Modelling BCG vaccination in the UK: *What is the impact of changing vaccination policy?*

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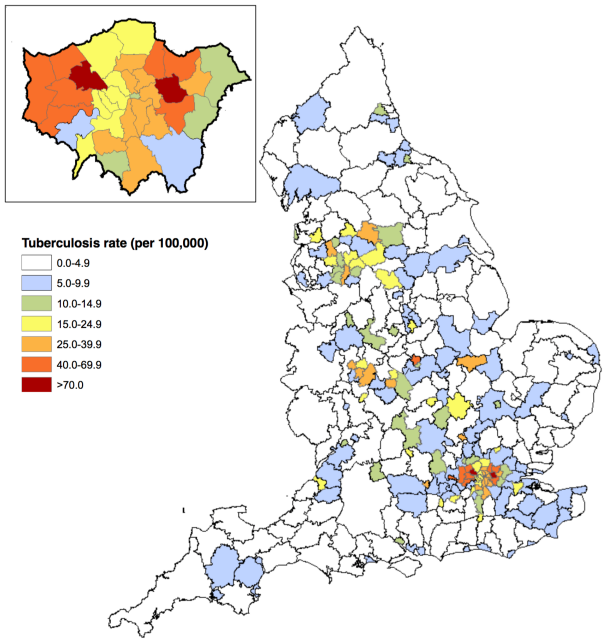
The natural history and epidemiology of Tuberculosis

- Primarily a respiratory disease caused by Mycobacterium tuberculosis
- Active TB may follow shortly after an initial infection or many years later due to endogenous reactivation or after reinfection [1]
- Risk of developing active disease is age dependent
- Globally Tuberculosis is the second most common cause of death from infectious disease, after HIV

Tuberculosis incidence in the UK

- Incidence rates have declined over the last 50 years
- However, TB continues to be an important PH problem in the UK.
- Some evidence this decline has slowed/stopped in the last 20 years.
- The majority of cases occur in the non-UK born [2]
- 70% of all cases occurred in the 40% most deprived households



1. Lambert, M. L., Hasker, E., Van Deun, A., Roberfroid, D., Boelaert, M., & Van der Stuyft, P. (2003). Recurrence in tuberculosis: Relapse or reinfection? *Lancet Infectious Diseases*, *3*(5), 282–287. https://doi.org/10.1016/S1473-3099(03)00607-8
2. PHE. (2016). Tuberculosis in England 2016 Report (presenting data to end of 2015). *Public Health England*, *Version 1.*, 173.

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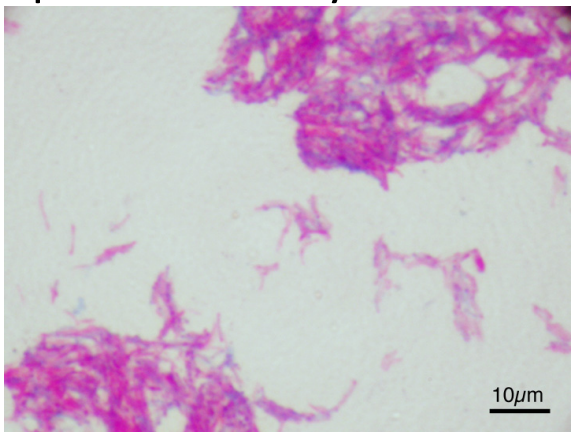
Bacillus Calmette–Guérin (BCG) vaccine:

- In use since 1921, with roughly **260 million** doses ordered a year
- Currently the **only licensed vaccine** for TB
- Thought to primarily prevent the transition from **latent to active TB**, although some evidence it reduces transmission
- 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 (little evidence of protection beyond 15 years)

Vaccination Policy:

- **Universal** vaccination introduced in 1953, via schools scheme
- Switched to **targeted** vaccination of infants in high risk groups in 2005
- Areas with incidence levels above **40/100,000** should vaccinate all infants.



Microscopic image of the Calmette-Guérin bacillus

1. Hart, P. D. A., & Sutherland, I. A. N. (1972). BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. *Bulletin of the World Health Organization*, *46*(3), 371–385. https://doi.org/10.1136/bmj.2.6082.293
2. Trunz, B. B., Fine, P., & Dye, C. (2006). Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*, *367*(9517), 1173–1180. https://doi.org/10.1016/S0140-6736(06)68507-3

Motivation and Research objectives

- TB continues to be an important PH problem in UK
- BCG only vaccine available: universal > targeted programme

Research Objectives

1. Investigate the evidence used to justify the policy change from universal school age to selective neonatal vaccination, and estimate the present and future impact of this change
2. Determine the evidence for associations between BCG vaccination and outcomes for active TB cases
3. Forecast the impact of BCG shortages, optimise the policy response to these shortages, suggest policy changes to limit future shortages

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

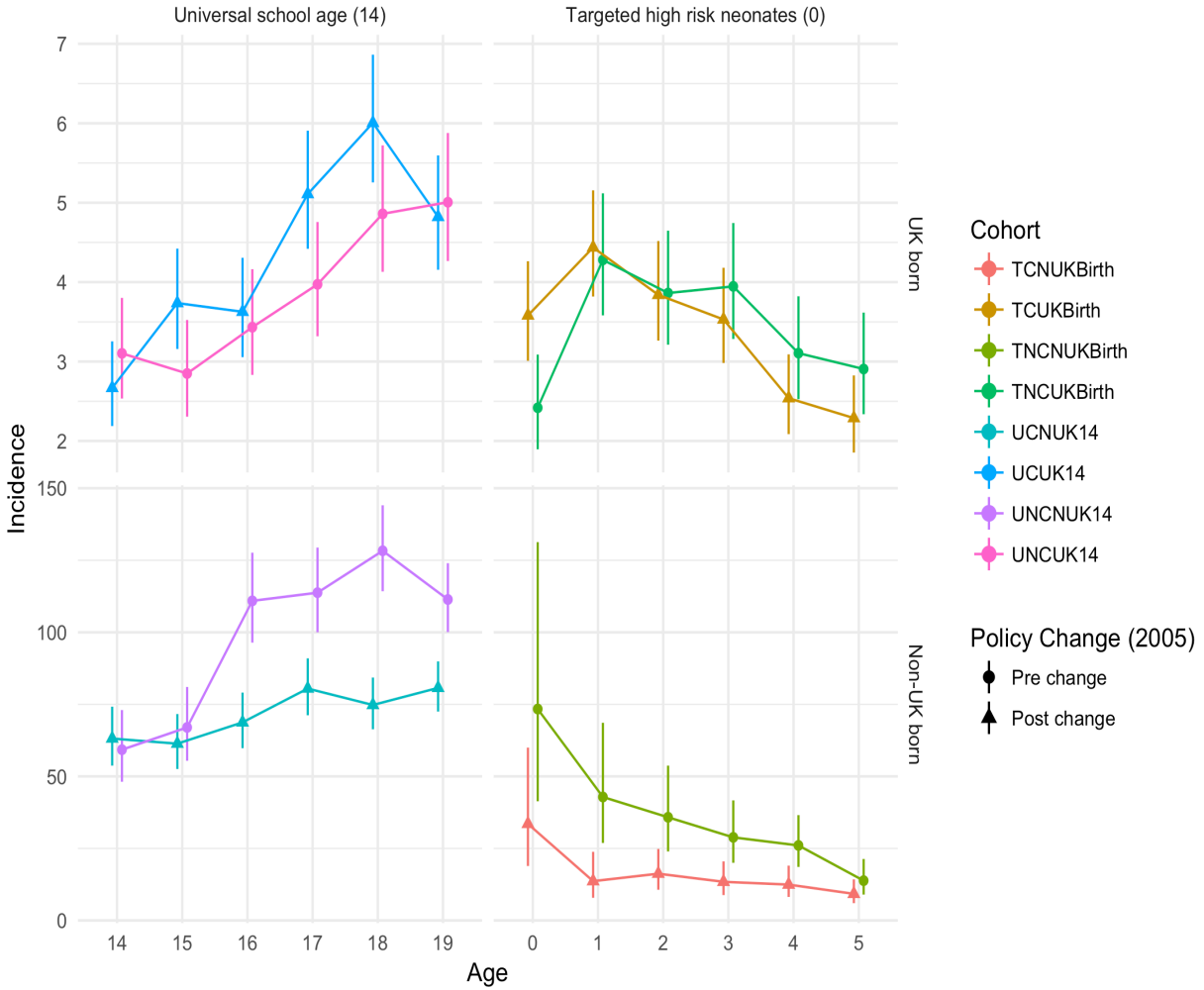
- Combined notification data and demographic data from the labour force survey (English population stratified by UK birth status)
- Constructed retrospective cohorts and estimated incidence over a 5 year period post eligibility for entry to a vaccination scheme.
- Estimated incidence rates and conducted a descriptive analysis
- Used Poisson models to estimate the change in incidence associated with the change in vaccination policy for each directly effected age group.
- Used a multi-model approach as the role of confounders was unclear. We discussed all results in the context of this approach.

Results – Incidence rates (per 100,000)

- Incidence decreased in all age groups.
- There appears to be weak coupling within age groups.
- Both directly effected populations have some evidence of post policy change increases in incidence.

Results – Incidence rates in the retrospective cohorts

- Stratified by scheme eligible for and UK birth status
- Some evidence that the ending the school age programme was associated with a reduction in incidence rates
- Less clear evidence for the association of the neonatal programme with reduced rates



Results – Poisson Models

- School age vaccination:
  - Across all models evidence of a modest increase in incidence rates
  - Univariable: 12% (95% CI 3% to 21%) increase
  - Fully adjusted: 17% (95% CI -7% to 47%) increase
  - Adjusting for non-UK born rates increased the effect size
  - Little evidence of an effect in the non-UK born population
- Neonatal vaccination:
  - Evidence variable across all models
  - Univariable: Little evidence for any effect
  - Fully adjusted: 19% (95% CI -1% to 35%) decrease
  - Required adjustment for non-UK born effects for there to be an association with a decrease in incidence rates
  - Some evidence of a reduction in incidence in non-UK born neonates

Discussion

- Appears to be some evidence of the expected effects of the change in policy in both populations
- The effect was highly confounded in neonates, with evidence indicating that non-UK born incidence should be adjusted for.
- Evidence of an effect in the non-UK born neonates who should not have been exposed to the program – unclear what mechanism is behind this.
- We have not accounted for indirect effects and changes in transmission.

Modelling

Accounting for Indirect Effects!!

Research Question

1. What were the indirect effects in England of the 2005 change in BCG vaccination policy
    1. What are the dynamics of direct versus indirect protection via BCG vaccination
    2. Modelling the indirect effects of the 2005 change in BCG vaccination policy in England

What are the dynamics of direct versus indirect protection via BCG vaccination

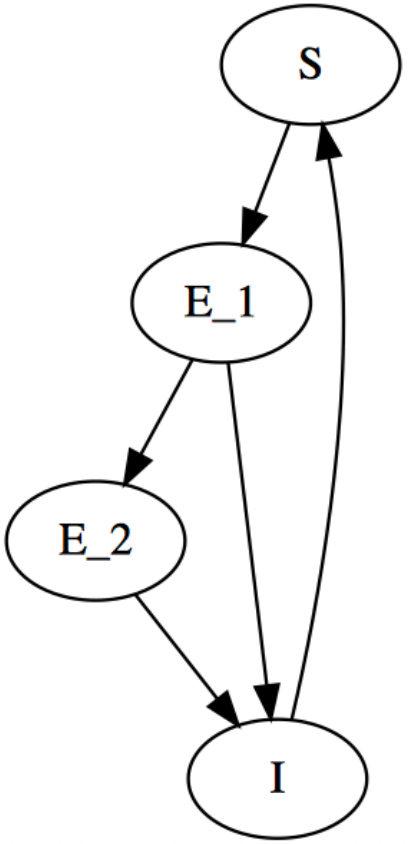
- Aim: Examine the transmission threshold at which point direct vaccination of at risk neonates is more beneficial than indirect protection via vaccination of those most at risk of onwards transmission.
- Assumptions:
  - The BCG programme only effects the UK born
  - Prior to 2000 there were no UK born cases (no reservoir population – highly conservative!)
  - Non-UK born cases are constant post 2015
  - Universal vaccination
- Scenario analysis:
  - Varying transmission rate.
  - Comparing school age, neonatal and no vaccination.
  - Varying non-UK born cases projection assumption.

Modelling the indirect effects of the 2005 change in BCG vaccination policy in England

- Aim: Modelling the indirect effects of the 2005 change in BCG vaccination policy in England
- Assumptions:
  - Fit to data from 2000 to 2004 (i.e pmcmc)
  - Assume school age policy was in effect
  - Assume that post 2004 estimated vaccine effectiveness and coverage can be applied to neonates.
  - Universal vaccination
  - Non-UK born cases are constant post 2015
- Scenario analysis:
  - School age vs. neonatal vs. no vaccination
  - The effects of vaccine effectiveness increases in neonates/changes in coverage
  - Compare with observed incidence
  - Varying non-UK born cases projection assumption.

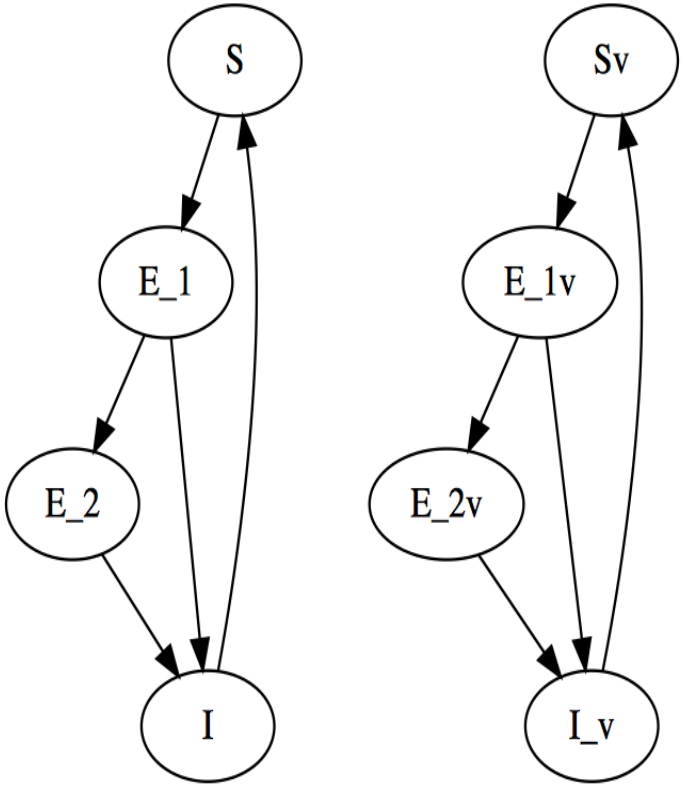
Tuberculosis model

- A parsimonious model:
  - Susceptible, high risk latents, low risk latents, infected (recover to susceptible)
  - Found to be the simplest model able to reproduce latent dynamics with transmission data (Ragonnet et al. 2017)
  - Non-UK born cases are not modeled
  - An external force of infection is applied representing the non-UK born population: Gamma white noise process * non-UK born incidence * period infectious, with non-UK born cases smoothed using a spline
  - More features: TB mortality, treated compartment etc. added if required.



Vaccination Model

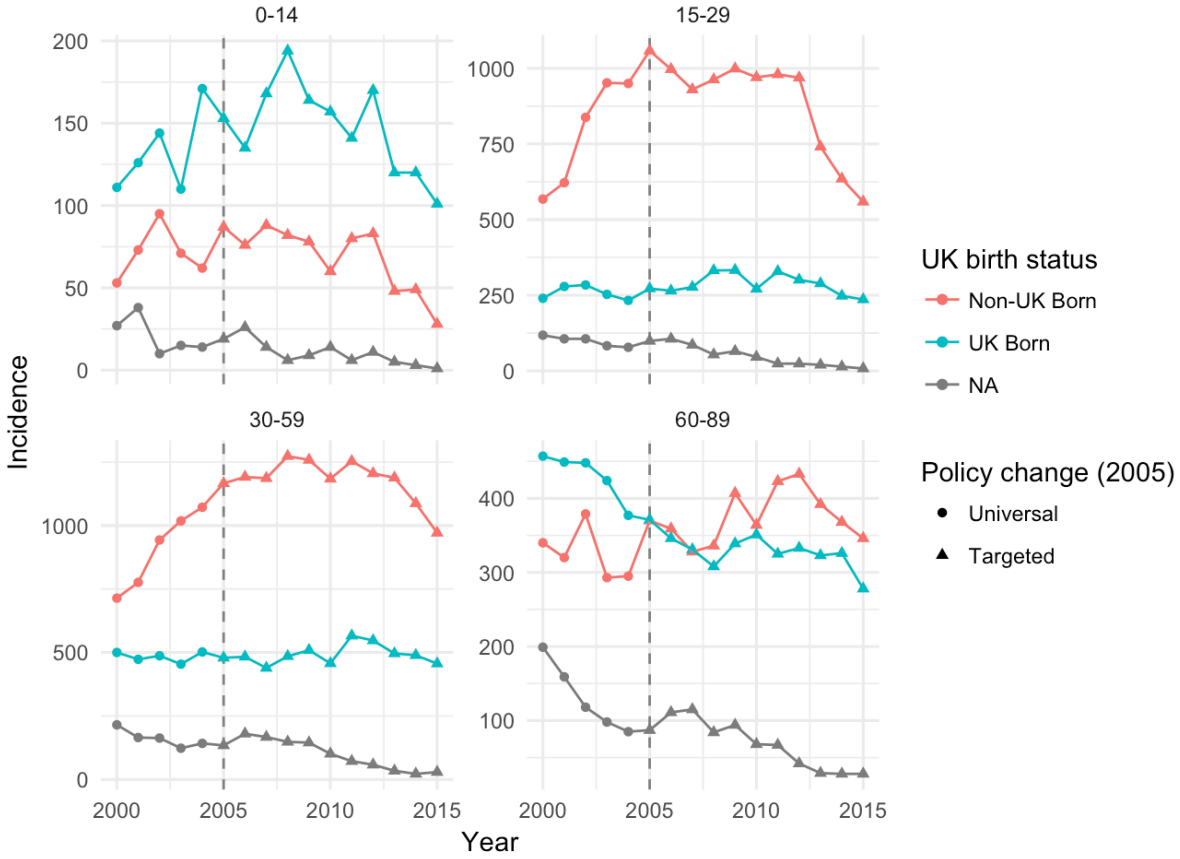
- Vaccination given on entry to a sub-population (i.e age group)
- Vaccination has imperfect protection
- Vaccination acts to reduce transmission from both high risk and low risk latent compartments to active disease
- Vaccination waning modelled via a step function across age groups (currently steps from full effectiveness to zero effectiveness)



Demographic Model

- No diagram ☹
- Age groups:
  - Children (0-14), young adults (15-29), adults (30-59), older adults (60-89)
  - Children are considered at risk of negative outcomes
  - Young adults more likely to onwards transmit
  - Older adults have different contact patterns, mortality rates etc
- Contact matrix: Polymod or approx Polymod.
- Births: Introduced as a smoothed covariate, using observed and projected births from ONS
- Mortality Rates: Smoothed age specific mortality rates estimated from ONS age specific mortality rates, assumed to be constant post 2015
- Continuous ageing
- Population limited to those under 90 due to poor data, ageing out of the older adults class is effectively untracked mortality.

An aside: Incidence in modelled age groups



Model Equations/ Simulation

1. Deterministic simulation via R-K
2. Stochastic simulation via the Euler-Maruyama method (this may change – comments?)
3. Stochastic model for analysis, deterministic for sanity checks!

The force of infection (λ_j, with $j = 0, 1, .., A$) is defined as follows, for a model with A age groups;

$$\lambda_j = \frac{\beta}{N} \sum_{k=1}^{A} C_{jk} \left(\frac{\iota_k \zeta(t)}{\nu} + \sum_{i=u,v} I_k^i \right)$$

The equations for the SEI model with vaccination are as follows;

$$\frac{dS_j^u}{dt} = (1 - sgn(j))(1 - \gamma_j)\omega - \lambda_j S_j^u + \nu I_j^u - \theta_j S_j^u + sgn(j)(1 - \gamma_j)\theta_{j-1} S_{j-1}^u - \mu_j S_j^u$$

$$\frac{dE_{1j}^u}{dt} = \lambda_j S_j^u - \epsilon_1 E_{1j}^u - \kappa E_{1j}^u - \theta_j E_{1j}^u + sgn(j)\theta_{j-1} E_{1j-1}^u - \mu_j E_{1j}^u$$

$$\frac{dE_{2j}^u}{dt} = \kappa E_{1j}^u - \epsilon_2 E_{2j}^u - \theta_j E_j^u + sgn(j)\theta_{j-1} E_{j-1}^u - \mu_j E_j^u$$

$$\frac{dI_j^u}{dt} = \epsilon_1 E_{1j}^u + \epsilon_2 E_{2j}^u - \nu I_j^u - \theta_j I_j^u + sgn(j)\theta_{j-1} I_{j-1}^u - \mu_j I_j^u$$

$$\frac{dS_j^v}{dt} = (1 - sgn(j))\gamma_j\omega - \lambda_j S_j^v + \nu I_j^v - \theta_j S_j^v + sgn(j)\theta_{j-1}(S_{j-1}^v + \gamma_j S_{j-1}^u) - \mu_j S_j^v$$

$$\frac{dE_{1j}^v}{dt} = \lambda S_j^v - (1 - \alpha_j)\epsilon_1 E_{1j}^v - \kappa E_{1j}^v - \theta_j E_{1j}^v + sgn(j)\theta_{j-1} E_{1j-1}^v - \mu_j E_{1j}^v$$

$$\frac{dE_{2j}^v}{dt} = \kappa E_{1j}^v - (1 - \alpha_j)\epsilon_2 E_{2j}^v - \theta_j E_{2j}^v + sgn(j)\theta_{j-1} E_{2j-1}^v - \mu_j E_{2j}^v$$

$$\frac{dI_j^v}{dt} = (1 - \alpha_j)(\epsilon_1 E_{1j}^v + \epsilon_2 E_{2j}^v) - \nu I_j^v - \theta_j I_j^v + sgn(j)\theta_{j-1} I_{j-1}^v - \mu_j I_j^v$$

Where u, v represent the unvaccinated and vaccinated populations respectively. The total population is the sum of all compartments such that;

$$N = \sum_{i=u,v} S^i + E_1^i + E_2^i + I^i$$

The signum function used above is defined as follows;

$$sgn(x) := \begin{cases} -1 & \text{if } x < 0, \\ 0 & \text{if } x = 0, \\ 1 & \text{if } x > 0. \end{cases}$$

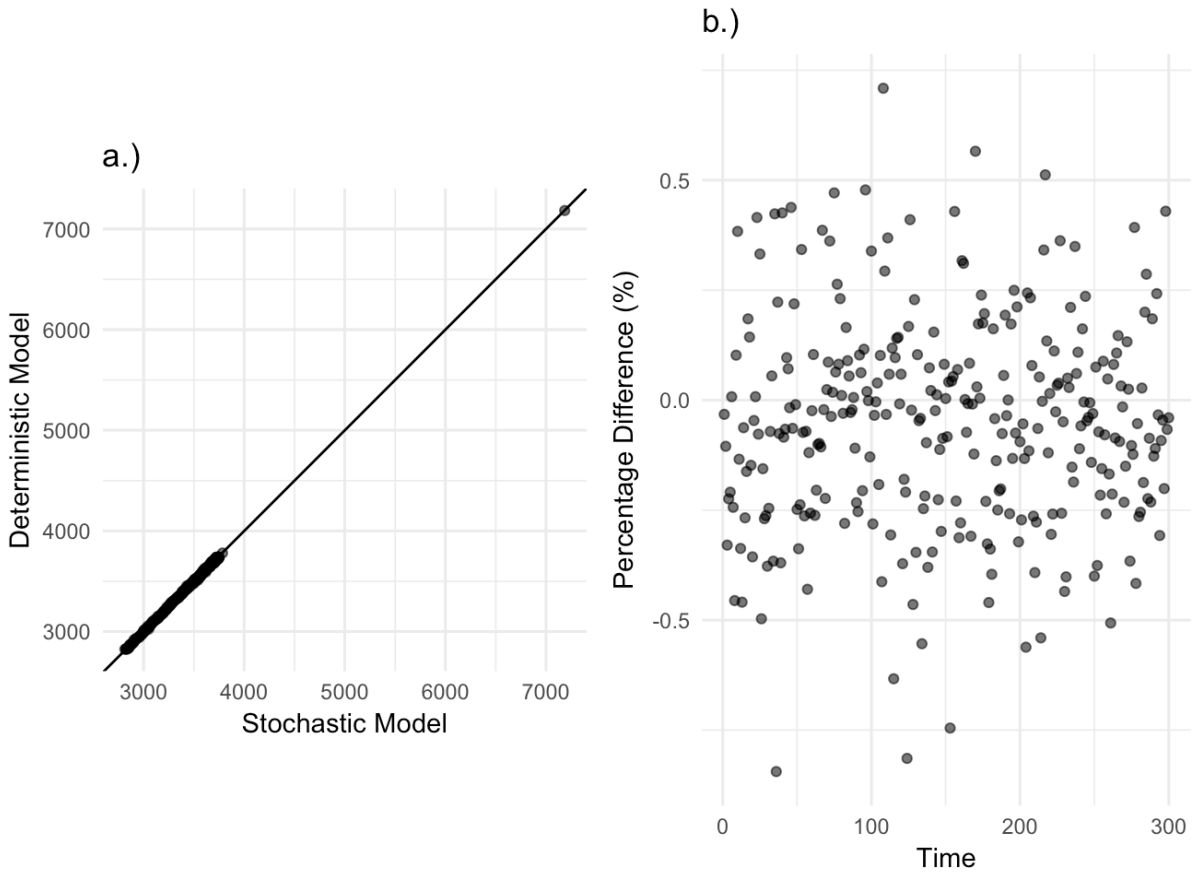
Parameters:

Parameter	Interpretation
β	The infectiousness of each case
ϵ_1	The rate of transition to active disease during high risk latency
κ	1 / the average high risk latent period
ϵ_2	1 / the average low risk latent period
ν	1 / the average infectious period
ι	The number of cases imported into the population
σ_{SE}	Intensity of the white noise process
γ	The proportion vaccinated in each age group
α	The vaccine effectiveness (VE) in each age group
C	The contact matrix of contact rates between each age group
μ	1 / the average life expectancy
N	The population size

Developments

- Switching from a white noise process if it proves hard to parameterize (parameterized using noise in the ETS dataset - not implemented yet)
- Initialise model with age distribution from 2000, for burn-in set births/deaths to maintain static distribution (any suggestions for another approach).
- Additional disease complexity: Treatment, re-activation etc.
- Increasing the number of age compartments if model is not producing realistic dynamics.
- More realistic assumptions about non-UK born rates.
- PMCMC particle calibration and model fitting (approach may be changed if computation is infeasible).
- Shiny app containing slimmed down scenario analysis, example trajectories etc (framework made, waiting on model initialization).

Model checking – How do you check models?



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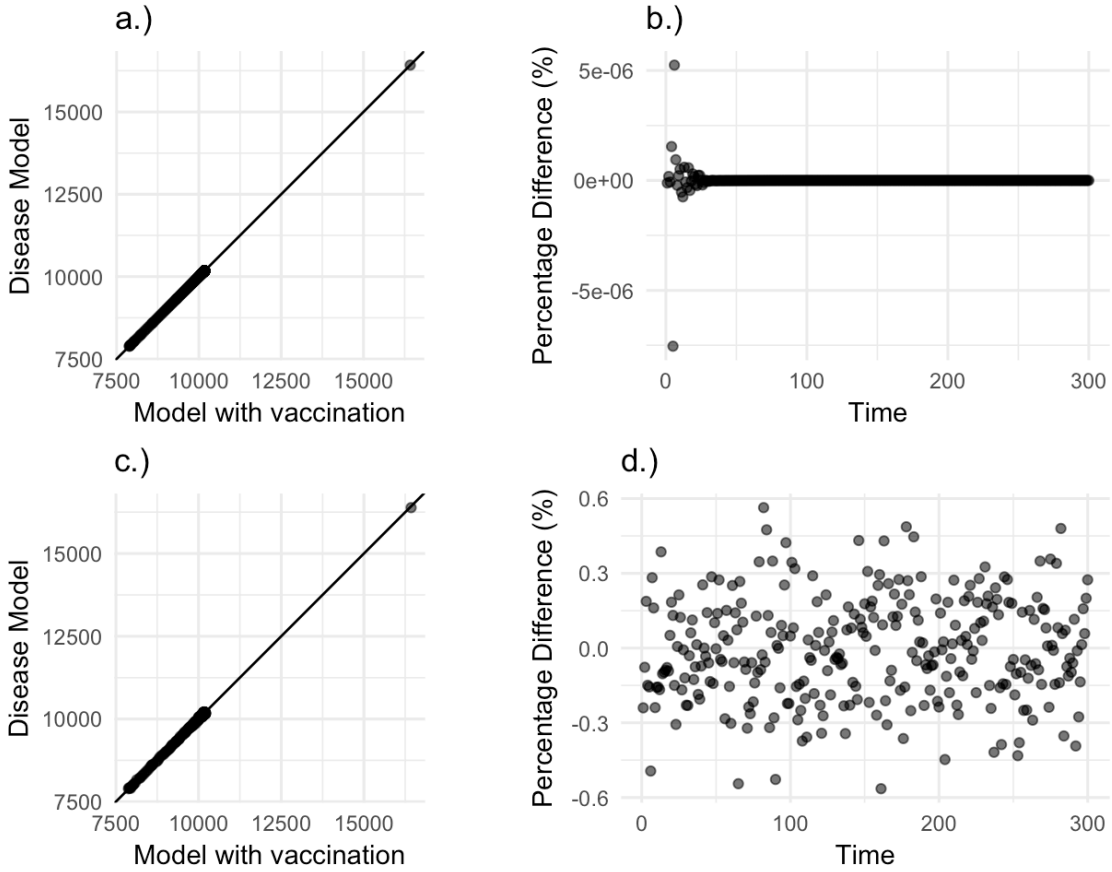

R packages

- Idmodelr – R package containing generic modelling tools, plot model trajectories, manage multidimensional models, generate parameter permutations, run scenario analysis, and coming soon analysis of scenario analysis.
- Prettypublisher – R package to facilitate easy formatting of output, pretty odds ratios, percentages, effect sizes and more.
- Both available via GitHub (www.github.com/seabbs) or my website (www.samabbott.co.uk)

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