Modelling the effect of discontinuing universal Bacillus Calmette-Guérin vaccination in an intermediate tuberculosis burden setting

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ABSTRACT

Background

Bacillus Calmette-Guérin (BCG) vaccination is a widely-used public health intervention for tuberculosis (TB) control. In Taiwan, like other intermediate TB burden settings, steadily declining TB incidence raises important questions on whether universal BCG vaccination should be discontinued. Recent surveys on adverse events following immunisation, such as BCG-induced osteomyelitis/osteitis, also suggest a need to re-evaluate the vaccination programme.

Methods

We developed an age-structured transmission dynamic model, calibrated to population demography and age-specific TB notification rates in Taiwan. We adopted ‘weak-protection’ and ‘strong-protection’ scenarios, representing a range of characteristics including the duration of BCG protection and vaccine efficacies against TB infection and progression. We estimated averted disability-adjusted life years (DALYs) and incremental costs over 10 years after discontinuing universal BCG vaccination in 2018, 2035, and 2050. We also examined the potential impact of ‘surveillance-guided’ discontinuation, triggered once notification rates fall to a given threshold.

Results

In the weak-protection scenario, discontinuing BCG would result in 2.8 (95% uncertainty range: 2.3, 3.1) additional notified TB cases and -4.1 (-7.7, 0.8) net averted DALYs over 2018-2027. In the strong-protection scenario, 82.9 (72.6, 91.6) additional cases and -402.7 (-506.6, -301.2) averted DALYs would be reported, suggesting a robustly negative health impact. However, in this vaccine scenario, there could be an overall health benefit if BCG is discontinued once TB notification falls below 5 per 100,000 population. The most influential
vaccine characteristic for the net health impact is the vaccine efficacy against progression to pulmonary TB. In financial terms, the eliminated cost of the vaccination programme substantially outweighed the incremental cost for TB treatment regardless of BCG protection.

Conclusions

BCG discontinuation may be warranted in intermediate burden settings, depending on the quality of vaccine protection, and the potential for refocusing on other TB control activities for earlier detection and treatment.
INTRODUCTION

The Bacillus Calmette-Guerin (BCG) vaccine has been used to protect against tuberculosis (TB) since its introduction in humans in 1921 [1]. In a meta-analysis of randomised clinical trials, summary estimates of BCG efficacy were reported to be 69-92% against childhood meningeal and/or miliary TB and 28-65% against pulmonary TB [2]. In countries with high TB burden, the World Health Organization recommends that HIV-negative infants should be given BCG as soon as possible after birth [3]. On the other hand, low burden countries should consider discontinuing universal BCG vaccination if their TB burden is low enough to meet the criteria of the International Union Against Tuberculosis and Lung Disease (IUATLD) (Box 1) [4].

In most countries with intermediate TB burden, where the annual incidence is between 10 and 100 per 100,000 population, BCG has been routinely offered to neonates [5]. However, unlike high burden settings, TB cases in intermediate burden countries are usually concentrated in older adults [6, 7]. This raises an important question about the need for continuing universal BCG vaccination, which shows little evidence for preventing TB in older adults [8]. Like other intermediate burden countries, Taiwan has shown a high BCG coverage (98%) [9] and a decreasing trend of TB notification rates, from 72 to 43 per 100,000 population over 2005-2016 [10]. In addition, even though the overall TB burden in Taiwan was not considered ‘low’ in the IUATLD criteria for BCG discontinuation [4], the annual notification rate of meningeal TB in children under 5 years old is now less than 0.1 per million general population. Another reason supporting the reassessment of the vaccination programme comes from recent surveys on BCG-induced osteomyelitis/osteitis (BCGO) following immunisation [11], which led to calls for a vaccine withdrawal because of safety
concerns. Although the occurrence of BCGO is rare, it is nonetheless comparable to the childhood TB notification rate (both ≤ 5 per 100,000 population) [10].

In such a context, discontinuing BCG may result in an increase of TB burden, so the decision must be weighed systematically against costs and adverse events associated with the vaccination programme. The situation is further complicated by the uncertainty of BCG protection, such as the duration of protection. Indeed, estimates of vaccine efficacy (VE) can vary by settings [2]. Mathematical modelling offers a helpful tool for capturing these complexities together with TB transmission dynamics, as well as for identifying which uncertainties are most critical to address. Thus, using Taiwan as a case study, we applied modelling techniques, in combination with economic analysis, to tackle the challenges in the policy decision on BCG discontinuation.
METHODS

Model description

We developed a deterministic compartmental model to represent the dynamics of TB transmission in Taiwan. The model was divided into three age groups – children (0-14 years old), adults (15-64), and elders (65 and above). To capture TB natural history, the model was also stratified into distinct states, which can be briefly categorised as Susceptible, Latent, Diseased and Recovered, as illustrated in Figure 1. In the first two years of infection, individuals are categorised as ‘fast-latent’ and suffer from a higher risk of developing active TB disease. After two years, ‘fast-latent’ individuals move to ‘slow-latent’ state and their risk of TB progression reduces [12]. In the diseased states, we distinguish pulmonary and extra-pulmonary TB cases, with only pulmonary TB being infectious. Through successful treatment or spontaneous recovery, diseased individuals then convert to the recovered state. However, recovered individuals may relapse and return to the diseased states. We did not address HIV-infected and multidrug-resistant TB cases in our model because of their low incidences in Taiwan [9].

The model captures the dynamics of TB transmission through the force-of-infection, assumed to be proportional to the pulmonary TB prevalence at a given time. Exogenous reinfection can be acquired in slow-latent and recovered individuals, who then have a reduced risk of developing TB disease [12]. The fast-latent individuals cannot be reinfected because they either develop TB or stabilise to ‘slow-latent’ state within a relatively short period. Annual rates of transition between states were informed by the literature review and country-based statistics (Appendix S2).

Effects of BCG vaccination
We specified a sigmoid function to model the rapid-growing coverage of the BCG programme from 1940 in Taiwan (Appendix S3). Vaccination was assumed to provide ‘leaky’ protection: that is, providing partial protection to all the vaccinated individuals, rather than complete protection to only a proportion [13]. We also assumed that BCG provides protection only against primary infection but not reinfection [8]. To address the uncertainty in BCG protection, we set up ‘weak-protection’ and ‘strong-protection’ scenarios, constituting plausible ranges in a series of vaccine characteristics including duration of protection (10 vs 40 years), and VEs against infection (0 vs 22%), progression to pulmonary TB (0 vs 54%), and progression to extrapulmonary TB (29 vs 54%) (Table 1). These quantitative estimates were chosen to capture the upper and lower limits of overall VE against TB disease summarised by a systematic review [8, 14]. In addition to the protective effects, we included the harmful effect of BCGO, the primary adverse events observed from BCG vaccination in this setting. As there is no evidence to suggest a temporal trend in annual BCGO incidence, we assumed that it occurs at a constant rate among vaccinated neonates [11].

Model calibration

To capture the correct age structure, we applied the annual birth rates and age-specific death rates since 1900 in a transmission-free model, according to the Taiwan Department of Household Registration [15] (Appendix S1). The age distributions of the population in 2000, 2010 and 2015 were fitted by modifying transition rates between age compartments. Using a Bayesian framework, we then calibrated the model to the age-specific TB notification rates over 2005-2016 with Markov chain Monte Carlo techniques (Appendix S3). Probability densities for calibration targets were assumed to be normally distributed, with 95% confidence intervals representing an assumed ±10% of notification error. To model the
disproportionately high TB burden in the elderly, we incorporated an age-structured infection matrix, to reflect differential mixing between age groups, as well as potential age-specific variation in infectiousness of TB cases. We modelled a time-varying treatment initiation rate, using a piecewise linear function with two separate slopes to reflect improvements in TB services after the Taiwan National Health Insurance (NHI) launched in 1995. In addition to these two assumptions, we also incorporated uncertainty in TB natural history parameters in the calibration.

**Economic analysis**

We quantified health impacts through disability-adjusted life years (DALYs), consisting of years of life lost (YLL) and years lived with disability (YLD). We calculated YLLs due to TB by multiplying the number of TB deaths and the year difference between the life expectancy in 2016 and the median age of each age group. YLDs due to TB disease were derived from the product of TB patient-years in the model and the disability weight of non-HIV-infected TB patients in the GBD 2013 study [16]. For BCGO, we included only YLDs in children, as disease-specific deaths and adult cases were not identified in the literature [17]. The duration of illness in BCGO cases was assumed to be 7.5 months based on the average treatment period needed for symptom relief [18]. In the absence of data, we assigned the disability weight of moderate osteoarthritis for BCGO [19], as both conditions share similar symptoms.

For the cost analysis, we took the perspective of the Taiwan Centers for Disease Control (Taiwan CDC), the agency with the principal role in decision-making for TB control, and only included direct medical costs (Appendix S5). Unit costs relating to TB treatment and BCG vaccination were extracted from local databases and then converted from Taiwan New Dollars to US Dollars at an exchange ratio of 29.6:1 in April 2018. We defined costs for
medical prescriptions and procedures by the Taiwan NHI claim prices [20, 21]. The cost for
BCG vaccines was extracted from the Taiwan CDC budget report [22]. We additionally
estimated the compensatory expense for BCGO cases, while noting that this expense is not
paid from public funds, but separately supplied by vaccine manufacture companies. A
constant discounting rate of 3% per year was applied to both DALYs and costs from the year
of BCG discontinuation.

Future projections

In both the weak- and strong-protection scenarios described in Table 1, we projected the TB
and BCGO notification rates. For these projections, we fixed the birth rate, age-specific
death rates, and treatment initiation rate at the levels in the final year of calibration, to
control for demographic changes and new interventions. In the economic evaluation, we
calculated the averted DALYs and the incremental costs over 10 years following BCG
discontinuation, compared with continuing BCG. We combined the outputs of model
calibration with uncertainty in economic inputs, such as the BCGO incidence rate and
disability weights, to find overall uncertainty in averted DALYs and incremental costs
(Appendix S2 & 4). To explore the temporal effect, the health and cost impacts were
evaluated in different years that BCG discontinuation begins (2018, 2035, and 2050).
Additionally, we examined potential policies where discontinuation is triggered by declining
TB notification rates reaching a certain threshold level. We allowed TB burden to decline
indefinitely over time in this simulation, by modelling a hypothetical future scenario with
the treatment initiation rate increasing indefinitely. With this background process, we
simulated a policy where BCG discontinuation is implemented (and maintained indefinitely
thereafter) at different notification thresholds between 5 to 55 per 100,000 population; we
examined the health impact over the 10 years after discontinuation.
Sensitivity analyses

Partial rank correlation coefficients were calculated to identify the most influential factors relating to the decision of BCG discontinuation. We additionally explored the most important characteristic of BCG protection in the weak- and strong-protection scenarios, by changing each of the characteristics in Table 1 at a time. We also examined the sensitivity of model projections to Poisson-distributed notification rates specified in model calibration. All the analyses in this study were programmed in MATLAB.
RESULTS

Table 2 presents model projections of the TB and BCGO burden following BCG discontinuation in 2018. Discontinuing BCG would result in 2.8 (95% uncertainty range: 2.3, 3.1) and 82.9 (72.6, 91.6) additional, cumulative TB cases over 2018-2027 in the weak- and strong-protection scenarios, respectively. These are both small increases, relative to the 10,234 TB cases that were notified in 2016 alone [10]. Declining trends in notifications would remain despite BCG discontinuation. On the other hand, the numbers of averted BCGO cases over the 10 years following BCG discontinuation are similar in both the scenarios.

The upper panel of Figure 2 shows the potential health implications of discontinuing BCG vaccination. In the weak-protection scenario, the net averted DALYs over 2018-2027 after discontinuing BCG would be -4.1 (-7.7, 0.8), compared with continuing BCG. This negative value of averted DALYs suggests a small but increased health burden. However, the uncertainty ranges do not exclude a net positive health impact. Postponing the discontinuation to 2035 and 2050 would result in -1.9 (-3.9, 1.1) and -0.9 (-2.2, 1.0) averted DALYs over the subsequent 10 years, an increasing health gain of the central estimates. On the other hand, in the strong-protection scenario, BCG discontinuation would result in a small but robustly negative net health impact of -402.7 (-506.6, -301.2) and -128.4 (-163.6, -94.1) net averted DALYs in 2018 and 2050, respectively. Considering the health impact by age (Appendix S6), in the weak-protection scenario we found that children would receive health benefits (positive averted DALYs) from preventing BCGO cases, but would also bear the most health burden (negative averted DALYs) caused by additional TB cases. By contrast in the strong-protection scenario, as BCG protection is longer-lasting, adults would have the most TB burden following discontinuation.
The lower panel of Figure 2 addresses the cost implications of discontinuing BCG and shows cost-saving results in both the weak- and strong-protection scenarios. Among the cost items, the key driver is the nationwide BCG immunisation programme. In line with the slightly increased TB health burden following BCG discontinuation, the incremental cost of TB treatment is small compared to the reduced expenses from the immunisation programme and BCGO treatment. Moreover, the inclusion of the BCGO compensatory fee (paid from industry rather than public funds), would not change these overall cost trends but would increase the saving even more (Appendix S6).

We next examined the implications of a vaccination policy to trigger BCG discontinuation when a TB notification rate falls below a threshold level. Figure 3 demonstrates an inverse relationship between the thresholds of notification rates and the ten-year health benefits following BCG discontinuation. Lower notification thresholds (that is, more stringent conditions for discontinuation) would result in an increase of averted DALYs. Discontinuing BCG would bring health benefits approximately at a TB notification rate of 40 and 5 per 100,000 population in the weak- and strong-protection scenarios, respectively.

In the sensitivity analysis, we concentrated on the health impact of BCG discontinuation in 2018 (Appendix S7). In both the weak- and strong-protection scenarios, parameters for economic evaluation and the recent increase in treatment initiation rate were found to be most influential. In addition, net averted DALYs in the weak-protection scenario were particularly sensitive to parameters related to extrapulmonary TB, while pulmonary TB mortality rate had a greater effect in the strong-protection scenario. This reflected the different degrees of vaccine protection against pulmonary and extrapulmonary TB involved in the two scenarios.
Figure 4 explores model sensitivity to the characteristics of BCG protection shown in Table 1. If we could only modify a single characteristic, whether or not the vaccine protects against pulmonary TB was identified as the most critical component in estimating the health impact of BCG discontinuation. However, in the strong-protection scenario, under a BCG vaccine that does not protect against TB infection, the net health impact would not change much, compared to adding this protection in the weak-protection scenario. This may be explained by the concurrent assumption of the long duration of protection, which is able to prevent TB progression in latently-infected adults and elders.
Integrating information on TB transmission and demographic structure in Taiwan, we developed an analytical framework to assess the population-level impact of discontinuing universal BCG vaccination. We showed that, even though BCG discontinuation is currently recommended for low TB burden settings, it may also be considered in intermediate burden settings with an incidence between 10 to 100 per 100,000 population. In particular, in settings where VE for BCG is at the upper end of earlier estimated ranges [8], BCG discontinuation would have a small but robustly negative health impact, as the additional TB burden outweighs the benefits of averting BCG side-effects. In settings where VE is at the lower end of earlier estimated ranges, any net health effect from BCG discontinuation is small compared to model uncertainty (Figure 2). In either scenario, postponing discontinuation until TB burden falls to a given threshold is likely to mitigate negative health impacts (Figure 4), possibly even to the extent that there arises a net health benefit from discontinuation.

To assess policy implications, we must also consider the economic outcomes arising from this work. In particular, BCG discontinuation is consistently cost-saving for the TB programme, and would, therefore, release public health resources for other TB control activities, which may be more effective in accelerating declines in TB burden. For example, our results illustrate that continuous improvement of early detection and treatment initiation could be more impactful than BCG vaccination (Appendix S8). Such impact may well compensate for any negative health effect from BCG discontinuation; addressing this issue will require a systematic analysis of the costs of refocusing TB control efforts from BCG vaccination to improved detection and treatment, an important question for future work.
A large geographic variation in BCG vaccine protection has been reported in the literature [2, 8], and it is also a major source of uncertainty in developing vaccination strategies for TB control [23-25]. As the two scenarios of BCG protection in our study led to different conclusions for BCG discontinuation, further country-based information on BCG protection is essential to improve the assessment of vaccination policies. With the characteristics of BCG protection embedded in our model structure (Table 1), economic evaluation can be efficiently updated once context-specific information on the characteristics of BCG protection is collected, potentially through a pilot study in which BCG is discontinued in a representative sample of a national population.

According to our findings, universal BCG vaccination would have a limited health impact on the future TB epidemic in Taiwan. Even in the strong-protection scenario, the declining trend of TB burden would not be offset by BCG discontinuation. This marginal health impact may be explained by the mismatch between the duration of BCG protection and the TB epidemiology in Taiwan, where more than 50% of the incident TB cases are in the elderly [10]. The nature of immunity waning suggests that the elderly are less or even not protected by BCG vaccination received at birth. Although a 40-year duration of BCG protection was assigned in the strong-protection scenario, elders would still be the age group least sensitive to the withdrawal of the BCG vaccination programme (Appendix S6). Our study results demonstrated the importance of involving age structure in order to characterise the distribution of health impacts in evaluating the population-impact of BCG vaccination policies.

As with any modelling exercise, there are limitations to note. First, we stratified the whole population into three age groups and details of age-related heterogeneity may not be fully captured. However, with this simple stratification, the model is capable of demonstrating
the heterogeneous demographics and transmission dynamics among children, adults and elders (Appendix S4). In addition, we modelled ageing using a per-capita rate of transition between the different age compartments, an approach that – while having the advantage of simplicity [26] – introduces an exponentially distributed ‘residence time’ in each age compartment. Nonetheless, because the health impact of BCG discontinuation is concentrated in the youngest age groups (Appendix S6), this is unlikely to substantially affect the model results.

In terms of the economic evaluation, there are limitations in the use of DALYs for public health decisions, for example, its restrictions in addressing different resource availability and country contexts [27]. Nonetheless, it remains helpful as a standard and widely-used measure of effectiveness in policy planning. Another limitation is that we assigned a single value of disability weight for all active TB cases. Further surveys on the distribution of symptom presentation will be essential to precisely assess the health burden caused by TB. Moreover, we did not take the societal perspective in the economic evaluation and thus patient costs such as transportation and absence at work during healthcare seeking were excluded, for lack of relevant surveys. However, in light of the small epidemiological impact, the substantial savings after BCG discontinuation are not likely to be affected.

The health benefits of BCG in our model may still be underestimated because we did not consider its protection against other health risks than TB. For example, BCG protection against leprosy has been reported, although its efficacy varied by settings [28]. Apart from disease-specific protection, a systematic review suggested that BCG was associated with reduced childhood all-cause mortality [29]. Receiving BCG at birth was also found with an increased antibody response to other immunisations [30]. Such benefits of BCG vaccination in the context of Taiwan will need further evaluation. On the other hand, important
questions about the health risks of BCG require further investigation. For example, the potential correlation between the strength of vaccine protection and the occurrence of BCGO was not addressed in this study, owing to a lack of systematic evidence [17]. Improved data on the incidence, severity and health impact of BCGO and other BCG-associated side-effects could have important implications for the development of future vaccination policies.

Rather than discontinuation at a national scale, selective BCG vaccination is an alternative strategy. Targeting 10% of infants at high risk in Finland, selective BCG vaccination was found cost-effective [31]. Similarly, Usher and colleagues [23] showed that additional protection from a universal BCG programme was limited compared to a selective one, where infants with parents from high TB incidence countries were vaccinated. In Taiwan, the potential value of selective BCG vaccination can be evaluated when the distribution of BCGO-associated risk factors become clearer. Additionally, our results suggest implications for future TB vaccines. Such vaccines may be expected to show higher performance than the strong-protection scenario listed in Table 1. In this case, the policy question shifts from the impact of BCG discontinuation to that of replacement by new vaccines or vaccination strategies. Nonetheless, additional cost – for example for introducing a booster vaccine - may also be an important concern for decision-makers.

After BCG discontinuation, a slight increase in active TB cases was observed in Sweden [32], while no additional meningeal TB cases were reported in a county in Beijing [33]. According to our modelled results, some children would certainly be exposed to the risk of TB if the routine BCG immunisation is withdrawn, even though the health burden caused by BCGO could be avoided. Constant surveillance of TB and BCGO will be critical for policy feedback and adjustment.
In summary, while the IAUTLD criteria (Box 1) were arguably informed by the experiences of the United Kingdom [34], Sweden [35] and other low burden European countries [36], our work highlights that it can be appropriate for intermediate TB burden countries to consider BCG discontinuation when protective and harmful effects of BCG, age-specific TB epidemiology and population dynamics are taken into account. As the downward trend of TB burden continues, more intermediate TB burden settings will face the need to re-evaluate their BCG vaccination policies in order to effectively allocate resources for TB control. The analytic framework applied in this study can be a useful reference for informing the decision-making of discontinuing universal BCG vaccination, with synthesised evidence based on a context-specific cost-effectiveness evaluation.
Box 1. IUATLD criteria for discontinuing universal BCG vaccination [4]

One of the following three criteria should be fulfilled for consideration of discontinuing a BCG Vaccination Programme in a country with a low TB prevalence:

- The average annual notification rate of sputum smear-positive pulmonary TB ≤ 5 cases per 100,000 population during the previous three years.
- The average annual notification rate of TB meningitis in children under 5 years old ≤ 1 case per million general population during the previous five years.
- The average annual risk of TB infection ≤ 0.1%. 
Table 1: Characteristics of BCG protection

<table>
<thead>
<tr>
<th>Characteristics Description</th>
<th>Weak-protection scenario</th>
<th>Strong-protection scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>$VE_{inf}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE against TB infection</td>
<td>0 %</td>
<td>22 %</td>
</tr>
<tr>
<td>$VE_{pgr,ptb}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE against TB progression for pulmonary TB cases</td>
<td>0 %</td>
<td>54 %</td>
</tr>
<tr>
<td>$VE_{pgr,etb}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE against TB progression for extrapulmonary TB cases</td>
<td>29%</td>
<td>54 %</td>
</tr>
<tr>
<td>$w$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waning rate of BCG protection (reciprocal of duration of protection)</td>
<td>$1/10$ year$^{-1}$</td>
<td>$1/40$ year$^{-1}$</td>
</tr>
</tbody>
</table>

The table shows the different types of VE, together with the duration of BCG immunity, corresponding to the ‘weak’ and ‘strong’ vaccine protection scenarios. A recent meta-analysis estimated VE against all TB morbidity to lie between 29% - 64% [8]. We constructed the weak- and strong-protection scenarios to cover this range. However, overall VEs ($VE_{all}$) are constituted from different types of vaccine protection, as $(1-VE_{all}) = (1-VE_{inf}) \times (1-VE_{pgr})$, where $VE_{inf}$ represents protection against infection, and $VE_{pgr}$ represents protection against progression. In the strong-protection scenario, we assumed the same VE against progression to pulmonary and extrapulmonary TB ($VE_{pgr} = VE_{pgr,ptb} = VE_{pgr,etb}$), whereas in the strong-protection scenario we assumed no protection against progression to pulmonary TB ($VE_{pgr,ptb} = 0, VE_{pgr,etb} = VE_{pgr}$). Further details on the methods of parameter specification can be found in Appendix S3. Abbreviations: BCG-Bacillus Calmette-Guérin vaccine, TB-tuberculosis, VE-vaccine efficacy.
Central estimates and their 95% uncertainty intervals of the health impact of discontinuing BCG in 2018 are shown. The estimates were derived by comparing the results between discontinuing and continuing BCG over 2018-2027. Note that the increased numbers of notified TB cases are small, compared to the 10,234 cases reported in Taiwan in 2016 alone. Positive values for ‘averted DALYs’ signify a net health gain, and vice versa. See Table 1 for the definition of the weak and strong-protection scenarios. Additionally, see Table S7.1 in the supplementary appendix for results of a sensitivity analysis where Poisson distribution was assumed to the notification rates in model calibration. Abbreviations: BCG-Bacillus Calmette-Guérin vaccination, BCGO-BCG-induced osteomyelitis/osteitis, DALYs-disability-adjusted life years, TB-tuberculosis.

<table>
<thead>
<tr>
<th>Cumulative difference over 2018-2027</th>
<th>Weak-protection scenario</th>
<th>Strong-protection scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional TB notified cases</td>
<td>2.8 (2.3, 3.1)</td>
<td>82.9 (72.6, 91.6)</td>
</tr>
<tr>
<td>Prevented BCGO cases</td>
<td>92.3 (40.8, 144.1)</td>
<td>92.3 (40.8, 143.7)</td>
</tr>
<tr>
<td><strong>Averted</strong></td>
<td>****</td>
<td>**</td>
</tr>
<tr>
<td>TB</td>
<td>-8.2 (-10.4, -6.3)</td>
<td>-407.3 (-510.7, -304.6)</td>
</tr>
<tr>
<td>BCGO</td>
<td>4.0 (1.5, 8.6)</td>
<td>4.0 (1.5, 8.7)</td>
</tr>
<tr>
<td><strong>Net</strong></td>
<td><strong>-4.1 (-7.7, 0.8)</strong></td>
<td><strong>-402.7 (-506.6, -301.2)</strong></td>
</tr>
</tbody>
</table>
Figure 1: Model structure for TB transmission and BCG vaccination
This is a simplified model structure showing the natural history of TB within a single age group. Each box represents mutually exclusive states (S-susceptible, Lf-latent with fast progression, Lref-latent with fast progression from reinfection, Ls-latent with slow progression, TB-active TB disease, R-recovered, and V-vaccinated). Arrows show transitions between states (A-birth, B-infection, C-stabilisation of latent infection, D-fast disease progression, E-slow disease progression, F-reinfection, G-recovery, and H-relapse). The coloured arrows highlight the transitions affected by BCG vaccination. The transitions of ageing, natural death and TB-specific death are not presented. Abbreviations: BCG-Bacillus Calmette-Guérin vaccine, TB-tuberculosis.
Figure 2: Health and cost impacts of discontinuing BCG under different scenarios

In the upper panel, averted DALYs were evaluated over a ten-year period following BCG discontinuation. Arising from BCG discontinuation, averted DALYs caused by TB (red bars) are negative as a result of the excess TB cases. In contrast, averted DALYs caused by BCGO (green bars) are positive as the burden from the adverse events of BCG immunisation were avoided. The net averted DALYs (black diamond) demonstrate the overall health impact and vary by the quality of BCG protection. Where this lies below 0, BCG discontinuation would lead to a net health loss and vice versa. In the lower panel, the cost impacts over the ten-year periods following BCG discontinuation are presented by source. There is a positive increase (red bars) in cost for TB treatment, while BCGO treatment, BCGO compensation, and BCG immunisation programme decrease the cost. The net incremental costs are negative (black diamonds), regardless of the discontinuing year and BCG protection. Abbreviations: BCG-Bacillus Calmette-Guérin vaccination, BCGO-BCG-induced osteomyelitis/osteitis, DALYs-disability-adjusted life years, TB-tuberculosis.
Figure 3: Relationship between TB notification rates and net averted DALYs
While Figure 2 addresses the potential health implications of discontinuation at different years, this figure instead takes the perspective of discontinuing BCG at a threshold level of TB notification rates (horizontal axis). The region above the horizontal black line denotes the condition where BCG discontinuation would have an overall beneficial health impact over the subsequent 10 years and vice versa. For clarity, we show only results arising from the ‘best fitting’ (likelihood maximising) parameter set. Abbreviations: BCG-Bacillus Calmette-Guérin vaccination, DALYs-disability-adjusted life years, TB-tuberculosis.
Figure 4: Relative health impact of the characteristics of vaccine protection
The averted DALYs after BCG discontinuation in 2018 are presented under different scenarios of protection afforded by the vaccine. The characteristics contributing to BCG protection are listed in Table 1. At the top of the figure, each column represents a scenario combining different elements of vaccine protection. Light-blue boxes denote a vaccine characteristic with the weak-protection scenario in effect (see also table 1), while dark-blue boxes indicate the strong-protection scenario being in effect. Asterisks denote those bars that show the largest change in the net health impact, indicating the most influential characteristic. In both of the scenarios, we varied one of the characteristics only in future projections by using the ‘best fitting’ (likelihood maximising) parameter set from model calibration. Abbreviations: BCG-Bacillus Calmette-Guérin vaccination, BCGO-BCG-induced osteomyelitis/osteitis, DALYs-disability-adjusted life years, TB-tuberculosis.
SUPPLEMENTARY FILES

Supplementary appendix
This document includes the model equations, parameter tables, calibration methods, sensitivity analyses and relevant details of this study.

CONFLICT OF INTEREST

All the authors have no conflict of interest to declare.

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