Mathematical modelling to estimate the impact of age of BCG vaccination on global paediatric TB mortality

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List of Abbreviations

BCG: Bacillus Calmette–Guérin

CI: Confidence interval

CFR: Case Fatality Ratio

DHS: Demographic & Health Survey

DTP1: First dose of Diphtheria-Tetanus-Pertussis Vaccine

EPI: Expanded Programme on Immunisation

HIV: Human Immuno-deficiency Virus

Hib: Haemophilus influenzae type b

HR: Hazard Ratio

MCV: Measles containing vaccine

M.tb: Mycobacterium tuberculosis

RCT: Randomised Controlled Trial

RR: Rate Ratio

SAGE: Scientific Advisory Group of Experts

TB: Tuberculosis

UR: Uncertainty Range

VE: Vaccine Efficacy

WHO: World Health Organization

UNPD: United Nations Population Division

UNICEF: United Nations Children's Fund

Abstract

Background

The World Health Organization (WHO) recommends that HIV-negative infants in high burden tuberculosis (TB) countries should receive a single dose of Bacillus Calmette–Guérin (BCG) vaccine as soon as possible after birth. However, globally 50% coverage is achieved at 3 – 4 weeks of age. The WHO is currently considering whether to update the recommended age of BCG vaccination. We therefore estimated the potential impact of changes to the age of BCG vaccination on global paediatric mortality.

Methods

A static mathematical model was created and calibrated to the number of global childhood TB deaths in 2015 (169 000; range: 145 000-194 000), assuming the current age distribution of BCG vaccination (reaching 89.4% coverage at 31 months of age). The number of TB deaths per global birth cohort over the first 15 years of life was estimated, for 12 hypothetical scenarios for age of BCG vaccination. Scenarios included recommending BCG vaccination either at birth, 6 weeks, 6 months or 1 year of age, with 2-4 implementation scenarios for each recommendation, which included BCG co-administration with the first dose of Diptheria-Tetanus-Pertussis vaccine (DTP1) or measles containing vaccine (MCV).

Results

BCG final coverage (89.4%) achieved at birth, was estimated to lead to 4 933 (95% UR: 198 – 12 089) or 2.9% (95% UR: 0.1% - 7.1%) fewer TB deaths. BCG co-administration with DTP1, recommended at 6 weeks of age, was estimated to lead to a 3 119 (95% UR: 125 – 7 643), or 1.8% (95% UR: 0.1% - 4.5%), increase in TB deaths, assuming BCG final coverage was not exceeded. However, BCG co -administration with DTP1 where BCG final coverage equalled DTP1 final coverage (92.9%) was estimated to result in 3 585 (95% UR: 139 – 9 111) or 2.1% (95% UR: 0.1% - 5.3%) fewer TB deaths. Vaccination starting at 6 months was estimated to lead to 19 707 (95% UR: 790 - 48 284) or 11.7% (95% UR: 0.5% - 28.2%) additional TB deaths. BCG co-administration with MCV, recommended at 9 or 12 months, was estimated to lead to 30 547 (95% UR: 1 224 – 74 840) or 18.1% (95% UR: 0.7% - 43.8%) additional TB deaths, assuming BCG final coverage could not be increased.

Conclusion

The greatest reduction in the global burden of childhood TB could be achieved if existing routine delays in BCG vaccination at birth could be eliminated. Most scenarios of delayed vaccination would be anticipated to increase global paediatric TB mortality. However, BCG co-administration with

DTP1, recommended at six weeks of age, may result in a small reduction in TB mortality if final BCG coverage were able to reach DTP1 coverage levels. WHO policy makers should consider the feasibility of achieving earlier vaccination or increased coverage if the current BCG recommendations are to be updated.

Introduction

Since its first use in humans in 1921, more than 3 billion people have been vaccinated with Bacillus Calmette-Guérin (BCG).(1) Today, approximately 100 million infants receive BCG vaccination every year as part of the World Health Organization's (WHO) Extended Programme on Immunisation (EPI).(2)

The WHO recommends that,

> "In countries with a high burden of TB [tuberculosis], a single dose of BCG vaccine should be given to all infants as soon as possible after birth". (3, p.27)

BCG vaccine has been shown to be highly effective at preventing severe forms of childhood tuberculosis (TB), reducing the risk from TB meningitis and miliary TB by 85% (RR 0.15 95% CI: 0.08 - 0.32) (4) or TB associated death by 66% (RR 0.34, 95% CI: 0.12 – 0.92). (5) BCG's effectiveness at preventing adult pulmonary disease is however less clear, with reported effectiveness ranging from 0 – 80%.(6, 7) Recently, it has also been suggested that BCG may have beneficial non-specific effects, conferring protection against diseases other than TB and leading to a reduction in all-cause mortality (8), though further research is required to understand the size and mechanism of this possible effect. (9)

In 2015, worldwide BCG coverage was estimated at 88% (10); however this global figure hides large disparities between TB endemic countries. For example, in 2015, within the WHO African Region, Nigeria had a coverage estimates of only 68% compared to 99% in Tanzania, whilst in the WHO Western Pacific Region, Papua New Guinea achieved just 65% coverage, compared to 99% in Malaysia. (10)

Furthermore, vaccination coverage estimates provide little information on the age at which vaccines are delivered. It has been shown that the timing of childhood vaccinations varies widely between and within countries, with delayed vaccination extremely common for many childhood vaccines, including BCG, Diptheria-Tetanus-Pertussis (DTP), and the Measles containing vaccine (MCV). (11) For BCG, the median age at vaccination was greater than 4.6 weeks in a quarter of low and middle income countries surveyed. (11)

There are several, often setting-specific, reasons why BCG vaccine may not be administered at birth. For example, children born at home may have infrequent contact with health workers, staff in small centres may only provide BCG vaccine once or twice a month to minimise wastage from multi-dose vials, and many countries operate a policy of delayed vaccination for low birth weight children. (12) In addition, manufacturing shortfalls recently led to global shortages in BCG supply. Modelling

suggests that such widespread shortages could lead to thousands of additional childhood TB deaths due to missed BCG vaccination.(13)

In 2005, the WHO Scientific Advisory Group of Experts (SAGE) highlighted the importance of regularly reviewing the evidence base for the EPI schedule in light of new vaccines, evolving health systems, and the changing epidemiology of the underlying diseases. (14). The WHO are now considering the evidence base around the timing of BCG vaccination, and whether to update the recommendation on what age BCG should be delivered during the EPI schedule.

As BCG vaccination forms a cornerstone of TB prevention policy, it follows that efforts to either increase BCG vaccination coverage or to improve the timing of vaccine delivery could lead to a reduction in disease burden. However, the magnitude of this impact has not been explored in the published literature. We therefore present results of mathematical modelling to explore the potential impact of changes to the recommended age of BCG vaccination on global numbers of TB deaths per birth cohort over the first 15 years of life.

Methods

Data inputs and assumptions

Population Estimates

The annual global BCG-eligible birth cohort was estimated at 130.04 million in 2015, based on the total number of births per annum from the 157 countries with a policy of universal neonatal BCG vaccination as listed in the BCG World Atlas (15) and WHO/UNICEF 2015 BCG coverage estimates. (10) The annual number of births in each country was estimated from the United Nations Population Division (UNPD) estimate of births from 2010 – 2015, assuming that births were distributed equally over this period. (16) For seven countries (Tuvalu, Saint Kitts & Nevis, Niue, Nauru, the Marshall Islands, Dominica, and the Cook Islands) without available UNPD data, annual births were estimated using the CIA World Factbook. (17) The birth cohort was not adjusted for children born with HIV infection - in whom BCG vaccine would be contraindicated (18) – due to lack of suitable data and the minimal estimated impact of this adjustment (<0.2% of the birth cohort)(19)

For this global birth cohort, 8.17m (6.28%) all-cause deaths were estimated to occur during childhood (0-14 years), using UNPD 2010-2015 data for 0-4, 5-9, and 10-14 year olds and assuming that annual deaths were distributed equally across 2010-2015.(20) To estimate the weekly risk of all-cause death, these estimates were also assumed to be equally distributed by week within each age group.

BCG Parameters

A systematic review of the literature exploring BCG vaccine efficacy by age of administration was conducted (see appendix A for search strategy and sifting diagram). Four original research articles, (8, 21-23) and one systematic review (9) were identified, but no conclusive evidence to suggest that BCG efficacy varies depending on age of vaccination was found. It was therefore assumed that the protective effect of BCG against TB associated death was equivalent whether given at birth or later.

A published meta-analysis of five randomised controlled trials estimated the rate ratio (RR) of TB death in BCG vaccinated neonates versus unvaccinated neonates as 0.34 (95% CI: 0.12 – 0.92), corresponding to a vaccine efficacy (VE) against TB death of 0.66 (95%CI: 0.08 – 0.88). (5) This parameter was incorporated into the model as 'all or nothing' protection (i.e. vaccine efficacy was assumed to be the proportion of vaccinated individuals who would be completely protected against TB death).

Evidence suggests that BCG vaccine may provide long lasting protection for up to 15-20 years. (5, 24) It was therefore assumed that the protective effect of BCG vaccine would last for the duration of the 15-year model time horizon, with no waning of vaccine efficacy over this time-period.

Vaccine coverage by age

A study by Clark and Sanderson estimated vaccination coverage by age in low and middle income countries. (11) They used the most recent household surveys (US AID Demographic & Health Survey or UNICEF Multiple Indicator Cluster Survey) from 66 countries between 2005 and 2012, to determine the exact age at which children received their vaccines. From this data, vaccine coverage was estimated - by week during the first year of life, and by month for the two years thereafter – for each country surveyed and for eleven global regions based on WHO mortality strata.

Using 2015 WHO / UNICEF coverage estimates (10) and vaccine coverage by age data for the 157 countries that make up the global birth cohort,(11) the proportion of the global birth cohort that had been vaccinated with BCG, DTP1 and MCV by age was estimated. This was used to create the hypothetical scenarios of BCG vaccination age (below).

The Clark study (11) did not include high-income countries, yet five high-income countries have a policy of universal vaccination (Brunei Darussalam, Ireland, Japan, Portugal and Singapore), which together represent 0.975% of the BCG eligible global birth cohort. For these countries, a proxy measure - UK vaccine coverage by age data for DTP1 vaccine - was used instead. DTP1 vaccine is universally offered in the UK (unlike BCG vaccine) from 2 months of age, so the cumulative figure for week 8 in the DTP1 coverage distribution was taken to represent the proportion that would receive BCG in the first week of life in these five countries. MCV coverage by age data were not available for these five high income countries, so the global MCV coverage distribution is based on data from 152 low and middle-income countries.

TB Mortality & Incidence

Worldwide, there were an estimated 169 000 (range: 145 000– 194 000) TB deaths in HIV-negative children aged 0-14 years in 2015, with an additional 41 000 (range: 35 000-47 000) deaths in HIV-positive children. (25) As BCG vaccine is contraindicated in HIV-infected infants, it was assumed that only HIV-negative paediatric deaths could potentially be averted, therefore only HIV-negative deaths were modelled. As per previous modelling studies, (26) it was assumed that the annual global

paediatric TB mortality in children aged 0-14 years (period mortality), was equivalent to the TB mortality of a single global cohort over the first 15 years of their life (cohort mortality).

The proportion of total childhood TB deaths that occurred in children aged 0-4 years was estimated from unpublished data (Peter Dodd, personal communication, 07 June 2017). (27) The total number of TB deaths in HIV-negative children aged 0-4 years was estimated as the sum of treated (2 690; 95% range: 1 850 – 4 150) and untreated (161 000; 95% range: 107 000 – 221 000) TB deaths in 0-4 year olds. Similarly, the total number of TB deaths in HIV-negative children aged 0-14 years was calculated from treated (4 810; 95% range: 3 710 – 6 550) and untreated (193 000; 95% range: 151 000 – 246 000) TB deaths in this age group. The proportion of childhood TB deaths occurring in children aged 0-4 years was estimated by dividing the total number of TB deaths in children aged 0-4 years by the total in children aged 0-14 years. This proportion was applied to distribute the WHO estimate of global paediatric TB deaths between 0-4 and 5-14 year olds.

To estimate the average global case fatality ratio (CFR) for children with TB, the WHO estimate for TB deaths in HIV-negative children was divided by estimated TB incidence in HIV-negative children.(24) As HIV-negative paediatric TB incidence is not directly estimated in the literature, WHO TB incidence estimates among male (470 000, range: 420 000 – 530 000) and female (480 000, range: 410 000 – 560 000) children in 2015 were employed to estimate overall paediatric incidence, and adjusted to remove HIV co-infected cases. (25, p.46) An estimated 11% (range 9 – 14%) of all incident cases of TB (in adults and children) were in persons living with HIV;(25, p.24) it was therefore assumed that this same proportion applied to incident TB in children living with HIV.

Mathematical Model & Baseline (no change in vaccination schedule) Scenario

A mathematical model was developed using Microsoft Excel (Microsoft Office 365, Microsoft) to estimate the following primary outcomes:

- The weekly risk of TB death in unprotected HIV-negative children during the first 15 years of life;
- The estimated change in global childhood TB deaths due to hypothetical changes in the age of BCG vaccination.

In addition, the following secondary outcome was explored:

- The estimated change in global childhood TB cases that would also occur due to hypothetical changes in the age of BCG vaccination.

A static modelling method was employed to estimate the direct effect of vaccination, as paediatric cases are generally minimally infectious,[28] so it was assumed that BCG protection during the first 15 years of life would not affect transmission of *M.tb* within the community.

The baseline (no change in vaccination schedule) scenario was generated using the 2015 global BCG vaccination 'coverage by age' distribution (above) and the 2015 global estimate of HIV-negative paediatric TB deaths. [25]

Firstly, the number of unprotected individuals by each week of age during the first 15 years of life was estimated. Unprotected individuals were defined as those either unvaccinated against TB, or vaccinated but having not mounted a sufficient immune response to confer protection against TB death (1 – vaccine efficacy (VE)). The global BCG vaccination coverage by age distribution was used to estimate the vaccination status of all children from the global birth cohort who were still alive by each week of age, and from this, the number of unprotected children by week of age was estimated. Weekly childhood all-cause deaths were assumed to be distributed proportionately between BCG vaccinated and unvaccinated individuals. This is summarised in equation 1, where n_t = number of unprotected children at age t (weeks), U_t = number of unvaccinated children at age t, V_t = number of vaccinated children at age t, VE = vaccine efficacy, BC = global number of BCG-eligible births, D_t = global number of all-cause deaths by age t, Cov_t = vaccination coverage at age t, and RR = rate ratio of TB death in BCG vaccinated neonates versus unvaccinated neonates.

Equation 1: $n_t = U_t + (V_t \times (1 - VE))$

where $U_t = ((BC - D_t) \times (1 - Cov_t))$,

$V_t = (BC - D_t) \times Cov_t$,

$VE = 1 - RR$

The weekly individual-level risk of TB death in unprotected children aged 0-4 years and 5-14 years (R_{0-4} and R_{5-14}) was calculated (equation 2) by dividing the 2015 estimate of HIV-negative paediatric TB deaths in each age group ($Mort_{0-4}$ or $Mort_{5-14}$) by the sum of the number of unprotected person-weeks in that age group ($\sum n_{0-4}$ or $\sum n_{5-14}$). Where a = age group:

Equation 2: $R_a = Mort_a / \sum n_a$

The average global paediatric case fatality ratio (CFR) was calculated in the baseline scenario for HIV-negative children with TB by dividing the number of TB deaths in HIV negative children (Mort) by the estimated number of TB cases in HIV negative children (Incidence).

Equation 3: CFR = Mort / Incidence

Scenarios of age of BCG vaccination

TB mortality in ten scenarios (B-K) for age of BCG vaccination were compared to the current age of BCG vaccination (scenario A: baseline (no change in vaccination schedule) scenario). These are summarised in Table 1 and Figure 1 below.

Table 1: Summary of age of BCG vaccination scenarios

| Scenario	Scenario Description
A	Baseline (no change in vaccination schedule) scenario
B	89.4% immediate coverage at birth
C	100% immediate coverage at birth
D	0% coverage until six weeks of age, then 89.4% immediate coverage at six weeks.
E	0% coverage until six weeks of age, then 89.4% final coverage delaying the baseline scenario BCG coverage distribution by six weeks.
F	DTP1 coverage distribution, capped when coverage reached 89.4%
G	0% coverage until six months of age then 89.4% immediate coverage at six months.
H	0% coverage until six months of age, then 89.4% final coverage delaying the baseline scenario BCG coverage distribution by six months.
I	0% coverage until 12 months of age, then 89.4% immediate coverage at 12 months.
J	0% coverage until 12 months of age, then 89.4% final coverage delaying baseline BCG coverage distribution by 12 months
K	MCV coverage distribution, capped when coverage reached 89.4%
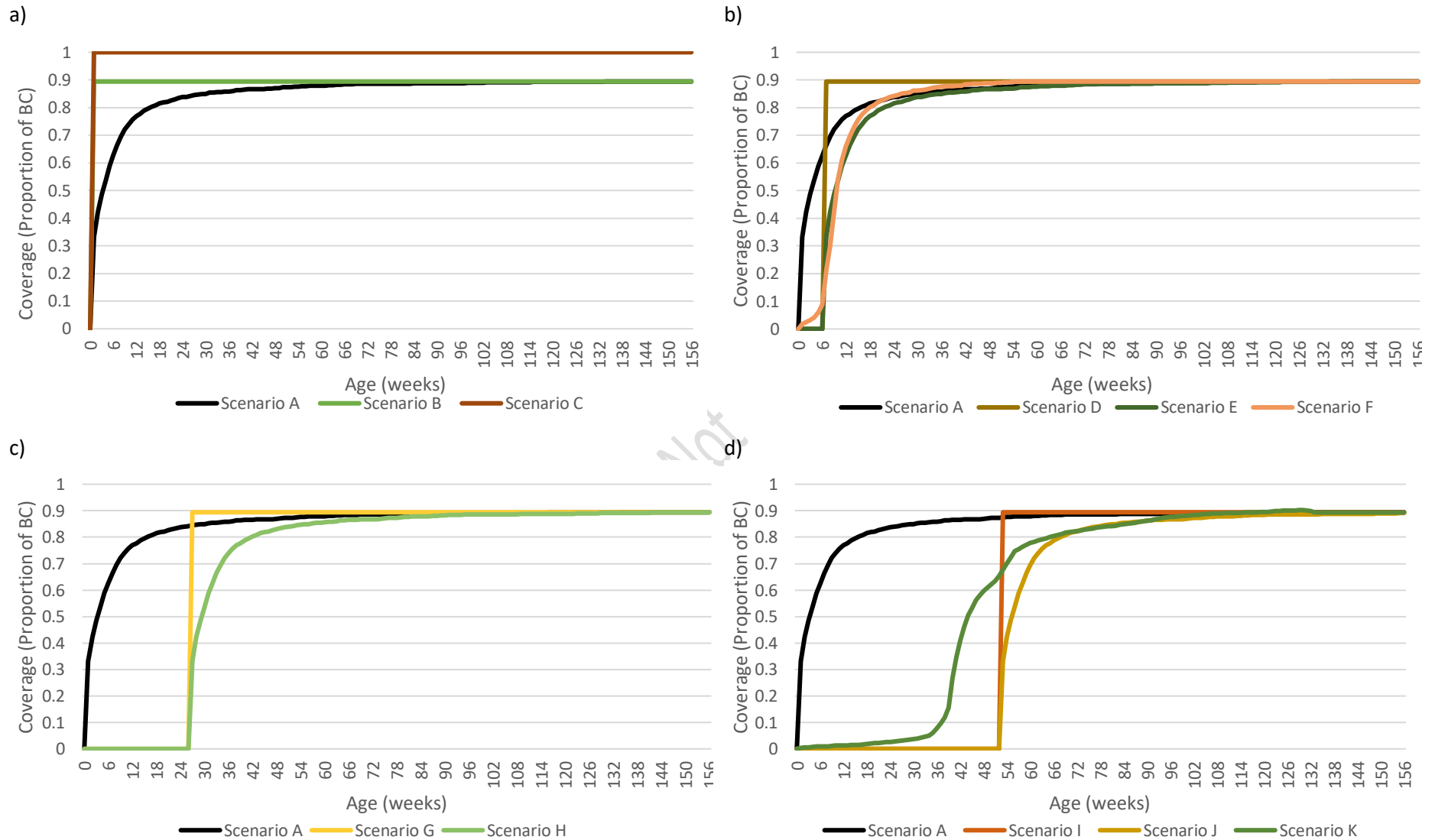
Figure 1: BCG vaccine coverage by age scenarios a) Implementation scenarios of vaccination at birth, b) Implementation scenarios of vaccination delayed by ~6 weeks of age, c) Implementation scenarios of vaccination delayed to ~6 months of age, d) Implementation scenarios of vaccination delayed by ~12 months of age. For scenario descriptions, see Table 1. BC = global BCG eligible birth cohort.

The baseline scenario (scenario A), represents the current global BCG distribution of coverage by age. BCG is recommended as soon as possible after birth, but due to delays in delivery, it was estimated that only 33% of the global BCG-eligible birth cohort received BCG in the first week of life, and 50% coverage was achieved between three and four weeks of age. 87.4% of the eligible global birth cohort received BCG by 52 weeks, with the final coverage estimate of 89.4% achieved by two years and seven months of age.

Two hypothetical 'at birth' scenarios were explored (B&C, Figure 1A). Scenario B assumed 89.4% coverage at birth, whilst scenario C assumed 100% coverage at birth.

Three implementation scenarios for vaccination recommended at 6 weeks were explored (D-F, Figure 1B). Scenario D was similar to scenario B, in that the current final coverage was achieved instantaneously at 6 weeks, whereas scenario E assumed the current BCG coverage distribution was shifted 6 weeks later. The vaccination scenario at 6 weeks, considered the most realistic (scenario F) estimated the impact of co-administering BCG vaccine with DTP1. DTP1 is recommended at six weeks of age, but it is estimated that 8.9% of children receive DTP1 before this age and final coverage (92.9%) is achieved by 3 years of age However, factors other than simply the recommended age of vaccination may influence the final coverage estimate for co-administered BCG, for example the issues of supply in 20-dose vials. Therefore, in the main analysis it was assumed that final BCG coverage would not be able to exceed current BCG coverage estimates, so the distribution in scenario F was capped at 89.4%. This assumption was explored in sensitivity analyses.

Two implementation scenarios for vaccination recommended at 6 months were explored (G-H, Figure 1C) and three implementation scenarios for vaccination recommended at 12 months (I-K, Figure 1D). Scenarios G and I were the equivalent to scenarios B and D, achieving 89.4% coverage immediately at 6 and 12 months, respectively. Scenarios H and I were similar to scenarios C and E above, assuming a shift of the current BCG vaccination distribution by 6 and 12 months, respectively. Scenario K, considered the most likely vaccination scenario for recommended vaccination around 12 months was co-administration with the MCV vaccine, and capped at the BCG final coverage of 89.4% similarly to scenario F. The MCV age of coverage distribution was composed of 70 countries that recommend MCV at 9 months and 75 countries that recommend MCV at 12 months of age, with a few countries that recommend it earlier than this (e.g. Malaysia and Papua New Guinea recommend MCV at 6 months), and a few later than this age (e.g. China recommends MCV at 18 months). Therefore, this scenario represents a WHO recommendation of BCG vaccination between 9 and 12

months, as opposed to at 12 months, but is a potential co-administration vaccine within the EPI schedule.

Vaccine efficacy was assumed unchanged by age of vaccination in childhood. However, changing the timing of BCG vaccination altered the number of unprotected individuals at a given age and the period for which they were unprotected. Therefore, for each scenario, the number of unprotected individuals at each week (n_t) was calculated using the coverage by age distribution (Cov_t) for that scenario in equation 1 (above). The weekly number of TB deaths in each scenario was estimated by multiplying the number of unprotected individuals at each week by the weekly estimated individual risk of TB death in the relevant age group (R_{0-4} and R_{5-14}), calculated using equation 2 for the baseline scenario and then applied to each of the alternative scenarios. The total number of paediatric TB deaths per birth cohort in the first 15 years of life (pTBD) in each scenario was the sum of these weekly estimates of TB deaths (equation 4):

Equation 4: $pTBD = \left(\sum_{t=0}^{t=259} n_t \times R_{0-4} \right) + \left(\sum_{t=260}^{t=782} n_t \times R_{5-14} \right)$

The change in the total number of TB deaths due to the altered timing of BCG vaccination was calculated by subtracting the baseline number of TB deaths (scenario A) from the TB deaths in each scenario (B to K). The change in the number of TB cases in each scenario was calculated by dividing the total number of HIV-negative deaths in each scenario by the CFR (estimated in equation 3), and subtracting the number of cases estimated in the baseline (scenario A).

Uncertainty Analysis

Uncertainty in model outcomes due to parameter uncertainty was estimated by sampling from the parameters in Table 2.

Table 2: Parameters and ranges for uncertainty analyses

No.	Parameter Description	Parameter range	Reference
1	Total number of childhood TB deaths in HIV negative individuals	145 000 – 194 000	(25, p.47)
2	Rate ratio of TB deaths in vaccinated vs. unvaccinated neonates	0.12 – 0.92	(5)
3	Number of TB deaths in children aged 0 – 4 who had received TB treatment	1 850 – 4 150	(27)
4	Number of TB deaths in children aged 0 – 4 who had not received TB treatment	107 000 – 221 000	(27)
5	Number of TB deaths in children aged 0 – 14 who had received TB treatment	3 710 – 6 550	(27)
6	Number of TB deaths in children aged 0 – 14 who had not received treatment	151 000 – 246 000	(27)
7	Number of incident cases of TB in male children	420 000 – 530 000	(25)
8	Number of incident cases of TB in female children	410 000 – 560 000	(25)
9	Percentage of incident TB cases in individuals living with HIV	7 – 11%	(25)

A log-normal distribution was employed for parameter 2, as the published confidence intervals were estimated using the DerSimonian and Laird method. (29) For the remainder, the underlying distributions were not published, therefore log-normal distributions were generated from each point estimate and 95% range, ensuring adequate sampling from the range of values provided whilst being bound by a lower limit of zero. A summary of each parameter and its associated distribution is in Appendix B. As per a previous modelling study, location and scale parameters for each distribution were estimated using the 2.5%, 50% and 97.5% quantiles in rriskDistributions package in the statistical programme R. (13)

Parameters 3 & 4, 3 & 5, 5 & 6 and 4 & 6 were assumed to be perfectly correlated. This was to ensure the number of deaths in children aged 0-4 years would not exceed the number of deaths in children aged 0-14 years, and because it was assumed that numbers of deaths in treated and untreated children would be correlated. Parameters 7 & 8 were assumed to be perfectly correlated as the ratio of incident cases between male and female children was estimated to be between 0.9 and 1.1 depending on WHO region. (25)

Oracle Crystal Ball (Release 11.1.2.4.850, Oracle) was used to generate 100 000 iterations of the model by sampling from each of these nine parameters. Median values and a 95% uncertainty range of the model outcomes are reported from these iterations.

Sensitivity Analysis

The following sensitivity analyses were performed to explore the impact of varying key model assumptions.

1. The WHO estimate for the total HIV-negative childhood TB deaths parameter was replaced by the estimate from the Dodd et al. unpublished study. (27)

2. The 89.4% cap was removed from the DTP1 distribution (scenario F) and the MCV distribution (scenario K). Instead, the reported global final coverage estimate of 92.9% was applied for DTP1, and 90.9% for MCV was reached at three years of age. This allowed exploration of the possibility that co-administration with these other high-coverage vaccines could lead to an increase in final BCG coverage.

3. The correlation between treated and untreated TB death input parameters (3&4 and 5&6) was removed,(27) allowing exploration of the possibility where they may be few TB deaths in children who received treatment, and a large number of deaths in those who had not received treatment, or vice-versa.

4. No paediatric-specific data on HIV-TB co-infection were identified, therefore it was assumed to be equal to the all-ages co-infection proportion in the main analysis. To explore the impact of varying this assumption, and given HIV prevalence is lower in children, the percentage of incident cases of TB in children living with HIV was halved to sample from the range 4.5-7%.

The model was run an additional 100 000 times in Oracle Crystal Ball for each of these sensitivity analyses. Median values and a 95% uncertainty range are reported from these iterations.

Results

Baseline - no change in vaccination schedule – scenario A

The modelled estimate for weekly risk of TB death for an unprotected child was 0.0000099503 (95% Uncertainty Range (UR): 0.0000043827 – 0.0000184722) between the ages of 0 and 4 years, and 0.0000010847 (95% UR: 0.0000003955 – 0.0000023858) for an unprotected child 5-14 years of age. This is equivalent to 10.0 TB deaths per week (95% UR: 4.4 – 18.5) for every 1 million unprotected children between the ages of 0 and 4 years of age, and 1.1 TB death per week (95% UR: 0.4 – 2.4) for every 1 million unprotected children aged 5-14 years.

As calibrated, the total number of HIV-negative TB deaths in the baseline scenario for one global cohort over the first 15 years of life was 168 926 (95% UR: 146 259 – 195 027). Based upon an estimated CFR of 0.2 (95% UR: 0.16 – 0.24), a total of 844 865 (95% UR: 735 744 – 970 554) incident TB cases in HIV-negative children were estimated.

Scenarios of BCG Timing

Results for all BCG timing scenarios are summarised in Table 3 and Figures 2 a-d.

Earlier vaccination scenarios – Scenarios B & C

By improving the current real-world delays that exist in delivering BCG vaccine, so that the estimated final coverage figure of 89.4% was reached in the first week of life (Scenario B), it was estimated that there would be a total of 163 675 (95% UR: 140 967 - 189 885) childhood TB deaths per birth cohort in the first 15 years of life. This represents 4 933 fewer TB deaths (95% UR: 198 – 12 089) than the baseline scenario where BCG was recommended at birth, but only 33.2% receive the vaccine during the first week of life, and 50% coverage was reached between week 3 and 4 of life. In scenario B, there were an estimated 818 739 (95% UR: 708 753 - 944 287) incident TB cases per birth cohort in the first 15 years of life, a reduction of 24 663 (95% UR: 989 – 60 398) compared to the baseline.

Furthermore, it was estimated that if 100% coverage was achieved in the first week of life (scenario C), that there would be 32 762 fewer TB deaths (95% UR: 1 295 - 80 484), and 163 674 (95% UR: 6 482 - 402 395) fewer TB cases per birth cohort over the first 15 years of life. This was equivalent to 19.4% (95% UR: 0.8% - 47.1%) fewer deaths compared to the baseline estimate.

Vaccination delayed by ~ 6 weeks – Scenarios D – F

Although the least likely of these three potential implementation scenarios, immediate coverage of 89.4% at 6 weeks (scenario D) would result in an estimated 370 (95% UR: 15 – 907) fewer childhood TB deaths, and 1 850 (95% UR: 74 - 4 531) fewer TB cases compared to the baseline scenario.

If the baseline BCG coverage distribution was shifted so that BCG was delayed by 6 weeks (Scenario E), it was estimated that an additional 4 557 (95% UR: 183 - 11 166) childhood TB deaths and 22 783 (95% UR: 913 to 55 788) childhood TB cases would occur compared to baseline per birth cohort in the first 15 years of life.

Co-administration of BCG with DTP1 recommended at 6 weeks and capped at 89.4% (scenario F), was considered to be the most realistic of the three potential 6-week implementation scenarios. In this scenario, it was estimated that there would be an additional 3 119 (95% UR: 125 - 7 643) TB deaths and an additional 15 594 TB cases (95% UR: 625 - 38 185) over the first 15 years of life compared to the baseline scenario – an increase of 1.8% (95% UR: 0.1% - 4.5%).

Vaccination delayed by ~ 6 months – Scenarios G – H

Only two scenarios were explored for vaccination at 6 months, as it would require implementation of a new EPI vaccination visit. Immediate coverage of 89.4% at 6 months (scenario G) was estimated to result in an additional 14 800 (95% UR: 593 – 36 263) TB deaths and an additional 73 991 (95% UR: 2 965 to 181 174) TB cases per cohort compared to baseline. Shifting the baseline BCG coverage distribution by 6 months (scenario H) would result in an even greater additional disease burden with 19 707 (95% UR: 790 - 48 284) extra TB deaths, and 98 522 (95% UR: 3 948 to 241 233) extra TB cases per birth cohort in the first 15 years of life compared to the baseline scenario. This was an increase of 11.7% (95 UR: 0.5 to 28.2%).

Vaccination delayed by ~ 12 months – Scenarios I – K

Scenarios I and J were similar to scenarios D/G and E/H, respectively, in that they explored either immediate coverage of 89.4% or shifting of the baseline BCG coverage distribution, but to 12 months. Under scenarios I or J there would either be an additional 34 428 (95% UR: 1 380 – 84 345) or 39 308 (95% UR: 1 575 – 96 298) childhood TB deaths, respectively, whilst there would also be either an additional 172 117 (95% UR: 6 897 to 421 387) or 196 515 (95% UR: 7 875 to 481 103) TB cases per birth cohort in the first 15 years of life compared to baseline (scenario A).

If BCG was recommended for co-administration with MCV (scenario K), which is recommended at 9 or 12 months in most low and middle-income countries, and capped to 89.4% coverage, it was estimated that that there would be additional 30 547 (95% UR: 1 224 – 74 840) childhood TB deaths and an additional 152 716 (95% UR: 6 120 – 373 900) TB cases per birth cohort over the first 15 years of life compared to the baseline scenario.

Table 3: Estimated TB mortality & TB cases per birth cohort in the first 15 years of life in different scenarios of BCG age of vaccination.

Timing of BCG vaccination scenario	Total number of childhood TB deaths per birth cohort in the first 15 years of life (Median, 95% UR)	Change in number of TB deaths compared to Scenario A (Median, 95% UR)	Percentage change in number of TB deaths compared to Scenario A (Median, 95% UR)*	Total number of childhood TB cases per birth cohort in the first 15 years of life (Median, 95% UR)	Change in number of TB cases compared to Scenario A (Median, 95% UR)
A. Baseline (no change in vaccination schedule) scenario	168 926 (146 259 to 195 027)	N/A	N/A	844 865 (735 744 to 970 554)	N/A
B. 89.4% immediate coverage at birth	163 675 (140 967 to 189 885)	-4 933 (-12 089 to -198)	-2.9 (-7.1 to -0.1)	818 739 (708 753 to 944 287)	-24 663 (-60 398 to -989)
C. 100% immediate coverage at birth	135 414 (87 661 to 176 291)	-32 762 (-80 484 to -1295)	-19.4 (-47.1 to -0.8)	677 509 (437 230 to 879 084)	-163 674 (-402 395 to -6 482)
D. 0% coverage until six weeks of age, then 89.4% immediate coverage at six weeks.	168 527 (145 923 to 194 600)	-370 (-907 to -15)	-0.2 (-0.5 to 0.0)	842 922 (734 106 to 968 333)	-1 850 (-4 531 to -74)
E. 0% coverage until six weeks of age, then 89.4% final coverage delaying the baseline BCG coverage distribution by six weeks.	173 739 (149 894 to 201 234)	4 557 (183 to 11 166)	2.7 (0.1 to 6.5)	868 880 (754 122 to 1 002 216)	22 783 (913 to 55 788)
F. DTP1 coverage distribution (capped when coverage reached 89.4%)	172 217 (148 848 to 199 120)	3 119 (125 to 7 643)	1.8 (0.1 to 4.5)	861 478 (748 733 to 991 643)	15 594 (625 to 38 185)
G. 0% coverage until six months of age then 89.4% immediate coverage at six months.	184 254 (155 526 to 219 936)	14 800 (593 to 36 263)	8.8 (0.4 to 21.2)	921 175 (781 800 to 1 095 608)	73 991 (2 965 to 181 174)
H. 0% coverage until six months of age, then 89.4% final coverage delaying the baseline BCG coverage distribution by six months	189 185 (157 428 to 230 080)	19 707 (790 to 48 284)	11.7 (0.5 to 28.2)	945 776 (790 834 to 1 147 796)	98 522 (3 948 to 241 233)
I. 0% coverage until 12 months of age, then 89.4% immediate coverage at 12 months.	203 761 (161 384 to 263 293)	34 428 (1 380 to 84 345)	20.4 (0.8 to 49.3)	1 018 760 (809 352 to 1 313 462)	172 117 (6 897 to 421 387)
J. 0% coverage until 12 months of age, then 89.4% final coverage delaying baseline BCG coverage distribution by 12 months	208 591 (162 355 to 274 791)	39 308 (1 575 to 96 298)	23.3 (0.9 to 56.3)	1 043 029 (813 554 to 1 370 950)	196 515 (7 875 to 481 103)
K. MCV coverage distribution (capped when coverage reached 89.4%)	199 985 (160 556 to 254 282)	30 547 (1 224 to 74 840)	18.1 (0.7 to 43.8)	999 517 (805 514 to 1 269 237)	152 716 (6 120 to 373 900)

*Percentage change in number of TB cases compared to Scenario A is the same as the percentage change in number of TB deaths so is not shown here.

Figure 2a. Median total childhood TB deaths per birth cohort in the first 15 years of life. 95% uncertainty ranges are represented by error bars. For full description of scenarios see table 2.
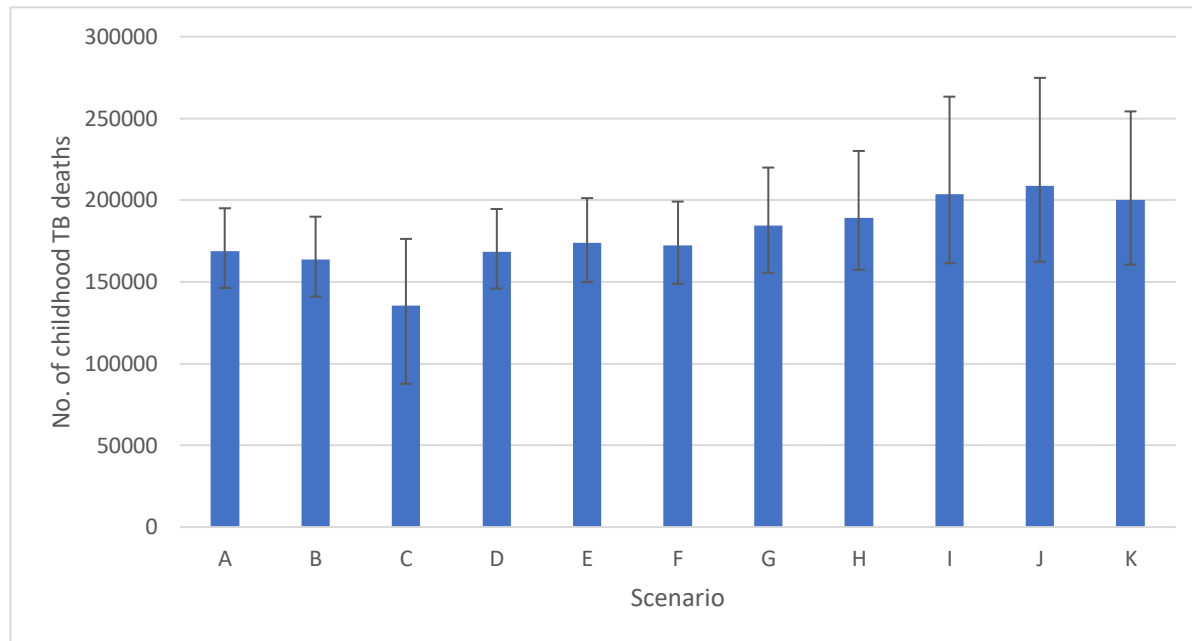

Figure 2b. Median total number of childhood TB cases per birth cohort in the first 15 years of life. 95% uncertainty ranges are represented by error bars. For full description of scenarios see table 2.
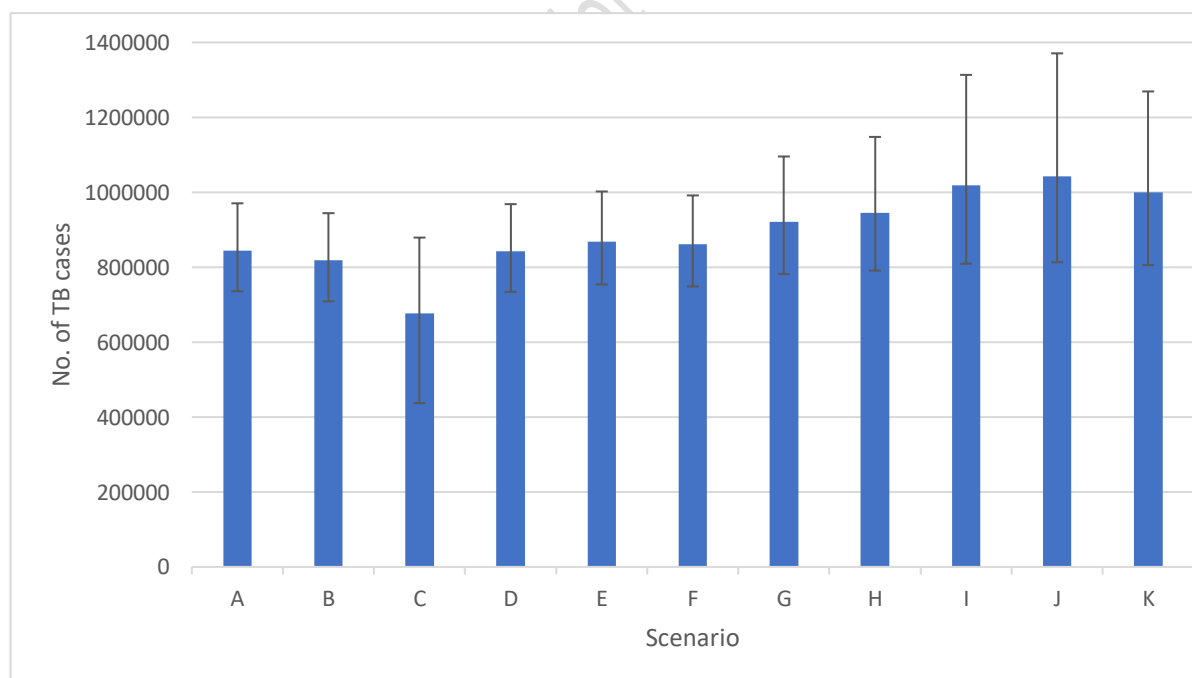
Figure 2c. Median change in number of TB deaths compared to Scenario A (baseline scenario). 95% uncertainty ranges are represented by error bars
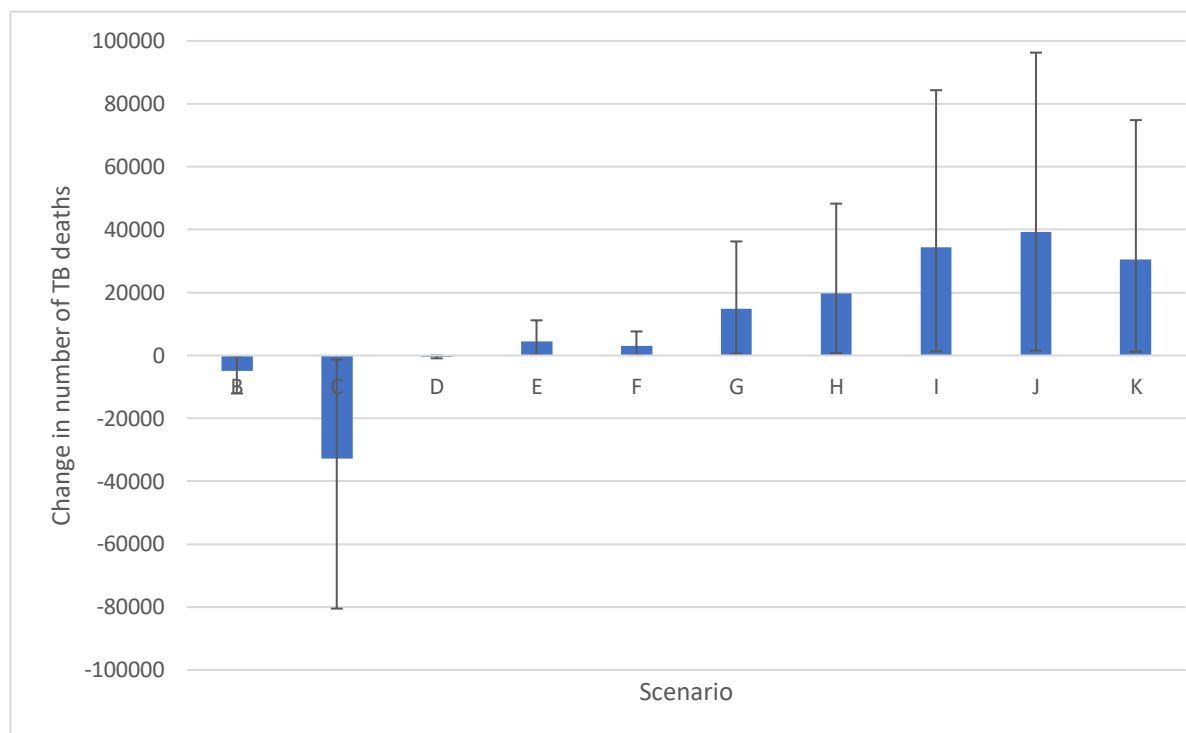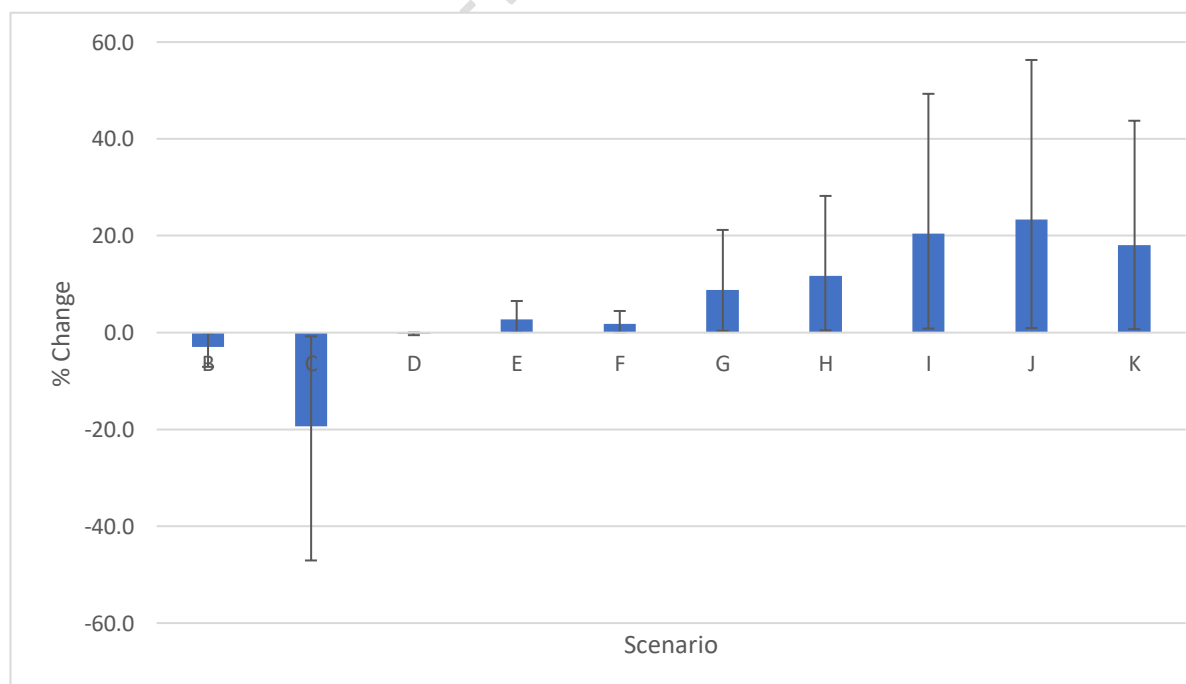

Figure 2d. Percentage change in number of TB deaths compared to scenario A (baseline scenario). 95% uncertainty ranges are represented by error bars

Sensitivity Analyses

Input parameter for HIV negative paediatric TB deaths

When assuming the Dodd et al. estimate for global paediatric HIV negative TB deaths as the main input parameter (27), the individual weekly risk of TB death was estimated to increase to 0.0000116193 (95% UR: 0.0000049325 - 0.0000231566) for unprotected children aged 0-4 years, and 0.0000012702 (95% UR: 0.0000005239 - 0.0000025048) for unprotected children aged 5 – 14 years.

As calibrated, there were 197 759 (95% UR: 154 816 – 252 567) HIV-negative childhood TB deaths, and 845 225 (95% UR: 735 891 – 970 278) HIV-negative incident cases in the baseline scenario. The results from the four main implementation scenarios (one for each timing scenario) are summarised in Table 4 below. These were considered the most realistic implementation scenario at each vaccination recommendation age. In all of the scenarios (including those displayed in the table), there were approximately 17% more deaths in the sensitivity (Dodd) analysis, than the main analysis. This demonstrates that if new estimates emerge for HIV-negative paediatric deaths, the main analysis can be adjusted by a factor of the change in this input parameter.

Table 4: Total childhood TB deaths in the main analysis and HIV negative paediatric TB deaths sensitivity analysis.

Scenario	Total childhood TB deaths (*Median, 95% UR*)	
	Main Analysis	Sensitivity analysis (Dodd et al. estimate, 26)
A. "Baseline (no change in vaccination schedule) scenario"	**168 926** (146 259 to 195 027)	**197 759** (154 817 to 252 568)
B. 89.4% immediate coverage at birth	**163 675** (140 967 to 189 885)	**191 556** (150 093 to 244 788)
F. DTP1 coverage distribution (capped when coverage reached 89.4%)	**172 217** (148 848 to 199 120)	**201 569** (157 485 to 258 133)
H. 0% coverage until 6 months of age, then 89.4% final coverage delaying the baseline scenario BCG coverage distribution by 6 months	**189 185** (157 428 to 230 080)	**221 358** (168 194 to 296 032)
K. MCV coverage distribution (capped when coverage reached 89.4%)	**199 985** (160 556 to 254 282)	**233 981** (173 031 to 324 546)

The input parameter for incident TB cases was not altered in this sensitivity analysis; therefore the estimated number of TB cases were similar to the main analysis and are not reported here.

DTP1 Distribution and MCV Distribution - 'capped' versus 'uncapped'

In the main analysis, the DTP1 coverage distribution (scenario F) and the MCV coverage distribution (scenario K) were capped at 89.4% (the final coverage estimate for BCG). When these coverage distributions were uncapped, DTP1 coverage reached 92.2% and MCV 90.9% respectively. This resulted in fewer childhood TB deaths and TB cases in both situations, as summarised in Table 5 below. Importantly, in the DTP1 sensitivity analysis the direction of impact compared to baseline changed from increased number of deaths (1.8%) to fewer TB deaths (-2.1%).

Table 5: TB deaths and TB cases in capped and uncapped DTP1 and MCV coverage scenarios

Scenario	Total number of childhood TB deaths (Median, 95% UR)	Total number of childhood TB Cases (Median, 95% UR)	Percentage change compared to baseline -Scenario A (Median, 95% UR)
F. DTP1 coverage distribution (capped when coverage reached 89.4%)	172 217 (148 848 to 199 120)	861 478 (748 733 to 991 643)	1.8 (0.1 to 4.5)
F2. DTP1 coverage distribution (uncapped – final coverage estimate of 92.9%)	165 091 (142 471 to 191 155)	825 688 (716 539 to 950 802)	-2.1 (-5.3 to -0.1)
K. MCV coverage distribution (capped when coverage reached 89.4%)	199 985 (160 556 to 254 282)	999 517 (805 514 to 1 269 237)	18.1 (0.7 to 43.8)
K2. MCV coverage distribution (uncapped – final coverage estimate of 90.9%)	197 735 (160 020 to 249 231)	988 300 (802 841 to 1 243 724)	16.8 (0.7 to 40.6)

Correlated versus uncorrelated input parameters

When the correlation between the number of childhood TB deaths in those that had and had not received treatment was removed (see table 7 in Appendix C), this had negligible effect on the estimates for total childhood TB deaths in each scenario.

Incident cases of TB in children living with HIV

When the estimated proportion of HIV co-infection in children developing TB was halved to sample from the range 4.5%-7%, the number of TB cases in HIV negative children rose by approximately 6% in each scenario compared to the main analysis. These results are summarised in table 8 in Appendix C.

Discussion

BCG final coverage (89.4%) achieved at birth, was estimated to lead to 4 933 (95% UR: 198 – 12 089) or 2.9% (95% UR: 0.1% - 7.1%) fewer TB deaths. BCG co-administration with DTP1, recommended at 6 weeks of age, was estimated to lead to a 3 119 (95% UR: 125 – 7 643), or 1.8% (95% UR: 0.1% - 4.5%), increase in TB deaths, assuming BCG final coverage was not exceeded. However, BCG co - administration with DTP1 where BCG final coverage equalled DTP1 final coverage (92.9%) was estimated to result in 3 585 (95% UR: 139 – 9 111) or 2.1% (95% UR: 0.1% - 5.3%) fewer TB deaths. Vaccination starting at 6 months was estimated to lead to 19 707 (95% UR: 790 - 48 284) or 11.7% (95% UR: 0.5% - 28.2%) additional TB deaths. BCG co-administration with MCV, recommended at 9 or 12 months, was estimated to lead to 30 547 (95% UR: 1 224 – 74 840) or 18.1% (95% UR: 0.7% - 43.8%) additional TB deaths, assuming BCG final coverage could not be increased.

The current WHO policy of recommending BCG vaccine as soon as possible after birth to all infants in countries with a high burden of TB averts a substantial number of additional childhood TB deaths and cases, compared to most scenarios of BCG recommended later in the vaccination schedule. However, the real-world effect of recommending BCG at a later time point in the vaccination schedule is difficult to predict, as it is likely that some children may receive the vaccine before the recommended age, whilst others will receive it on time or after the recommended age. We therefore explored a number of implementation scenarios to estimate the impact of recommending BCG at 6 weeks, 6 months or 1 year of age, most of which estimated a substantial increase in childhood TB deaths.

Scenarios B, D, G and I, assumed that at 89.4% coverage was achieved immediately at the recommended age, with no vaccination before the recommended age. This scenario is useful for estimating the effect of perfect implementation of BCG at a given time point, but is considered optimistic given the challenges of vaccine implementation in routine practice. Scenarios E, H & J model the potential impact of shifting the baseline BCG age of coverage distribution to a later time point. This is a more realistic assumption given that the distribution represents a possible distribution of uptake based upon current BCG timing of uptake. These scenarios, however, assume that no vaccination occurs before the recommended age, and therefore likely overestimate the number of additional deaths that may occur. The most realistic scenarios were considered scenarios F and K, which are based on real-world timing of vaccination data for DTP1 and MCV, respectively, both capped at the BCG final coverage (89.4%) as it was assumed that co-administration would have no effect on either vaccine efficacy or final BCG vaccine coverage. A sensitivity analysis explored this assumption by modelling the effect of implementing both timing and coverage data for DTP1 and

MCV. Given that the final coverage estimates for each of these vaccines was higher than for BCG, total TB deaths and TB cases were lower in this sensitivity analysis compared to scenarios F and K respectively. Importantly, in the DPT1 co-administration sensitivity analysis, allowing DTP1 final coverage instead of capping at the BCG final coverage caused a switch from a 1.9% increase to a 2.1% decrease in TB deaths. Therefore, implementation success in the 6-week vaccination scenarios appears to influence the overall positive or negative impact of the change in BCG vaccination timing. Co-administration with DTP1 may increase BCG coverage, but the current BCG multi-dose format may limit achievable increases in coverage, and could even plausibly reduce DTP coverage, therefore caution should be advised against concluding that co-administration would automatically lead to an increase in coverage.

Two key model inputs into were the WHO estimates for HIV-negative paediatric deaths and the WHO estimated incidence of TB in children. (25) Though estimation methods have greatly improved, it remains extremely challenging to reliably estimate the true burden of paediatric TB disease and deaths. Estimates of cases are limited by inadequate access to medical care, and many remain undetected due to difficulties in diagnosing childhood TB clinically or microbiologically. (30) Furthermore, it is simply not known the extent to which TB is the true underlying cause of childhood deaths that are reported as being due to HIV, pneumonia, malnutrition, or meningitis in vital registration data. (30, 31) In the sensitivity analysis, we used an alternative estimate for HIV-negative paediatric TB deaths that was 17% higher than the WHO estimate. (27) Estimated outcome values for each scenario were therefore also 17% higher in the sensitivity analysis than in the main analysis. In future, should any new estimates for global paediatric TB deaths emerge, our model could therefore simply incorporate this new value and re-estimate values for additional childhood TB deaths and disease in each scenario.

Strengths and limitations of the study

This model is based on the latest available estimates for both the number of childhood TB deaths (25), and for the proportion of those deaths that occur in children under five. (27) Our estimates for the individual risk of TB death in 0-4 years and 5-14 years benefit from using age specific vaccine coverage data to take into account routine delays in vaccination that are not captured by simple coverage estimates.

A number of alternate vaccine age of vaccination scenarios have been considered, including age of vaccination data for DTP1 and MCV, therefore several estimates are based on more reliable input parameters than simply hypothetical scenarios.

Like all modelling studies, this study is a simplification of a complex reality, and therefore has several limitations. Firstly, we have assumed that BCG vaccine efficacy is equivalent whether given at birth or at a later time point up to 12 months of age. This assumption was made after conducting a literature review that did not find any reliable evidence to the contrary. However, vaccine efficacy estimates against meningeal or miliary TB for vaccine delivered later than the neonatal period are higher in tuberculin test-negative than -positive children, suggesting that BCG has greater efficacy in individuals not previously sensitised to *Mycobacteria*. (4) It is biologically plausible, therefore, that in the scenarios where BCG is given some time after birth, that BCG vaccine efficacy may be reduced in individuals already sensitised to *M.tb.* This model has therefore potentially underestimated the additional deaths that would occur in these delayed vaccination scenarios. Although considered unlikely, if new research were to find vaccine efficacy to be higher when delivered at a later time point, further research would be required to estimate the impact of changing the timing of routine BCG vaccination.

Secondly, our model has not taken into account potential non-specific effects of BCG vaccine on diseases other than TB, as the evidence for this is still limited.(9) Not including non-specific effects in this model potentially underestimates the possible benefit of early BCG vaccination and the possible detrimental effects of delayed BCG vaccination.

Thirdly, data to inform how childhood TB deaths are distributed by age are limited. It is known that children under the age of two are most at risk of TB meningitis and miliary disease. (32) However, data limitations prevented estimating the risk of TB death in any greater granularity than the age categories 0-4 years and 5-14 years. If the true number of TB deaths in children under the age of two is greater than has been estimated in the model, then the risk of TB death in those years will have been underestimated, as will have the detrimental effects of delayed BCG vaccination and the benefits of improving coverage at birth. This is an important data gap in the field, therefore we encourage studies or improved availability of existing data to inform this distribution.

Fourthly, some sampling variability may have been introduced between the main analysis and the sensitivity analyses, which may have caused a small difference in the baseline number of deaths. The effect of this sampling variability was very small given that the model was run 100 000 times in each analysis.

Fifth, weekly all-cause deaths were assumed to occur proportionately between BCG vaccinated and BCG unvaccinated individuals as data limitations meant we could not determine the actual number of all-cause deaths in each of these groups. Therefore there would have been a very small over-allocation of deaths to the vaccinated cohort, producing a slight overestimate of individual risk of TB

death in the baseline scenario and the impact of changes in each of the subsequent scenarios. However, the actual number of individuals potentially misallocated is very small and therefore the effect on the model estimates would be minimal.

Lastly, the WHO estimates for incident cases of TB in children are not disaggregated by HIV status. For the purpose of calculating the CFR, we have therefore assumed that the proportion of incident cases of TB co-infected with HIV is equal to the proportion of HIV co-infection in incident TB cases in adults and children. This is likely to be an overestimate, given that there were only an estimated 150 000 incident cases of HIV in children in 2015 (19). This assumption is likely to have overestimated the CFR, and consequently underestimated additional cases of childhood TB in the delayed vaccination scenarios.

Collectively, these model limitations tend to underestimate the additional deaths and cases caused by delaying BCG vaccination, therefore estimates presented could be considered a conservative estimate of the additional disease burden that may result from vaccination delays.

Interpretation & Implications

Routine delays in BCG vaccination have been widely reported in the literature (11, 33), despite the WHO recommendation that BCG should be administered "as soon as possible after birth". (3) Our research found that in most scenarios, delaying BCG vaccination, could lead to a substantial increase in the number of childhood TB deaths. The only scenario in which delayed vaccination was potentially beneficial were if co-administration with DTP1 were to lead to increased coverage, but the social, technical and logistical aspects of such an assumption would require in-depth consideration. Therefore, in light of our study, WHO policy makers should consider the feasibility of achieving earlier vaccination or increased coverage if the current BCG recommendations are to be updated.

The underlying causes of delayed vaccination are likely to be multifactorial and context specific. However, the policy of 'restricted vial opening' - not opening a 20-dose vial of BCG vaccine until a sufficient number of children are present - is a widely adopted policy in many TB endemic regions to reduce potential wastage of unused vaccine, and is a known contributory cause of delayed BCG vaccination. (34) Production of individual or 10-dose vials of BCG vaccine could increase coverage, reduce wastage and, crucially, reduce delays in vaccination, thereby reducing preventable childhood TB mortality.

Data gaps and future research

Data limitations currently exist with regards to how childhood TB deaths are stratified by age. We would encourage further studies or further exploration of existing data in this area. This would enable the individual risk of TB death in the early stages of life to be estimated with greater accuracy than is currently possible.

If more robust data on the non-specific effects of BCG vaccine were to emerge, or if data to suggest differential vaccine efficacy by age of vaccination were to come to light, then further modelling could be conducted to explore the impact of these vaccine parameters on model outcomes.

Conclusion

BCG vaccine has been a part of the WHO EPI schedule since 1974, and remains a cornerstone of TB prevention policy. However, as with all EPI vaccines, the evidence base for BCG vaccine recommendations should be subject to regular review.

BCG is highly effective against the most severe forms of childhood TB, but routine delays in administering BCG vaccine exist across TB endemic settings.

The greatest reduction in the global burden of childhood TB could be achieved if existing routine delays in BCG vaccination at birth could be eliminated. Most scenarios of delayed vaccination would be anticipated to increase global paediatric TB mortality. However, BCG co-administration with DTP1, recommended at six weeks of age, may result in a small reduction in TB mortality if final BCG coverage were able to reach DTP1 coverage levels. WHO policy makers should consider the feasibility of achieving earlier vaccination or increased coverage if the current BCG recommendations are to be updated.

The WHO Roadmap for Childhood Tuberculosis has set a target of zero TB deaths among children. (31) Reducing delays in vaccination, and achieving coverage levels equal to that of other vaccines could therefore be valuable strategies to help achieve this goal.

Acknowledgements

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Appendix A: Search strategy & sifting process for literature review

Literature review to explore whether BCG vaccine efficacy varies by age of administration.

1. (bcg or bcg vaccin* or BCG immuni* or bacillus calmette guerin or bacillus calmette-guerin or bacillus calmette guerin vaccin* or bacillus calmette guerin immuni* or bacillus calmette-guerin vaccin* or bacillus calmette-guerin immuni* or tuberculosis vaccin* or tuberculosis immuni* or TB vaccin* or TB immuni*).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw]

2. exp tuberculosis vaccines/ or exp bcg vaccine/

3. (tuberculosis or tb or miliary tuberculosis or miliary TB or TB mening* or mening* TB or mycobacterium tuberculosis).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw]

4. exp Tuberculosis/ or exp Tuberculosis, Meningeal/ or exp Mycobacterium tuberculosis/ or exp Tuberculosis, Miliary/

5. (p?ediatric or child* or infan* or neonat*).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw]

6. exp Child, Preschool/ or exp Infant, Newborn/ or exp Child/ or exp Adolescent/ or exp Pediatrics/ or exp Infant/

7. (delay* or postpon* or catch-up or Catch-up or late or early).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw]

8. exp time/ or exp time factors/

9. 1 or 2

10. 3 or 4

11. 5 or 6

12. 7 or 8

13. 9 and 10 and 11 and 12

14. remove duplicates from 13

15. limit 14 to human

16. (delay* or postpon* or catch-up or Catch-up or late or early or tim*).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw]

17. 8 or 16

18. 9 and 10 and 11 and 17

19. limit 18 to humans

20. limit 19 to (clinical study or clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or systematic reviews)

21. remove duplicates from 20

Medline & Embase & Embase Classic: n = 303		Pubmed: n = 99

Total hits, n = 402	→	Studies removed at title level: 289

Records screened at abstract level, n = 113	→	Studies removed at abstract level: 91

Records screened at full text level, n = 12	→	Studies removed at full text level, n=9:

Studies included, n = 3		

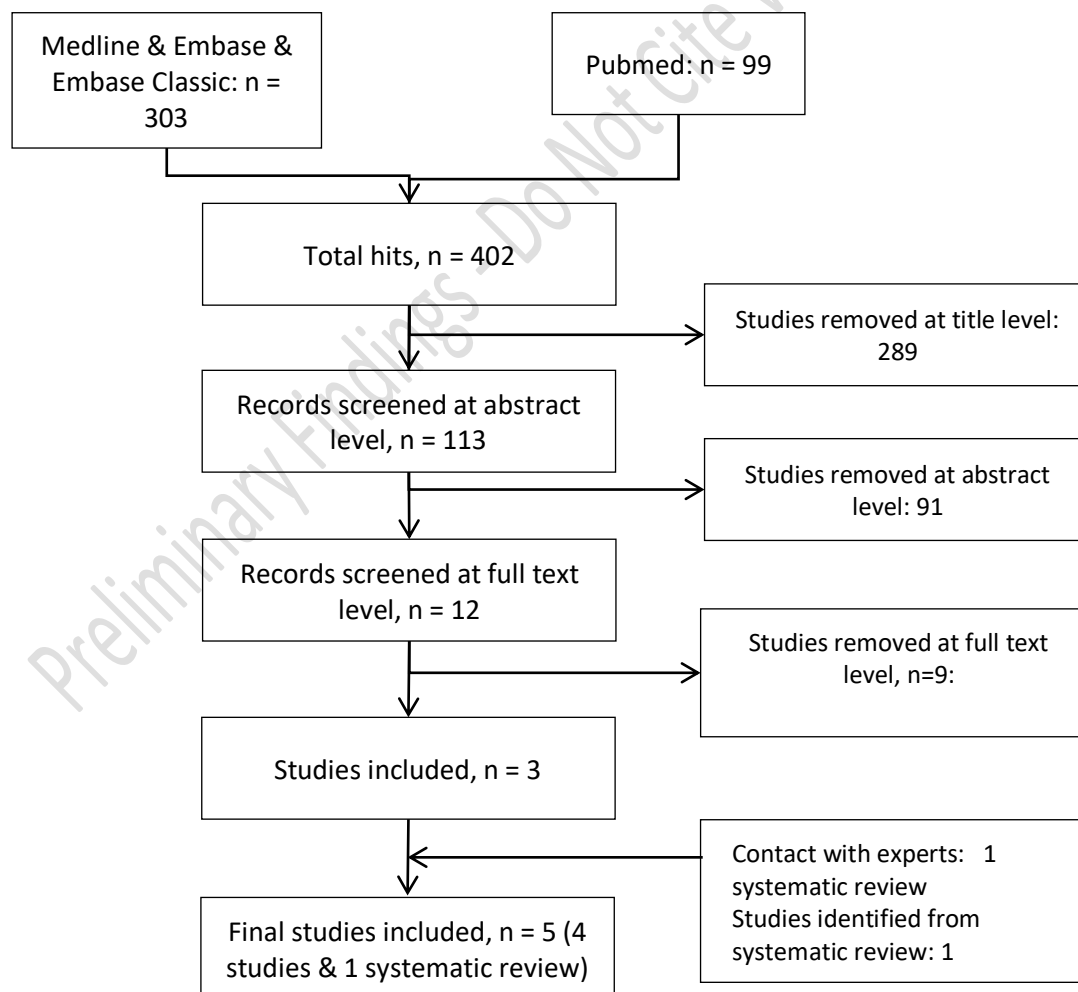| Final studies included, n = 5 (4 studies & 1 systematic review)	←	Contact with experts: 1 systematic review Studies identified from systematic review: 1

Figure 3: Sifting Process for literature review

Appendix B: Summary of model parameters used in uncertainty analysis.

Table 6: Summary of model parameters used in uncertainty analysis.

Parameter	Data source	Data mid-point estimate and range of values	Distribution used	Log mean (2dp)	Log standard deviation (2dp)	Mean value sampled from distribution (95% range)
HIV-negative TB deaths in children 0 – 14 years old	(25)	169 000 (145 000 to 194 000)	Log normal	12.03	0.07	169 397 (146 259 to 195 027)
Rate ratio of TB deaths in vaccinated vs. unvaccinated neonates	(5)	0.34 (0.12 to 0.92)	Log normal	-1.08	0.52	0.39 (0.12 to 0.94)
HIV-negative TB deaths in children aged 0 – 4 years who had received TB treatment	(27)	2690 (1 850 to 4 150)	Log normal	7.90	0.20	2 747 (1 819 to 3 994)
HIV-negative TB deaths in children aged 0 – 4 years who had not received TB treatment	(27)	161 000 (107 000 to 221 000)	Log normal	11.99	0.17	163 190 (115 165 to 225 079)
HIV-negative TB deaths in children aged 0 – 14 years who had received TB treatment	(27)	4810 (3 710 to 6 550)	Log normal	8.48	0.14	4 860 (3 663 to 6 335)
HIV-negative TB deaths in children aged 0 – 14 years who had not received TB treatment	(27)	193 000 (151 000 to 246 000)	Log normal	12.17	0.12	194 458 (151 442 to 246 275)
Number of incident cases of TB in male children 0 – 14 years	(25)	470 000 (420 000 to 530 000)	Log normal	13.06	0.06	470 936 (418 547 to 527 998)
Number of incident cases of TB in female children 0 – 14 years	(25)	480 000 (410 000 to 560 000)	Log normal	13.08	0.08	481 564 (410 556 to 561 236)
Proportion of incident TB cases in individuals living with HIV (main analysis)	(25)	0.11 (0.09 to 0.14)	Log normal	-2.21	0.11	0.11 (0.09 to 0.14)

Appendix C: Sensitivity analyses results

Table 7: Total number of TB deaths in main analysis and sensitivity analysis when the correlation between treated and untreated TB death input parameters (3&4 and 5&6) was removed. Median (95% UR)

	Main analysis	Sensitivity analysis using uncorrelated assumptions
Scenario	Total number of TB deaths (*Median, 95% UR*)	Total number of TB deaths (*Median, 95% UR*)
A. "Baseline (no change in vaccination schedule) scenario"	**168 926** (146 259 to 195 027)	169 049 (146 276 to 195 060)
B. 89.4% immediate coverage at birth	**163 675** (140 967 to 189 885)	163 730 (140 949 to 189 808)
F. DTP1 coverage distribution (capped when coverage reached 89.4%)	**172 217** (148 848 to 199 120)	172 386 (148 943 to 199 311)
H. 0% coverage until six months of age, then 89.4% final coverage delaying the baseline scenario BCG coverage distribution by six months.	**189 185** (157 428 to 230 080)	189 411 (157 717 to 230 576)
K. MCV coverage distribution (capped when coverage reached 89.4%)	**199 985** (160 556 to 254 282)	200 301 (160 841 to 254 884)

Table 8: Total number of TB cases in the main analysis and the sensitivity analysis in which the percentage of incident cases of TB in children living with HIV was halved to sample from the range 4.5-7%. Median (95% UR)

Scenario	Total number of TB cases (*Median, 95% UR*)	
	Main analysis	Sensitivity Analysis
A. Baseline (no change in vaccination schedule) scenario	**844 865** (735 744 to 970 554)	**897 673** (783 020 to 1 028 748)
B. 89.4% immediate coverage at birth	**818 739** (708 753 to 944 287)	**869 740** (754 567 to 1 001 331)
F. DTP1 coverage distribution (capped when coverage reached 89.4%)	**861 478** (748 733 to 991 643)	**915 347** (796 970 to 1 050 435)
H. 0% coverage until six months of age, then 89.4% final coverage delaying the baseline scenario BCG coverage distribution by six months.	**945 776** (790 834 to 1 147 796)	**1 005 242** (842 519 to 1 218 026)
K. MCV coverage distribution (capped when coverage reached 89.4%)	**999 517** (805 514 to 1 269 237)	**1 062 775** (857 923 to 1 348 126)