

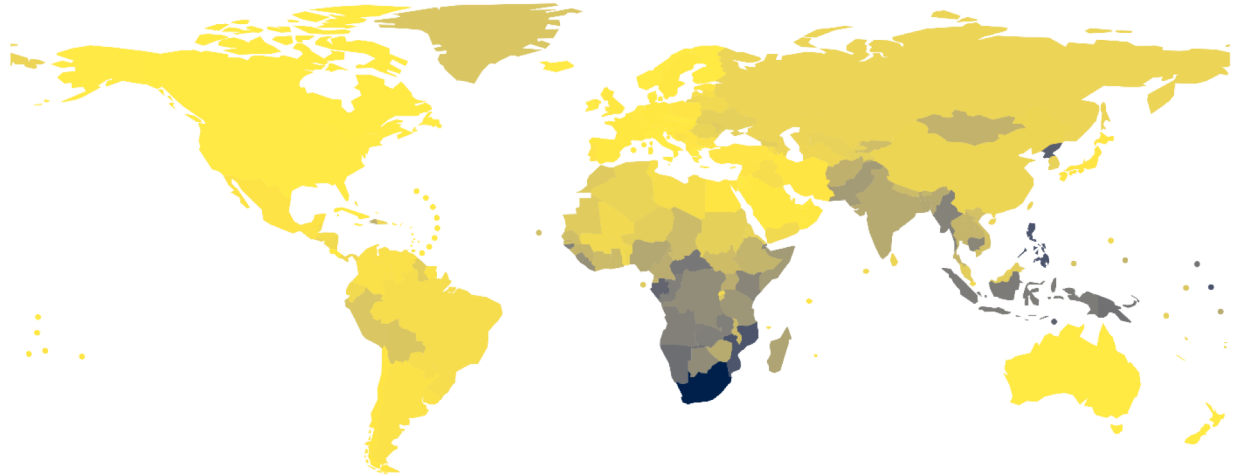
Estimating the effect of the 2005 UK BCG vaccination policy change: A retrospective cohort study using the Enhanced Tuberculosis Surveillance system, 2000-2015

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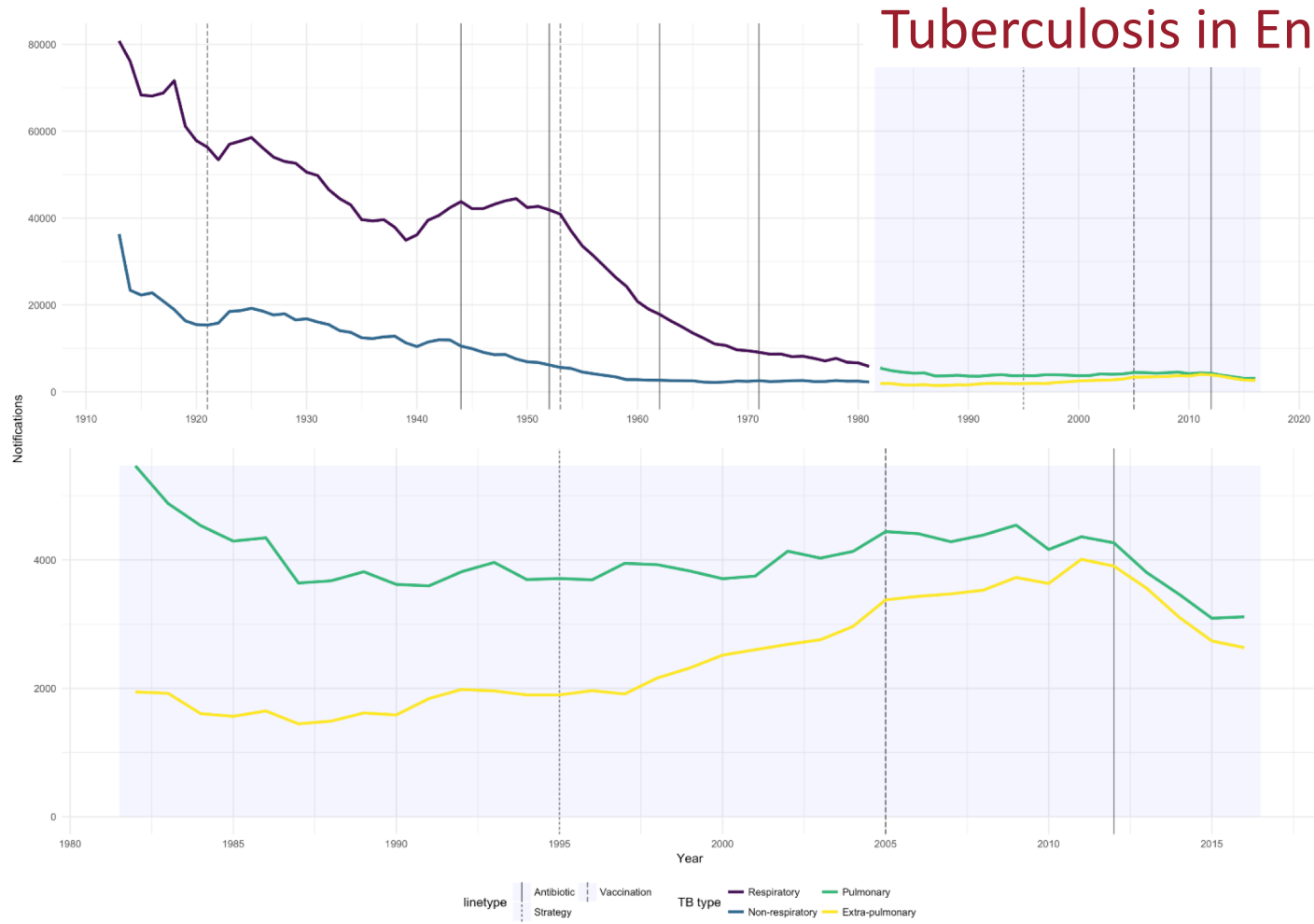
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Tuberculosis (TB) globally

- 10.4 million people fell ill with TB, and 1.7 million died from the disease in 2016 alone.
- Globally Tuberculosis is the second most common cause of death from infectious disease, after HIV.
- Respiratory disease
- Two latent stages, an initial period of high activation risk, followed by a longer period of low activation risk
- Risk of developing disease, likelihood of onwards transmission etc. are age dependent.



Tuberculosis Incidence by Type in England and Wales
From 1913 to 2016



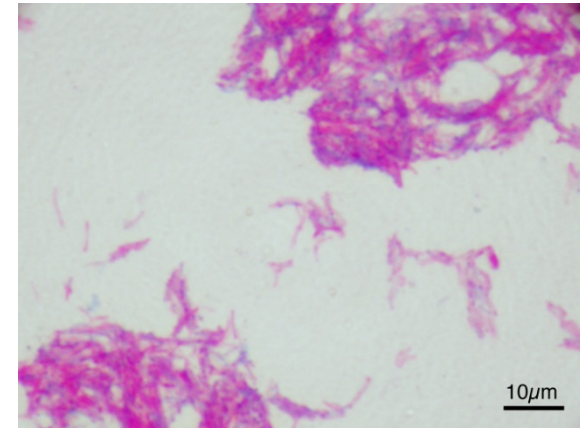
Shaded area shows incidence from 1984 to 2016. Source: Public Health England/Wikipedia

Bacillus Calmette–Guérin (BCG) vaccine:

- In use since 1921, with roughly **260 million** doses ordered a year
- Variable efficacy: (**0-80%**) In the UK estimated at **>75%** [1]
- Highly protective against TB and TB meningitis in children [2]
- Protection thought to wane with time – 15-20 years

Vaccination policy:

- **Universal** vaccination introduced in 1953, via schools scheme
- Switched to **targeted** vaccination of infants in high risk groups in 2005



Microscopic image of the Calmette-Guérin bacillus

Motivation

- The long term impacts of the 2005 change in vaccination policy have not been estimated.
- In order to understand the current epidemiology of TB in England it is important to understand the role of BCG vaccination.
- Evaluating previous vaccination policy decisions will help future decision making.

Aim: To estimate the direct effect on the eligible populations of the change in BCG vaccination policy from universal school-age vaccination to targeted vaccination of neonates.

Data Sources

Enhanced Tuberculosis Surveillance (ETS) system :

- Data on all notifications from the Enhanced Tuberculosis Surveillance (ETS) system from Jan 1, 2000 to Dec 31, 2015.
- The ETS is maintained by PHE, and collects demographic, clinical, and microbiological data on all notified cases in England, and is updated annually.

Labour Force Survey (LFS):

- Population estimates from the April to June (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.
 - The survey data was used to provide estimates of the population in England, stratified by UK birth status and age.
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Estimating TB incidence rates

- Estimated incidence rates (with 95% confidence intervals) stratified by UK birth status, age, and year of notification, with the epiR package.
- Then used descriptive analysis to describe the observed trends in age-specific incidence rates over the study period.
- Specifically, we compared incidence rates pre and post the change in BCG vaccination policy.

Retrospective cohorts

Cohort	Vaccination programme eligible for	Covered by programme	Birth status	Age at study entry	Year of study entry
UCUK14	Universal	Yes	UK born	14	2000-2004
UNCUK14	Universal	No	UK born	14	2005-2010
TCUKBirth	Targeted	No	UK born	Birth	2000-2004
TNCUKBirth	Targeted	Yes	UK born	Birth	2005-2010
UCNUK14	Universal	Yes	Non-UK born	14	2000-2004
UNCNUK14	Universal	No	Non-UK born	14	2005-2010
TCNUKBirth	Targeted	No	Non-UK born	Birth	2000-2004
TNCNUKBirth	Targeted	Yes	Non-UK born	Birth	2005-2010

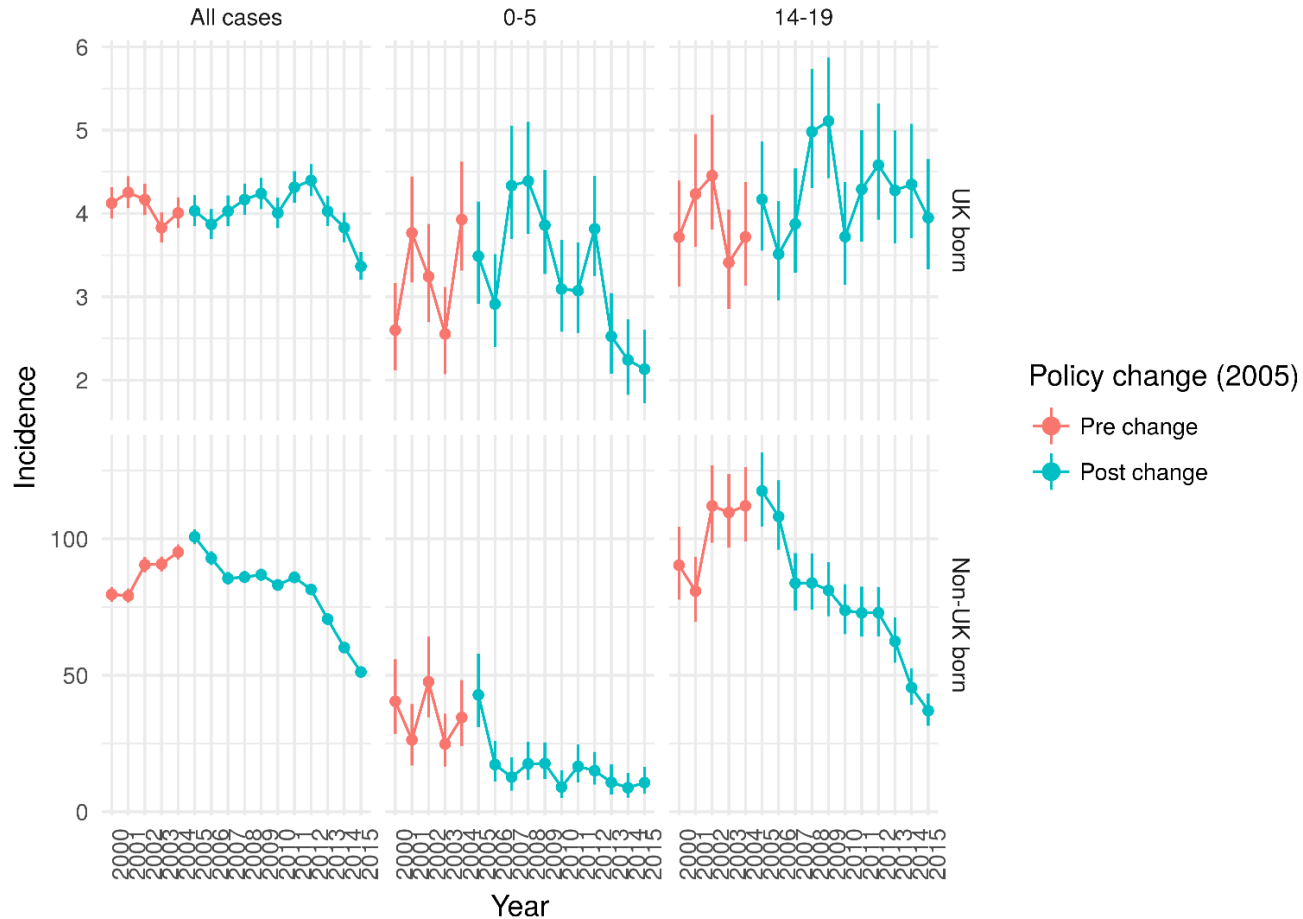
Model construction

- Considered a range of models, starting from a univariable Poisson model and adding complexity in a stepwise fashion.
- We considered:
 - The year of the policy change (2005).
 - Age.
 - UK born incidence rates.
 - Non-UK born incidence rates.
 - An interaction between UK born and non-UK born incidence rates.
 - Year of study entry (as a random effect).
- Two negative binomial models (which included all hypothesised confounders) were also evaluated.

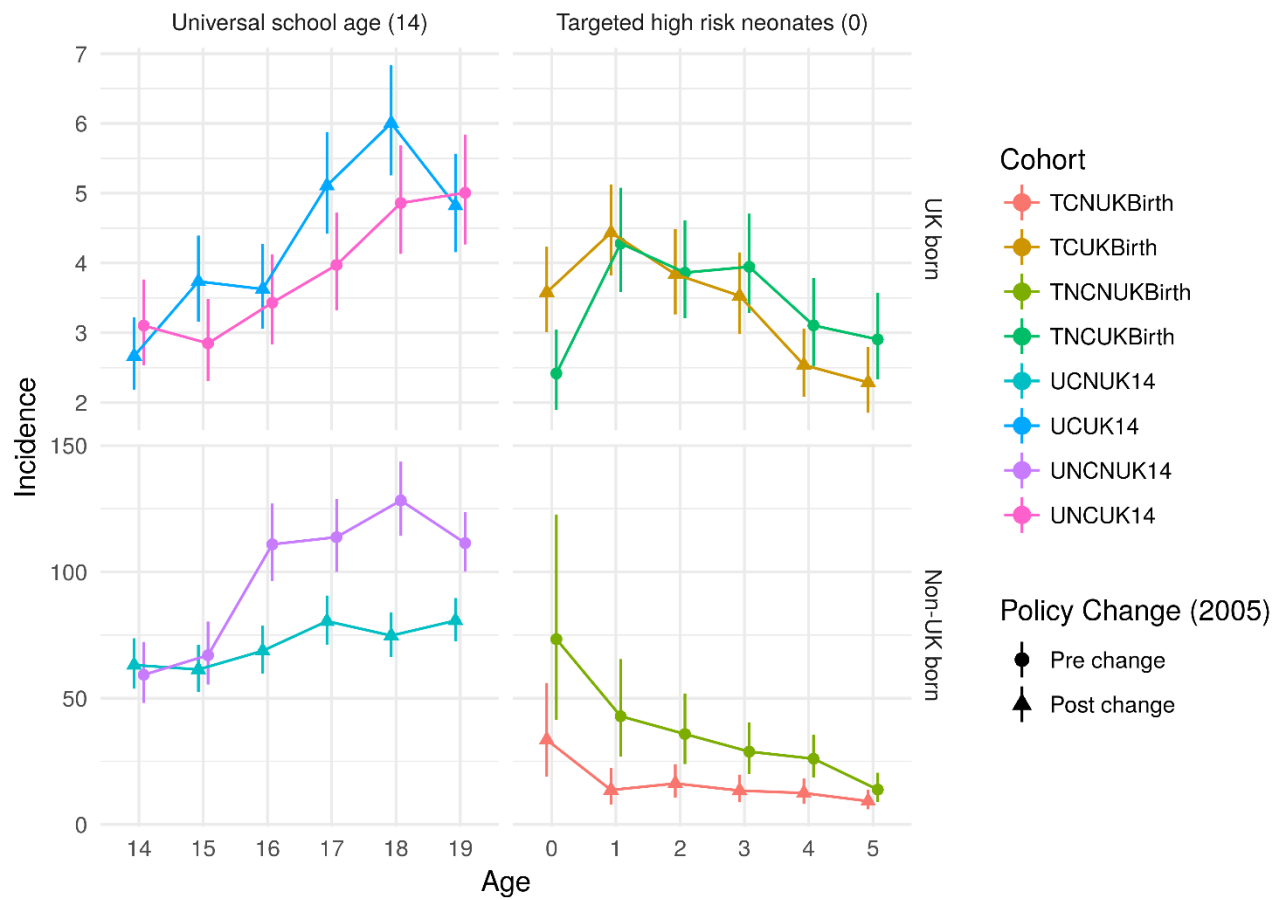
Model fitting and selection

- Models fit using MCMC with brms and stan
- 4 chains with a burn in of 25,000 and 25,000 sampled iterations
- Convergence assessed using trace plots and the R hat diagnostic.
- Models were then ranked by goodness of fit, assessed using the leave one out cross validation information criteria.
- Tiebreaks were resolved using the model degrees of freedom (with parsimonious models preferred).

Descriptive analysis of incidence rates



Incidence rates in the retrospective cohorts



Direct effects of ending the universal school-age programme

UK born:

- The best fitting model was a Poisson model.
- The model was adjusted with fixed effects for the change in policy, age, and incidence rates in the UK born population.
- There was some evidence that incidence rates increased after the change in policy with an Incidence Rate Ratio (IRR) of 1.07 - (95% CI: 0.98 to 1.16)

Non-UK born:

- The best fitting model was a Negative binomial model.
 - The model was adjusted with fixed effects for the change in policy, age, incidence rates in the UK born and non-UK born populations with incidence rates in the UK born and non-UK born populations as interaction terms.
- There was some evidence that incidence rates decreased after the change in policy with an IRR of 0.90 (95% CI: 0.79 to 1.01) .

Direct effects of introducing the targeted neonatal high risk program

UK born:

- The best fitting model was a Poisson model.
- The model had a random intercept for year of study entry, and was adjusted with fixed effects for the change in policy, age, and incidence rates in the UK born.
- There was weak evidence that incidence rates decreased after the change in policy with an Incidence Rate Ratio (IRR) of 0.92 (95% CI 0.78 to 1.10)

Non-UK born:

- The best fitting model was a Poisson model.
- The model was adjusted with fixed effects for the change in policy, age, and incidence rates in the non-UK born population.
- There was strong evidence that incidence rates decreased after the change in policy with an IRR of 0.59 (95% CI: 0.45 to 0.78) .

Discussion

- We found some evidence that the ending of the BCG schools scheme was associated with a small increase in incidence rates in the UK born at school-age. We also found a comparable decrease in incidence rates in the non-UK born at school-age.
 - We found weak evidence that the introduction of the targeted neonatal vaccination programme was associated with a small decrease in incidence rates in UK born neonates. However, we found strong evidence of a large decrease in incidence rates in non-UK born neonatal incidence rates.
 - We could not investigate the indirect effects of onwards transmission, as this would require a dynamic transmission disease model. Therefore we may have not captured the full effects of the change in vaccination policy.
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Tools:

- **getTBinR**: R package for accessing and visualising the WHO TB database (www.samabbott.co.uk/getTBinR)
 - **Explore Global TB**: Web app for exploring global TB (<http://seabbs.co.uk/shiny/ExploreGlobalTB/>).
 - **TB in England and Wales**: Web app for exploring TB in England and Wales (http://seabbs.co.uk/shiny/TB_England_Wales/).
 - **The Pebble Game**: Web app for understanding herd immunity (<http://www.seabbs.co.uk/shiny/thepebblegame/>)
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