Estimating the effect of the 2005 UK BCG vaccination policy change: A retrospective cohort study using the Enhanced Tuberculosis Surveillance system, 2000-2015

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**ABSTRACT**

**Background**

In 2005 the UK changed from a policy of universal school age Bacillus Calmette–Guérin (BCG) vaccination, to a policy of neonatal vaccination targeted at high risk neonates. Deployment of the BCG vaccine varies globally, with many countries adapting their vaccination programs over the past two decades. Little work has been done to assess the impact of switching BCG vaccination policies. **Methods**

We combined notification data from the Enhanced Surveillance system, with demographic data from the Labour Force Survey, to estimate the incidence rate of TB in both the UK born and non-UK born populations. We constructed retrospective cohorts of those eligible for both the universal, and targeted BCG vaccination programs between Jan 1, 2000 and Dec 31, 2010. To assess the evidence for an association between the change in vaccination policy and incidence rates we then investigated a range of poisson, and negative binomial models, which were assessed based on their goodness of fit, and epidemiological justifications.

**Results:** *copy in from bottom of paper*

**Conclusions:**

We found evidence across all models investigated that the ending of the BCG schools scheme was associated with an increase in incidence rates in the directly effected population. For models that adjusted for incidence rates in non-UK born population we found that the introduction of the neonatal vaccination program was associated with a decrease in incidence rates in the directly effected population. Understanding the trade-off's inherent to BCG vaccination targeting could inform future decision making.

**Keywords:**

BCG, surveillance, vaccination policy, neonatal

**What is the key question?**

**What is the bottom line?**

**Why read on?**

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**INTRODUCTION**

Bacillus Calmette–Guérin (BCG) remains the only licensed Tuberculosis (TB) vaccine, nearly a century after it's development[1], and remains in use throughout the world.[2] Globally vaccination policies differ, due to evidence of variable effectiveness in adults,[3] high effectiveness in children,[4,5] and evidence of interference with the standard skin test. The UK changed its vaccination policy in 2005 from a universal school age program to vaccination at birth for high risk neonates, due to evidence of reduced transmission,[6] and evidence of high effectiveness in children, compared to evidence of variable effectiveness in adults.[3] Little work has been done to evaluate the impact of this change in vaccination policy.

Notifications of TB in England and Wales increased from 6226, in 2000, to 8411, in 2011 but have have declined since, with incidence rates falling in both the non-UK born, and UK born populations.[6] After an initial infection with TB, an individual may rapidly develop active symptomatic disease, or the infection may enter a latent state which can develop into active disease many years later. This means that trends in TB notifications may not be directly linked to reducing transmission, and may instead be a product of changing TB incidence many years previously. Incidence in young children (0-14 years old) may be used as a proxy of TB transmission, as any active TB disease in this population may be attributable to reduced transmission, using this approach it is thought that TB transmission has been falling in England and Wales for the last 5 years; this has been supported using strain typing.[6] Unlike many vaccines BCG primarily functions by preventing the development of active, symptomatic disease, this means that direct effects of BCG vaccination may not be immediate, and therefore may not be readily detectable. Additionally any indirect effect of vaccination, via reducing ongoing transmission, will also be difficult to attribute to vaccination. However, some measure of the direct effect of BCG vaccination may be estimated by comparing populations pre and post vaccination, or the converse. This means that the 2005 change in UK vaccination policy represents an opportunity to estimate the direct effect of BCG vaccination on both neonates and those at school age, in a low incidence setting.

This study uses data on notifications from the Enhanced Tuberculosis Surveillance (ETS) system combined with population estimates stratified by UK birth status and age from the Labour Force Survey (LFS) to estimate the incidence of tuberculosis in England and Wales. Retrospective cohorts of those eligible for each scheme are then created to estimate the direct effect of the change in vaccination programs within the first 5 years of vaccination. The impact of the policy change is then estimated using a series of hypothesis driven models increasing in complexity from a simple Poisson model to a multilevel model, with a random intercept. Model fit is then assessed, with models being ranked in order of goodness of fit. Inferences are then made as to the impact of the vaccination policy change, using the results from all models tested.

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**METHODS**

**Enhanced Tuberculosis Surveillance (ETS) system**

Data on all notifications from the Enhanced Tuberculosis Surveillance (ETS) system from Jan 1, 2000 to Dec 31, 2015 were obtained from Public Health England (PHE). The ETS is maintained by PHE, and collects demographic, clinical, and microbiological data on all notified cases in England and Wales, and is updated annually with de-notifications, late notifications and other updates. A descriptive analysis of tuberculosis epidemiology in England is published each year, which fully details data collection, cleaning, and trends in TB incidence at both a national, and sub-national level.[6]

**Labour Force Survey (LFS)**

We obtained yearly population estimates from the April to June Labour Force Survey (LFS) for 2000-2015, the LFS is a study of the employment circumstances of the UK population, and provides the official measures of employment and unemployment in the UK. Reporting practices have changed with time so the appropriate variables for age, country of origin, country of birth, and survey weight were extracted from each yearly extract, standardised, and combined into a single tidy dataset.**???** The LFS data was then aggregated, accounting for survey weight, by year, age, and UK birth status to provide yearly estimates of the UK born/Non-UK born populations by age. As the LFS is based on a population sample these estimates are subject to sampling errors.

**Retrospective cohorts**

We assigned a year of eligibility to all cases; for both the universal school age, and targeted neonatal vaccination programs using age, and year of notification, and stratifying by UK birth status. Eligibility was defined as the final year in which an individual could have been vaccinated under either scheme; under 1 for the targeted neonatal program, and at 14 for the school age vaccination program. We then restricted the eligible years considered to be between 2000-2010, to ensure that all cohorts had an equivalent follow up time, and then followed up each cohort for 5 years recording the number of cases and the population in each year. To allow comparison between those eligible prior to the BCG vaccination policy change and those eligible post policy change each cohort was flagged as either pre or post policy change using a binary variable (Policy change; Pre change/Post change).

The above steps created two retrospective cohorts of cases and crude controls, one for those eligible for the schools scheme (vaccination at 14 years old) and one eligible for the universal scheme (vaccination at birth); with the UK born as the population exposed to UK vaccination policy, and therefore eligible, and the Non-UK born cohorts acting as unexposed crude controls. The structure of each retrospective cohort is summarised in table 1.

**Table 1:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Cohort | Birth status | Study arm | Eligiblity criteria (age) | Eligible entry years | Years of follow up |
| Eligible for universal school age vaccination | UK born | Case | 14 | 2000-2010 | 5 |
|  | Non-UK born | Control | 14 | 2000-2010 | 5 |
| Eligible for targeted neonatal vaccination | UK born | Case | < 1 | 2000-2010 | 5 |
|  | Non-UK born | Control | < 1 | 2000-2010 | 5 |

**Confounding variables**

As each cohort is followed up starting from a different year of entry there is a strong likelihood of a time bias between cohorts, this potential for bias is strengthened further as the aim of this study is to compare incidence rates prior to 2005, and incidence rates post 2005. This confounding cannot be completely adjusted for as variation between years of eligibility, before, and after the policy change is the exposure that we are investigating. However it can be mitigated, by accounting for other known confounding, by using a model that includes a random intercept for each cohort, and assuming that any residual effect is associated with the change in vaccination policy. Additionally, evidence indicates that TB incidence varies with age[6]; as we have restricted entry to each cohort by age, years of follow up acts as a proxy for age and therefore should be adjusted for. Finally, as TB is an infectious disease cases are not independent of each other, and are instead due to contact between individuals. Incidence rates of TB vary with time, and when incidence is high individuals in our study populations may be at a higher risk of being infected. To account for this the number of cases, and population size of the background population should be adjusted for. TB is heterogeneously distributed across the population[6], and there is some evidence that case importation drives incidence rates, therefore incidence in the study population maybe associated with both the background rate in the UK born population, and in the non-UK born population. There may also be an additional interaction between the rate in the UK born population and in the Non-UK born population.

**Model definitions**

As model building can be subjective and because differences between models can be informative we considered a range of models, motivated by the possible confounding outlined above. The simplest model included in the analysis was a univariable analysis of the policy change; in a poisson framework. Additionally variables were then added to account for possible confounding. As the follow up for each cohort began in a different year models with a random intercept for year of entry were included, again with a range of model complexities. Finally evidence of over-dispersion was tested for by using comparable negative binomial models for both the most complex fixed and random effect models. Table 2 outlines the details of each model included in the analysis.

**Table 2:** Model definitions, specifying if the adjustment has a fixed or random effect. The models are ordered by complexity.

|  |  |
| --- | --- |
| Model | Description |
| Model 1 | Poisson framework; Adjusting with fixed effects for policy change. |
| Model 2 | Poisson framework; Adjusting with fixed effects for policy change, and years of follow up. |
| Model 3 | Poisson framework; Adjusting with fixed effects for policy change, years of follow up, background cases, and background population. |
| Model 4 | Poisson framework; Adjusting with fixed effects for policy change, years of follow up, background cases, and background population with background cases:population as interaction terms. |
| Model 5 | Poisson framework; Adjusting with fixed effects for policy change, years of follow up, UK born-UK born cases, and UK born-UK born populations. |
| Model 6 | Poisson framework; Adjusting with fixed effects for policy change, years of follow up, UK born-UK born cases, and UK born-UK born populations with UK born cases:population, and non-UK born cases:population as interaction terms. |
| Model 7 | Poisson framework; Adjusting with fixed effects for policy change, years of follow up, UK born-UK born cases, and UK born-UK born populations with UK born cases:population, non-UK born cases:population, and UK born incidence:non-UK born incidence as interaction terms. |
| Model 8 | Negative binomial framework; Adjusting with fixed effects for policy change, years of follow up, UK born-UK born cases, and UK born-UK born populations with UK born cases:population, non-UK born cases:population, and UK born incidence:non-UK born incidence as interaction terms. |
| Model 9 | Poisson framework; Random intercept for year of entry, adjusting with fixed effects for policy change. |
| Model 10 | Poisson framework; Random intercept for year of entry, adjusting with fixed effects for policy change, and years of follow up. |
| Model 11 | Poisson framework; Random intercept for year of entry, adjusting with fixed effects for policy change, years of follow up, background cases, and background population. |
| Model 12 | Poisson framework; Random intercept for year of entry, adjusting with fixed effects for policy change, years of follow up, background cases, and background population with background cases:population as interaction terms. |
| Model 13 | Poisson framework; Random intercept for year of entry, adjusting with fixed effects for policy change, years of follow up, UK born-UK born cases, and UK born-UK born populations. |
| Model 14 | Poisson framework; Random intercept for year of entry, adjusting with fixed effects for policy change, years of follow up, UK born-UK born cases, and UK born-UK born populations with UK born cases:population, and non-UK born cases:population as interaction terms. |
| Model 15 | Poisson framework; Random intercept for year of entry, adjusting with fixed effects for policy change, years of follow up, UK born-UK born cases, and UK born-UK born populations with UK born cases:population, non-UK born cases:population, and UK born incidence:non-UK born incidence as interaction terms. |
| Model 16 | Negative binomial framework; Random intercept for year of entry, adjusting with fixed effects for policy change, years of follow up, UK born-UK born cases, and UK born-UK born populations with UK born cases:population, non-UK born cases:population, and UK born incidence:non-UK born incidence as interaction terms. |

**Model assumptions**

In order to model the estimated effect of the vaccination policy change, we have made several simplifying assumptions. Firstly we have assumed that the incidence of TB in the UK born and non-UK born adequately represents the exposure to TB for the study population, this assumes that contact rates between age groups have not changed during the course of the study, and that heterogeneities in contact rates, given changing age specific incidence, do not bias the results. We have also assumed that there were no systematic changes in vaccination for the non-UK born population, that were comparable to those seen in the UK born population. Additionally, unmeasured confounding variables may cause bias as in any observational study, however this is mitigated as it unlikely that these variables have changed systematically over time, and in accounting for multiple years of eligibility we are adjusting for random variation. Due to the complexity of the targeted neonatal vaccination program no data is available on the number of individuals eligible under this scheme in each year, therefore we have made the simplifying assumption that the entire population of neonates was eligible for vaccination. Finally, we have assumed that the retrospective cohorts pre and post policy changes are comparable, and that after adjustment for confounding any residual differences between cohorts are due to the effect of changing vaccination policy. This assumption limits the amount of within year of eligibility confounding that can be accounted for, as each year of eligibility can only have data on either vaccination pre policy change or vaccination post policy change.

**Statistical methods**

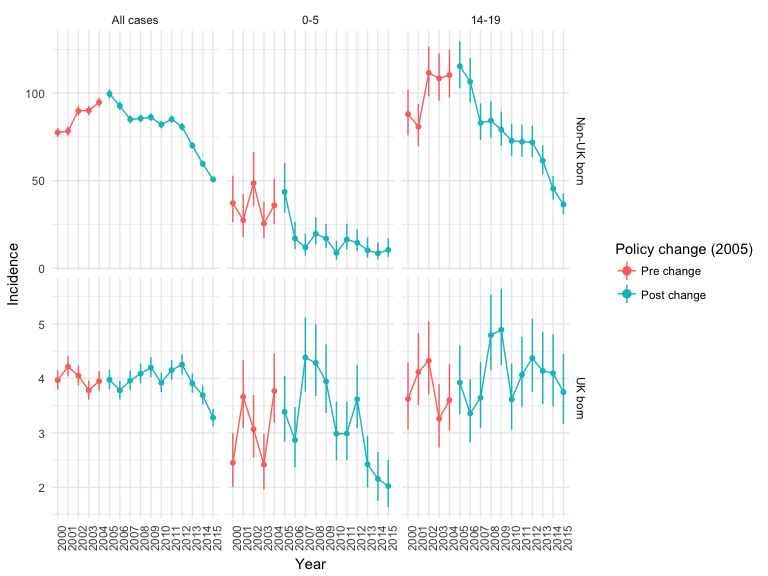
We estimated incidence rates (with 95% confidence intervals) stratified by UK birth status, year of eligibility to either scheme, and years of follow up using estimates of TB notifications from the ETS, and population estimates from the LFS, with the epiR package.[7]. The brms package, with default weakly informative priors, was used to perform MCMC fitting using STAN for all models.[8,9] Models were run until convergence (4 chains with a burn in of 50,000, and 50,000 sampled iterations each), with convergence being assessed using trace plots and the R hat diagnostic.[9] Model fit was assessed using the leave one out cross validation information criterion (LOOIC).[10] Models were then ranked by LOOIC, with the best fitting models presented in full. All numeric confounders were centred and scaled by their standard deviation, therefore their coefficients can be interpreted as the change per standard deviation. As there is little justification for assuming a linear association between years of follow up and incidence, each follow up year has been adjusted for independently.

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**RESULTS**

Between Jan 1, 2000 and Dec 31, 2015 there were 117436 notifications of TB in England and Wales, of which 93% (109067/117436) had their birth status recorded. Of those with a known birth status 28% (30286/109067) were UK born, and of these 1659 cases were eligible for the universal schools scheme, and 1380 were eligible for the targeted neonatal scheme during the study period. For those eligible for the universal schools scheme between 2000 and the end of the scheme in 2005 the incidence of TB was 3.71 (95% CI 3.45, to 3.99), with incidence increasing after the ending of the scheme to 4.16 (95% CI 3.90, to 4.43). Prior to the introduction of the targeted neonatal vaccination program, the incidence rate of TB was 3.32 (95% CI 3.06, to 3.60), compared to 3.31 (95% CI 3.09, to 3.55) after the introduction the scheme.

* discuss trends in incidence for UK born 14-19 year olds and 0-5 year olds and how this compares to general incidence



**Figure 1:** Incidence rates for non-UK born/UK born population, those aged 0-5 and therefore directly effected by the targeted neonatal vaccination program, and those aged 14-19 and therefore directly effected by the universal school age scheme.

**UK born cohort eligible for universal school age vaccination**

In the UK born cohort eligible for universal vaccination, across all models fitted, there was evidence that ending the scheme was associated with an increase in TB rates (table 3). Across all models, the effect size of the change in policy increased as confounding variables were adjusted for, although the width of the credible intervals also increased. In the univariable model (Model 1), the ending of the scheme was associated with an increased incidence rate of TB (0.11 (0.03, to 0.20)). Whilst in Model 15, which included adjustment for all hypothesised confounding, there was reduced evidence of an association but the estimated increase in incidence rates was larger (0.14 (-0.09, to 0.37)).

The LOOIC goodness of fit metric suggested that models that did not adjust for years of follow up fitted the data best, with all other models having a comparable fit to the data. Adjusting for the incidence rate in the general UK born population increased the magnitude of the effect size across all models compared to models that did not adjust for this confounding. Negative binomial models (Models 8 and 16) estimated comparable effect sizes, with increased credible intervals, but there was no clear evidence that they provided a significantly improved fit to the data when compared to Poisson models.

For the non-UK born cohorts there was little evidence of an effect of the policy change in all models that adjusted for incidence rate in the general non-UK born population, however in models that did not adjust for this there was some evidence that the policy change was associated with reduced incidence rates (supplementary table S1. There was little evidence that the estimated effects of the policy change in the non-UK born cohorts were comparable to those in the UK born cohorts.

**Table 3:** Comparision of models fitted to incidence rates for the UK born population that was eligible for the universal vaccination program of those at school age (14). Models are ordered by the goodness of fit as assessed by LOOIC.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Effect (CI 95%) | Years of follow up | Years of eligibility | UK born rates | Non-UK born rates | Degrees of freedom | LOOIC (se) |
| Model 9 | 0.12 (0.00, to 0.23) | No | Yes | No | No | 14 | -260 (16) |
| Model 1 | 0.11 (0.03, to 0.20) | No | No | No | No | 2 | -256 (5.18) |
| Model 10 | 0.11 (0.00, to 0.23) | Yes | Yes | No | No | 19 | -223 (16) |
| Model 2 | 0.11 (0.03, to 0.20) | Yes | No | No | No | 7 | -222 (10.6) |
| Model 15 | 0.14 (-0.09, to 0.37) | Yes | Yes | Yes | Yes | 26 | -219 (19.1) |
| Model 16 | 0.14 (-0.12, to 0.38) | Yes | Yes | Yes | Yes | 27 | -218 (14.5) |
| Model 13 | 0.15 (-0.08, to 0.38) | Yes | Yes | Yes | Yes | 23 | -218 (17) |
| Model 7 | 0.15 (-0.01, to 0.32) | Yes | No | Yes | Yes | 14 | -218 (15.5) |
| Model 8 | 0.14 (-0.07, to 0.34) | Yes | No | Yes | Yes | 15 | -218 (12.2) |
| Model 14 | 0.14 (-0.09, to 0.36) | Yes | Yes | Yes | Yes | 25 | -217 (17.8) |
| Model 5 | 0.14 (-0.03, to 0.31) | Yes | No | Yes | Yes | 11 | -217 (13.3) |
| Model 11 | 0.15 (0.00, to 0.30) | Yes | Yes | Yes | No | 21 | -217 (15.1) |
| Model 6 | 0.15 (-0.02, to 0.32) | Yes | No | Yes | Yes | 13 | -216 (14.3) |
| Model 3 | 0.15 (0.03, to 0.27) | Yes | No | Yes | No | 9 | -216 (11.4) |
| Model 12 | 0.13 (-0.01, to 0.28) | Yes | Yes | Yes | No | 22 | -216 (15.1) |
| Model 4 | 0.13 (0.01, to 0.25) | Yes | No | Yes | No | 10 | -214 (11.7) |

**UK born cohort eligible for targeted neonatal vaccination**

In the UK born cohort eligible for targeted vaccination the evidence for, and direction of, an effect of the vaccination policy was variable across the models assessed (table 4). For the univariable model (Model 1), there was little evidence that the introduction of targeted neonatal vaccination was associated with any change in incidence rates for the directly effected population (0.00 (-0.09, to 0.09)). However, after adjusting for all hypothesised confounding (Model 15), there was some evidence to suggest that the introduction of the policy was associated with reduced incidence rates (-0.17 (-0.40, to 0.06)).

As for the cohort eligible for universal vaccination, the LOOIC goodness of fit metric suggested that models that did not adjust for years of follow up fitted the data best, that models that did not adjust for population incidence rates fitted better than those that did, and that all other models had a comparable fit. For models that did not adjust for population incidence rates there was little evidence of any association between incidence rates and the introduction of the neonatal vaccination program. When only the incidence rates in the general UK born population were adjusted for there was some evidence that the introduction of the policy was associated with an increase in incidence rates. However, for models that also adjusted for the incidence rates in the non-UK born population, the direction of the effect was reversed and there was some evidence that the introduction of the policy was associated with a reduction of incidence rates in the directly effected population. Negative binomial models (Models 8 and 16) estimated comparable effect sizes, with increased credible intervals, but there was no clear evidence that they provided a significantly improved fit to the data when compared to Poisson models.

For the non-UK born cohorts, there was some evidence that the introduction of the neonatal vaccination campaign was associated with a decrease in incidence rates across all models assessed. After adjusting for both incidence rates in the UK born, and non-UK born population there remained some evidence that the change in policy decreased incidence rates in non-UK born neonates with a greater effect size than in the UK born population, although the credible intervals were large (supplementary table S1. Whilst there was some evidence that the effect of the policy change was comparable in the UK born and non-UK born populations, the large degree of uncertainty in the effect size estimates for the non-UK born cohorts makes drawing inferences difficult.

**Table 4:** Comparision of models fitted to incidence rates for the UK born population that was eligible for the targeted vaccination program of neonates. Models are ordered by the goodness of fit as assessed by LOOIC.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Effect (CI 95%) | Years of follow up | Years of eligibility | UK born rates | Non-UK born rates | Degrees of freedom | LOOIC (se) |
| Model 1 | 0.00 (-0.09, to 0.09) | No | No | No | No | 2 | -242 (4.93) |
| Model 9 | 0.01 (-0.17, to 0.19) | No | Yes | No | No | 14 | -242 (19.2) |
| Model 2 | 0.00 (-0.09, to 0.09) | Yes | No | No | No | 7 | -223 (11.9) |
| Model 10 | 0.01 (-0.17, to 0.18) | Yes | Yes | No | No | 19 | -220 (20) |
| Model 4 | 0.12 (-0.01, to 0.25) | Yes | No | Yes | No | 10 | -210 (12.3) |
| Model 3 | 0.12 (0.00, to 0.25) | Yes | No | Yes | No | 9 | -209 (11.3) |
| Model 13 | -0.15 (-0.40, to 0.14) | Yes | Yes | Yes | Yes | 23 | -203 (14.2) |
| Model 12 | 0.18 (-0.05, to 0.44) | Yes | Yes | Yes | No | 22 | -203 (15.9) |
| Model 11 | 0.19 (-0.04, to 0.45) | Yes | Yes | Yes | No | 21 | -202 (15.4) |
| Model 5 | -0.19 (-0.37, to 0.00) | Yes | No | Yes | Yes | 11 | -202 (11.1) |
| Model 16 | -0.17 (-0.42, to 0.08) | Yes | Yes | Yes | Yes | 27 | -201 (12.3) |
| Model 8 | -0.18 (-0.38, to 0.03) | Yes | No | Yes | Yes | 15 | -201 (11) |
| Model 15 | -0.17 (-0.40, to 0.06) | Yes | Yes | Yes | Yes | 26 | -200 (14.8) |
| Model 7 | -0.18 (-0.37, to 0.00) | Yes | No | Yes | Yes | 14 | -199 (12.8) |
| Model 14 | -0.16 (-0.39, to 0.07) | Yes | Yes | Yes | Yes | 25 | -199 (13.4) |
| Model 6 | -0.17 (-0.36, to 0.00) | Yes | No | Yes | Yes | 13 | -198 (11.4) |

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**DISCUSSION**

**Summary**

**Strengths and Weaknesses**

**Meaning of the study**

**Extensions and possible further work**

**Acknowledgements**

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**Conflicts of interest**

* statements needed

**Accessibility of data and programming code**

The code, and interim results, for this analysis can be found at: *link not yet available*

**Results:** *copy to top of paper*

Of the 30286 UK born TB cases in England, and Wales between 2000, and 2015, 1659 cases were eligible for the universal schools scheme, and 1380 were eligible for the targeted neonatal scheme between 2000, and 2010. We found that across all models investigated there was evidence that ending the schools scheme was associated with an increase in incidence rates. We found that the ending of the scheme was associated with an increase in incidence of 0.11 (0.03, to 0.20) in the univariable model, and of 0.14 (-0.09, to 0.37) in the fully adjusted model. We found more variable evidence for an association between the high risk neonatal program and reduced incidence, with only models that included non-UK born incidence rates estimating a reduction in incidence. In the univariable model there was little evidence of an association (0.00 (-0.09, to 0.09)). However, in the fully adjusted model there was evidence that the introduction of the scheme was associated with a reduction in incidence of -0.17 (-0.40, to 0.06). In the non-UK born cohorts we found little evidence that the ending of the school scheme was associated with incidence rates, but there was some evidence that introduction of the targeted high risk program reduced incidence in the eligible population.

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**REFERENCES**

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## Online supplementary appendix: Estimating the effect of the 2005 UK BCG vaccination policy change: A retrospective cohort study using the Enhanced Tuberculosis Surveillance system, 2000-2015

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**Non-UK born model comparision**

**Supplementary table S1:** Comparision of models fitted to incidence rates for the Non-UK born population that was eligible for the universal vaccination program of those at school age (14). Models are ordered by the goodness of fit as assessed by WAIC.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Effect (CI 95%) | Years of follow up | Years of eligibility | UK born rates | Non-UK born rates | Degrees of freedom | LOOIC (se) |
| Model 1 | 0.00 (-0.09, to 0.09) | No | No | No | No | 2 | -242 (4.93) |
| Model 9 | 0.01 (-0.17, to 0.19) | No | Yes | No | No | 14 | -242 (19.2) |
| Model 2 | 0.00 (-0.09, to 0.09) | Yes | No | No | No | 7 | -223 (11.9) |
| Model 10 | 0.01 (-0.17, to 0.18) | Yes | Yes | No | No | 19 | -220 (20) |
| Model 4 | 0.12 (-0.01, to 0.25) | Yes | No | Yes | No | 10 | -210 (12.3) |
| Model 3 | 0.12 (0.00, to 0.25) | Yes | No | Yes | No | 9 | -209 (11.3) |
| Model 13 | -0.15 (-0.40, to 0.14) | Yes | Yes | Yes | Yes | 23 | -203 (14.2) |
| Model 12 | 0.18 (-0.05, to 0.44) | Yes | Yes | Yes | No | 22 | -203 (15.9) |
| Model 11 | 0.19 (-0.04, to 0.45) | Yes | Yes | Yes | No | 21 | -202 (15.4) |
| Model 5 | -0.19 (-0.37, to 0.00) | Yes | No | Yes | Yes | 11 | -202 (11.1) |
| Model 16 | -0.17 (-0.42, to 0.08) | Yes | Yes | Yes | Yes | 27 | -201 (12.3) |
| Model 8 | -0.18 (-0.38, to 0.03) | Yes | No | Yes | Yes | 15 | -201 (11) |
| Model 15 | -0.17 (-0.40, to 0.06) | Yes | Yes | Yes | Yes | 26 | -200 (14.8) |
| Model 7 | -0.18 (-0.37, to 0.00) | Yes | No | Yes | Yes | 14 | -199 (12.8) |
| Model 14 | -0.16 (-0.39, to 0.07) | Yes | Yes | Yes | Yes | 25 | -199 (13.4) |
| Model 6 | -0.17 (-0.36, to 0.00) | Yes | No | Yes | Yes | 13 | -198 (11.4) |

**Supplementary table S2:** Comparision of models fitted to incidence rates for the Non-UK born population that was eligible for the targeted vaccination program of neonates. Models are ordered by the goodness of fit as assessed by WAIC.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Effect (CI 95%) | Years of follow up | Years of eligibility | UK born rates | Non-UK born rates | Degrees of freedom | LOOIC (se) |
| Model 9 | -0.75 (-1.03, to -0.47) | No | Yes | No | No | 14 | -164 (9.66) |
| Model 1 | -0.75 (-0.96, to -0.54) | No | No | No | No | 2 | -162 (3.52) |
| Model 15 | -0.34 (-0.87, to 0.18) | Yes | Yes | Yes | Yes | 26 | -153 (20.3) |
| Model 14 | -0.34 (-0.87, to 0.18) | Yes | Yes | Yes | Yes | 25 | -153 (18.8) |
| Model 16 | -0.33 (-0.93, to 0.29) | Yes | Yes | Yes | Yes | 27 | -152 (17) |
| Model 12 | -0.28 (-0.81, to 0.24) | Yes | Yes | No | Yes | 22 | -152 (15.3) |
| Model 10 | -0.80 (-1.08, to -0.52) | Yes | Yes | No | No | 19 | -152 (13.8) |
| Model 7 | -0.34 (-0.79, to 0.12) | Yes | No | Yes | Yes | 14 | -151 (17.7) |
| Model 13 | -0.35 (-0.87, to 0.19) | Yes | Yes | Yes | Yes | 23 | -151 (16.2) |
| Model 6 | -0.34 (-0.79, to 0.11) | Yes | No | Yes | Yes | 13 | -151 (16.1) |
| Model 8 | -0.32 (-0.84, to 0.21) | Yes | No | Yes | Yes | 15 | -151 (15.3) |
| Model 11 | -0.25 (-0.76, to 0.26) | Yes | Yes | No | Yes | 21 | -150 (13.8) |
| Model 2 | -0.80 (-1.01, to -0.59) | Yes | No | No | No | 7 | -150 (9.41) |
| Model 4 | -0.29 (-0.72, to 0.15) | Yes | No | No | Yes | 10 | -150 (12.5) |
| Model 5 | -0.35 (-0.80, to 0.10) | Yes | No | Yes | Yes | 11 | -149 (13.5) |
| Model 3 | -0.24 (-0.67, to 0.19) | Yes | No | No | Yes | 9 | -149 (10.8) |

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