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**

The Bacillus Calmette–Guérin (BCG) vaccine is the mostly widely used vaccine globally, however its efficacy remains contentious. In 2005, England changed from universal vaccination of school-age children to targeted vaccination of high-risk children at birth, identified by local Tuberculosis (TB) incidence and by the parents’ country of origin. The impact of this policy change has not been evaluated.

**Methods**

We combined notification data from the Enhanced Surveillance system, with demographic data from the Labour Force Survey to construct retrospective cohorts of individuals in England eligible for both the universal, and targeted vaccination programmes between Jan 1, 2000 and Dec 31, 2010. For each cohort, we estimated the incidence over a 5 year period and used Poisson and Negative Binomial regression models in order to estimate the impact of the change in policy on TB burden in England.

**Results:**

We found consistent evidence that ending universal vaccination was associated with a 7% (95% CI -2% to 16%) increase in incidence rates in the UK born school-age population eligible for the programme. We found more variable evidence for an association between the high risk neonatal programme and small reduction in incidence rates of 8% (95% CI -10% to 22%) in UK born neonates eligible for the programme. For both those at school-age and neonates, who were non-UK born, we found consistent evidence for an association between a reduction in incidence rates and the the change in vaccination policy (School-age: 15% (95% CI 3% to 25%), Neonates: 41% (95% CI 22% to 55%)).

**Conclusions:**

The introduction of the targeted BCG vaccination programme and withdrawal of universal vaccination was associated with increased incidence rates in the UK born at school age, and decreased incidence rates in the non-UK born, both in neonates and for those of school-age. Understanding the trade-offs inherent to vaccination targeting could inform future decision-making.

**Keywords:**

BCG, surveillance, vaccination policy, neonatal

**What is the key question?**

What was the effect of changing from universal school age BCG vaccination to high risk neonatal BCG vaccination on incidence rates in the populations directly affected by the vaccination programmes.

**What is the bottom line?**

There was evidence that the change in policy was associated with an increase in incidence rates in those eligible for the universal school age scheme, with little evidence of a decrease in incidence rates in those eligible for the high risk neonatal vaccination scheme, and strong evidence of large decreases in incidence rates in non-UK born neonates and those at school-age.

**Why read on?**

These results provide an important evaluation of the direct effects of both withdrawing, and implementing a BCG vaccination programme in a low incidence country, whilst also enabling a more accurate estimate of TB transmission to be made in England.

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**INTRODUCTION**

In 2005, England changed its Bacillus Calmette–Guérin (BCG) vaccination policy in 2005 from a universal school age programme to vaccination at birth for high risk neonates, due to evidence of reduced tuberculosis (TB) transmission,[1–3] and evidence of high effectiveness in children,[4–6] compared to evidence of variable effectiveness in adults.[7] Little work has been done to evaluate the impact of this change in vaccination policy.

The number of notifications of TB in England increased from 6044 in 2000 to 8280 in 2011 but have since declined.[1] Trends in TB incidence may not be directly linked to transmission as after an initial infection an individual may either develop active disease, or enter a latent stage which then may later develop into active disease. Incidence in young children (0-14 years old) is a proxy of TB transmission, as any active TB disease in this population is attributable to recent 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.[1] However, this conclusion does not take account of the change in BCG vaccination policy and therefore may be an overestimate of the reduction in TB transmission, as high risk young children are now more likely to be less susceptible to active TB disease due to BCG vaccination.

Although the long term effects of BCG vaccination such as reducing the reactivation of latent cases and decreasing onwards transmission are not readily detectable over short time scales the direct effects of vaccination on incidence rates can be estimated in vaccinated populations, when compared to comparable unvaccinated populations.[8] We aimed to estimate the impact of ending the BCG schools scheme on incidence rates in those at school-age who were UK born and who were non-UK born, by comparing comparable populations before and after the change in vaccination policy. Using a similar approach, we also aimed to estimate the impact of the targeted neonatal vaccination programme on population level incidence rates in both UK born neonates and non-UK born neonates. We made use of routinely collected surveillance data and Bayesian model selection methods to estimate the impact of the BCG policy change, these estimates may be used to inform future decision making and provide context to observed changes in TB incidence rates.

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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 is updated annually. 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.[1]

**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 data-set. The LFS data was then aggregated 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.

**Estimating age-specific incidence rates**

We estimated incidence rates (with 95% confidence intervals) stratified by UK birth status, age, and year of notification, with the epiR package.[9] We then used a 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**

Cases were identified as being eligible for either the universal programme or the targeted programme, between 2000 and 2010, based on date of birth and date of TB notification. For the universal programme we defined eligibility as being aged 14 between 2000-2010, and having been notified whilst aged 14-19 years old. Similarly, for the targeted programme we defined eligibility as being born between 2000-2010, and having been notified whilst aged 0-10 years old. Cases that were eligible for the universal programme were defined to be covered by it if they were aged 14 between 2000-2004, and otherwise were defined to have not been covered. Similarly, cases that were eligible for the targeted programme were defined to be covered by it if they had been born between 2005-2010, and were defined to be not covered if they had been born prior to this. Cases were then stratified by UK birth status, with non-UK born cases assumed to have not been exposed to England’s BCG vaccination policy, and UK born cases assumed to have exposed if eligible and covered by the relevant programme. This gave comparable non-UK born and UK born cohorts. The LFS population estimates were similarly classified; resulting in 8 population level cohorts, each with 5 years of follow up (table 1).

Table 1: Summary of eligibility criteria for each cohort.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 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 |
| UCNUK14 | Universal | Yes | Non-UK born | 14 | 2000-2004 |
| UNCNUK14 | Universal | No | Non-UK born | 14 | 2005-2010 |
| TCUKBirth | Targeted | No | UK born | Birth | 2000-2004 |
| TNCUKBirth | Targeted | Yes | UK born | Birth | 2005-2010 |
| TCNUKBirth | Targeted | No | Non-UK born | Birth | 2000-2004 |
| TNCNUKBirth | Targeted | Yes | Non-UK born | Birth | 2005-2010 |
| \* Coverage signifies that the cohort fit the criteria for the programme and entered the study during the time period it was in operation not that the cohort was vaccinated by the programme. | | | | | |

**Confounding variables**

We adjusted for incidence rates in both the UK born and non-UK born as incidence rates in neonates and those at school age are likely to be partially driven by transmission from the wider population. We also included an interaction between incidence rates in UK born and non-UK born as it is thought that the majority of transmission is due to imported cases.[1] We adjusted for age as evidence indicates that TB incidence varies with age,[1] and that the effectiveness of the BCG vaccine may vary with time post vaccination.[7] We could not fully adjust for year of study entry as including this variable would fully capture variation pre and post policy change. We therefore investigated the inclusion of a random intercept for the year of study entry, this adjusts for baseline differences between cohorts without explaining all variation.

**Model construction**

We considered a range of models, motivated by the confounding structure outlined above. Multiple models were considered as the precise structure and magnitude of the confounding was uncertain, and because by comparing different model results inferences can be made. We first investigated a univariable Poisson model, additional confounding variables were then added sequentially both with and without a random effect for year of study entry. We also investigated comparable Negative Binomial models. Supplementary Table S1 outlines the details of each model included in the analysis.

**Statistical methods**

We estimated incidence rates for those eligible for both the universal and targeted vaccination programmes within the study period, stratified by year of study entry, UK birth status, scheme coverage, and age. We summarised these incidence rates across years of study entry to provide mean incidence rates for each age group in each cohort. We then estimated Incidence Rate Ratios (IRR), from each model, for the strength of the association between the change in vaccination policy for both the UK born and non-UK born populations that were eligible for the universal programme, and for the targeted programme. The brms package, with default weakly informative priors, was used to perform Markov Chain Monte Carlo fitting using STAN for all models.[10,11] Models were run until convergence (4 chains with a burn in of 25,000, and 25,000 sampled iterations each), with convergence being assessed using trace plots and the R hat diagnostic.[11] Model fit was assessed using the leave one out cross validation information criterion (LOOIC).[12] Models were then ranked by goodness of fit, using their LOOIC. Ties were resolved using the degrees of freedom, with the simplest model selected. If any ties remained the model with the strongest apriori hypothesis was preferred. 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 age and incidence, each age group has been adjusted for independently. R was used for all analysis.[13]

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**RESULTS**

**Descriptive analysis of age-specific incidence rates**

Between Jan 1, 2000 and Dec 31, 2015 there were 114,820 notifications of TB in England, of which 93% (106765/114820) had their birth status recorded. Of notifications with a known birth status 27% (29096/106765) were UK born. From 2000 until 2012 incidence rates in the UK born remained relatively stable, since when they have fallen from 4.40 (Per 100,000; 95% CI 4.21 to 4.59), to 3.37 (Per 100,000; 95% CI 3.20 to 3.54) in 2015 (figure 1; see online supplementary table S2). In comparison incidence rates in the non-UK born increased from 79.63 (Per 100,000; 95% CI 76.97 to 82.36) in 2000, to 100.71 (Per 100,000; 95% CI 98.01 to 103.47) in 2005, since when they have decreased to 51.21 (Per 100,000; 95% CI 49.67 to 52.80) in 2015 (figure 1; see online supplementary table S3).

We found that incidence rates in those aged 14-19, who were UK born, have remained relatively stable since 2000. However incidence rates did increase from 3.72 (Per 100,000; 95% CI 3.14 to 4.38) in 2004, to a maximum of 5.11 (Per 100,000; 95% CI 4.42 to 5.87) in 2009; 4 years after the ending of the BCG schools scheme. This trend was not observed in the non-UK born population aged 14-19, were incidence rates reached a peak of 117.54 (Per 100,000; 95% CI 104.52 to 131.75), in 2005, since when they have declined year on year to 37.04 (Per 100,000; 95% CI 31.51 to 43.28) in 2015. Whilst there is some evidence that incidence rates have fallen since 2012 in the UK born population aged 14-19, the magnitude of this trend does not match that seen in the corresponding non-UK born population, or in the population as a whole (figure 1; see online supplementary table S2 and supplementary table S3).

In those aged 0-5, who were UK born, incidence rates increased after the introduction of the high risk neonatal vaccination program from 3.93 (Per 100,000; 95% CI 3.31 to 4.62) in 2004 to a maximum of 4.39 (Per 100,000; 95% CI 3.76 to 5.10) in 2008, since when they have declined to 2.13 (Per 100,000; 95% CI 1.72 to 2.61) in 2015. This does not match with the observed trend in incidence rates in the non-UK born population, aged 0-5, which declined from 42.83 (Per 100,000; 95% CI 30.99 to 57.91) in 2005, to 17.32 (Per 100,000; 95% CI 11.13 to 25.93) in 2006 since when it has continued to decrease. However, the decline in incidence rates observed since 2012 does correspond with the decline in incidence rates for all cases observed in both UK and non-UK born populations (figure 1; see online supplementary table S2 and supplementary table S3).

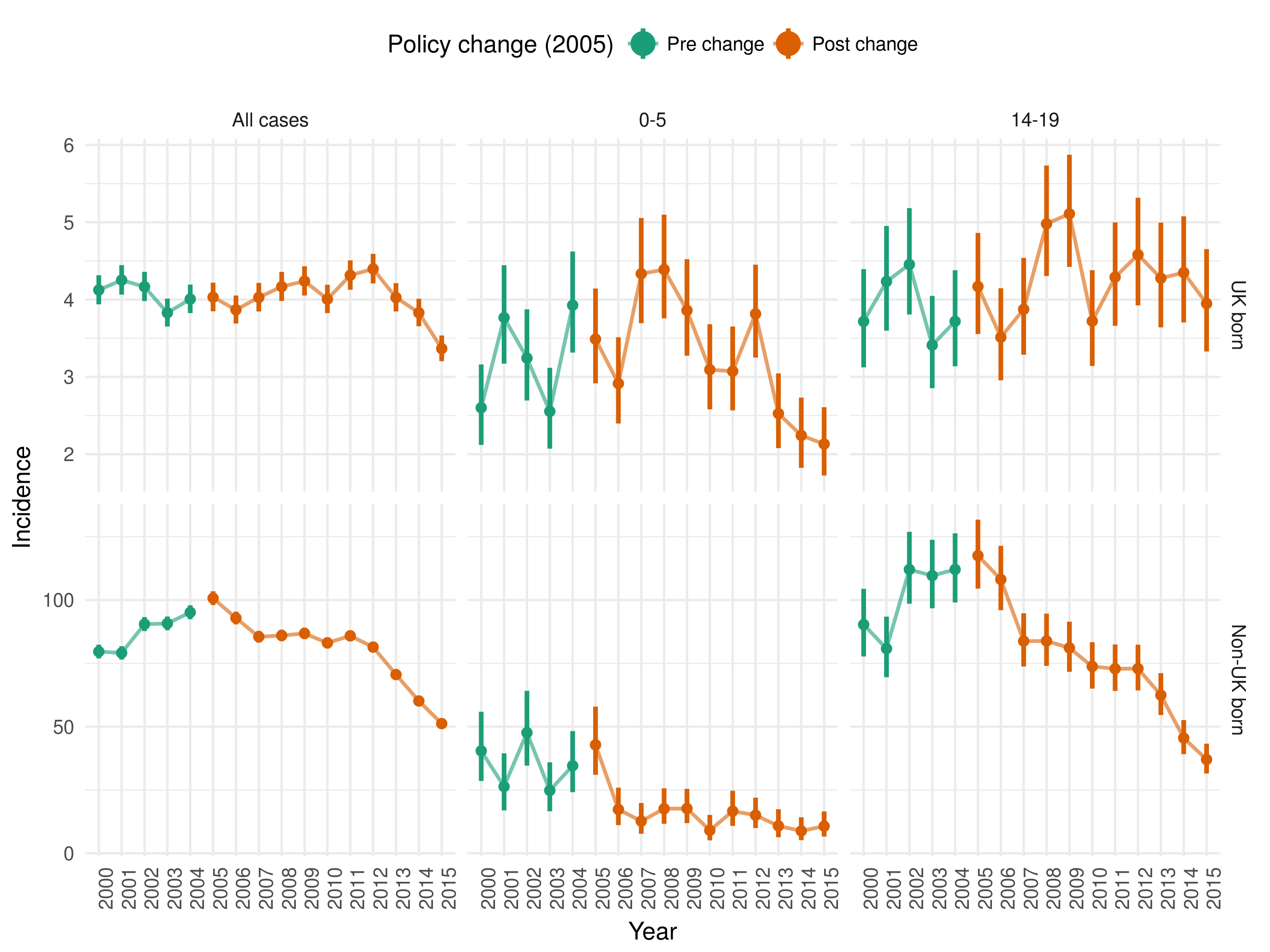


Figure 1: Incidence rates per 100,000 for non-UK born/UK born population, those aged 0-5 and therefore directly affected by the targeted neonatal vaccination programme, and those aged 14-19 and therefore directly affected by the universal school age scheme.

**Summarised incidence rates in the retrospective cohorts**

Between 2000 and 2015 there were 1624 UK born cases eligible for the universal schools scheme, and 1338 UK born cases eligible for the targeted neonatal scheme between 2000 and 2010, with 5 years of follow up. For UK born cases eligible for the universal schools scheme between 2000 and the end of the scheme in 2005 the yearly average incidence of TB, after 5 years of follow up, was 3.87 (Per 100,000; 95% CI 3.59 to 4.16), with incidence increasing after the ending of the scheme to 4.32 (Per 100,000; 95% CI 4.05 to 4.60). This trend was not observed in the non-UK born who would have been eligible for the universal programme (figure 2). Prior to the introduction of the targeted neonatal vaccination program, the yearly average incidence of TB for UK born cases eligible for the targeted program after 5 years of follow up was 3.43 (Per 100,000; 95% CI 3.17 to 3.72), compared to 3.37 (Per 100,000; 95% CI 3.13 to 3.61) after the introduction of the scheme. There was some evidence that incidence rates in the non-UK born population that would have been eligible for the targeted neonatal programme also followed this trend (figure 2).

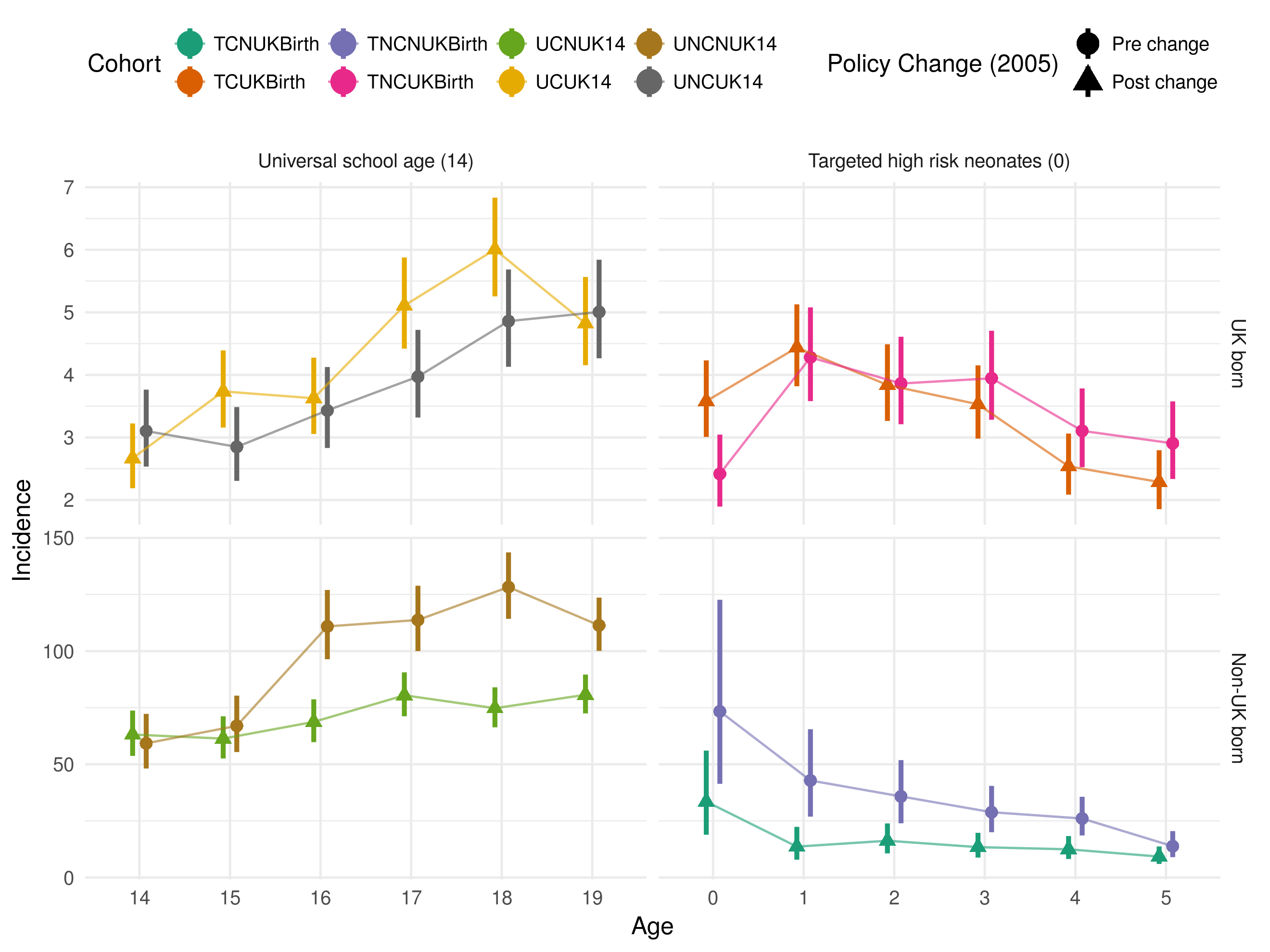


Figure 2: Incidence rates per 100,000 for each retrospective cohort.

**Direct effects of ending the universal school age programme**

In the UK born cohorts eligible for universal vaccination there was evidence, across all models, that ending the scheme was associated with a modest increase in TB rates (supplementary table S4) in those eligible for the schools programme. The IRR for the change in policy increased as variables were added to the model, although the uncertainty of the effect estimate also increased. Using the LOOIC goodness of fit criteria the best fitting model was found to be a Poisson model, which adjusted for the change in policy, age, and incidence rates in the UK born (table 2). In this model there was an estimated 7% (95% CI -2% to 16%) increase in incidence rates in those at school-age, who were UK born, associated with the change in policy. Models which adjusted for the change in policy, age, and UK born incidence rates had similar LOOIC scores and comparable IRR estimates. Models which did not adjusted for UK born incidence rates estimated a larger impact from ending the school-age scheme, but were consistently found to fit the data worse than models which did not.

For the comparable non-UK born cohort who were eligible for universal vaccination there was evidence, in the best fitting model, that ending the scheme was associated with a decrease in incidence rates of 15% (95% CI 3% to 25%) (supplementary table S5) in the non-UK born at school-age. The best fitting model adjusted for the change in policy, age, incidence rates in the non-UK born, and year of eligibility as a random effect. All models which had comparable LOOIC scores estimated nearly comparable IRRs, although several estimated a slightly attenuated effect (supplementary table S6).

Table 2: Summary table of effect sizes, in the UK born cohort eligible for the universal scheme, with the best fitting model as determined by comparision of the LOOIC. The best fitting model is summarised as follows; Model 8: Poisson model; Adjusting with fixed effects for the change in policy, age, and incidence rates in the UK born.

|  |  |
| --- | --- |
| Term | Effect (95% CI) |
| Policy Change | 1.07 (0.98 to 1.16) |
| Age |  |
| 14 | *Reference* |
| 15 | 1.15 (0.98 to 1.36) |
| 16 | 1.22 (1.04 to 1.42) |
| 17 | 1.59 (1.36 to 1.84) |
| 18 | 1.90 (1.64 to 2.20) |
| 19 | 1.74 (1.49 to 2.02) |
| UK born incidence rate (per standard deviation) | 1.09 (1.05 to 1.14) |

**Direct effects of introducing the targeted neonatal programme**

For the UK born cohorts eligible for targeted neonatal vaccination the evidence across all models was mixed with several models estimating a small decrease in incidence rates, several models estimating a small increase in incidence rates, and several models estimating little impact of the change in policy (see online supplementary table S7). All models had wide credible intervals compared to models in the UK born cohort eligible for universal school-age vaccination (see online supplementary table S4). As in the UK born cohort eligible for universal school-age vaccination the best fitting model adjusted for the change in policy, age and UK born incidence rates, but also adjusted for the year of study entry with a random effect (table 4). This model estimated an 8% (95% CI -10% to 22%) decrease in incidence rates in UK born neonates associated with the introduction of the targeted neonatal vaccination programme, although the credible intervals were wide. The next best fitting model, with a comparable LOOIC score and which adjusted for non-UK born incidence rates rather than UK born incidence rates, estimated that the introduction of the targeted program was association with only a 4% (95% CI -14% to 20%) decrease in incidence rates.

For the comparable non-UK born cohort who were eligible for targeted neonatal vaccination there was evidence, across all models, that introducing the programme was associated with a large decrease in incidence rates. Several models had equivalent LOOIC scores, meaning that the simplest model with the strongest apriori hypothesis was selected. This model, which adjusted for the change in policy, age, and non-UK born incidence rates, estimated that a 41% (95% CI 22% to 55%) decrease in incidence rates in non-UK born neonates was associated with the change in vaccination policy (supplementary table S8). All models which had comparable LOOIC scores estimated a slightly increased effect of the change in policy in comparison to the best fitting model (supplementary table S9).

Table 4: Summary table of effect sizes, in the UK born cohort eligible for the targeted scheme, with the best fitting model as determined by comparision of the LOOIC. The best fitting model is summarised as follows; Model 20: Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, age, and incidence rates in the UK born.

|  |  |
| --- | --- |
| Term | Effect (95% CI) |
| Policy Change | 0.92 (0.78 to 1.10) |
| Age |  |
| 0 | *Reference* |
| 1 | 1.41 (1.20 to 1.64) |
| 2 | 1.22 (1.04 to 1.43) |
| 3 | 1.18 (1.01 to 1.39) |
| 4 | 0.89 (0.75 to 1.05) |
| 5 | 0.84 (0.70 to 1.00) |
| UK born incidence rate (per standard deviation) | 1.12 (1.06 to 1.18) |
| Year of study elibility, group level |  |
| Intercept (standard deviation) | 1.15 (1.05 to 1.28) |
| Year of study elibility, individual level |  |
| 2000 | 0.82 (0.67 to 0.98) |
| 2001 | 0.93 (0.78 to 1.08) |
| 2002 | 1.10 (0.95 to 1.31) |
| 2003 | 1.06 (0.91 to 1.25) |
| 2004 | 1.12 (0.97 to 1.32) |
| 2005 | 1.07 (0.93 to 1.25) |
| 2006 | 1.04 (0.90 to 1.20) |
| 2007 | 0.96 (0.83 to 1.11) |
| 2008 | 1.00 (0.87 to 1.16) |
| 2009 | 0.99 (0.85 to 1.14) |
| 2010 | 0.94 (0.80 to 1.08) |

**DISCUSSION**

We found consistent evidence that the withdrawal of the BCG schools scheme was associated with a modest increase in incidence rates in the UK born population who were eligible for the scheme and a decrease of approximately twice the magnitude in incidence rates in the non-UK born population who were also eligible for the scheme, after 5 years of follow up. In the cohorts eligible for the targeted neonatal programme we found weak evidence that the programme was associated with a reduction in incidence rates in UK born neonates after 5 years of follow up. However, we found consistent evidence for a large decrease in incidence rates in non-UK born neonates, after 5 years of follow up, associated with the introduction of the targeted neonatal vaccination programme.

Tuberculosis is a complex disease, with poorly understood epidemiology. Similarly the BCG vaccine is known to offer imperfect protection, which has been shown to vary both spatially and with time since vaccination.[14,15] By focusing on the impact of the change in policy on the directly affected populations within a short period of time, and by employing a multi-model approach we have limited the potential impact of these issues and explored the potential confounding in detail. Our study was based on a routine observational data set (ETS), and a repeated survey (LFS) both of which may have introduced bias. Whilst the LFS is a robust data source, widely used in academic studies,[16–18] it is susceptible to sampling errors particularly in the young, and in the old; which may have biased the estimated incidence rates. However as the LFS is a well established survey it is unlikely that these biases have varied with time, therefore they should not impact our analysis as we have investigated trends in incidence rates, rather than absolute incidence rates. As the ETS system is a routine surveillance data set, some level of under-reporting is likely,[19] as is some level of missing data; for which we cannot discount an unknown missing not at random mechanism. However, UK birth status is relatively complete (93% (106765/114820)), and it is likely that under-reporting has decreased as the ETS has developed. It is possible that UK birth status is subject to misclassification bias, particularly in those notified when very young, or very old, but there is little evidence to suggest the direction, or magnitude of this bias. Finally we have been unable to adjust for known demographic risk factors for TB, notably socio-economic status,[20,21] and ethnicity.[20–22] However, unless there have been systematic changes to risk factors over time, this confounding is likely to be mitigated as we have compared multiple cohorts. In order to model the estimated effect of the BCG vaccination policy change we made several simplifying assumptions. Firstly we 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. Due to the complexity of the targeted neonatal vaccination programme no reliable data is available on the number of individuals eligible in each year, therefore we have made the simplifying assumption that the entire population of neonates was eligible for vaccination. This means that we have estimated the affect of the scheme at a population level, and not within the high risk population, in which the effect may have been greater than estimated. 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 affect of changing vaccination policy.

Vaccination programmes are rarely rolled back and then both re-implemented in a different target population and with a different scope, therefore few studies exist evaluating this process. Whilst we were unable to estimate the effectiveness of the BCG vaccine as the vaccine status of TB cases was unknown as was the coverage of both the universal schools scheme, and the targeted neonatal programme. We were able to establish estimates for the percentage change in incidence rates due to the change of policy at the population level. This may be used as a lower bound for the effectiveness of the BCG vaccine in the UK born population in England, which can then be compared to results from other studies. Although it is likely to be an underestimate in both cases, as it assumes 100% coverage, which for the universal scheme is unlikely and for the targeted scheme is known to not be the case. An MRC trial in the 1950’s found that BCG effectiveness was 77% in white school age children in England.[23] More recent studies have found wide variation with estimates of BCG effectiveness ranging from 0% to 78%.[7]. Whilst our estimate of protection in young adults was substantially lower than that estimated in the MRC trial, it is uncertain to what extent this is due to our necessary assumption of complete coverage. However our result does give some measure of the population wide effectiveness of the school age BCG programme, indicating that it did have some measurable impact. Consistently protection has been found to be stronger in young children than in adults,[4–6] this is consistent with our results in non-UK born neonates but not with our estimates for the UK born neonates. We also found that the association between BCG vaccination and incidence rates in neonates was highly sensitive to confounding whilst the association with incidence rates in school age children was not.

This study indicates that the change in England’s vaccination policy was associated with a modest increase in incidence in the UK born that were eligible for the school age vaccination programme, and with a small reduction in incidence in the UK born that were eligible for the high risk neonatal vaccination programme. This result corresponds with the expected effect of the change in vaccination policy, but serves to quantify the trade-offs involved. Unexpectedly, we found evidence of an association between the change in policy and a decrease in incidence rates in the non-UK born that were eligible for the universal school-age scheme and a large decrease in incidence rates in the non-UK born that were eligible for the targeted neonatal vaccination programme. This suggests that the change of vaccination policy to target high risk neonates may have resulted in an increased focus on high risk non-UK born individuals who may not have been the direct targets of the vaccination programme. The incidence rate in young children is often used as an informal proxy of TB transmission,[1] this result allows the effect of BCG vaccination to be adjusted for, which may lead to more accurate estimates of ongoing TB transmission in England. Further validation is required using alternative study designs, but this result should be considered when vaccination policy changes are being considered.

It is well established that interventions against infectious diseases, such as TB, should be evaluated not only for their direct effects but also for future indirect effects via ongoing transmission. Statistical approaches such as those used in this paper are not appropriate for capturing these future indirect effects, and instead dynamic disease models should be used. In addition this study could not evaluate the impact of the neonatal programme on the high risk population it targets, due to a lack of reliable data. Improved coverage data for the BCG programme is required to more fully evaluate it’s ongoing impact.

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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*

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##### PAGEBREAK

## 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

Sam Abbott, Hannah Christensen, Ellen Brooks-Pollock

**Model Definitions**

Supplementary Table S1: Full definition of each model, ordered by increasing complexity.

|  |  |
| --- | --- |
| Model | Description |
| Model 1 | Poisson model; Adjusting for no fixed effects. |
| Model 2 | Poisson model; Adjusting with fixed effects for the change in policy. |
| Model 3 | Poisson model; Adjusting with fixed effects for the change in policy, incidence rates in the UK born. |
| Model 4 | Poisson model; Adjusting with fixed effects for the change in policy, incidence rates in the non-UK born. |
| Model 5 | Poisson model; Adjusting with fixed effects for the change in policy, incidence rates in the UK born and non-UK born populations. |
| Model 6 | Poisson model; Adjusting with fixed effects for the change in policy, 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. |
| Model 7 | Poisson model; Adjusting with fixed effects for the change in policy, and age. |
| Model 8 | Poisson model; Adjusting with fixed effects for the change in policy, age, and incidence rates in the UK born. |
| Model 9 | Poisson model; Adjusting with fixed effects for the change in policy, age, and incidence rates in the non-UK born. |
| Model 10 | Poisson model; Adjusting with fixed effects for the change in policy, age, incidence rates in the UK born and non-UK born populations. |
| Model 11 | Poisson model; Adjusting 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. |
| Model 12 | Negative binomial model; Adjusting 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. |
| Model 13 | Poisson model; Random intercept for year of study entry, adjusting for no fixed effects. |
| Model 14 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy. |
| Model 15 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, incidence rates in the UK born. |
| Model 16 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, incidence rates in the non-UK born. |
| Model 17 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, incidence rates in the UK born and non-UK born populations. |
| Model 18 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, 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. |
| Model 19 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, and age. |
| Model 20 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, age, and incidence rates in the UK born. |
| Model 21 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, age, and incidence rates in the non-UK born. |
| Model 22 | Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, age, incidence rates in the UK born and non-UK born populations. |
| Model 23 | Poisson model; Random intercept for year of study entry, adjusting 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. |
| Model 24 | Negative binomial model; Random intercept for year of study entry, adjusting 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. |

**Incidence estimates for all cases, those aged 0-5 and those aged 14-19**

Supplementary Table S2: Incidence rates per 100,000 in the UK born for all cases, those aged 0-5, and those aged 14-19, who were directly effected by the change in vaccination policy in 2005

|  |  |  |  |
| --- | --- | --- | --- |
| Year eligible for vaccination | Age group | | |
| All cases\* | 0-5\* | 14-19\* |
| 2000 | 4.12 (3.94 to 4.31) | 2.60 (2.12 to 3.16) | 3.72 (3.12 to 4.39) |
| 2001 | 4.25 (4.06 to 4.45) | 3.77 (3.17 to 4.44) | 4.23 (3.60 to 4.95) |
| 2002 | 4.17 (3.98 to 4.36) | 3.24 (2.69 to 3.87) | 4.45 (3.81 to 5.18) |
| 2003 | 3.83 (3.65 to 4.01) | 2.55 (2.07 to 3.12) | 3.41 (2.85 to 4.05) |
| 2004 | 4.01 (3.83 to 4.19) | 3.93 (3.31 to 4.62) | 3.72 (3.14 to 4.38) |
| 2005 | 4.03 (3.85 to 4.22) | 3.49 (2.92 to 4.14) | 4.17 (3.55 to 4.86) |
| 2006 | 3.87 (3.69 to 4.05) | 2.91 (2.40 to 3.51) | 3.51 (2.96 to 4.15) |
| 2007 | 4.03 (3.85 to 4.22) | 4.33 (3.69 to 5.05) | 3.87 (3.29 to 4.54) |
| 2008 | 4.17 (3.98 to 4.36) | 4.39 (3.76 to 5.10) | 4.98 (4.30 to 5.73) |
| 2009 | 4.24 (4.05 to 4.43) | 3.86 (3.27 to 4.52) | 5.11 (4.42 to 5.87) |
| 2010 | 4.01 (3.83 to 4.19) | 3.09 (2.58 to 3.68) | 3.72 (3.14 to 4.38) |
| 2011 | 4.31 (4.13 to 4.51) | 3.07 (2.57 to 3.65) | 4.29 (3.66 to 5.00) |
| 2012 | 4.40 (4.21 to 4.59) | 3.82 (3.25 to 4.45) | 4.58 (3.92 to 5.32) |
| 2013 | 4.03 (3.85 to 4.21) | 2.53 (2.08 to 3.04) | 4.28 (3.64 to 5.00) |
| 2014 | 3.83 (3.65 to 4.01) | 2.24 (1.82 to 2.73) | 4.35 (3.70 to 5.08) |
| 2015 | 3.37 (3.20 to 3.54) | 2.13 (1.72 to 2.61) | 3.95 (3.33 to 4.65) |
| \* Incidence rate per 100,000, with 95% confidence intervals | | | |

Supplementary Table S3: Incidence rates per 100,000 in the non-UK born for all cases, those aged 0-5, and those aged 14-19, who would have been directly effected by the change in vaccination policy in 2005 had they been UK born

|  |  |  |  |
| --- | --- | --- | --- |
| Year eligible for vaccination | Age group | | |
| All cases\* | 0-5\* | 14-19\* |
| 2000 | 79.63 (76.97 to 82.36) | 40.45 (28.56 to 55.88) | 90.31 (77.70 to 104.43) |
| 2001 | 79.11 (76.51 to 81.78) | 26.36 (16.95 to 39.47) | 80.81 (69.52 to 93.44) |
| 2002 | 90.47 (87.75 to 93.26) | 47.63 (34.62 to 64.16) | 112.05 (98.55 to 126.92) |
| 2003 | 90.75 (88.09 to 93.48) | 24.81 (16.59 to 35.94) | 109.63 (96.75 to 123.77) |
| 2004 | 95.14 (92.42 to 97.92) | 34.58 (24.13 to 48.25) | 112.07 (99.05 to 126.35) |
| 2005 | 100.71 (98.01 to 103.47) | 42.83 (30.99 to 57.91) | 117.54 (104.52 to 131.75) |
| 2006 | 92.89 (90.39 to 95.44) | 17.32 (11.13 to 25.93) | 108.13 (95.99 to 121.40) |
| 2007 | 85.50 (83.19 to 87.85) | 12.69 (7.74 to 19.87) | 83.76 (73.75 to 94.78) |
| 2008 | 86.00 (83.74 to 88.31) | 17.59 (11.66 to 25.67) | 83.83 (74.00 to 94.63) |
| 2009 | 86.81 (84.58 to 89.09) | 17.69 (11.92 to 25.44) | 81.10 (71.66 to 91.46) |
| 2010 | 83.07 (80.91 to 85.28) | 9.07 (5.11 to 15.16) | 73.78 (65.05 to 83.38) |
| 2011 | 85.87 (83.73 to 88.06) | 16.65 (10.82 to 24.70) | 72.86 (64.14 to 82.47) |
| 2012 | 81.42 (79.36 to 83.52) | 15.05 (9.97 to 21.96) | 72.92 (64.32 to 82.37) |
| 2013 | 70.58 (68.70 to 72.50) | 10.80 (6.36 to 17.41) | 62.46 (54.61 to 71.14) |
| 2014 | 60.15 (58.44 to 61.90) | 8.82 (5.19 to 14.22) | 45.51 (39.15 to 52.62) |
| 2015 | 51.21 (49.67 to 52.80) | 10.69 (6.62 to 16.54) | 37.04 (31.51 to 43.28) |
| \* Incidence rate per 100,000, with 95% confidence intervals | | | |

**Direct effects of the change in policy on the UK born cohorts - results from all models**

Supplementary Table S4: Comparision of models fitted to incidence rates for the UK born population that was eligible for the universal vaccination programme of those at school age (14). Models are ordered by the goodness of fit as assessed by LOOIC, the degrees of freedom are used as a tiebreaker.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model | IRR (CI 95%)\* | Variables | | | | | Model Fit Metrics | | |
| Policy Change | Age | UK born rates | Non-UK born rates | Year of study entry | DoF\*\* | LPD† | LOOIC (se)†† |
| Model 8 | 1.07 (0.98 to 1.16) | Yes | Yes | Yes | No | No | 8 | -204 | 429 (14) |
| Model 20 | 1.07 (0.95 to 1.20) | Yes | Yes | Yes | No | Yes | 20 | -201 | 430 (14) |
| Model 10 | 1.08 (0.97 to 1.21) | Yes | Yes | No | Yes | No | 9 | -204 | 431 (14) |
| Model 11 | 1.08 (0.97 to 1.20) | Yes | Yes | Yes | Yes | No | 10 | -203 | 431 (14) |
| Model 22 | 1.07 (0.94 to 1.23) | Yes | Yes | No | Yes | Yes | 21 | -201 | 433 (14) |
| Model 23 | 1.06 (0.93 to 1.22) | Yes | Yes | Yes | Yes | Yes | 22 | -200 | 433 (13) |
| Model 9 | 1.18 (1.07 to 1.31) | Yes | Yes | No | Yes | No | 8 | -209 | 439 (17) |
| Model 7 | 1.12 (1.03 to 1.22) | Yes | Yes | No | No | No | 7 | -210 | 440 (17) |
| Model 19 | 1.12 (0.99 to 1.26) | Yes | Yes | No | No | Yes | 19 | -205 | 442 (17) |
| Model 21 | 1.17 (1.03 to 1.33) | Yes | Yes | No | Yes | Yes | 20 | -205 | 442 (17) |
| Model 5 | 1.00 (0.90 to 1.10) | Yes | No | No | Yes | No | 4 | -242 | 503 (22) |
| Model 6 | 0.99 (0.90 to 1.09) | Yes | No | Yes | Yes | No | 5 | -240 | 504 (21) |
| Model 3 | 1.07 (0.98 to 1.17) | Yes | No | Yes | No | No | 3 | -245 | 505 (22) |
| Model 17 | 0.97 (0.82 to 1.13) | Yes | No | No | Yes | Yes | 16 | -231 | 509 (24) |
| Model 18 | 0.96 (0.81 to 1.13) | Yes | No | Yes | Yes | Yes | 17 | -229 | 509 (23) |
| Model 15 | 1.07 (0.95 to 1.21) | Yes | No | Yes | No | Yes | 15 | -239 | 512 (23) |
| Model 2 | 1.12 (1.03 to 1.22) | Yes | No | No | No | No | 2 | -251 | 513 (26) |
| Model 1 | 0.00 (0.00 to 0.00) | No | No | No | No | No | 1 | -254 | 514 (27) |
| Model 4 | 1.08 (0.98 to 1.19) | Yes | No | No | Yes | No | 3 | -250 | 515 (25) |
| Model 14 | 1.12 (0.99 to 1.26) | Yes | No | No | No | Yes | 14 | -244 | 521 (27) |
| Model 16 | 1.05 (0.90 to 1.22) | Yes | No | No | Yes | Yes | 15 | -239 | 521 (27) |
| Model 13 | 0.00 (0.00 to 0.00) | No | No | No | No | Yes | 13 | -243 | 522 (28) |
| \* Incidence Rate Ratio, with 95% credible intervals, \*\* Degrees of Freedom, † Computed log pointwise predictive density, †† Leave one out information criterion, with standard error | | | | | | | | | |

Supplementary Table S7: Comparision of models fitted to incidence rates for the UK born population that was eligible for the targeted vaccination programme of neonates. Models are ordered by the goodness of fit as assessed by LOOIC, the degrees of freedom are used as a tiebreaker.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model | IRR (CI 95%)\* | Variables | | | | | Model Fit Metrics | | |
| Policy Change | Age | UK born rates | Non-UK born rates | Year of study entry | DoF\*\* | LPD† | LOOIC (se)†† |
| Model 20 | 0.92 (0.78 to 1.10) | Yes | Yes | Yes | No | Yes | 20 | -192 | 416 (14) |
| Model 22 | 0.96 (0.80 to 1.14) | Yes | Yes | No | Yes | Yes | 21 | -192 | 419 (15) |
| Model 8 | 0.93 (0.84 to 1.02) | Yes | Yes | Yes | No | No | 8 | -200 | 421 (18) |
| Model 10 | 0.98 (0.88 to 1.10) | Yes | Yes | No | Yes | No | 9 | -199 | 421 (18) |
| Model 23 | 0.95 (0.79 to 1.13) | Yes | Yes | Yes | Yes | Yes | 22 | -192 | 421 (15) |
| Model 11 | 0.98 (0.88 to 1.10) | Yes | Yes | Yes | Yes | No | 10 | -199 | 423 (18) |
| Model 9 | 1.06 (0.95 to 1.18) | Yes | Yes | No | Yes | No | 8 | -203 | 429 (19) |
| Model 19 | 0.98 (0.84 to 1.15) | Yes | Yes | No | No | Yes | 19 | -198 | 431 (15) |
| Model 21 | 1.05 (0.90 to 1.22) | Yes | Yes | No | Yes | Yes | 20 | -198 | 431 (16) |
| Model 7 | 0.98 (0.90 to 1.07) | Yes | Yes | No | No | No | 7 | -205 | 432 (18) |
| Model 5 | 1.04 (0.93 to 1.17) | Yes | No | No | Yes | No | 4 | -216 | 444 (20) |
| Model 6 | 1.04 (0.93 to 1.16) | Yes | No | Yes | Yes | No | 5 | -216 | 446 (20) |
| Model 17 | 1.04 (0.89 to 1.22) | Yes | No | No | Yes | Yes | 16 | -208 | 447 (17) |
| Model 18 | 1.04 (0.88 to 1.23) | Yes | No | Yes | Yes | Yes | 17 | -208 | 449 (17) |
| Model 4 | 1.12 (1.01 to 1.25) | Yes | No | No | Yes | No | 3 | -220 | 452 (19) |
| Model 3 | 0.92 (0.84 to 1.01) | Yes | No | Yes | No | No | 3 | -221 | 454 (20) |
| Model 15 | 0.92 (0.78 to 1.09) | Yes | No | Yes | No | Yes | 15 | -211 | 454 (18) |
| Model 16 | 1.13 (0.97 to 1.32) | Yes | No | No | Yes | Yes | 15 | -213 | 456 (17) |
| Model 1 | 0.00 (0.00 to 0.00) | No | No | No | No | No | 1 | -230 | 464 (21) |
| Model 2 | 0.98 (0.90 to 1.07) | Yes | No | No | No | No | 2 | -229 | 467 (21) |
| Model 13 | 0.00 (0.00 to 0.00) | No | No | No | No | Yes | 13 | -220 | 468 (19) |
| Model 14 | 0.99 (0.85 to 1.16) | Yes | No | No | No | Yes | 14 | -219 | 471 (19) |
| \* Incidence Rate Ratio, with 95% credible intervals, \*\* Degrees of Freedom, † Computed log pointwise predictive density, †† Leave one out information criterion, with standard error | | | | | | | | | |

**Best fitting models for the non-UK born cohorts**

Supplementary Table S5: Summary table of effect sizes, in the non-UK born cohort eligible for the universal scheme, with the best fitting model as determined by comparision of the LOOIC. The best fitting model is summarised as follows; Model 21: Poisson model; Random intercept for year of study entry, adjusting with fixed effects for the change in policy, age, and incidence rates in the non-UK born.

|  |  |
| --- | --- |
| Term | Effect (95% CI) |
| Policy Change | 0.85 (0.75 to 0.97) |
| Age |  |
| 14 | *Reference* |
| 15 | 1.02 (0.88 to 1.18) |
| 16 | 1.37 (1.19 to 1.56) |
| 17 | 1.55 (1.36 to 1.77) |
| 18 | 1.64 (1.44 to 1.87) |
| 19 | 1.69 (1.48 to 1.92) |
| Non-UK born incidence rate (per standard deviation) | 1.17 (1.11 to 1.22) |
| Year of study elibility, group level |  |
| Intercept (standard deviation) | 1.10 (1.04 to 1.19) |
| Year of study elibility, individual level |  |
| 2000 | 1.08 (0.98 to 1.22) |
| 2001 | 1.01 (0.91 to 1.12) |
| 2002 | 1.05 (0.95 to 1.18) |
| 2003 | 0.94 (0.83 to 1.03) |
| 2004 | 0.93 (0.83 to 1.03) |
| 2005 | 0.94 (0.83 to 1.04) |
| 2006 | 1.12 (1.00 to 1.27) |
| 2007 | 1.01 (0.91 to 1.13) |
| 2008 | 0.95 (0.85 to 1.05) |
| 2009 | 0.98 (0.87 to 1.08) |
| 2010 | 1.01 (0.91 to 1.14) |

Supplementary Table S8: Summary table of effect sizes, in the non-UK born cohort eligible for the targeted neonatal scheme, with the best fitting model as determined by comparision of the LOOIC. The best fitting model is summarised as follows; Model 8: Poisson model; Adjusting with fixed effects for the change in policy, age, and incidence rates in the UK born.

|  |  |
| --- | --- |
| Term | Effect (95% CI) |
| Policy Change | 0.42 (0.34 to 0.53) |
| Age |  |
| 0 | *Reference* |
| 1 | 0.49 (0.31 to 0.78) |
| 2 | 0.49 (0.32 to 0.76) |
| 3 | 0.40 (0.26 to 0.62) |
| 4 | 0.36 (0.24 to 0.56) |
| 5 | 0.23 (0.15 to 0.36) |
| Non-UK born incidence rate (per standard deviation) | 1.17 (1.04 to 1.32) |

**Direct effects of the change in policy on the non-UK born cohorts - results from all models**

Supplementary Table S6: Comparision of models fitted to incidence rates for the non-UK born population that was eligible for the universal vaccination programme of those at school age (14). Models are ordered by the goodness of fit as assessed by LOOIC, the degrees of freedom are used as a tiebreaker.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model | IRR (CI 95%)\* | Variables | | | | | Model Fit Metrics | | |
| Policy Change | Age | UK born rates | Non-UK born rates | Year of study entry | DoF\*\* | LPD† | LOOIC (se)†† |
| Model 21 | 0.85 (0.75 to 0.97) | Yes | Yes | No | Yes | Yes | 20 | -221 | 482 (15) |
| Model 22 | 0.89 (0.77 to 1.02) | Yes | Yes | No | Yes | Yes | 21 | -220 | 483 (15) |
| Model 10 | 0.90 (0.82 to 0.99) | Yes | Yes | No | Yes | No | 9 | -228 | 484 (17) |
| Model 9 | 0.86 (0.80 to 0.94) | Yes | Yes | No | Yes | No | 8 | -229 | 485 (17) |
| Model 23 | 0.89 (0.77 to 1.02) | Yes | Yes | Yes | Yes | Yes | 22 | -220 | 486 (15) |
| Model 11 | 0.90 (0.82 to 0.99) | Yes | Yes | Yes | Yes | No | 10 | -228 | 487 (17) |
| Model 19 | 0.71 (0.60 to 0.84) | Yes | Yes | No | No | Yes | 19 | -228 | 510 (21) |
| Model 20 | 0.70 (0.60 to 0.83) | Yes | Yes | Yes | No | Yes | 20 | -228 | 514 (22) |
| Model 7 | 0.71 (0.67 to 0.76) | Yes | Yes | No | No | No | 7 | -249 | 530 (26) |
| Model 8 | 0.71 (0.66 to 0.75) | Yes | Yes | Yes | No | No | 8 | -248 | 534 (25) |
| Model 16 | 0.76 (0.64 to 0.89) | Yes | No | No | Yes | Yes | 15 | -257 | 565 (27) |
| Model 14 | 0.70 (0.59 to 0.84) | Yes | No | No | No | Yes | 14 | -258 | 566 (31) |
| Model 4 | 0.78 (0.73 to 0.85) | Yes | No | No | Yes | No | 3 | -276 | 568 (30) |
| Model 13 | 0.00 (0.00 to 0.00) | No | No | No | No | Yes | 13 | -258 | 569 (31) |
| Model 15 | 0.70 (0.59 to 0.84) | Yes | No | Yes | No | Yes | 15 | -258 | 570 (32) |
| Model 17 | 0.76 (0.65 to 0.89) | Yes | No | No | Yes | Yes | 16 | -256 | 570 (28) |
| Model 5 | 0.79 (0.73 to 0.86) | Yes | No | No | Yes | No | 4 | -275 | 571 (30) |
| Model 18 | 0.76 (0.64 to 0.89) | Yes | No | Yes | Yes | Yes | 17 | -256 | 574 (28) |
| Model 6 | 0.79 (0.73 to 0.86) | Yes | No | Yes | Yes | No | 5 | -275 | 576 (30) |
| Model 2 | 0.71 (0.67 to 0.76) | Yes | No | No | No | No | 2 | -284 | 581 (35) |
| Model 3 | 0.70 (0.66 to 0.75) | Yes | No | Yes | No | No | 3 | -283 | 584 (35) |
| Model 1 | 0.00 (0.00 to 0.00) | No | No | No | No | No | 1 | -322 | 654 (45) |
| \* Incidence Rate Ratio, with 95% credible intervals, \*\* Degrees of Freedom, † Computed log pointwise predictive density, †† Leave one out information criterion, with standard error | | | | | | | | | |

Supplementary Table S9: Comparision of models fitted to incidence rates for the non-UK born population that was eligible for the targeted vaccination programme of neonates. Models are ordered by the goodness of fit as assessed by LOOIC, the degrees of freedom are used as a tiebreaker.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model | IRR (CI 95%)\* | Variables | | | | | Model Fit Metrics | | |
| Policy Change | Age | UK born rates | Non-UK born rates | Year of study entry | DoF\*\* | LPD† | LOOIC (se)†† |
| Model 9 | 0.59 (0.45 to 0.78) | Yes | Yes | No | Yes | No | 8 | -137 | 295 (18) |
| Model 8 | 0.42 (0.34 to 0.53) | Yes | Yes | Yes | No | No | 8 | -137 | 295 (18) |
| Model 10 | 0.51 (0.38 to 0.69) | Yes | Yes | No | Yes | No | 9 | -136 | 295 (17) |
| Model 11 | 0.50 (0.37 to 0.68) | Yes | Yes | Yes | Yes | No | 10 | -134 | 295 (16) |
| Model 7 | 0.47 (0.38 to 0.59) | Yes | Yes | No | No | No | 7 | -139 | 298 (19) |
| Model 20 | 0.42 (0.31 to 0.56) | Yes | Yes | Yes | No | Yes | 20 | -134 | 298 (19) |
| Model 22 | 0.50 (0.36 to 0.72) | Yes | Yes | No | Yes | Yes | 21 | -134 | 298 (18) |
| Model 23 | 0.48 (0.34 to 0.69) | Yes | Yes | Yes | Yes | Yes | 22 | -132 | 298 (17) |
| Model 21 | 0.58 (0.42 to 0.81) | Yes | Yes | No | Yes | Yes | 20 | -135 | 299 (19) |
| Model 19 | 0.47 (0.35 to 0.63) | Yes | Yes | No | No | Yes | 19 | -136 | 301 (20) |
| Model 4 | 0.72 (0.55 to 0.94) | Yes | No | No | Yes | No | 3 | -149 | 307 (18) |
| Model 5 | 0.65 (0.48 to 0.89) | Yes | No | No | Yes | No | 4 | -148 | 309 (18) |
| Model 6 | 0.65 (0.48 to 0.88) | Yes | No | Yes | Yes | No | 5 | -147 | 310 (18) |
| Model 16 | 0.72 (0.53 to 0.99) | Yes | No | No | Yes | Yes | 15 | -147 | 310 (19) |
| Model 17 | 0.65 (0.46 to 0.92) | Yes | No | No | Yes | Yes | 16 | -146 | 312 (19) |
| Model 18 | 0.64 (0.45 to 0.90) | Yes | No | Yes | Yes | Yes | 17 | -145 | 314 (19) |
| Model 3 | 0.45 (0.36 to 0.56) | Yes | No | Yes | No | No | 3 | -153 | 316 (22) |
| Model 2 | 0.49 (0.40 to 0.61) | Yes | No | No | No | No | 2 | -156 | 319 (22) |
| Model 15 | 0.44 (0.33 to 0.60) | Yes | No | Yes | No | Yes | 15 | -149 | 319 (23) |
| Model 14 | 0.49 (0.37 to 0.65) | Yes | No | No | No | Yes | 14 | -152 | 322 (23) |
| Model 13 | 0.00 (0.00 to 0.00) | No | No | No | No | Yes | 13 | -150 | 330 (25) |
| Model 1 | 0.00 (0.00 to 0.00) | No | No | No | No | No | 1 | -171 | 346 (27) |
| \* Incidence Rate Ratio, with 95% credible intervals, \*\* Degrees of Freedom, † Computed log pointwise predictive density, †† Leave one out information criterion, with standard error | | | | | | | | | |