards (figure 2, appendix). We noted some statistical evidence that change in HRs between time intervals was not log-linear (p=0·012). Time-specific VE estimated either assuming those with missing BCG

date were vaccinated as soon as they reached the eligible age or with use of PMM imputation were consistent with the complete data analysis beyond the first 10 years after vaccination (appendix). Sensitivity estimates for the first 10 years were lower and less precise than were the complete data.

Discussion

Findings from our study show that BCG vaccination was associated with an almost halving of the risk of tuberculosis during a 40 year period after vaccination. If examined by decades, we noted that BCG was associated with about a 60% reduction in risk during the first two decades after vaccination. VE was about 40% between 20 years and 40 years after vaccination, although the evidence was weaker. The vaccine seemed to reduce the risk of pulmonary tuberculosis, the infectious form of the disease, more than it did of all tuberculosis. These results are only the second, to our knowledge, to present evidence in support of BCG protection against tuberculosis during a period of 40 years or longer, the first being follow-up of participants in the Native American and Alaska Natives BCG trial,[16] and our results are the first in a European population.

Advantages of our study included the large sample size, good documentation of TST and BCG vaccination status, and linkage to 50 years of good routine tuberculosis surveillance and various administrative databases. The study also had limitations: it had few cases in each time period due to low tuberculosis rates in Norway since the 1960s[30,31] (due to, in turn, an effective nationwide tuberculosis control programme in the 1940s to 1970s and improvement in living conditions)[27] and a lower stringency of TST than in trials (people were tested only once at each screening round, and the aP test could have been less sensitive than was the Mantoux test,[32] whereas some trials used high tuberculin doses and two-stage testing[5,7]); this lower stringency of TST than in trials would cause non-differential inclusion of some TST positives and, thus, an underestimation of VE. The low VE estimate in the first 5 years is consistent with this hypothesis. The higher VE obtained if excluding tuberculosis cases in the first 2 years than if not excluding them suggests that TST sensitisation was more often due to infection with *M tuberculosis* than to environmental mycobacteria.

Potential exists for selection bias and confounding. Those who declined vaccination might have had a higher tuberculosis risk than did the general population, leading to an overestimation of VE. The information available did not support this assumption: age-adjusted all-cause mortality and loss to follow-up through emigration were similar in unvaccinated and vaccinated individuals, as were most baseline sociodemographic characteristics. The unvaccinated group was, however, older than was the vaccinated group, so was likely to have been exposed to higher risk of tuberculosis earlier in their life; however,

these individuals also remained TST negative at several successive screening rounds and were therefore more likely to be at a lower risk of tuberculosis. We therefore deem that the study underestimates BCG effectiveness. Nonetheless, we acknowledge that, in our study, as in most observational studies, a potential for residual confounding exists, including from unmeasured confounders.

Our estimates of BCG effectiveness in the first 5 years were lower than were previous estimates in similar populations. BCG effectiveness was about 90% with use of data from the Norway routine school vaccination programme,[21] although those investigators used a case-population approach known to slightly overestimate VE. Trials in the UK, USA, and Canada yielded VEs of 70–80%.[5,15,33] The difference might partly be attributable to lower stringency of TST and selection through repeated screening of unvaccinated individuals at lower risk of tuberculosis in this study, both discussed earlier; similarly low VE was reported in a previous trial[34] without stringent tuberculin testing before randomisation. Another factor might be that revaccination might have been captured in the database as a first vaccination; revaccination was not uncommon in individuals who were TST negative despite previous vaccination.[18,19] Postvaccination TST induration is not associated with BCG efficacy,[35] and evidence suggests that revaccination has no to, at most, a slight boosting effect on BCG-derived immunity.[36,37] In such revaccinated individuals, VE at the start of follow-up could have already decreased since their first vaccination, thus underestimating VE.

BCG effect beyond 5 years was consistent with literature reports from similar settings. VE 5–10 years after vaccination was similar to estimates in cohorts from Norway[21] and France,[38] and consistent with the Native American and Alaska Natives[16] and British Medical Research Council[5] BCG trials. The overlap between our estimates and those from these two trials continued 10–15 years after vaccination, although these two trials had higher point estimates and narrower CIs than our study had, consistent stringent TST, and complete case ascertainment. The other trials in the northern hemisphere above the tropics had too few tuberculosis episodes beyond 10 years to measure VE.[15] The Native American and Alaska Natives trial[16] measured BCG efficacy 15–20 years after vaccination at 52% (95% CI 28–68), the sole trial with enough data beyond 15 years. This finding is similar to ours and to those of Gernez-Rieux and Gervois[38] who reported a VE of 51% during the same interval in a French cohort. Overall, the VE estimated in our study during the first 20 years after vaccination seems consistent with the scientific literature.

In a systematic review,[15] only investigators of the Native American and Alaska Natives trial were noted to have measured BCG effectiveness beyond 20 years after vaccination. VE was 55% (95% CI 31–77) after 60 years of follow-up, similar to ours after 40 years, with estimates 20–30 years and 30–40 years after vaccination of about 62% (–5 to 88).[16] A comparison of our VE with that of the Native American and Alaska Natives trial is given in the appendix. We had less power than did the Native American and Alaska Natives trial beyond 20 years because of the very high tuberculosis incidence in their trial population, but findings from both studies showed persistence of BCG protection against tuberculosis beyond 20 years after vaccination.

VE seemed to wane beyond the first 20 years after vaccination, although the low study power precluded statistical evidence. A similar trend was noted in the Native American and Alaska Natives trial and is consistent with a review[15] of duration of BCG protection. Two hypotheses could explain a decrease in VE estimates with time—namely, reduction in the unvaccinated individuals' susceptibility or waning of the vaccinated individuals' immunity. Cross-immunity from sensitisation by environmental mycobacteria in unvaccinated individuals might progressively mask persistent BCG effect, therefore giving the false impression of decreasing VE. The fall could also be caused by waning of BCG-derived immunological memory, one of the premises for development of BCG booster vaccines.[14] These two hypotheses are not mutually exclusive and both might have played some part in our findings.

Our results are consistent with long-lived BCG-derived immunity, adding to the evidence that BCG vaccination of individuals not yet infected by *M tuberculosis* nor sensitised by environmental mycobacteria might confer some protection against tuberculosis for at least 20 years.[15] Besides the emerging evidence that BCG vaccination might also protect against *M tuberculosis* infection itself,[10,11] a longer duration of protection than that previously assumed would imply that the vaccine is more cost effective than was previously estimated. In the absence of any new and more effective tuberculosis vaccine than the BCG vaccine, the first pillar of WHO's new End Tuberculosis Strategy recognises the potential contribution of continued BCG vaccination of individuals at high risk of tuberculosis to their vision of a "world free of tuberculosis",[39,40] a contribution that is strengthened by BCG's long protection. Furthermore, in view of how widely BCG has been used across the world and the possibility that it may interact with future tuberculosis vaccines, such long-lived effect should be accounted for during development of new tuberculosis vaccines.

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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Manuscript:

Duration and change in BCG effectiveness against tuberculosis with time since vaccination: evidence from a Norwegian population-based cohort study.

<u>Online–Only Supplements</u>

eFigure1: **Age-adjusted cumulative survival probability during follow-up by vaccination status**

The graph suggests that the age-adjusted survival is broadly similar between the BCG vaccinated and unvaccinated subjects, in spite of the age difference at start of follow-up. This supports the fact that analysis using a Cox model adjusted for age as a time updated variable (i.e. fitting the model on the age (in years) time scale) provided a reasonable control for confounding by age.
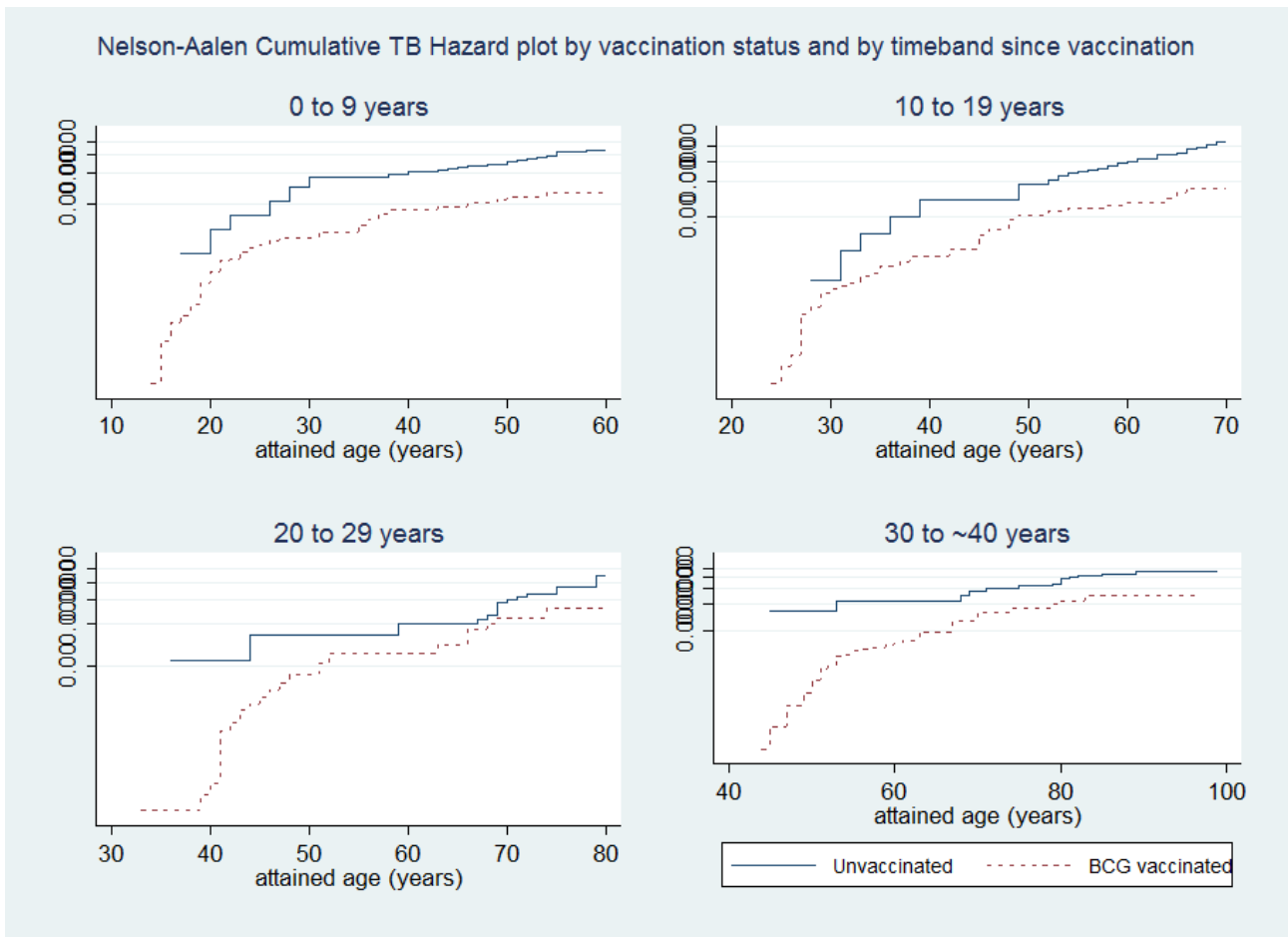
eFigure 2: Nelson-Aalen Cumulative Hazard plot by vaccination status

The solid blue and dashed red lines respectively represent cumulative TB hazards in unvaccinated and BCG vaccinated subjects for successive 10-year bands since vaccination, after adjustment for current age. The Nelson-Aalen plots of cumulative hazard by vaccination status for each time band suggest that overall, there is no gross violation of the proportionality assumption.
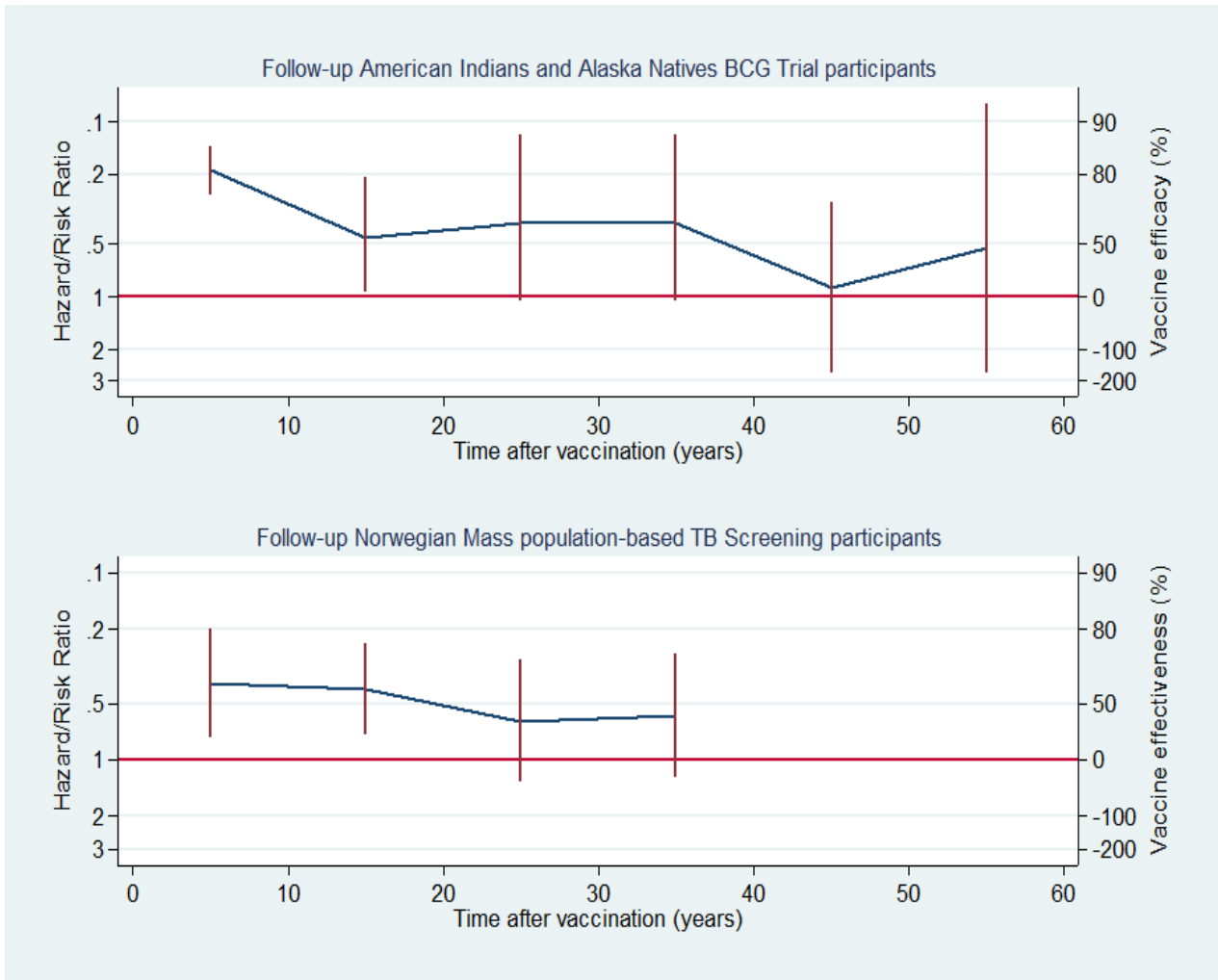
eFigure 3: BCG effectiveness against all tuberculosis - results from Norwegian cohort compared to 60-year follow-up of American Indians and Alaska Natives BCG Trial[1] *(Vertical bars represent 95% confidence intervals; TB cases occuring in first 2 years after screening are excluded)*

eTable 1: Age-adjusted association of baseline characteristics to risk of all type of tuberculosis among unvaccinated study participants

	TB rate per 100,000pyr (# / pyrs)	Hazard Ratio (95%CI)
Sex		
Female	2.2 (47/2126580)	-
Male	5.6 (56/1005338)	2.46 (1.67;3.62)
Marital status		
Married	3.1 (77/2451020)	-
Single/Other	3.8 (26/680898)	0.85 (0.54;1.36)
Education level of head of household[1]		
Lower secondary or less	3.3 (65/1953514)	-
Higher secondary	3.1 (33/1073866)	0.92 (0.61;1.40)
Tertiary / Vocational / Post-2ry	4.8 (5/104538)	1.41 (0.46;3.52)
Type of Municipality at entry (Urban/Rural)		
Rural	2.9 (39/1363433)	-
Urban	3.6 (64/1768485)	1.26 (0.84;1.87)
Number of residents in household at entry		
0-2	4.0 (27/674049)	-
3-4	2.9 (46/1565386)	0.73 (0.45;1.18)
5-6	3.3 (24/723736)	0.82 (0.47;1.43)
7+	3.6 (6/168747)	0.87 (0.36;2.13)
Occupation category of head of household at entry		
Manufacture, construction, mining	3.4 (45/1314856)	-
Technical, scientific, humanities	2.7 (5/185927)	0.79 (0.31;1.98)
Administration, sales, services	2.9 (13/444628)	0.86 (0.46;1.59)
Agriculture, forestry, fishing	3.2 (20/623615)	0.94 (0.56;1.60)
Trade, transport, communication	3.3 (17/510265)	0.97 (0.56;1.70)
Military, Other	5.7 (3/52627)	1.64 (0.51;5.28)
Annual TB rates 1965		
<20per100000	3.4 (53/1550626)	-
20-25per100000	3.5 (23/649109)	1.03 (0.63;1.68)
26+per100000	2.9 (27/932183)	0.83 (0.52;1.33)

All Hazard Ratios adjusted for current age

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[1] In absence of detailed information on income for all members of the household and given the fact we used census data from 1960 and 1970, the head of household was defined for practical purpose as (husband if married (or own if husband is unemployed)), father if <21 or in school (or mother if father is unemployed or not available) or own otherwise). This is as close as we could to definitions in place in Norway in the 1960-70s (oldest person in household – Keilman – Household Statistics in Europe – consequences of different definitions http://www.ssb.no/a/histstat/aap/aap_befolkning_199203.pdf retrieved on 03Dec2013).

eTable 2: BCG Effectiveness per stratum and adjusted for age and potential baseline confounders

	BCG vaccine		No BCG vaccine		Stratum-specific age adjusted VE (%) (95%CI)[2]	p-value (test homogeneity)	Bivariable adjusted VE (%) (95%CI)
Characteristics	# TB	Rate[3]	# TB	Rate[3]			
Overall ('Crude')	157	1.3	103	3.3	64 (52 to 73)		64 (52 to 73)
Sex							
Female	73	1.1	47	2.2	59 (38 to 73)		
Male	84	1.5	56	5.6	70 (56 to 80)	0.25	65 (54 to 74)
Marital status							
Married	37	1.2	77	3.1	63 (44 to 75)		
Single/Other	120	1.3	26	3.8	62 (40 to 75)	0.91	62 (49 to 72)
Education level of head of household at entry							
Lower secondary or less	93	1.5	65	3.3	52 (32 to 66)		
Higher secondary	55	1.1	33	3.1	72 (54 to 94)	0.02	61 (49 to 71)
Tertiary / Vocational / Post-2ry	9	0.9	5	4.8	89 (65 to 99)		
Type of Municipality of Residence							
Rural	66	1.3	39	2.9	60 (38 to 74)		
Urban	91	1.3	64	3.6	51 (50 to 76)	0.63	63 (51 to 72)
Number of residents in household at entry							
0-2	12	1.5	27	4.0	56 (09 to 78)		
3-4	57	1.0	46	2.9	64 (46 to 76)	0.94	63 (50 to 72)
5-6	63	1.4	24	3.3	66 (41 to 81)		
7+	25	1.7	6	3.6	59 (-8 to 85)		
Occupation category of head of household at entry							
Manufacture, construction, mining	53	1.1	45	3.4	69 (51 to 80)		
Technical, scientific, humanities	8	0.8	5	2.7	80 (23 to 95)		
Administration, sales, services	14	0.9	13	2.9	69 (24 to 87)	0.74	64 (52 to 73)
Agriculture, forestry, fishing	38	1.7	20	3.2	58 (19 to 78)		
Trade, transport, communication	35	1.7	17	3.3	49 (3 to 73)		
Military, Other	9	2.1	3	5.7	54 (-56 to 87)		
County-level Annual TB rates 1965							
<20per100000	58	1.1	53	3.4	69 (53 to 80)		
20-25per100000	30	0.9	23	3.5	74 (53 to 86)	0.06	63 (51 to 72)
26+per100000	69	1.8	27	2.9	39 (0 to 64)		

[2] VE = Vaccine effectiveness; 95%CI = 95% Confidence Interval
[3] Rate of tuberculosis per 100,000 person-years

eTable 3: BCG vaccine effectiveness against all TB with 5-year bands break down for initial 20 years after vaccination

Time since vaccination	# TB cases/pyears	Rate (per 100,000pyears)	'Crude' HR (95%CI)	Crude VE (95%CI) (%)	p-value	Adjusted HR (95%CI)	Adjusted VE (%)(95%CI)	p-value
0-4 years								
Unvaccinated	9/406289	2.2 (1.2;4.3)						
BCG vaccinated	19/1463866	1.3 (0.8;2.0)	0.65 (0.26;1.60)	35 (-60 to 74)	0.35	0.79 (0.31;2.02)	21 (-102 to 69)	0.62
0-4 years (excluding TB events occurring in first 2 years)								
Unvaccinated	7/406285	1.7 (0.8;3.6)						
BCG vaccinated	9/1463850	0.6 (0.3;1.2)	0.52 (0.18;1.49)	48 (-49 to 82)	0.22	0.58 (0.19;1.76)	42 (-76 to 81)	0.34
5-9 years								
Unvaccinated	20/405715	4.9 (3.2;7.6)						
BCG vaccinated	27/1456931	1.9 (1.3;2.7)	0.33 (0.17;0.66)	67 (34 to 83)	0.002	0.39 (0.19;0.83)	61 (17 to 81)	0.01
10-14 years								
Unvaccinated	19/398866	4.8 (3.0;7.6)						
BCG vaccinated	24/1444728	1.7 (1.1;2.5)	0.36 (0.18;0.72)	64 (28 to 82)	0.004	0.43 (0.21;0.89)	57 (11 to 79)	0.02
15-19 years								
Unvaccinated	25/385974	6.5 (4.4;9.6)						
BCG vaccinated	21/1429846	1.5 (1.0;2.3)	0.33 (0.17;0.64)	67 (36 to 83)	0.001	0.43 (0.21;0.89)	57 (11 to 79)	0.02
20-29 years								
Unvaccinated	15/704774	2.1 (1.3;3.5)						
BCG vaccinated	29/2794374	1.0 (0.7;1.5)	0.72 (0.36;1.43)	28 (-43 to 64)	0.35	0.62 (0.28;1.31)	38 (-31 to 71)	0.22
30-~40 years								
Unvaccinated	15/830300	1.8 (1.1;3.0)						
BCG vaccinated	37/3835528	1.0 (0.7;1.3)	0.71 (0.35;1.46)	29 (-46 to 65)	0.35	0.58 (0.27;1.23)	42 (-23 to 73)	0.16

Crude means adjusted only for current age (in years) (Cox model fitted on age timescale)
Fully adjusted for current age, calendar time, and baseline characteristics

eTable 4: BCG Vaccine Effectiveness against Pulmonary TB

Time since vaccination	# PTB cases/pyears	Rate (per 100,000pyears)	'Crude' HR* (95%CI)	Crude VE* (95%CI) (%)	p-value	Adjusted HR~ (95%CI)	Adjusted VE~ (%)(95%CI)	p-value
Overall								
Unvaccinated	78/3131442	2.5 (2.0;3.1)	-					
BCG vaccinated	121/12424654	1.0 (0.8;1.2)	0.36 (0.26;0.49)	64 (51 to 74)	<0.001	0.45 (0.30;0.68)	55 (32 to 70)	<0.001
0-9 years								
Unvaccinated	20/811781	2.5 (1.6;3.8)						
BCG vaccinated	32/2920511	1.1 (0.8;1.5)	0.43 (0.22;0.85)	57 (15 to 78)	0.02	0.43 (0.20;0.92)	57 (8 to 80)	0.03
0-9 years (excluding TB events occurring in first 2 years)								
Unvaccinated	19/811779	2.3 (1.5;3.7)						
BCG vaccinated	26/2920500	0.9 (0.6;1.3)	0.36 (0.18;0.74)	64 (26 to 82)	0.005	0.33 (0.15;0.73)	67 (27 to 85)	0.006
10-19 years								
Unvaccinated	38/784707	4.8 (3.5;6.7)						
BCG vaccinated	36/2874390	1.3 (0.9;1.7)	0.31 (0.18;0.54)	69 (46 to 82)	<0.001	0.37 (0.20;0.68)	63 (32 to 80)	0.002
20-29 years								
Unvaccinated	11/704697	1.6 (0.9;2.8)						
BCG vaccinated	22/2794270	0.8 (0.5;1.2)	0.67 (0.30;1.50)	33 (-50 to 70)	0.33	0.50 (0.21;1.19)	50 (-19 to 79)	0.12
30+ years								
Unvaccinated	9/830257	1.1 (0.6;2.1)						
BCG vaccinated	31/3835483	0.8 (0.6;1.1)	0.79 (0.34;1.87)	21 (-87 to 66)	0.60	0.60 (0.24;1.46)	40 (-46 to 76)	0.26

*'Crude' HRs are in fact adjusted for current age (in years) (Cox model fitted on age timescale)

~Fully adjusted for current age, calendar time, and baseline characteristics. Test for log-linear trend in HRs by timeband p=0.012

	BCG date recorded (N=297,905)	BCG date missing (N=24957)
Sex		
Female (%)	163634 (54.9%)	11535 (46.2%)
Male (%)	134271 (45.1%)	13422 (53.8%)
Marital status		
Married	78321 (26.7%)	2414 (9.7%)
Single/Other	216162 (73.3%)	22266 (89.2%)
Missing	3422 (1.1%)	277 (1.1%)
Education level of head of household		
Lower secondary or less	151968 (51.0%)	12459 (49.9%)
Higher secondary	120522 (40.4%)	10864 (43.5%)
Tertiary / Vocational / Post-secondary	24383 (8.2%)	1486 (6.0%)
Missing	1032 (0.4%)	148 (0.6%)
Type of Municipality at entry (Urban/Rural)		
Urban	171916 (57.7%)	15791 (63.3%)
Rural	125580 (42.2%)	9109 (36.5%)
Missing	409 (0.1)	57 (0.2%)
Number of residents in household at entry		
0-2	21002 (7.0%)	2073 (8.3%)
3-4	132790 (44.6%)	11165 (44.7%)
5-6	109416 (36.7%)	8785 (35.2%)
7+	34276 (11.6%)	2876 (11.5%)
Missing	421 (0.1%)	58 (0.2%)
Occupation category of head of household at entry		
Manufacture, construction, mining	119232 (40.0%)	9724 (39.0%)
Technical, scientific, humanities	24814 (8.3%)	1989 (8.0%)
Administration, sales, services	38234 (12.8%)	3889 (15.6%)
Agriculture, forestry, fishing	54497 (18.3%)	3449 (13.8%)
Trade, transport, communication	49356 (16.6%)	4417 (17.7%)
Military, Other	10136 (3.4%)	1300 (5.2%)
Missing	1636 (0.6%)	189 (0.8%)
Annual TB rates 1965		
<20per100000	127961 (43.0%)	10705 (42.9%)
20-25per100000	78637 (26.4%)	4152 (16.6%)
26+per100000	91300 (30.6%)	10097 (40.4%)

The date of vaccination was missing in 173,384/940,584 (18.4%) subjects, some of whom would have been vaccinated after 1962 hence eligible for the study. As mentioned in the methods section, individuals aged 13 years or more after 1962 were more likely to have been vaccinated as soon as they became eligible (i.e. when they turned 13-14 years). 24,957/173,384 (14%) people with missing BCG date were 13 years old or less in 1962, and therefore included in a sensitivity analysis making the pragmatic assumption that they received BCG when aged 13 years. The distribution of baseline characteristics in these subjects, including socio-demographic and other TB risk factors is presented in the supplementary table 4 above.

eTable 6: Sensitivity analysis of BCG effectiveness against all TB

Time since vaccination	Adjusted HR (95%CI)	p-value	VE (%) (95%CI)
Complete data analysis results			
0 to 9 years	0.49 (0.26;0.93)	0.03	51 (7 to 74)
0 to 9 years excl TB in first 2 years	0.39 (0.20;0.76)	0.006	61 (24 to 80)
10 to 19 years	0.42 (0.24;0.73)	0.002	58 (27 to 76)
20 to 29 years	0.62 (0.29;1.32)	0.22	38 (-32 to 71)
30 to ~40 years	0.58 (0.27;1.24)	0.16	42 (-24 to 73)
Pragmatic Assumption*: BCG vaccinated subjects with missing value for year of vaccination were vaccinated when they reached 13 years old if did so after 1962			
0 to 9 years	0.48 (0.25;0.91)	0.025	52 (9 to 75)
0 to 9 years excl TB in first 2 years	0.38 (0.19;0.75)	0.005	62 (25 to 81)
10 to 19 years	0.44 (0.25;0.76)	0.003	56 (24 to 75)
20 to 29 years	0.62 (0.29;1.33)	0.22	38 (-33 to 71)
30 to ~40 years	0.56 (0.26;1.20)	0.13	44 (-20 to 74)
Multiple Imputation using Predictive Mean Matching			
0 to 9 years	0.68 (0.37;1.25)	0.22	32 (-25 to 63)
0 to 9 years excl TB in first 2 years	0.50 (0.26;0.98)	0.04	50 (2 to 74)
10 to 19 years	0.42 (0.25;0.73)	0.002	58 (27 to 75)
20 to 29 years	0.59 (0.28;1.26)	0.17	41 (-26 to 72)
30 to ~40 years	0.55 (0.26;1.17)	0.12	45 (-17 to 74)

Under the pragmatic assumption, 24957 BCG vaccinated subjects with year of vaccination missing are included in analysis, as detailed in eTable 5.

eTable 7: Sensitivity Analysis of BCG effectiveness against Pulmonary Tuberculosis

Time since vaccination	Adjusted HR (95%CI)	p-value	VE (%) (95%CI)
Complete data analysis			
0 to 9 years	0.43 (0.20;0.92)	0.03	57 (8 to 80)
0 to 9 years excl TB in first 2 years	0.33 (0.15;0.73)	0.006	67 (27 to 85)
10 to 19 years	0.37 (0.20;0.68)	0.002	63 (32 to 80)
20 to 29 years	0.50 (0.21;1.19)	0.12	50 (-19 to 79)
30 to ~40 years	0.60 (0.24;1.46)	0.26	40 (-46 to 76)
Pragmatic Assumption*: BCG vaccinated subjects with missing value for year of vaccination were vaccinated when they reached 13 years old if did so after 1962			
0 to 9 years	0.42 (0.32;0.90)	0.026	58 (10 to 68)
0 to 9 years excl TB in first 2 years	0.32 (0.15;0.71)	0.005	68 (29 to 85)
10 to 19 years	0.38 (0.21;0.71)	0.002	62 (29 to 79)
20 to 29 years	0.51 (0.21;1.20)	0.12	49 (-20 to 79)
30 to ~40 years	0.57 (0.23;1.41)	0.22	43 (-41 to 77)
Multiple Imputation using Predictive Mean Matching			
0 to 9 years	0.62 (0.30;1.30)	0.20	38 (-30 to 70)
0 to 9 years excl TB in first 2 years	0.46 (0.21;0.99)	0.05	54 (1 to 79)
10 to 19 years	0.37 (0.20;0.66)	0.001	63 (34 to 80)
20 to 29 years	0.49 (0.21;1.15)	0.10	51 (-15 to 79)
30 to ~40 years	0.57 (0.23;1.40)	0.22	43 (-40 to 77)

*Under the pragmatic assumption, 24957 BCG vaccinated subjects with year of vaccination missing are included in analysis, as detailed in eTable 5.

References

1.   Aronson NE, Santosham M, Comstock GW, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: A 60-year follow-up study. *JAMA : the journal of the American Medical Association.* 2004;291(17):2086-2091.

10. General Discussion and Conclusions

10.1 Introduction

Whilst the burden of tuberculosis in England is lower than in most low-income developing countries, it remains relatively higher than in developed nations with comparable economic standing (1, 2). Until the recent 2 years, TB notification rates had not significantly declined for nearly three decades (3), with TB rates in the country's largest city, London, amongst the highest in Western European and North American major cities, and earning London the unenviable label of "*TB capital of Western Europe*" for over a decade. By comparison, before the 1980s, England had experienced nearly 80 years of sustained decline in TB rates, with steady progress towards the disease's elimination as a public health problem (4). The pace of decline slowed in the early 1980s, with TB rates plateauing soon after. The stagnation in national rates has been attributed to the high TB incidence among migrants from high TB burden parts of the world, and the resurgence of the disease in segments of the UK-born population (5).

In the first part of my thesis, I examined the long-term trends in TB notifications in England over 30 years, and I explored the association between tuberculosis and deprivation in the UK-born population at the ecological and individual levels. I also measured the association of TB to some intermediate social determinants of health inequalities (SDH) as possible pathways through which poverty may partly affect the TB risk in a subsection of this population. I dedicated the second part of my thesis to BCG vaccination, one of the longstanding prevention tools, that has been less examined than case finding and treatment recently. Like several other low TB burden countries, England reviewed their BCG vaccination policy in the early 2000s to take into account changes to the disease epidemiology in the country. In light of the low incidence in the general population, and the limited impact of the HIV pandemic on the local TB epidemiology, the programme of routine universal vaccination of schoolchildren was replaced by targeted vaccination of infants at high risk (6). I presented a national survey of how the 2005 change in policy was implemented at the local level, and I estimated the vaccine uptake after the policy change as well as explore how it related to some area-level factors. Lastly, I performed analyses measuring the long-term duration of BCG-derived protection against tuberculosis. Findings from the latter study, together with the growing body of additional evidence on BCG, are potentially relevant to vaccination policy as well as the ongoing research and development efforts to find new and more effective TB-vaccines.

In the following sections, I summarise the key findings from the different result chapters with comments on how they relate and flow from each other. I subsequently discuss some of the strengths and limitations of the works presented in this thesis. I then offer some reflections on the relevance of my findings to policy and potential implications, as well as proposing future line of enquiries that may build on these works.

10.2 Key findings by research questions

Tuberculosis notifications in England between 1983 and 2014

The first result chapter of this thesis examined the trends in TB notifications in England and Wales over three decades, from 1983 to 2014, contrasting the pattern in foreign-born and UK-born populations by age and ethnicity. The aim was to help provide some insight into how the interplay between these factors may have affected the TB resurgence in England from the mid-1980s as well as recent trends, especially in the UK-born population.

My analysis suggested that a relatively complex dynamic underscored recent trends in TB notifications. The failure of overall TB rates to continue to decline from the mid-1980s appeared to be mostly attributable to a steep increase of TB rates in the foreign-born population from Black ethnicity and the fact that TB rates in foreign-born subjects from the Indian Sub-Continent (ISC, mainly Indians, Pakistani and Bangladeshi) ceased to decline. However, there was also a non-negligible contribution from the UK-born population, in which the rapid decrease in TB notification rates observed for most of the 20th century progressively slowed until rates stopped declining from the 1980s. I also found that whereas TB rates in the foreign-born population appear to have been declining since 2006, TB rates in the UK-born population have remained mostly stagnant. My results also show that TB rates in older individuals have been declining consistently over the past three decades, whereas they have increased then stabilised in UK-born young adults. Furthermore, I found that the decline in TB rates observed in the foreign-born population since 2006 is mirrored in the TB rates in UK-born individuals from ethnic minority groups, whereas rates seem to have plateaued in the White ethnic group. Tuberculosis being a classic poverty-related disease, I therefore wanted to explore the role of socio-economic deprivation and poverty-related determinants of health in halting the progress towards the control of TB in a country where resources exist to effectively eliminate the disease as a public health problem.

An ecological analysis of the association between tuberculosis notification rates in England between 2008 and 2012 and small area-level deprivation

Following the findings in the first result chapter, that TB rates in the UK-born population have been mostly stagnant until recent years, especially in the White ethnic population, in the second result chapter, I investigated the association between TB notification rates in recent years (2008-2012) and area-level deprivation level, stratified by place of birth (UK-born versus foreign-born populations). The intention was to attempt to disentangle the potential role of deprivation from that of place of birth (and associated TB risk) in driving variations in TB risk across the country.

I found that even after accounting for confounding by age, sex, urban/rural area classification and the area-level proportion of non-White residents, area-level deprivation remained positively associated with overall TB rates, with higher notifications in most deprived areas. The results also suggested a stronger association between the area-level deprivation and TB rates in the UK-born compared to the foreign-born population. After adjusting for confounding, TB notification rates in UK-born subjects living in the most deprived quintile areas of England were about two-and-a-half times higher than the least deprived quintile areas, whereas the magnitude of the equivalent association in the foreign-born population was just about an 80% increase in those from the most deprived quintile areas compared to those in the least deprived quintile areas. The analyses also revealed a strong association (nearly three times higher rates in the most deprived quintile areas compared to least deprived) between area-level deprivation and TB rates in children aged 0-14 years, a group mostly UK-born and in which the majority of TB cases are likely to result from recent infection.

Social determinants of tuberculosis in UK-born adults: a case-control study

The third result chapter built on the results from the analysis of TB trends in England (Manuscript 1) that suggested low, but stubbornly stagnant TB notification rates in the UK-born population, notably young adults from White ethnic background; and the ecological analyses reported in chapter 2 that showed a strong gradient in TB notification rates across small-area level deprivation in the UK-born population. These results supported the need to further assess the association between socio-economic status (SES)

and TB at the individual level, and investigate some underlying determinants. Here, I conducted secondary analyses of data collected as part of an England-wide population-based case-control study on the duration of BCG effectiveness against tuberculosis. Information was collected on a range of social-determinants of health inequalities (SDH) in young adults UK-born TB cases from White ethnic background and randomly selected community-based controls. My main objective was to use a formal causal framework to disaggregate and measure the respective association between those individual-level social-determinants of health and TB, in an attempt to help map out how SES overall may affect the risk of TB along some of these pathways. Using education level as a proxy-measure for socio-economic status, the study showed that the risk of TB in subjects with none or education below O-level was about four times higher compared to those with a degree or higher qualification. The results also suggested that besides small-area deprivation level in the place of residence, the intermediate social determinants of health associated with higher risk of TB included tobacco smoking, misuse of controlled drugs, and history of homelessness. The Population Attributable Fraction (PAF) estimates suggested that interventions to reduce tobacco smoking and drug use may respectively contribute to preventing up to 18% and 15% TB cases in young UK-born adults, thus supporting the case for integrated health and social services in high-risk young adult population groups.

A National survey of the implementation of childhood BCG vaccination policy at the local level in England

The fourth and fifth result chapters of my thesis focused on BCG, the sole preventive vaccine with proven effectiveness against TB in several settings including the UK. Considering the stagnation of TB rates over decades, the rationale for this part of my thesis was to examine the effectiveness and service delivery of one part of the TB control toolkit that has been relatively neglected in recent years. The fourth chapter specifically reports a survey of BCG vaccination policy in England following the major change in policy in 2005 from routine universal vaccination of schoolchildren to targeted vaccination of high-risk infants. I also used routinely available data to estimate the BCG vaccination uptake in the target population in the 3-year period after the change (2006-2008) and the association between uptake and some area characteristics, including the vaccination policy and main delivery pathway, deprivation level, and percentage of minority ethnic births in the area.

The BCG vaccination policy in England changed in 2005, when routine universal vaccination of schoolchildren was discontinued and replaced by targeted vaccination of

infants at higher risk of TB (6). The recommended approaches to implementing the new policy of targeted vaccination included universal vaccination of all infants in areas with higher TB rates, and selective vaccination of specific groups in areas with lower TB rates, with the area-level TB rates cut-off threshold set at 40 cases per 100,000. I contributed to a national survey on the state of the implementation of the new recommendations at local level by years 2010-2011. We found that the new policy had been implemented in most areas in the country in line with recommendations, with about 7 in 10 areas using selective vaccination of high-risk children and the rest using universal vaccination. The survey also highlighted the heterogeneity in health care delivery pathways between areas, as well as some complexities and challenges in the identification of, and services delivery to high-risk groups. For example, areas using selective vaccination of high-risk groups employed a wider variety of channels (e.g. maternity records, baby's hospital notes, child health record, birth notification records etc.) to identify 'at-risk' children as well as to administer the vaccine (such as postnatal ward, community clinics, chest clinics, paediatric clinics), compared to areas using universal vaccination of all infants, where there was no need to identify 'at-risk' infants, and vaccination is mostly offered through community clinics. The multiple pathways in selective vaccination areas has the potential to result in missed opportunities for vaccination due to lack of clear responsibilities, as well as a greater risk of failure of linkage to care. Other examples of challenges in implementing the policy included shortages in staff with suitable training to administer BCG intra-dermally, and unclear or lack of service-level agreement to organise vaccination for babies born in maternities with catchment areas enclosing different primary care areas with different healthcare pathways for BCG vaccination.

Estimation of BCG vaccine uptake following a major change in policy

There in currently no routine denominator data for the continuous monitoring of BCG vaccine uptake in England since the 2005 policy change to targeted vaccination of high-risk infants. In the fifth result chapter, I used routinely available administrative data on the number of BCG doses administered and the number of live-births by areas to estimate infant-BCG vaccine uptake in the 3-year period (2006-2008) after the change in policy. I also explored the association between uptake levels and some area-level factors (current and past vaccination policy and main place of vaccine delivery, deprivation rank, and percentage of ethnic minority birth in the area). These analyses suggested that nearly a third of eligible infants may have missed BCG vaccination during the study period (average

uptake 68%), and that vaccine uptake was slightly higher in areas using universal vaccination (72%), compared to those using selective vaccination of high-risk groups (66%). The vaccine uptake not surprisingly also appeared to be better in areas primarily delivering the vaccine immediately after birth, in post-natal wards (73%), compared to those having to come to community clinics for vaccination some weeks later (64%).

A population-based cohort study of the duration of BCG-derived protection against tuberculosis

In the fifth and final result chapter of my thesis, I used readily available linked-register data from Norway, a European country with relatively low-TB incidence in the native population as in England, to conduct a population-based historical cohort study measuring the duration of BCG-derived protection against tuberculosis.

Overall, the follow-up of nearly 300,000 BCG vaccinated and 83,000 tuberculin-negative unvaccinated individuals over more than 40 years suggested that BCG provide an average 60% protection against tuberculosis in the first 20-year post-vaccination, possibly waning to about 40% vaccine effectiveness 20-40 years after vaccination. The protection levels found in my analysis were similar to observations from a North American BCG trial with long follow-up, and consistent with the hypothesis of a long-lived BCG-derived immunity against TB.

The evidence generated may be relevant to the cost-effectiveness assessment of BCG vaccination strategies in such settings, thus policy planning, as well as to ongoing efforts to develop new and more effective TB vaccines, whose potential interaction with BCG may be important to consider in view of the widespread use of BCG across the world.

10.3 Strengths and limitations of the research presented

The respective methodological strengths and limitations specific to the studies included in his thesis have been discussed in more detail in the relevant sections of each manuscript. More generally, a feature common to most analyses presented here is their reliance, fully or in part, on routine surveillance data. These data had the advantage of being readily available and relatively inexpensive, thus allowing for a rapid exploration of the research questions that I set out to explore, and potentially contributing to the evidence at a lower cost, compared to purposefully designed prospective data collection. The fact that these

were nationwide data and of reasonably good quality adds confidence to the validity of the inference made, and the findings' generalisability to the target populations. The analyses of long-term trends in TB notifications may have been more complete if detailed annual surveillance data with patients' place of birth and ethnicity were readily available at the national level prior to 1999 when the central surveillance system was established. However, the comprehensive nature and rigorous methods of the 5-yearly periodic national TB surveys has provided us with useful snapshots of the TB situation over these years.

The focus of my thesis was on TB in the UK-born population of England, in which rates have been stagnant for decades. In line with some of the strategies proposed by WHO to achieve the long-term goal of TB elimination in a near future, one of my main aims was to help understand how social determinants of health inequalities (SDH) may contribute to increased TB risk in the target population. The availability of detailed information on several SDH at the individual-level in the nationwide case-control study reported in the thesis provided an opportunity to explore this research question at a deeper level. There are some limitations, not least because the study was not primarily designed to explore this research question. More detailed information on the overall social-economic status (e.g. income, social class etc.) and some potentially relevant determinants of TB could have been measured, for example the nutritional status. Furthermore, the retrospective data collection added difficulties in establishing the temporal sequence between the risk factors examined and the risk of TB. However, the consistency of findings with existing knowledge and the biological plausibility contribute to their robustness.

The survey of the implementation of the BCG vaccination policy at the local level, and the estimation of vaccine uptake, were both conducted just before a substantial re-organisation of England's health system architecture. At the time of the studies, vaccinations were organised through 152 Primary Care Trusts (PCTs), which is the administrative level at which analyses were done. However, since 2013, PCTs have been abolished, and routine vaccinations and other public health activities are delivered through Clinical Commissioning Groups (CCGs), with England divided into 211 CCGs as of 2015. This has had implications in terms of local vaccination policies that may warrant an update to the survey. The Cover of Vaccine Rapidly Evaluated (COVER) service of Public Health England (PHE) has also been developing a system for continuous monitoring of BCG vaccine uptake, which eventually will inform the evaluation of the vaccination programme; however, the system is still being tested (PHE 2016).

10.4 Recommendation for research and potential future studies

Besides stagnant TB rates in the UK-born population, the analyses of TB trends in England also showed an interesting steep decline in TB rates in the foreign-born population in recent years, which was beyond the scope of my thesis to investigate further. The explanation for these recent trends are unclear and may warrant further exploration to help policy and planning. Notably, it would be important to apportion the respective roles of local TB control measures from that of global TB trends (thus emphasising the impact on local TB epidemiology of the UK contribution to global TB control) and trends in population movements.

The pathways through which poverty affect the risk of TB could also benefit from additional exploration, including prospective data collection for a better measurement of the role of various social determinants of health inequalities (SDH). In the context of a study prospectively collecting more detailed data, it may also be helpful to conduct a formal mediation analysis to quantify the respective contributions of intermediate SDH to the poverty-related TB risk, which could help policy makers focus the resources where they are likely to have the biggest impact.

As mentioned in section 10.3, the survey implementation of BCG vaccination policy requires an update given the re-organisation of England's health-care system since the survey reported in this thesis. The Cover of Vaccine Rapidly Evaluated (COVER) service of Public Health England (PHE) has been developing a system for continuous monitoring of BCG vaccine uptake. The first experimental data were published in 2016, limited to data from areas that offer universal neonatal BCG vaccination (10 out of more than 150 local authorities) (7). This is a welcome development, although the system is new and does not yet cover the whole country, and data quality is still variable. Until the system is more stable and established, and include areas with selective vaccination of children at higher risk, it might be useful to explore if any available routine data could be used to obtain a recent picture of the vaccine coverage in the country since the re-organisation of care.

Finally, results from my study of duration of BCG-derived protection against TB can be included in the most recent systematic review on the duration of BCG protection (8), to update the meta-analyses and provide more robust evidence on which to base any new BCG or new TB vaccines policy.

10.5 Reflections on relevance of findings to policy and potential implications

My findings from the examination of TB trends appear to challenge the assumption that TB rates in the UK-born population are mostly driven by an aging population and increasing population of UK-born subjects with family ties to high-TB burden parts of the world. The long-term trends show that TB rates have continued to decline in older UK-born subjects at a similar pace over the past 30 years, and that rates in young-adult UK-born from ethnic minorities have be decreasing steadily in the past decade, mirroring the trends in foreign-born populations. The later observation is likely explained by the fact that a substantial driver of the TB risk in UK-born subjects from ethnic minority is their family ties to high-TB burden parts of the world. On the other hand, TB rates in UK-born young adults from White ethnicity seem stagnant. I also show that the association between deprivation and TB is stronger in the UK-born population, and the case-control analysis suggest that the deprivation-related increased in TB risk may be explained in part at the individual-level by SDH like tobacco smoking and use of controlled-drugs, as well as homelessness and possibly history of stay in prison. In spite of their limitations, those findings are intuitively consistent with other more direct observations on recent social changes. There have been several reports of rising social inequalities and deprivation in England since the 1980s, including higher prevalence of homelessness among young adults (9), and decline in the quality of accommodation in metropolitan areas (10). There is also a large body of evidence linking poverty and deprivation to higher prevalence of a number of habits potentially deleterious to health, including tobacco smoking (e.g. (11)).

The recent WHO's post-2015 End-TB strategy appreciates the imperative need to address social inequalities as part of any efforts to eliminate TB as a public health problem (12). While the reduction of social injustice and related health inequalities is a long-term and much more complex goal to achieve, a better understanding of some of the pathways through which poverty affects the risk of tuberculosis can help inform and/or improve targeted interventions that are within the grasp of public health, such as tobacco smoking cessation, prevention of drug use etc. The findings presented in this thesis lend support to the idea that innovative approaches may be required in combatting TB, including for example integrated approaches that support individuals, not as patients screened and/or diagnosed with a specific disease, but as whole entities whose health and other social needs should be better understood and supported. Such integration of services may also

prove more cost-effective, as many of the health determinants prevalent in the vulnerable populations with high TB burden as also risk factors for several other diseases.

Regarding the place of BCG vaccination in TB prevention among UK-born subjects in England, the revision of policy in 2005 was motivated by changes to the TB epidemiology, including relatively lower incidence rate in the general population, as well as a judgment on the benefit compared to the risk of BCG-related adverse events. However, there has since been new evidence emerging of BCG vaccination that is relevant to policy. For example, whereas it was assumed that BCG does not protect against infection, a number of studies and a meta-analysis have suggested that BCG offer some protection against infection (13), which is important in view of the spread of multi-drug resistant strains. Another interesting development was the development of a new laboratory test for the diagnosis of latent TB infection (LTBI), the Interferon Gamma Release Assay (IGRA), which unlike the tuberculin skin test (TST), is specific to *Mycobacterium tuberculosis* and is unaffected by BCG vaccination (14). While the assay remains relatively costlier than the TST and is more labour-intensive, this development may warrant the reconsideration of the argument upon which BCG vaccination had to be balanced against a compromised ability to screen for LTBI as part of TB control efforts in low-incidence settings.

In the same vein as these new facts of BCG, some findings from my thesis are consistent with a duration of BCG-derived protection against TB longer than previously assumed. This information is directly relevant to calculations of the cost-effectiveness of the vaccine, thus of vaccination strategies. A further development with relevance to BCG vaccination policy is the fact that whereas there was great hope that a new and more effective TB would quickly become available, there is greater now appreciation that several gaps remain in the understanding of the immune response to *Mtb*, and vaccine development efforts will likely be more laborious than initially thought. The most promising TB vaccine candidate, the MVA85A BCG-booster vaccine, underwent human phase 3 trial, unfortunately providing little to no more additional protection than BCG alone (15). Of the thirteen vaccine candidates currently at various stage of development, only two (M72 adjuvant fusion protein and *Mycobacterium vaccae* lysate) are undergoing human efficacy testing (16). BCG is therefore likely to remain for the near future the sole TB prevention vaccine, and the emerging evidence as new developments discussed should help reconsider the role and potential contribution of BCG to TB control efforts.

The review of local vaccination policy also highlighted how heterogeneities and complex delivery pathways at the local level may lead to missed vaccination opportunities for high-risk children, and this was reflected in the estimates of vaccine uptake. In recently

published data on BCG uptake in areas with universal neonate vaccination in 2015, Public Health England estimated that in 24 London local authorities with data available, BCG uptake varied from 2.4% to 94.7%, with uptake in the nine areas with highest TB rates varying from 32.3% to 91.6% (7). The vaccine uptake may have been affected by the global shortage in BCG supply in the past few years (17) and possibly unstable data from the new monitoring system. However, the low uptake in some areas and the large variation in the estimated local uptakes should be reason for concern and prompt a review of the approach to vaccine delivery and perhaps more harmonisation of care pathways across areas.

10.6 Conclusion

High-income countries like the UK are in a better position to achieve TB elimination in a near future compared to low-income countries where resources are more constrained. However, the research reported in this thesis highlighted the stagnant TB rates in the UK born White population of England, notably in young adults, an age group that has received less attention than TB in the foreign-born population. My investigations also suggested that deprivation and the related harms remain associated with TB in this population group, which is a concern in view of the upswing in poverty noted in recent years. Further studies are warranted to examine the underlying social determinants of TB in this population, while addressing the limitations of the results presented in my thesis.

My research also put the spotlight on BCG vaccination, an often-neglected part of the TB control toolkit, which despite its shortcomings remains the sole effective TB vaccine available. I showed that the current vaccination programme faced several challenges to service delivery, which may have affected the vaccine uptake in the current target population. I also found that the vaccine efficacy lasts longer than previously estimated, albeit at moderate levels. In an era when Multi-Drug Resistance is spreading, this information, combined to the emerging evidence that BCG may also protect against *Mtb* infection, points to a further relevance of the vaccine for vulnerable groups from the general population in which the poverty-related risk of TB could last from infancy until adulthood.

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Appendices

Appendix 1: NHS England Research Ethics Approval for the studies reported Manuscript 3 and 4

Appendix 2: Health Protection Agency (HPA) Research Approval for the studies reported Manuscript 3 and 4

Appendix 3: LSHTM Ethics Approval for the studies reported Manuscript 3 and 4

Appendix 4: Questionnaire used for face-to-face interviews in the case control study reported in Manuscript 3

Appendix 5: Norwegian Research Ethics Committee Approval for the cohort study reported in Manuscript 6

Appendix 6: Norwegian Institute of Public Health Data Access agreement and authorisation for the cohort study reported in Manuscript 6

NHS

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02 June 2011

Professor Laura Rodrigues
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Dear Professor Rodrigues

Study title:	**CASE-CONTROL STUDY OF CHANGES IN THE EFFICACY OF BCG WITH TIME SINCE VACCINATION FOR PREVENTING TUBERCULOSIS IN THE UK**
REC reference:	**11/H1102/11**

Thank you for your letter of 19 May 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair's Panel.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

<u>Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.</u>

This Research Ethics Committee is an advisory committee to the South East Coast Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter		05 January 2011
Evidence of insurance or indemnity		13 December 2010
Investigator CV		20 December 2010
Other: Letter of invitation to participants - Adult (incl young adult) controls	2	28 March 2011
Other: Letter of invitation to participants - Adult (incl young adult) cases	2	28 March 2011
Other: Letter of invitation to participants - Child cases	2	28 March 2011
Other: Letter on invitation to participants - Child controls	2	28 March 2011
Participant Consent Form: For Examining Upper Arm & Linking to Records - Adult	3	18 April 2011
Participant Consent Form: For Examining Upper Arm & Linking to Records - Child	3	18 April 2011
Participant Consent Form: Interview Consent - Adults	1	18 April 2011
Participant Consent Form: Interview Consent - Parents	1	18 April 2011
Participant Information Sheet: Adult Cases	4	16 May 2011
Participant Information Sheet: Adult Controls	4	16 May 2011
Participant Information Sheet: Child Cases	4	16 May 2011
Participant Information Sheet: Child Controls	4	16 May 2011
Participant Information Sheet: Young Adult Cases	4	16 May 2011
Participant Information Sheet: Young Adult Controls	4	16 May 2011
Participant Information Sheet: Adult Cases	4 (without photo)	16 May 2011
Participant Information Sheet: Adult Controls	4 (without photo)	16 May 2011
Participant Information Sheet: Child Cases	4 (without photo)	16 May 2011
Participant Information Sheet: Child Controls	4 (without photo)	16 May 2011
Participant Information Sheet: Young Adult Cases	4 (without	16 May 2011

		photo)	
Participant Information Sheet: Young Adult Controls		4 (without photo)	16 May 2011
Protocol		1	20 December 2010
Questionnaire: Interviewer administered		1	20 December 2010
REC application			11 January 2011
Referees or other scientific critique report			01 May 2009
Response to Request for Further Information		2	28 March 2011
Response to Request for Further Information			18 April 2011
Response to Request for Further Information			19 May 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

      Notifying substantial amendments
      Adding new sites and investigators
      Progress and safety reports
      Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/H1102/11	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

**Dr L. Alan Ruben
Chair**

Email: sophievella@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Punam Mangtani*
Professor John Stephenson Executive Director, Research &
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13/10/2011

Re: **Title of Research Project:** Case control study of changes in the efficacy of BCG
with time since vaccination for preventing TB in the UK

Date of permission: 22 July 2011

Dear Dr Abubakar,

I am pleased to inform you that permission has been granted for the Health Protection Agency
to act as a participating organisation in the above study, based on information supplied in the
REC form (dated 11/01/2011) and protocol (dated 20/12/2010).

Permission is only granted for the activities for which a favourable opinion has been given by
the REC.

Yours sincerely,

Dr John Stephenson
Director of R&D
Chair of RSRSG
Health Protection Agency
john.stephenson@hpa.org.uk

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

ETHICS COMMITTEE

APPROVAL FORM
Application number: **5996**

Name of Principal Investigator	**Professor Laura Rodrigues and Dr Punam Mnagtani**
Faculty	**Epidemiology and Population Health**
Head of Faculty	**Professor Laura Rodrigues**

Title: **CASE CONTROL STUDY OF CHANGES IN THE EFFICACY OF BCG WITH TIME SINCE VACCINATION FOR PREVENTING TUBERCULOSIS IN THE UK**

This application is approved by the Committee.

Chair of the Ethics Committee

Date ....27 June 2011 ……………………………………….

Approval is dependent on local ethical approval having been received.

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form.

BCG case control study questionnaire_v1_20_12_2010

Note 1: This questionnaire is to be used for both cases and controls, for adults and children. The questionnaire will be administered using computer aided interviewing, which allows questions to be altered depending on the age of the subject. For children under the age of 16, the questions will be asked of the parent, and the words 'were/did /have/do you' will be replaced with 'was/did/has/does your child' throughout. For children under the age of 16, questions relating to occupation will be asked of/about the parent.
For questions to 16 to 22 year olds related to vaccine history will be asked of the parent – if necessary by use of a form for the information, which can be shown to the parent, or posted.

Note 2: Some questions are only asked of particular groups. Where this is the case, it is indicated in italics before the question or questions that it applies to.

SECTION A   INTRODUCTION AND EARLY HISTORY

A1   INTERVIEWER – RECORD RESPONDENT'S NAME

A2   INTERVIEWER – ASK OR RECORD RESPONDENT'S SEX
Male
Female

A3   What is your date of birth?
ENTER DATE IN NUMBERS , E.G. 02/01/1972.
IF (Name) DOES NOT KNOW HIS/HER DATE OF BIRTH, PLEASE GET AN ESTIMATE.

IF DATE GIVEN AT A3
A4   Can I just check, what was your age last birthday?

IF A4 = NOT KNOWN/REFUSED
A5   What do you estimate your age to be?

ASK ALL
A6   Were you born in the United Kingdom? This includes England, Scotland, Wales or Northern Ireland?
Yes
No

(IF NO, EXPLAIN THAT FOCUS OF STUDY IS ON UK HEALTH POLICY FOR BABIES AND CHILDREN, SO R NOT ELIGIBLE. THANK AND END INTERVIEW.)

ASK ALL
A7   We are interested in the immunisations that people received when they were babies and children. Immunisation policies have changed over time and may also vary according to where you live. We would like to know where you were living at different times when you might have been offered certain immunisations.
First, could you tell me the town or city where you were born? *(INTERVIEWER: RECORD NAME OF THE TOWN AND THE COUNTY. IF A LARGE CITY, ASK:)* In which borough or district were you live?

(INTERVIEWER: RECORD NAME OF TOWN AND COUNTY.)

IF AGE<23
A8	Were you born in a hospital?
	Yes
	No
	Don't know

IF A8=YES
A9	What was the name of the hospital where you were born? *(INTERVIEWER: RECORD NAME OF HOSPITAL IN FULL)*

ASK IF AGE <22 YEARS
A10	Where did you live when you were a baby, from when you were born to when you were 4 years old? That is before *<DATE OF R'S 4ᵀᴴ BIRTHDAY>*? *(IF MORE THAN ONE PLACE)* Where did you live for the longest time? *(INTERVIEWER: RECORD NAME OF THE TOWN AND THE COUNTY. IF A LARGE CITY, ASK:)* In which borough or district did you live?

A11	Did you move to a different area between the ages of 4 and 11? That is between *<DATE OF R'S 4ᵀᴴ BIRTHDAY>* and *<DATE OF R'S 11ᵀᴴ BIRTHDAY>*.
	Yes
	No

IF A11=YES, ASK
A12	Where did you live between the ages of 4 and 11?	*(IF MORE THAN ONE PLACE)* Where did you live for the longest time? *(INTERVIEWER: RECORD NAME OF THE TOWN AND THE COUNTY. IF A LARGE CITY, ASK:)* In which borough or district did you live?

ASK ALL
 A8	Where did live between the ages of 11 and 14? That is between *<DATE OF R'S 11ᵀᴴ BIRTHDAY>* and *<DATE OF R'S 14ᵀᴴ BIRTHDAY>*. *(IF MORE THAN ONE PLACE)* Where did you live for the longest time? *(INTERVIEWER: RECORD NAME OF THE TOWN AND THE COUNTY. IF A LARGE CITY, ASK:)* In which borough or district did you live?

SECTION B   IMMUNISATION HISTORY

ASK IF UNDER 2 YEARS OLD
B1	Has *(CHILD'S NAME)* had any immunisations yet?
	Yes
	No

IF B1= YES OR AGE>2 AND <16
B2	*(INTERVIEWER: SHOW EXAMPLE RED BOOK)* When children are given immunisations, these are usually marked in a red Child Health Record Book (or Red Book) which is kept by the parent or guardian at home. Do you have *(CHILD'S NAME)*'s red book to hand?
INTERVIEWER: IF YES, ASK PARENT TO GET BOOKLET AND ENCOURAGE THEM TO CONSULT IT TO FIND OR CHECK RESPONSES. CODE WHETHER BOOK AVAILABLE AND USED.
	Red book available and consulted
	Red book not available/not used

IF AGE>=16 AND <=22 YEARS THEN
B3   The next questions are about immunisations, including some that are usually given to babies and small children. If there are any immunisations that you are not sure of, may we have your permission to ask your parents? *INTERVIEWER CODE:*
        Parent(s) present, able to answer questions now in person
        Parents able to answer questions now on phone
        Parents live with respondent – can leave form and come back/call back for information
        Parents live elsewhere – respondent gives permission to contact them
        Respondent doesn't give permission for parental contact

ASK ALL
B4   *SHOW CARD A*
As far as you are aware, have you had any of the immunisations on this card?
(If you need to, please refer to the red (Child Health Record) book to check.)
        Yes
        No

IF B4 = YES
B5   *SHOW CARD A*
Which ones have you had?
INTERVIEWER: CODE ALL THAT APPLY. IF HAD SEPARATE JABS FOR MEASLES, MUMPS AND/OR RUBELLA (INSTEAD OF ALL THREE COMBINED (MMR) DO NOT USE CODE 45, BUT CODE THESE AS SEPARATE.
        Diphtheria/ Tetanus/ Whooping Cough
        Polio
        Hib (Haemophilus Influenzae type b)
        5-in-1 injection: Diptheria/ Tetanus/ Whooping Cough/ Polio/ Hib (Haemophilus Influenzae type b)
        Measles, Mumps, Rubella combined (MMR)
        Meningococcal C
        Pneumococcal vaccine (Pneomococcal conjugate vaccine, PCV)
        CODE IF APPLICABLE: Measles as a separate immunisation
        CODE IF APPLICABLE: Mumps as a separate immunisation
        CODE IF APPLICABLE: Rubella as a separate immunisation
        CODE IF APPLICABLE: Don't know

IF B5=DON'T KNOW
B6   As far as you aware, do you think you probably had *(READ OUT)* ...
        all the usual infant vaccinations
        some of the usual infant vaccinations, or
        none of the usual infant vaccinations.
        CODE IF APPLICABLE: Don't know

ASK ALL:
B7   (As far as you know), did you have the BCG vaccination when you were a baby, that is, before your first birthday?
(INTERVIEW CHECK RED BOOK, IF AVAILABLE (PAGE 11B – BCG VACCINATION.
PROMPT IF NECESSARY): The BCG vaccination is given in the upper arm. Sometimes it causes a spot or sore that lasts for a few weeks, and sometimes it leaves a permanent scar.
        Yes
        No

Don't know

IF B7=YES
B8   Where were you given the BCG vaccination? Were you *(READ OUT)* ...
        in hospital,
        in a hospital outpatient clinic (for example, a chest clinic)
        at your GP's surgery
        at another clinic or health centre (not your GP) , or
        somewhere else?
        (DO NOT READ OUT) Don't know/can't recall

IF B8=SOMEWHERE ELSE
B9   Where were you given the BCG vaccination? *(INTERVIEWER: WRITE IN)*

IF B2=RED BOOK AVAILABLE AND CONSULTED
B10   We are interested in the vaccination policies in different areas. Can I check the red
book to see whether any reason was given when the BCG was given to *<NAME>*?
*(INTERVIEWER: CODE 'REASON FOR BCG' FROM PAGE 11B OF RED BOOK. CODE ALL
THAT APPLY. DO NOT ASK FAMILY. NOT ALL COPIES OF THE RED BOOK HAVE THIS
SECTION.)*
        Reason not recorded in book
        All babies in the area were vaccinated (called "universal neonatal programme")
        Parent/grandparent born in a country with a high TB rate
        TB in a relative or close contact
        Travel to a country with a high TB rate
        Born or lived in a country with a high TB rate
        Other (specify at next question)

IF B10=OTHER
B11   INTERVIEWER WRITE IN REASON WHY BCG GIVEN

IF B7=NO OR DON'T KNOW & AGED OVER 11 YEARS
B12   Some people who did not have the BCG as a baby were given it later on at school. As
far as you remember, were you given the BCG at school when you were aged between 11 and
13? *(INTERVIEWER PROMPT IF NECESSARY)* The BCG vaccination is given in the upper
arm. Sometimes it causes a spot or sore that lasts for a few weeks, and sometimes it leaves a
permanent scar.
        Yes
        No
        Don't know

IF B7=NO OR DON'T KNOW & AGED <=11 YEARS OR B12 = NO
B13   Do you remember having the BCG vaccination at any other age, or somewhere other
than school?
        Yes
        No
        Don't know

IF B13=YES
B14   How old were you when you had the BCG vaccination?

B15   Where were you given the BCG vaccination? Were you *(READ OUT)* …
        in hospital,
        in a hospital outpatient clinic (for example, a chest clinic)
        at your GP's surgery
        at another clinic or health centre (not your GP) , or
        somewhere else?
        (DO NOT READ OUT) Don't know/can't recall

IF B15=SOMEWHERE ELSE
B16   Where were you given the BCG vaccination? *(INTERVIEWER: WRITE IN)*

IF AGE >=23 YEARS
B17   Before the BCG immunisation is given to school children a test is usually done which involves an injection with one needle, or with 6 pins in a circle, into the inside of the lower arm (interviewer to show on place on their own arm). Do you remember having a test like this when you were at school?
        Yes
        No
        Don't know

IF B17=YES
B18   Did you receive the BCG immunisation as a second injection a few weeks after this test?

        Yes
        No

IF B18=NO
B19   Was this because *(READ OUT)* ….
        you were told you did not need a BCG vaccine as a result of the test
        you refused to have the second injection, or
        you missed the second injection?
        (DO NOT READ OUT) Don't know/can't recall

ASK ALL:
B20   If you had the BCG vaccination it may have left a small scar on the upper left arm. Would you mind If we looked at your upper arm to see if there is a BCG scar? *INTERVIEWER RECORD:*
        Respondent agreed
        Respondent refused

IF B20=RESPONDENT AGREED
B21   *INTERVIEWER RECORD RESULT OF INSPECTION*
        BCG scar identified
        No BCG scar visible
        Not sure – a scar is present, but not in the normal place
        Not sure – a scar is present, but looks more like a cut
        Not sure – a scar is present, but is raised rather than indented
        Not sure – some other reason
        Not examined

B22   Would you be willing for us to take a photograph of your arm?

INTERVIEWER RECORD:
    Respondent agreed
    Respondent refused

IF B22=RESPONDENT AGREED
B23   *INTERVIEWER RECORD TIME AND DATE OF PHOTOGRAPH OR 'NOT TAKEN'.*
THANK RESPONDENT.

SECTION C   GENERAL HEALTH

ASK ALL
C1   Did a doctor or nurse ever tell you that you had asthma?
    Yes
    No

IF C1 = YES
C2   How old were you when you were first told by a doctor or nurse that you had
asthma? *(ENTER AGE IN YEARS)*

ASK ALL
C3   Did a doctor ever tell you that you had pneumonia?
    Yes
    No

IF C3= YES
C4   How old were you when you when you were first told by a doctor that you had
pneumonia? *(ENTER AGE IN YEARS)*

ASK ALL
C5   Are you currently being treated for diabetes?
    Yes
    No

IF C5= YES
C6   How old were when you were told that you had diabetes? *(ENTER AGE IN YEARS)*

C7   How is your diabetes currently being managed? *(INTERVIEWER: CODE ALL THAT*
APPLY.)
    Injections
    Tablets
    Diet

SECTION D   TB HISTORY

ASK ALL
D1   Have you ever been treated for TB (Tuberculosis)?
    Yes
    No
D2   How old were when you were treated for TB? *(ENTER AGE IN YEARS)*

IF D1= YES

D3   Have you been treated for TB (Tuberculosis) in the last five years?
    Yes
    No

IF D3= YES
D4   What year was this? (*INTERVIEWER RECORD YEAR*)

D5   Which type of health service did you go to first when you became ill with TB? Was it *(READ OUT)* ...
    a GP
    an NHS Walk-in centre
    a Hospital A&E department
    via NHS Direct (the NHS phone helpline), or
    somewhere else?
    (DO NOT READ OUT) Don't know/can't recall

IF D5=SOMEWHERE ELSE
D6   Which type of health service did you go to first when you became ill with TB? *(INTERVIEWER: WRITE IN)*

D7   *SHOWCARD B*
Who was the first person to suggest that your illness might be TB? *(INTERVIEWER: CODE ONE ONLY)*
    Family member (for example, parent, husband or wife, brother or sister)
    Friend
    Other non-medical person (for example a colleague, acquaintance)
    GP
    Doctor or nurse at an NHS Walk-in centre
    Doctor or nurse at a hospital A&E department
    Advisor on NHS Direct (the NHS phone helpline)
    Someone else

IF D7=SOMEONE ELSE
D8   Who was the first person to suggest that your illness might be TB? *(INTERVIEWER: WRITE IN)*

D9   There are several different types of treatment you may have for TB. Some people take one type of tablet only, and other people take two or more tablets every day. When you started your treatment for TB, did you just take one type of tablet or were you prescribed two or more different tablets to take every day?
    One type of tablet throughout the treatment
    Two or more different tablets every day

D10   Before you had TB did you know anyone else who had TB?
    Yes
    No

IF D10=YES
D11   Was that person someone who lived in the same household as you, or someone who lived elsewhere?
    Someone in household

Someone who lived elsewhere

SECTION E   RISKS (SELF-COMPLETION MODULE)

ASK IF AGED >23
To be completed by respondents. Interviewers will not see answers.
This module will include opening questions explaining how to complete and locking answers at the end so that they are not accessible to the interviewer. Respondents will be given a set of showcards.

E1   Which one of these best describes you?
I smoke daily
I smoke, but not every day
I used to smoke but do not smoke at all now
I have never smoked

IF E1=I SMOKE DAILY, OR I SMOKE BUT NOT EVERY DAY
E2   On average, how many cigarettes do you currently smoke in a day?
Less than one per day
1 to 4 per day
5 to 9 per day
10 to 19 per day
20 to 39 per day
40 or more per day

E3   How long have you smoked cigarettes? PLEASE TYPE IN THE NUMBER OF YEARS. IF LESS THAN ONE YEAR, CODE 0.

IF E1= I USED TO SMOKE
E4   When did you last smoke a cigarette? PLEASE TYPE IN YEAR (for example, 1998).

E5   On average, when you used to smoke how many cigarettes did you smoke in a day?
Less than one per day
1 to 4 per day
5 to 9 per day
10 to 19 per day
20 to 39 per day
40 or more per day

E6   How long in total did you smoke cigarettes? PLEASE TYPE IN THE NUMBER OF YEARS. IF LESS THAN ONE YEAR, CODE 0.

ASK ALL:
E7   PLEASE LOOK AT SHOWCARD S1.
[showcard options: In own home, in other people's homes, while travelling by car, other places indoors, other places out of doors]
Are you regularly exposed to other people's tobacco smoke indoors in any of these places?
Yes
No

E8   Do you currently drink alcohol, including drinks you brew or make at home?
      Yes, I currently drink alcohol
      No, I used to drink alcohol but I don't drink now
      No, I have never drunk alcohol

IF E8=YES, I CURRENTLY DRINK ALCOHOL
E9   On average, how often do you have a drink containing alcohol?
      Four or more times a week
      Once or twice a week
      Two to four times a month
      Monthly
      Less often

E10   PLEASE LOOK AT SHOWCARD S2. THIS SHOWS DIFFERENT TYPES OF DRINK,
EQUIVALENT TO A SINGLE STANDARD DRINK
[Showcard lists equivalents to a standard drink: half a pint of beer, a single measure of spirits or a small glass of wine] .
How many standard drinks do you have on a typical day when you drink alcohol?
      One or two drinks
      Three or four drinks
      Five or six drinks
      Seven to nine drinks
      Ten or more drinks

IF E8=NO, I USED TO DRINK ALCOHOL BUT I DON'T DRINK NOW
E11   When did you last have an alcoholic drink? PLEASE TYPE IN YEAR (for example, 1998).

E12   On average, how often did you have a drink containing alcohol?
      Four or more times a week
      Once or twice a week
      Two to four times a month
      Monthly
      Less often

E13   PLEASE LOOK AT SHOWCARD S2. THIS SHOWS DIFFERENT TYPES OF DRINK,
EQUIVALENT TO A SINGLE STANDARD DRINK
[Showcard lists equivalents to a standard drink: half a pint of beer, a single measure of spirits or a small glass of wine] .
How many standard drinks did you have on a typical day when you LAST DRANK alcohol?
      One or two drinks
      Three or four drinks
      Five or six drinks
      Seven to nine drinks
      Ten or more drinks

ASK ALL
E14   PLEASE LOOK AT SHOW CARD S3.
[Showcard lists common non-Class A drugs: cannabis, qat, glue, gas, solvents] .
Have you ever taken any of the following drugs without a prescription?

    Yes
    No

IF E14=YES
E15   When was the last time you took any of these drugs? PLEASE TYPE IN YEAR (for example, 1998).

ASK ALL
E16   PLEASE LOOK AT SHOW CARD S4.
[Showcard lists common Class A drugs: ecstasy, cocaine, crack, heroin, LSD, magic mushrooms speed or other amphetamines,] .
Have you ever taken any of the following drugs without a prescription?
    Yes
    No

IF E16=YES
E17   When was the last time you took any of these drugs? PLEASE TYPE IN YEAR (for example, 1998).

E18   Have you ever smoked or inhaled any of these drugs?
    Yes
    No

E19   Have you ever injected any of these drugs?
    Yes
    No

ASK ALL
E20   PLEASE LOOK AT SHOW CARD S5.
[Showcard lists different types of homelessness: e.g. sleeping rough, living in a temporary hostel]
Have you ever lived in one of these situations for a week or more?
    Yes
    No

IF E20=YES
E21   When was the last time you lived in one of these situations for a week or more?
PLEASE TYPE IN YEAR (for example, 1998).

E22   In total for how long did you live in one or more of these situations? PLEASE TYPE IN THE NUMBER OF WEEKS:
    1 month = 4 weeks
    6 months = 26 weeks
    1 year = 52 weeks
    2 years = 104 weeks

ASK ALL
E23   In the last ten years, have you been detained in prison in the UK? This includes time spent on remand or after conviction.
    Yes
    No

E24   In the last ten years, have you been detained in prison outside the UK? This includes time spent on remand or after conviction.
        Yes
        No

End of self-completion section. Instructions on how to save and lock answers.

SECTION F   ETHNIC BACKGROUND AND FOREIGN TRAVEL

ASK ALL
F1   SHOWCARD C
Which of these best describes your ethnic background?
        White British
        White Irish
        Any other white background
        Mixed White and Black Caribbean
        Mixed White and Black African
        Mixed White and Asian
        Any other mixed background
        Indian
        Pakistani
        Bangladeshi
        Any other Asian/Asian British background
        Black Caribbean
        Black Africa
        Any other Black/Black British background
        Chinese
        Any other ethnic group

IF F1=ANY OTHER WHITE BACKGROUND OR ANY OTHER MIXED BACKGROUND OR ANY OTHER ASIAN/ASIAN BRITISH BACKGROUND OR ANY OTHER BLACK/BLACK BRITISH BACKGROUND OR ANY OTHER ETHNIC GROUP
F2   Please can you describe your ethnic group. *INTERVIEWER: RECORD VERBATIM.*

ASK ALL
F3   SHOWCARD D
        Were your parents or your grandparents born in any of these regions? *(IF YES)* Where was that?
        INTERVIEWER IF ASKED – 'PARENTS' REFERS TO THE PERSON WHO BROUGHT UP R – NOT NECESSARILY THE BIOLOGICAL PARENT.
        CODE ALL THAT APPLY.
        Africa
        Asia
        The Caribbean
        Central or Eastern America
        Eastern Europe
        (INTERVIEWER CODE) None of these

F4   Are there any countries outside the outside the UK that you travel to regularly? (By regularly I mean every few years or more often)?
        Yes

No

F5   Which country? *INTERVIEWER: PROBE:* Any others?

ASK ALL
F6   (Apart from those countries), have you ever stayed in any country outside the UK for 3 months or more?

F7   Which country? *INTERVIEWER: PROBE:* Any others?

SECTION G   CLASSIFICATORY QUESTIONS

G1 SHOW CARD E
Which of these descriptions applies to what you were doing last week?
CODE FIRST TO APPLY
        Going to school or college full-time (including on vacation)
        In paid employment or self-employment (or away temporarily)
        On a Government scheme for employment training
        Doing unpaid work for a business that you own, or that a relative owns
        Waiting to take up paid work already obtained
        Looking for paid work or a Government training scheme
        Intending to look for work but prevented by temporary sickness or injury
        (INTERVIEWER: CHECK 28 DAYS OR LESS)
        Permanently unable to work because of long-term sickness or disability
        Retired from paid work
        Looking after the home or family
        Doing something else

IF G1= LOOKING FOR PAID WORK OR G1=WAITING TO TAKE UP PAID WORK ALREADY OBTAINED
G2   How long have you been looking for paid work or a place on a government training scheme?
        Not yet started
        Less than 1 month
        1 month but less than 3 months
        3 months but less than 6 months
        6 months but less than 12 months
        12 months or more

IF G1 = GOING TO SCHOOL OR COLLEGE FULL TIME, OR DOING UNPAID WORK, OR ON A GOVERNMENT SCHEME, OR NTENDING TO WORK BUT TEMPORARILY SICK OR INJURED, ORPERMANENTLY UNABLE TO WORK, OR RETIRED FROM PAID WORK, OR LOOKING AFTER HOME OR FAMILY, OR DOING SOMETHING ELSE
G3   Have you ever had a paid job, apart from casual or holiday work?
        Yes
         No

IF G3=YES
G4   How long ago did you last have a paid job?

Within past 12 months
1 year, less than 5 years
5 years, less than 10 years
10 years or more
Can't say

IF G1=IN PAID EMPLOYMENT OR SELF-EMPLOYMENT OR G3=YES
G5   What did the firm or organisation you work(ed) for mainly make or do (at the place where you last worked)?
DESCRIBE FULLY - PROBE MANUFACTURING OR PROCESSING OR DISTRIBUTING ETC.AND MAIN GOODS PRODUCED, MATERIALS USED, WHOLESALE OR RETAIL ETC.

G6   What was your (main) job (last week)?
ENTER JOB TITLE

G7   What did you mainly do in your job?

G8   Were you working as an employee or were you self-employed?
Employee
Self-employed

IF G8=EMPLOYEE
G9   In your job, did you have formal responsibility for supervising the work of other employees?
DO NOT INCLUDE PEOPLE WHO ONLY SUPERVISE CHILDREN, E.G. TEACHERS, NANNIES, CHILDMINDERS, OR ANIMALS, SECURITY OR BUILDINGS, E.G.CARETAKERS, SECURITY GUARDS
Yes
No

G10   How many people worked for your employer at the place where you worked?
Were there (*READ OUT)...*
1 to 24
25 to 499
or 500 or more employees?

IF G8=SELF-EMPLOYED
G11   Were you working on your own or did you have employees? *ASK OR RECORD*
On own/with partner(s) but no employees
With employees

IF G11=WITH EMPLOYEES
G12   How many people did you employ at the place where you worked?
Were there *(READ OUT)...*
1 to 24
25 to 499, or
500 or more employees

IF G8=EMPLOYEE OR G3=YES
G13   In your (main) job were you working...*(READ OUT)*
full time

or part-time?

ASK ALL
G14   At what age did you finish continuous full-time education at school or college?
(*RECORD AGE IN YEARS*)

ASK ALL AGED 23+
G15   SHOW CARD F
Which of these qualifications do you have? *CODE THE FIRST THAT APPLIES*
        Degree level qualification
        Teaching qualification, HNC/HND, BEC/TEC Higher, BTEC Higher, NVQ level 4
        A Levels, SCE Higher, ONC/OND/BEC/TEC, City & Guilds Advanced Final Level,
        NVQ Level 3
        O Levels Grades A-C, GCSE Grades A-C, City & Guilds Craft/Ordinary Level, NVQ
        Level 2
        GCE Grades D or E, GCSE Grades D-G, NVQ Level 1
        Other Qualifications.
        None of these

ASK ALL
G16   We would like to know a bit about the secondary schools you attended as a child.
What was the name of the first secondary school you attended at the age of 11?
INTERVIEWER RECORD SCHOOL NAME AND TOWN.

G17   How old were you when you started at that school?

G18   How old were you when you left that school?

IF G18<14 OR CURRENT AGE (WHICHEVER IS LOWEST)
G19   What was the name of the next secondary school you attended?
INTERVIEWER RECORD SCHOOL NAME AND TOWN.

G20   How old were you when you left that school?

*[INTERVIEWER: REPEAT FOR NEXT SCHOOL UNTIL AGE OF 14 OR CURRENT AGE
REACHED]*

ASK ALL
G21   SHOWCARD G
        Which of these describes the way your household occupies this accommodation?
        Own it (includes homes being bought with a mortgage)
        Pay part rent and part mortgage (shared ownership)
        Rented from a private landlord
        Rented from local authority or housing association
        Other

G22   Do you have any close family members, for example brothers, sisters, or cousins who
live nearby and who are about the same age as you (up to two years younger or older)?
(INTERVIEWER: INCLUDE PEOPLE WHO LIVE IN THE SAME HOUSEHOLD.)
        Yes
        No

Don't know

IF G22=YES
G23   How many close family members of about your age live nearby?

H   Nominated controls for infant BCG vaccination study

Note 1: These questions will be asked of the sample of cases (that is people identified through HPA records).
Note 2: Questions vary according to type of sample.

IF R PART OF THE INFANT IMMUNISATION SAMPLE AND CONTROL REQUIRES ETHNIC MATCHING
H1   A final set of questions now. As part of the study we would like speak to the parents of other children with a similar immunisation history. When your child was born in *[NAME OF DISTRICT]*, children in that area whose parents or grandparents were born in *[PART OF WORLD – SEE QUESTION F3]* received additional immunisations.

In order to see how effective these were, we are looking for parents of other children who were born in [DISTRICT] between (2 years before case) and (2 years after case), and whose parents were born in ....

Would you know any people like this?
        Yes
        No
        Don't know

IF R PART OF THE INFANT IMMUNISATION SAMPLE AND CONTROL DOES NOT REQUIRE ETHNIC MATCHING
H2   A final set of questions now. As part of the study we would like speak to the parents of other children with a similar immunisation history. We are looking for parents of other children who were born in *[NAME OF DISTRICT]* between (2 years before case) and (2 years after case).

Would you know any people like this?
        Yes
        No
        Don't know

IF R PART OF THE SCHOOL IMMUNISATION SAMPLE, check that (s)he was not born in any of the infant immunisation sample areas.
H3   A final set of questions now. As part of the study we would like speak to other people who went to secondary school in the same area as you.

We are looking for people who were born between (2 years before case) and (2 years after case).

Would you know any people like this?
        Yes
        No
        Don't know

IF H1= YES OR H2=YES or H3=YES
H4	*GIVE RESPONDENT COPY OF LETTER AND INFORMATION SHEET.*
Would you be willing to help us make contact with people like this? We are looking for one to five people. We would send them this letter and information sheet to ask if they would like to take part. It says that they have been suggested as someone who could help with this study of past immunisations in the area where you were born/went to school. Your responses today would remain confidential and would not be shared with anyone. We would not say that we chose you from health records, or anything about your health.

Would you be willing for us to contact anyone you know using this letter?
	Yes
	No
	Unsure

IF H4= YES
H5	Would be willing to give us details of anyone we could contact straight away?
	Yes
	No
	Unsure

IF H5= NO OR UNSURE
H6	Would you be willing to consider giving us details of anyone once you have had a chance to speak to them and ask their permission? Can we contact you again in a week or so? *INTERVIEWER: NOTE THAT YOU WILLCONTACT RESP AGAIN IN A WEEK FOR DETAILS (E.G. IF NEED TIME TO FIND THEM, OR UNCOMFORTABLE GIVING DETAILS WITHOUT PERMISSION)*
	Yes
	No

IF H6=YES, REPEAT FOR UP TO FIVE CONTACTS
H7	INTERVIEWER RECORD PERSON'S NAME, OR LEAVE BLANK IF RETURNING FOR THIS INFORMATION LATER.

H8	INTERVIEWER RECORD PERSON'S PHONE NUMBER, OR LEAVE BLANK IF RETURNING FOR THIS INFORMATION LATER.

H9	INTERVIEWER RECORD PERSON'S ADDRESS, OR LEAVE BLANK IF RETURNING FOR THIS INFORMATION LATER.

H10	INTERVIEWER RECORD PERSON'S E-MAIL ADDRESS, OR LEAVE BLANK IF RETURNING FOR THIS INFORMATION LATER.

H11	INTERVIEWER RECORD ANY OTHER USEFUL INFORMATION ABOUT CONTACTING THIS PERSON, OR LEAVE BLANK IF RETURNING FOR THIS INFORMATION LATER.

ASK ALL
H12	With your permission, we would like to consult the records held by the NHS Child or School Health Service to confirm whether or not if you had the BCG vaccine.

Please read this form, it explains more about what is involved.
INTERVIEWER: GIVE THE RESPONDENT THE CONSENT FORM AND ALLOW THEM TIME
TO READ THE INFORMATION.
        Consent given
        Consent not given

IF H12= CONSENT GIVEN
H13   Before I can pass your details on, I have to obtain written consent from you.
ENTER THE RESPONDENT'S SERIAL NUMBER ON THE TOP OF THE CONSENT FORMS.
ASK RESPONDENT TO SIGN AND DATE BOTH FORMS.
GIVE THE SECOD COPY OF THE FORM TO THE RESPONDENT.
CODE WHETHER SIGNED CONSENT OBTAINED.
        Consent signed
        No signed consent

Region:	Saksbehandler:	Telefon:		Vår dato:	Vår referanse:
REK nord	Veronica Sørensen	77620758		27.06.2012	2012/755/REK nord
				Deres dato:	**Deres referanse:**
				15.06.2012	

Vår referanse må oppgis ved alle henvendelser

Ibrahim Abubakar

Respiratory Diseases Department, Health Protection Agency, London

2012/755 Kohortstudie om varigheten av BCG-vaksinens beskyttelse

Forskningsansvarlig institusjon: Health Protection Agency, United KingdomIbrahim v/Abubakar, Punam Mangtani, Einar Heldal
Prosjektleder: Einar Heldal

Vurdering
Vi viser til prosjektendring av 15.06.2012 vedlagt cv og skjema for tilbakemelding av 19.06.2012.

REK anser at endring av prosjektleder er i tråd med de merknader komiteen gav i sitt utsettelsesvedtak av 05.06.2012 og har vurdert at Einar Heldal har tilstrekkelig kompetanse til å kunne stå som prosjektleder.

Videre har Rek vurdert tilbakemeldingen og anser at denne er dekkende for de merknader komiteen gav i sitt utsettelsesvedtak av 05.06.2012.

Etter fullmakt har komiteen fattet slikt:

Vedtak
Med hjemmel i helseforskningsloven § 10 og forskningsetikkloven § 4 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding på eget skjema senest et halvt år etter prosjektslutt,jf.helseforskningslovens § 12.
Prosjektleder skal sende søknad om prosjektendring til REK dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. helseforskningslovens § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. helseforskningslovens §10,3 ledd og forvaltningslovens § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette e- brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at tilbakemeldinger til komiteen og prosjektendringer sendes inn på skjema via vår saksportal:

http://helseforskning.etikkom.no.

Øvrige henvendelser sendes på e-post til post@helseforskning.etikkom.no.

Besøksadresse:
TANN-bygget Universitetet i Tromsø 9037 Tromsø

Telefon: 77646140
E-post: rek-nord@fagmed.uit.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK nord og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK nord, not to individual staff

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Veronica Sørensen
rådgiver

Kopi til: *ibrahim.abubakar@hpa.org.uk; punam.mangtani@lshtm.ac.uk; folkehelseinstituttet@fhi.no*

folkehelseinstituttet
www.fhi.no

Emne:	Kohortstudie om varigheten av BCG-vaksinens beskyttelse	**Ref. nr. Web-sak:** 12/700 **PDB:**
Til	Prosjektleder Ibrahim Abubakar	
Kopi til:		
Fra:	Avdeling for prosjektstøtte og – økonomi (SIPS)	**Dato:** 18. april 2012

Tilrådning fra Avdeling for prosjektstøtte

Saken gjelder søknad om prosjektgodkjenning fra REK for prosjektet "Kohortstudie om varighetene av BCG-vaksinens beskyttelse". Prosjektet utføres i regi av Nasjonalt folkehelseinstitutt i samarbeid med forskere fra Health Protection Agency i London og London School of Hygiene and Tropical Medicine.

Det søkes om forhåndsgodkjenning av prosjektet og dispensasjon fra taushetsplikt for kobling av data samlet inn i helsetjenesten med data fra sentrale helseregistre og om tillatelse til ny og endret bruk av data samlet inn i helsetjenesten etter helseforskningsloven § 35.

Formål
Prosjektet er en statistisk kohortstudie som skal undersøke hvor lenge BCG-vaksinasjon beskytter mot tuberkuloseinfeksjon. Funnene i studien vil ha stor betydning i forbindelse med planlegging, vurdering og gjennomføring av vaksinasjonsprogrammet i Norge og for liknende vaksinasjonsprogrammer internasjonalt. Studien vil gi nyttig informasjon om varighet av beskyttelse og om eventuell endring av beskyttelseseffekt over tid.

Utvalg
Utvalget vil bestå av 715000 individer fra den norske populasjonen. Studiecohorten vil hovedsakelig bli rekruttert ved å bruke screeningdata fra fødselscohortene som var med i massescrenningen som foregikk i perioden 1948 til 1975. Noe vil i tillegg bli rekruttert fra skolescreeningprogrammet som ble gjennomført for 9. klassinger i perioden fra 1975 til 1997.

Metode/design
Prosjektet er en historisk kvantitativ populasjonsbasert studie og vil kun benytte data som allerede er samlet inn i forbindelse med rutinemessig screeing/overvåking av forekomst, i regi av helsetjenesten og i sentrale helseregistre. Ved å koble data fra Tuberkuloseregisteret og Vaksinasjonsregisteret (SYSVAK) med screeningdata og sosioøkonomiske data om utdanning og inntekt fra SSB vil man kunne studere vaksineeffekten i opp til 35 år etter vaksinasjonstidspunktet.

Personvern og informasjonssikkerhet
Dataene som inngår i prosjektet vil bli behandlet i overensstemmelse med *Sikkerhetsmål og strategi for nasjonalt folkehelseinstitutt*, FHI R 501, samt underliggende sikkerhetsdokumentasjon. Forskningsdata vil bli oppbevart på et dedikert område i FHIs servere under streng tilgangskontroll. Forskere vil kun bearbeide avidentifiserte data og prosjektet vil ikke ta kontakt med studiepopulasjonen.
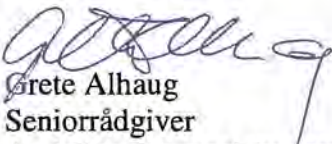
Vurdering

Formålet med studien er å undersøke effekten av BCG-vaksinen og beskyttelsens varighet. Funnene i studien vil kunne bidra med nyttig informasjon til helsemyndighetene både i Norge og i andre land hvor tuberkulose er langt mer utbredt enn i Norge. Studier som dette bidrar med opplysninger som kan gjøre helsemyndighetene bedre rustet til å foreta kost-nytte vurderinger av vaskinasjonsstrategien og dette vil være en fordel for samfunnet, helsemyndighetene og for befolkningen. Å benytte data som allerede er samlet inn i forbindelse med screeningprogrammer til dette formålet er etter vårt skjønn lite inngripende med tanke på de registrertes personvern sammenliknet med samfunnet og befolkningens nytte av å vurdere den faktiske effekten av vaksiner som tilbys i vaksinasjonsprogrammet.

Basert på foreliggende utkast til REK-søknad og forskningsprotokoll finner Avdeling for prosjektstøtte å kunne gi tilrådning til at prosjektet gjennomføres.

Eventuelle endringer i prosjektet skal meldes til avdeling for prosjektstøtte.

Med vennlig hilsen

Grete Alhaug
Seniorrådgiver
Avdeling for prosjektstøtte og -økonomi