

Disregarding the restrictive vial-opening policy for BCG vaccine in Guinea-Bissau: impact and cost-effectiveness for tuberculosis mortality and all-cause mortality in children aged 0–4 years

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ABSTRACT

Objective BCG vaccination is frequently delayed in low-income countries. Restrictive vial-opening policies, where a vial of BCG vaccine is not opened for few children, are a major reason for delay. During delays, children are unprotected against tuberculosis (TB) and deprived of non-specific effects of BCG. We assessed the potential effect and cost-effectiveness of disregarding the restrictive vial-opening policy, on TB and all-cause mortality, in children aged 0–4 years in Guinea-Bissau.

Methods Using static mathematical models, we estimated the absolute and percentage change in TB and all-cause deaths, in children aged 0–4 years, between the current BCG vaccine restrictive-opening policy scenario, and a non-restrictive policy scenario where all children were vaccinated in the first health-facility contact. Incremental cost-effectiveness was estimated by integration of vaccine and treatment costs.

Findings Disregarding the restrictive BCG vial-opening policy was estimated to reduce TB deaths by 11.0% (95% uncertainty range (UR):0.5%–28.8%), corresponding to 4 (UR:0–15) TB deaths averted per birth cohort in Guinea-Bissau, resulting in incremental cost-effectiveness of US\$ 911 per discounted life-year gained (LYG) (UR:145–9142). For all-cause deaths, the estimated reduction was 8.1% (UR:3.3%–12.7%) corresponding to 392 (UR:158–624) fewer all-cause deaths and an incremental cost-effectiveness of US\$ 9 (UR:5–23) per discounted LYG.

Conclusions Disregarding the restrictive BCG vial-opening policy was associated with reductions in TB deaths and all-cause deaths and low cost-effectiveness ratios. Our results suggest that it would be cost-effective to disregard the restrictive vial-opening policy. Other settings with similar practice are also likely to gain from disregarding this policy.

INTRODUCTION

The BCG vaccine was developed to protect against tuberculosis (TB), and is currently the

Key questions

What is already known?

- ▶ BCG is the only improved vaccine against tuberculosis (TB). However, BCG vaccination is often delayed in low-income countries, and a major cause of delay in Guinea-Bissau is the restrictive vial-opening policy, where a vial of BCG is not opened unless 10–12 children are present for vaccination at the same time.
- ▶ We identified one mathematical modelling study that estimated the global impact of different BCG coverage scenarios on TB mortality in children aged 0–14 years, which concluded that improving timeliness of BCG vaccination at birth was associated with reductions in TB deaths.
- ▶ We found no study estimating the health economic impact of increasing timeliness, the impact of improving BCG timeliness on all-cause mortality, nor any studies assessing the impact at the country level.

What are the new findings?

- ▶ In this study, we provide the first country-level estimates of the impact of change in BCG coverage and timeliness. We estimated that disregarding the restrictive vial-opening policy and vaccinating every child at the first contact with a health facility in Guinea-Bissau could reduce TB and all-cause mortality.
- ▶ Our study provides the first effect and cost-effectiveness estimates for this easily implementable intervention of disregarding the restrictive vial-opening policy, and our estimates show that it is both effective and cost-effective to disregard the restrictive vial-opening policy.

only approved TB vaccine.¹ The efficacy and effectiveness of BCG against TB varies considerably between studies and populations,² however, neonatal BCG has consistently been associated with reduced prevalence of TB disease.²

Key questions

What do the new findings imply?

- ▶ Existing empirical evidence has demonstrated the importance of early BCG vaccination for TB control and that early BCG may reduce all-cause mortality. Our study strongly supports disregarding the restrictive vial-opening policy, as we find that this would reduce child mortality and be cost-effective.
- ▶ Since Guinea-Bissau is not the only setting with this restrictive vial-opening policy and delays in BCG vaccination, other settings are likely to also gain by disregarding the restrictive vial-opening policy.

TB is estimated to be among the top ten causes of death worldwide.³ In 2015, global paediatric all-cause mortality was estimated at 5.9 million deaths,⁴ and 191 000 (95% CI: 132 000 to 257 000) of these were estimated as attributable to TB.⁵ As paediatric TB is difficult to diagnose, prevention may be more feasible than cure, particularly in settings with high TB burden and few resources. Vaccination is part of the WHO strategy for reducing TB deaths by 95% between 2015 and 2035.^{1 6} Recent estimates suggested that increasing global BCG coverage from 92% final coverage to an immediate 92% coverage at birth could reduce TB deaths <15 years by 5449 per global birth cohort (95% uncertainty range (UR): 218–15 071).⁷

BCG may have beneficial non-specific effects (NSEs), protecting against disease unrelated to TB.^{8–11} In 2014, a WHO-commissioned review concluded that BCG may have beneficial NSEs reducing all-cause child mortality.¹² Thus, BCG delays may be important for both TB-specific mortality and all-cause mortality.

BCG is recommended at birth, and although global coverage is estimated at 88% by 12 months,¹³ this does not reveal underlying vaccination delays. To meet vaccine wastage targets, local practices of not opening a vial of BCG unless a sufficient number of children are present for vaccination have arisen (restrictive vial-opening policy) and BCG is consequently delayed in many low-income countries.^{14–16}

The restrictive vial-opening policy is imposed with the goal of using scarce resources effectively. However, this saving may come at a cost and the impact has not been examined. The objective of this study was to estimate the epidemiological impact and cost-effectiveness of disregarding the restrictive BCG vial-opening policy in Guinea-Bissau, considering both the TB-specific and all-cause mortality effects.

METHODS

We developed two static mathematical models, one for TB deaths based on a model developed by Roy *et al*⁷ and one for all-cause deaths, both in Microsoft Excel 2013 (figure 1A,B). The model by Roy assumed all-or-nothing efficacy, where a proportion (corresponding to the vaccine efficacy) of BCG-vaccinated children are assumed

to be fully protected, and the remainder are assumed to be unprotected. However, the mechanism of efficacy is unknown. As it is unrealistic to assume complete protection against all-cause mortality, we assumed leaky BCG vaccine efficacy in both models, that is, all BCG-vaccinated children are assumed partly protected corresponding to the vaccine efficacy (online supplemental appendix 3.1).

The primary outcomes were absolute and percentage change in TB deaths and all-cause deaths averted among children <5 years per birth cohort due to disregarding the restricted BCG vial-opening policy (vial-policy change). The current scenario with restrictive BCG vial-opening policy (baseline) was compared with the non-restrictive scenario, defined as a scenario in which every child was BCG vaccinated at the first registered health facility contact.

Data inputs and assumptions

Where data were available, we used country-specific estimates for Guinea-Bissau. Parameter values and data sources are summarised in table 1.

Population estimates

We used routine 2012–2017 surveillance data from the Bandim Health Project's (BHP) urban and rural Health and Demographic Surveillance Systems (HDSS) to estimate the daily individual risk of all-cause mortality and all-cause hospital admission in children aged 0–4 years (table 1, online supplemental appendix 1.2.1). We used WHO/UNICEF birth cohort estimates (online supplemental appendix 1.1) and World Bank estimate of 57 years life-expectancy in Guinea-Bissau in 2017.¹⁷

TB data

For TB incidence and TB mortality, we used the 2016 Guinea-Bissau Global Burden of Disease¹⁸ (GBD) estimates, as reported TB data from Guinea-Bissau are likely underestimates. Using this information, we calculated a TB case fatality rate (CFR) of 0.21 (table 1). We assumed that all reported paediatric TB¹⁹ cases were hospitalised [personal communication: Victor Gomes, Programmatic Manager of MDR-TB, National TB Programme]. We calculated the proportion of hospitalised TB cases as reported cases divided by the GBD case estimate.

BCG coverage and timeliness

Using BHP routine data, we estimated BCG coverage and timeliness for the restrictive scenario using current estimates, and in the non-restrictive scenario using first health facility contact (figure 2, online supplemental appendix 1.2.2).

BCG vaccine efficacy

We used a BCG vaccine efficacy against TB death of 66% (95% CI: 8% to 88%).²⁰ We assumed vaccine efficacy was constant regardless of age of administration.⁷ BCG protection may last for up to 15 years²⁰, we, therefore, assumed no waning of protection between the ages 0 and 4 years. As children rarely contribute to transmission,²¹

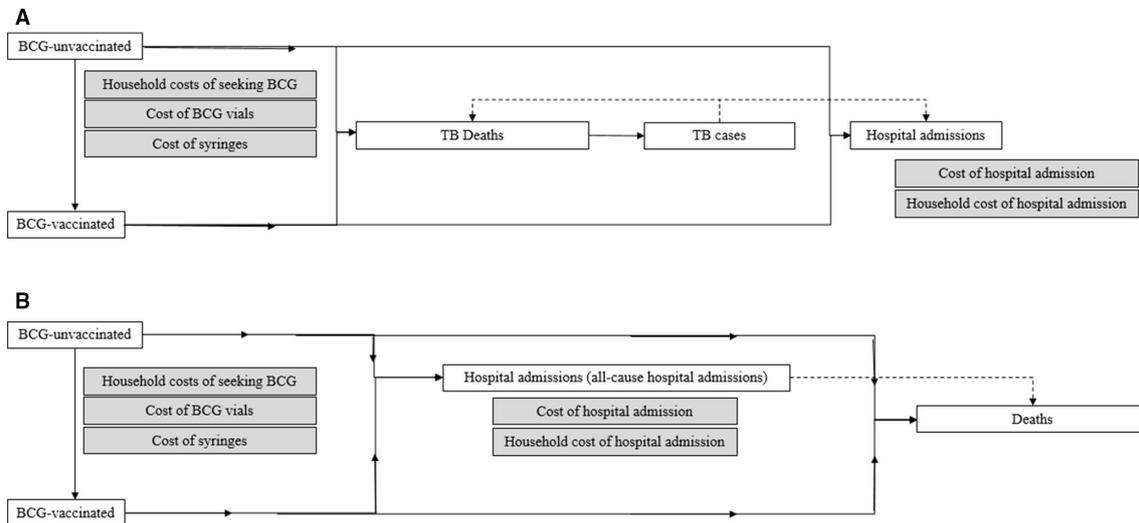


Figure 1 (A) Structure of the TB model. White boxes indicate stages in the model. Grey boxes indicate the included costs. Full arrows indicate the model flow, while dashed lines indicate the flow in the real world. All children enter the model as BCG unvaccinated. Children are counted as BCG vaccinated from the registration of a BCG vaccine (restrictive scenario) or registration of first health facility contact (non-restrictive scenario). In each scenario, we estimated the number of TB deaths. Based on a case-fatality rate, we calculated the number of TB cases. Using national data on the number of identified TB cases, we assumed that all identified TB cases were admitted, we estimated the number of TB hospital admissions in each scenario. (B) Structure of the all-cause model. White boxes indicate stages in the model. Grey boxes indicate the included costs. Full arrows indicate the model flow, while dashed lines indicate the flow in the real world, but in the models, there were no direct link, as the numbers were derived and calculated separately, and we only used the data on admission to be able to include these in the cost analyses. All children enter the model as BCG unvaccinated. Children are counted as BCG vaccinated from the registration of a BCG vaccine (restrictive scenario) or registration of first health facility contact (non-restrictive scenario). In each scenario, we estimated the number of all-cause hospital admissions, and included cost of hospital admissions incurred by the healthcare system and household cost of hospital admission (time spent in the hospital). We estimated the number of all-cause deaths and calculated the cost-effectiveness of disregarding the restrictive vial-opening policy.

we assumed that a vial-policy change would not affect transmission.

We undertook a meta-analysis of seven studies from Guinea-Bissau (online supplemental appendix 1.2.3), and obtained a vaccine efficacy against all-cause death of 42% (95%CI:19% to 58%) (figure 3). For all-cause hospital admission, we used a vaccine-efficacy from a meta-analysis (3%, 95% CI:-31% to 28%).²² Vaccine efficacies were assumed constant regardless of age at administration with no waning of protection before 5 years of age.

Costs

Costs were calculated using 2017 US dollar (US\$) values. We included vaccination costs (including materials and freight), household costs of seeking BCG (US\$ 1.92 per child,²³ online supplemental appendix 1.2.5), costs incurred by the health system per hospital bed day (US\$ 15.58,²⁴ online supplemental appendix 1.2.6), and time spent accompanying the child to the hospital (US\$ 2.98 per hospital bed day,²⁵ online supplemental appendix 1.2.6). Hospital admissions are free for children <5 years in Guinea-Bissau,²⁶ so we assumed no out-of-pocket payments for treatment. We assumed 50% vaccine wastage in the restrictive scenario, as a 20-dose vial is usually opened if 10 or more children are present. We assumed 95% wastage in the non-restrictive scenario, equivalent to vaccinating only one child per vial.

Mathematical model

TB deaths model

We developed a static cohort Markov model to calculate the absolute and relative difference in TB death between the restrictive and non-restrictive scenarios (online supplemental appendix 2.1). We estimated the daily risk of TB death in vaccinated and unvaccinated children in the restrictive scenario based on the total number of TB deaths (0–4 years), vaccine efficacy and the number of children BCG vaccinated and unvaccinated by age (table 1). To calculate the cumulative number of TB deaths per birth cohort in the first 5 years of life in each scenario, we applied the daily individual risk of TB among vaccinated children to the number of vaccinated children, and likewise for unvaccinated children. These risks were assumed constant between the ages 0 and 4 years. The population at risk was adjusted for all-cause deaths by day; assuming BCG had no effect on all-cause mortality.

The number of TB cases per birth cohort in the first 5 years of life in each scenario was estimated by dividing the number of TB deaths in each scenario by CFR of 0.21 (table 1). To estimate TB hospital admissions, the proportion of TB cases identified through national TB surveillance was applied to the model-estimated number of TB cases in each scenario, assuming all identified TB cases were admitted.

Table 1 Data inputs and assumptions

Variable	Estimate	Source	Distribution
Population characteristics			
Population at risk—birth cohort (2017)	69 212	Joint Reporting Form data from Guinea-Bissau*	Fixed
Life expectancy at birth	57 years	World Bank 2017†	Fixed
Estimated no of TB cases in males aged 0–4 in 2016	74 (37–121)	Global Burden of Disease Results Tool‡	Log-normal
Estimated no of TB cases in females aged 0–4 in 2016	89 (47–145)	Global Burden of Disease Results Tool‡	Log-normal
Estimated no of TB deaths in males aged 0–4 in 2016	16 (8–36)	Global Burden of Disease Results Tool‡	Log-normal
Estimated no of TB deaths in females aged 0–4 in 2016	17 (5–52)	Global Burden of Disease Results Tool‡	Log-normal
Reported TB cases aged 0–4 years in Guinea-Bissau	46	Annual TB report 2017, Guinea-Bissau§	Fixed
Case-fatality rate	0.21	Estimated from Global Burden of Disease estimates (See online supplemental appendix 1.3.1)	Fixed
TB estimates used in sensitivity analyses			
Estimated no of TB cases in males aged 0–4 in 2016	290 (270–310)	WHO TB data¶	Log-normal
Estimated no of TB cases in females aged 0–4 in 2016	240 (220–250)	WHO TB data¶	Log-normal
Estimated no of TB deaths in children aged 0–4 years in 2016	238 (48–518)	Dodd, Lancet Global Health, 2017**	Log-normal
Individual daily all-cause mortality risk			
Day 0	0.014184 (0.012901–0.015632)	BHP HDSS routine data††	Log-normal
Day 1	0.003370 (0.002757–0.004165)	BHP HDSS routine data††	Log-normal
Day 2	0.002100 (0.001646–0.002724)	BHP HDSS routine data††	Log-normal
Day 3	0.001090 (0.000772–0.001592)	BHP HDSS routine data††	Log-normal
Day 4	0.001123 (0.000799–0.001630)	BHP HDSS routine data††	Log-normal
Day 5	0.000787 (0.000518–0.001259)	BHP HDSS routine data††	Log-normal
Day 6	0.001110 (0.000785–0.001624)	BHP HDSS routine data††	Log-normal
Day 7	0.000547 (0.000319–0.001024)	BHP HDSS routine data††	Log-normal
Day 8–28	0.000142 (0.000115–0.000179)	BHP HDSS routine data††	Log-normal
Day 29–365	0.000054 (0.000049–0.000058)	BHP HDSS routine data††	Log-normal
Day 366–1826	0.000018 (0.000017–0.000020)	BHP HDSS routine data††	Log-normal
Individual daily risk of all-cause hospital admission			
Day 0–28	0.000083 (0.000065–0.000107)	BHP HDSS routine data††	Log-normal
Day 29–365	0.000080 (0.000074–0.000085)	BHP HDSS routine data††	Log-normal
Day 366–1826	0.000042 (0.000039–0.000044)	BHP HDSS routine data††	Log-normal
BCG coverage distribution in baseline scenario	figure 1	BHP HDSS routine data‡‡	Fixed
BCG coverage distribution disregarding the vial-opening policy	figure 1	BHP HDSS routine data‡‡	Fixed
Vaccine characteristics TB-specific			
Risk ratio of BCG on TB deaths	0.34 (0.12–0.92)	Abubakar, Health Technol Assess, 2013\$\$\$	Log-normal
Duration of protection	>5 years	Abubakar, Health Technol Assess, 2013\$\$\$	Fixed
Waning of protection	None	Assumption	Fixed

Continued



Table 1 Continued

Variable	Estimate	Source	Distribution
Prevention of transmission by BCG	None	Assumption	Fixed
Vaccine characteristics all-cause effects			
Risk ratio of BCG on all-cause deaths	0.58 (0.42–0.81)	Meta-estimate of studies from Guinea-Bissau¶¶	Log-normal
Risk ratio of BCG on all-cause hospital admissions	0.97 (0.72–1.31)	Meta-estimate of studies from Guinea-Bissau***	Log-normal
Duration of protection	>5 years	Assumption	Fixed
Waning of protection	None	Assumption	Fixed
Prevention of transmission by BCG	None	Assumption	Fixed
Cost estimates			
BCG vaccine price per dose incl. freight	0.20 USD	National department of the Expanded Programme on Immunisation*	Fixed
Injection syringe price incl. freight	0.05 USD	National department of the Expanded Programme on Immunisation*	Fixed
Mixing syringe price incl. freight	0.03 USD	National department of the Expanded Programme on Immunisation*	Fixed
Safety box	0.67 USD	National department of the Expanded Programme on Immunisation*	Fixed
Median bed day per TB hospital admission	60 days	Personal communication: Victor Gomes, National TB Programme§	Fixed
Median bed day per all-cause hospital admission	5 days	BHP HDSS hospital admission data†††	Fixed
Costs per hospital bed day incurred by health system	15.58 USD	Enemark, in preparation, 2019‡‡‡	Fixed
Household productivity costs per bed day hospital admission	2.98 USD	Knight, PNAS, 2014§§§	Fixed
Household costs of seeking BCG vaccination	1.92 USD	Thyssen, Vaccine, 2019¶¶¶¶	Fixed
Average no of times seeking BCG vaccination—restrictive (baseline) scenario	1.26	Thyssen, Vaccine, 2019¶¶¶¶	Fixed
Average no of times seeking BCG vaccination—non-restrictive scenario	1	Assumption	Fixed
Vaccine wastage—restrictive (baseline) scenario	50%	Assumption	Fixed
Vaccine wastage—non-restrictive scenario	95%	Assumption	Fixed

*Personal communication: Carifitos Bale, Director of the Expanded Programme on Immunisation in Guinea-Bissau.

†World Bank.¹⁷

‡Institute for Health Metrics and Evaluation.¹⁸

§Personal communication: Victor Gomes, Programmatic Manager of MDR-TB, National TB Programme.

¶WHO.³¹

**Dodd PJ *et al*⁶

††online supplemental appendix 1.2.1.

‡‡online supplemental appendix 1.2.2.

§§Abubakar I *et al*²⁰

¶¶online supplemental appendix 1.2.3, figure 2.

***Schaitz-Buchhoizer F *et al*²²

†††online supplemental appendix 1.2.6.

‡‡‡Enemark U *et al*²⁴

§§§Knight GM *et al*²⁵

¶¶¶Thyssen SM *et al*²³

BHP, Bandim Health Project's; HDSS, Health and Demographic Surveillance Systems; TB, tuberculosis.

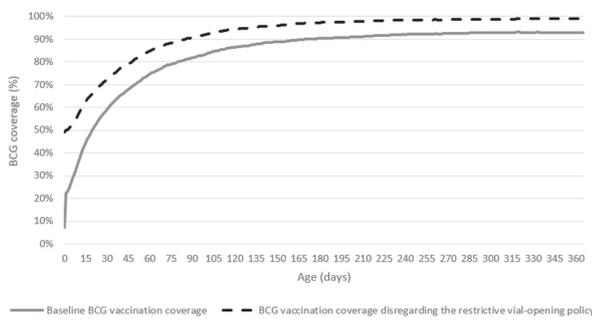


Figure 2 BCG coverage estimates in Guinea-Bissau in the restrictive (baseline) scenario and when disregarding the restrictive BCG vial-opening policy.

All-cause deaths model

We developed a static cohort Markov model to calculate the absolute and relative difference in all-cause death between the two scenarios (online supplemental appendix 2.2). We estimated daily, age-specific risk of all-cause death using the BHP routine all-cause mortality data (online supplemental appendix 1.2.1). Applying similar methods as the TB model, we used baseline data on BCG coverage by age, vaccine efficacy meta-estimate for all-cause death (online supplemental appendix 1.2.3), and the daily risk of all-cause death to calculate the daily risk of all-cause death in BCG-vaccinated children and in BCG-unvaccinated children, respectively.

We applied the estimated daily individual risk of all-cause mortality among BCG-vaccinated children to the

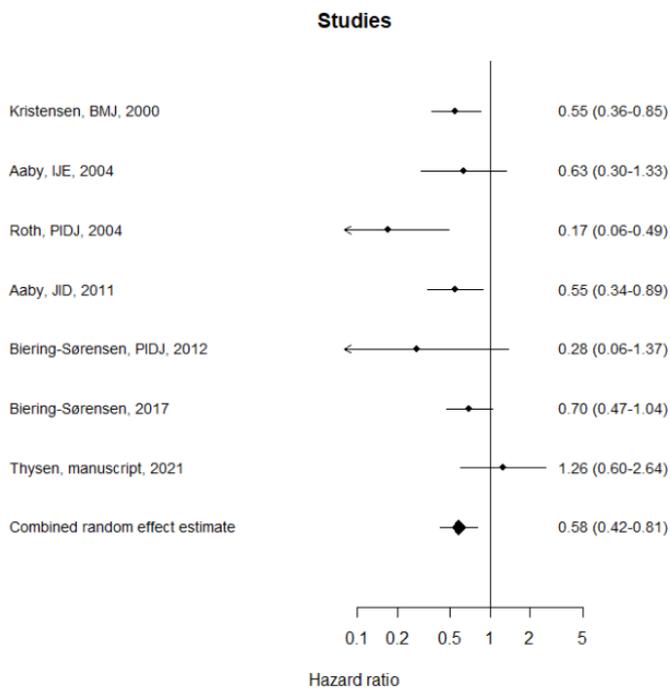


Figure 3 Meta-analysis of the effect of BCG on all-cause mortality in Guinea-Bissau HRs below 1 indicate that BCG vaccine is associated with lower mortality. HRs above 1 indicate that BCG vaccination is associated with higher mortality. 1: Kristensen *et al*⁹, 2: Aaby *et al*³⁴, 3: Roth *et al*³⁵, 4: Aaby *et al*³⁶, 5: Biering-Sørensen *et al*³⁷, 6: Biering-Sørensen *et al*⁸, 7: Thysen *et al*³⁸

number of BCG-vaccinated children, and likewise for unvaccinated children, and estimated daily and cumulative all-cause deaths between 0 and 4 years under the restrictive and non-restrictive scenarios (online supplemental appendix 2.2). Using a similar approach, we calculated the absolute and relative difference in all-cause hospital admissions between scenarios (online supplemental appendix 2.3).

Increasing evidence suggests that vaccines may interact.^{12 27} We, therefore, conducted a secondary analysis to assess outcomes only in the period prior to receipt of other vaccines (0–6 weeks of age).

Cost-effectiveness analyses

Cost-effectiveness was assessed from a societal perspective, including total population-level vaccination costs, household costs of seeking BCG vaccination, and costs of hospital admission incurred by the health system and the household (online supplemental appendix 2.4).

We added the number of deaths per year between the ages 0 and 5 years in 1-year intervals, to calculate the total number of deaths averted. Life-years gained (LYG) in the non-restrictive scenario were calculated in each model by multiplying the number of TB deaths or all-cause deaths averted per year of life by the remaining life expectancy.¹⁷ As WHO recommends,²⁸ we discounted future costs and life years by 3%/year. We calculated incremental cost-effectiveness ratios (ICERs) of a vial-policy change. We used Wood’s purchasing power parity adjusted cost-effectiveness threshold for Guinea-Bissau of US\$22–US\$645.²⁹

Urban versus rural subanalyses

Vaccination opportunities, healthcare-seeking behaviour and number of children present at health centres are likely to differ between the urban and rural population, resulting in different effects of a vial-policy change. We, therefore, calculated separate estimates for urban and rural Guinea-Bissau. We used the same approaches, but substituted risk of all-cause mortality, risk of all-cause hospital admission, BCG coverage, and birth cohort estimates with regional estimates.

Uncertainty and sensitivity analyses

We performed a probabilistic uncertainty analysis using Oracle Crystal Ball (Release 11.1.2.4.850, Oracle, USA), where a statistical distribution was set for each parameter with a reported UR (table 1). Location and scale parameters were estimated using the 2.5%, 50% and 97.5% percentiles in the ‘riskDistributions’ R package. Parameters with fixed values were not considered uncertain. A total of 100 000 parameter sets and model outputs were generated through Monte-Carlo simulations. Median and 95% URs were calculated from the 100 000 model outputs.

In sensitivity analyses, we assessed the impact of assuming leaky BCG vaccine efficacy by adapting the TB model to all-or-nothing efficacy, as in previous

models^{7 30} (online supplemental appendix 2.5). We evaluated the impact of using GBD estimates of TB mortality in two sensitivity analyses, using WHO TB incidence³¹ combined with CFR estimates from Jenkins,³² and using modelled estimates of TB mortality from Dodd.⁵ We also varied the assumption of perfect correlation between (1) male and female TB estimates, and (2) age-wise mortality estimates, to be uncorrelated in sensitivity analyses. We assumed very high wastage (95%) in the non-restrictive scenario, and therefore conducted sensitivity analyses with wastage assumptions in the restrictive scenario from 35% to 60% with 5% intervals, and in the non-restrictive scenario from 70% to 90%.

Patient and public involvement

The communities were involved in locating households for the HDSS data collection, when the BHP HDSS was setup. No participant was involved in setting the research question or the outcome measure, nor were they involved in developing the models, or design of the study. No participant was asked to advise on interpretation or writing up the results. The results are

disseminated to the national public health institute. There are no plans to disseminate the results of the research to study participants or the community.

RESULTS

Effects of a vial-policy change on TB-specific outcomes

Disregarding the restrictive vial opening policy was estimated to reduce TB deaths, admissions and cases by 11.0% (95% UR: 0.5%–28.8%). The number of TB deaths was 33 (UR: 13–89) per birth cohort in the restrictive scenario and 29 (UR: 11–79) in the non-restrictive scenario, averting 4 (UR: 0–15) TB deaths per birth cohort in the first 5 years of life. TB cases were reduced from 162 (UR: 96–273) to 142 (UR: 82–245), and TB hospital admissions from 46 to 41 (table 2).

Effects of a vial-policy change on all-cause outcomes

The vial-policy change was estimated to reduce all-cause mortality by 8.1% (UR: 3.3%–12.7%), from 4820 (UR: 4309–5425) all-cause deaths in the restrictive scenario to 4429 (UR: 3920–5028) all-cause deaths in the non-restrictive

Table 2 Effects of disregarding the restrictive BCG vial-opening policy in Guinea-Bissau

	Restrictive (baseline) scenario	Non-restrictive scenario	Absolute change	Percentage change
	Median (95% uncertainty range)	Median (95% uncertainty range)	Median (95% uncertainty range)	Median (95% uncertainty range)
TB-specific effects				
Total no of paediatric TB deaths	33 (13 to 89)	29 (11 to 79)	−4 (−15 to 0)	−11.0% (−28.8% to −0.5%)
Total no of paediatric TB cases	162 (96 to 273)	142 (82 to 245)	−18 (−54 to −1)	−11.0% (−28.8% to −0.5%)
Total no of paediatric TB hospital admissions	46*	41 (33 to 46)	−5 (−13 to 0)	−11.0% (−28.8% to −0.5%)
Sub-analysis stratifying urban and rural regions				
Total no of paediatric TB deaths—urban data	8 (3 to 22)	8 (3 to 21)	0 (−1 to 0)	−2.6% (−8.3% to −0.1%)
Total no of paediatric TB deaths—rural data	26 (10 to 69)	21 (8 to 57)	−4 (−17 to 0)	−16.4% (−38.6% to −0.8%)
All-cause effects				
Total no of all-cause deaths	4820 (4309 to 5425)	4429 (3920 to 5028)	−392 (−624 to −158)	−8.1% (−12.7% to −3.3%)
Total no of all-cause hospital admissions	5926 (5538 to 6346)	5940 (5532 to 6380)	18 (−125 to 133)	0.4% (−2.6% to 2.8%)
Subanalysis stratifying urban and rural regions				
Total no of all-cause deaths urban data	1071 (897 to 1302)	961 (795 to 1180)	−111 (−172 to −47)	−10.4% (−15.3% to −4.5%)
Total no of all-cause deaths rural data	3787 (3303 to 4386)	3467 (2992 to 4048)	−319 (−527 to −124)	−8.4% (−13.5% to −3.3%)

*The number of paediatric TB hospital admissions is the reported number of TB cases from Guinea-Bissau in 2017 (Programa Nacional de Luta contra a Tuberculose. Relatório anual de tuberculose 2017: Ministério da Saúde Pública da Guiné-Bissau, 2018).
TB, tuberculosis.

scenario, averting 392 (UR: 158–624) all-cause deaths per birth cohort in the first 5 years of life (table 2). There was an estimated 0.4% (UR: –2.6 to 2.8%) increase in all-cause hospital admissions, due to more children surviving and becoming admitted to hospital (table 2).

Costs and cost-effectiveness of a vial-policy change

In both models, the vial-policy change resulted in higher BCG-vaccination costs and lower household costs.

Accounting only for the TB-specific effects, the 95 (UR: 4–397) discounted LYG resulted in an ICER of US\$ 911 (UR: 145–9142) per discounted LYG and US\$ 26 527 (UR :4225–266291) per discounted TB death averted (table 3).

Including all-cause effects of BCG, the number of discounted LYG were 10 605 (UR: 4279–16,896), resulting in an ICER of US\$9 (UR: 5–23) per discounted LYG and

Table 3 Cost-effectiveness of disregarding the restrictive BCG vial-opening policy for the Guinea-Bissau birth cohort in 2017

	Restrictive (baseline) scenario	Non-restrictive scenario
No of children born in health facilities	33354	33354
No of children BCG-vaccinated at birth	13438	33354
No of children not BCG-vaccinated at birth	55774	35858
BCG coverage at 12 months of age	93 %	99 %
Total household costs of seeking BCG vaccination	US\$134631	US\$68694
Total BCG vaccine costs	US\$26221	US\$279769
Total injection supply costs	US\$3909	US\$6640
TB-specific effects only	Median (95% uncertainty range)	Median (95% uncertainty range)
No of paediatric TB deaths	33 (13 to 89)	29 (11 to 79)
LYG by averted TB death	–	195 (7 to 817)
LYG by averted TB death—discounted	–	95 (4 to 397)
No of paediatric TB hospital admissions	46*	41 (33 to 46)
Costs of TB hospital admissions	US\$51207	US\$45557
Costs of TB hospital admissions discounted	US\$47011	US\$41813
Incremental costs of disregarding the restrictive vial-opening policy (including vaccination costs, household costs and costs averted by TB hospital admissions)	–	US\$184692
Incremental costs of disregarding the restrictive vial-opening policy discounted	–	US\$185144
ICER per LYG (USD)	–	440 (69 to 4440)
ICER per LYG discounted (USD)	–	911 (145 to 9142)
ICER per TB death averted (USD)	–	24269 (3827 to 244869)
ICER per TB death averted discounted (USD)	–	26527 (4225 to 266291)
All-cause effects	Median (95% uncertainty range)	Median (95% uncertainty range)
No of all-cause deaths	4820 (4309 to 5425)	4429 (3920 to 5028)
LYG by averted all-cause deaths	–	22166 (8949 to 35288)
LYG by averted all-cause deaths—discounted	–	10605 (4279 to 16896)
No of all-cause hospital admissions	5926 (5538 to 6346)	5940 (5532 to 6380)
Costs of all-cause hospital admissions	US\$549815	US\$551478
Costs of all-cause hospital admissions discounted	US\$508556	US\$510076
Incremental costs of disregarding the restrictive vial-opening policy (including vaccination costs, household costs and costs averted by hospital admissions)	–	US\$192005
Incremental costs of disregarding the restrictive vial-opening policy discounted	–	US\$191863
ICER per LYG (USD)	–	4 (3 to 11)
ICER per LYG discounted (USD)	–	9 (5 to 23)
ICER per all-cause death averted (USD)	–	249 (144 to 615)
ICER per all-cause death averted discounted (USD)	–	259 (150 to 639)

*The number of paediatric TB hospital admissions is the reported number of TB cases from Guinea-Bissau in 2017 (Programa Nacional de Luta contra a Tuberculose. Relatório anual de tuberculose 2017: Ministério da Saúde Pública da Guiné-Bissau, 2018). ICER, incremental cost-effectiveness ratio; LYG, life-year gained; USD, US dollar 2017 value.

US\$259 (UR: 150–639) per discounted all-cause death averted (table 3).

Effects of a vial-policy change in urban and rural health regions

The vial-policy change in urban Guinea-Bissau was estimated to have a smaller effect on TB mortality, with 2.6% (0.1%–8.3%) fewer TB deaths, corresponding to less than 1 TB death per birth cohort (table 2). There was, however, a larger impact in the all-cause model with 111 (UR: 47–172) fewer deaths and 10.4% (UR: 4.5%–15.3%) estimated lower mortality, as many children had vaccination opportunities within the first days of life, where all-cause mortality is highest. Including all-cause effects, the estimated ICERs were US\$10 (UR: 6–23) per discounted LYG and US\$280 (UR: 173–653) per discounted all-cause death averted (online supplemental appendix 3.4).

In the rural population, the policy change was estimated to reduce TB deaths by 16.4% (0.8%–38.6%), corresponding to 4 (UR: 0–17) fewer TB deaths. The

resulting ICERs were US\$524 (UR: 77–5455) per discounted LYG and US\$15 272 (UR: 2245–159 037) per TB death averted. The estimated reduction in all-cause mortality was 8.4% (3.3%–13.5%) corresponding to 319 (UR: 124–527) fewer all-cause deaths (table 4). The resulting ICERs were US\$8 (UR: 4–20) per discounted LYG and US\$221 (UR: 120–567) per discounted all-cause death averted (online supplemental appendix 3.4).

Sensitivity analyses

Structural

Adapting the TB model structure from a model assuming leaky vaccine efficacy (main analysis) to all-or-nothing efficacy did not alter results (table 4). Similarly, assuming no correlations between mortality estimates yielded similar results (online supplemental appendix 3.5). The vial-policy change was cost saving in both TB and all-cause models when vaccine wastage was 80% or less in the non-restrictive scenario (online supplemental appendix 3.6).

Table 4 Effects of disregarding the restrictive BCG vial-opening policy in Guinea-Bissau—sensitivity analyses

	Restrictive (baseline) scenario	Non-restrictive scenario	Absolute differences	Percentage change*
	Median (95% uncertainty range)	Median (95% uncertainty range)	Median (95% uncertainty range)	Median (95% uncertainty range)
TB-specific effects				
Total no of paediatric TB deaths - main analysis	33 (13 to 89)	29 (11 to 79)	-4 (-15 to 0)	-11.0% (-28.8% to -0.5%)
Sensitivity to BCG mode of action model structure				
Total no of paediatric TB deaths—all-or-nothing BCG effectiveness	33 (13 to 89)	29 (11 to 79)	-4 (-15 to 0)	-11.0% (-28.8% to -0.5%)
Sensitivity to calibration data				
Total no of paediatric TB deaths—WHO† and Jenkins‡ data	231 (196 to 272)	204 (156 to 252)	-25 (-68 to -1)	-11.0% (-28.8% to -0.5%)
Total no of paediatric TB deaths—P. Dodd§ data	238 (110 to 519)	209 (94 to 463)	-25 (-94 to -1)	-11.0% (-28.8% to -0.5%)
All-cause effects				
Total no of all-cause deaths day—main analysis	4820 (4309 to 5425)	4429 (3920 to 5028)	-392 (-624 to -158)	-8.1% (-12.7% to -3.3%)
Subanalysis limiting follow-up to scheduled age of next vaccination				
Total no of all-cause deaths day 0–42	1922 (1612 to 2318)	1648 (1352 to 2028)	-277 (-415 to -120)	-14.5% (-20.7% to -6.3%)
Subanalysis excluding day 0				
Total no of all-cause deaths day 1–1826	3838 (3417 to 4345)	3621 (3208 to 4112)	-216 (-373 to -80)	-5.6% (-9.5% to -2.1%)

*Percentage change comparing the non-restrictive scenario with the restrictive scenario.

†WHO.³¹

‡Jenkins HE *et al*³²

§Dodd PJ *et al*⁵

TB, tuberculosis.

Source of TB data

Both the WHO TB incidence³¹ combined with Jenkins CFR³² and the Dodd estimates⁵ resulted in 25 averted TB deaths per birth cohort in the first 5 years of life. However, UR were greater when using Dodd estimates (table 4).

Prior to other routine vaccines

Limiting the analyses to the period prior to other scheduled routine vaccines, the policy change was estimated to reduce all-cause mortality by 14.5% (UR: 6.3%–20.7%) (table 4).

DISCUSSION

Main findings

Disregarding the restrictive BCG vial-opening policy was estimated to reduce TB deaths by 11.0% (UR: 0.5%–28.8%) corresponding to 4 (UR: 0–15) TB deaths averted per birth cohort. All-cause death estimates were reduced by 8.1% (UR: 3.3%–12.7%) corresponding to 392 (UR: 158–624) all-cause deaths per birth cohort. The ICER of the vial-policy change was estimated as US\$911 (UR: 145–9142) per discounted LYG by averting TB deaths. The estimated ICER considering all-cause mortality was considerably lower: US\$9 (UR: 5–23) per discounted LYG. Compared with Wood's purchasing power parity adjusted cost-effectiveness threshold for Guinea-Bissau (US\$22–US\$645),²⁹ the most conservative wastage assumption (95% in the non-restrictive scenario) may not lead to the conclusion that the policy was cost effective assuming effect only on TB deaths. However, at less conservative wastage assumptions, the cost declined markedly and despite few TB deaths averted, changing the policy could be cost-effective for TB deaths, and the policy was highly cost-effective including the effect on all-cause deaths, demonstrating the potential importance of considering all-cause effects in vaccine cost-effectiveness evaluations. Importantly, in the non-restrictive scenario, increased costs were incurred by the health system, while household costs were reduced. Hence, the intervention is likely to increase equity.

The vial-policy change was associated with larger impact in rural than urban Guinea-Bissau, as vaccination delays are greater in rural Guinea-Bissau and mortality is higher.

Comparisons and perspectives

Previously, Roy estimated that increasing BCG coverage to 92% at birth globally could reduce TB deaths <15 years of age by 2.8%.⁷ We found a greater percentage reduction in TB deaths (11.0%, UR: 0.5%–28.8%) by improving timeliness of BCG vaccination. Greater delays in BCG vaccination in the restrictive scenario and more precise estimates of BCG coverage in Guinea-Bissau contribute to the difference.

In recent years, manufacturing problems have created BCG shortages, estimated to be associated with 7433 (UR: 320–19 477) excess TB deaths in 0–14 year olds per global birth cohort,³⁰ but potential excess all-cause deaths were not included. Our results suggest that if all-cause deaths

had been estimated, the assessed public health impact of these shortages would have been substantially higher, and emphasise the importance of including all-cause mortality to inform the full impact of a policy change.

Strengths and limitations

We present the first model assessing impact and cost-effectiveness of the vial-opening policy change on all-cause mortality, and first country-level model assessing impact and cost-effectiveness of this change on any outcome. The BHP HDSS data allowed for country-representative age-specific estimates based on individual level data, which are more accurate than the aggregated data usually available. Results were robust to sensitivity analyses conducted.

Increasing vaccination coverage is usually resource demanding, but using the first registered health-facility contact to provide BCG could easily be implemented without additional initiatives. Thus, the high coverage in the non-restrictive scenario would be realistic if enough vaccines were available.

TB surveillance in Guinea-Bissau is limited and TB is likely underdiagnosed. Due to uncertainty in estimates of TB incidence and mortality, we assessed robustness of our results to the TB-calibration data by conducting sensitivity analyses using other data sources. The main estimates of absolute TB deaths averted were likely conservative, as using other data sources resulted in more TB deaths averted. The efficacy estimates of BCG against TB have varied between studies and populations,^{2 20} and thus the meta-analysed estimates have wide URs. We assumed that TB mortality was constant in 0–4 years old, since age-stratified data were not available. The estimates of TB cases and hospital admissions should be interpreted with caution as they are calculated based on different data sources assuming comparability.

The vaccine efficacy on all-cause deaths was estimated from trials in low-weight neonates and observational studies from Guinea-Bissau, which provided similar mortality estimates. More data from normal birth weight children would be of value. The current level of evidence is not sufficient to conclude on the duration of NSEs.

Cost estimates were derived from Guinea-Bissau. Household costs of seeking BCG vaccination²³ and health system costs per hospital bed day were included.²⁴ Out-of-pocket payments for treatment were not included, but as hospital admission for children is free, we expect out-of-pocket payments to be few. In main analyses, we conservatively assumed only one child was vaccinated per vial in the non-restrictive scenario, therefore likely overestimating the costs of the intervention, as more than one child would likely be vaccinated per vial. Sensitivity analyses showed that the intervention would potentially be cost saving, if on average four children were vaccinated per vial. However, we did not calculate URs for sensitivity analyses on wastage assumptions, and this conclusion should therefore be interpreted with caution.

Our models only included Guinea-Bissau. However, the restrictive vial-opening policy is not limited to Guinea-Bissau.^{15 33} While the exact impact and cost-effectiveness estimates are not directly transferable to other countries, the conclusions of the study are likely to be generalisable. Thus, important gains are likely to be possible in other settings with a similar practice.

CONCLUSION

Disregarding the restrictive vial-opening policy in Guinea-Bissau was estimated to result in small reductions in TB deaths and substantial reductions in all-cause deaths. Our results support that it would be cost-effective to disregard the restrictive vial-opening policy.

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Supplementary material

Disregarding the restrictive vial-opening policy for BCG vaccine in Guinea-Bissau: impact and cost-effectiveness for tuberculosis mortality and all-cause mortality in children aged 0-4 years

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Harris

Appendix

1. Details on data sources	2
1.1 Population estimates	2
1.2 Details on data derived from the BHP's urban and rural HDSS sites	2
1.2.1 All-cause mortality and all-cause hospital admissions	2
1.2.2 BCG coverage	2
1.2.3 Meta-analysis of BCG studies	3
1.2.4 Vaccination costs	3
1.2.5 Household costs of seeking BCG	4
1.2.6 Costs of hospital admissions	4
1.3 Details on TB estimates	4
1.3.1 Calculation of Case Fatality Ratio (CFR)	4
2. Details on model and model equations	5
2.1 TB deaths model with equations	5
2.2 All-cause deaths model with equations	6
2.3 All-cause hospital admission model with equations	8
2.4 Details on incremental costs and cost-effectiveness of disregarding the restrictive vial-opening policy with equations	10
2.5 Details on TB model assuming all-or-nothing BCG vaccine efficacy	12
3. Supplementary Figures and tables	14
3.1 All-or-nothing and leaky vaccine efficacy	14
3.2 BCG coverage estimates in urban Guinea-Bissau in the baseline scenario and the non-restrictive scenario	15
3.3 BCG coverage estimates in rural Guinea-Bissau in the baseline scenario and the non-restrictive scenario	16
3.4 Cost-effectiveness analyses of disregarding the restrictive BCG vial-opening policy by urban and rural population	17
3.5 Main results of disregarding the restrictive vial-opening policy with and without assumed correlation of mortality estimates and TB incidence estimates	19
3.6 Tables of incremental cost-effectiveness ratios (ICERs) in USD by varying vaccine wastage assumptions	20
References	22

1. Details on data sources

1.1 Population estimates

We used data from the WHO/UNICEF Joint Reporting Forms 2017 to obtain the annual birth cohort in Guinea-Bissau [personal communication: Carlitos Bale, Director of the Expanded Programme on Immunization in Guinea-Bissau].

1.2 Details on data derived from the BHP's urban and rural HDSS sites

1.2.1 All-cause mortality and all-cause hospital admissions

The daily individual risk of all-cause mortality was estimated based on data from 2012 to 2017. In survival models with age as underlying time scale, we assessed the daily risk of dying between 0-4 years of age using Kaplan-Meier estimates. Since mortality declines rapidly early in life, we estimated the risk of dying on a daily basis in the first week (day 0 to day 7), and in intervals: day 8 to 28, day 29 to 365, and finally day 366 to 1826. Children entered the analysis on January 1, 2012, registration in the HDSS, or birth, whichever came last. Children were followed until death, 5 years of age, or December 31, 2017, whichever came first.

Likewise, we estimated the individual risk of all-cause hospital admission on data from 2012 to 2017. The risk of hospital admission was estimated in survival models with age as underlying time scale in the following intervals: day 0 to 28, day 29 to 365, and day 366 to 1826. Children entered the analysis on January 1, 2012, registration in the HDSS, or birth, whichever came last. Children were followed until death, migration, 5 years of age, or December 31, 2017, whichever came first. After a hospital admission, children re-entered the analysis, and were able to contribute with more than one event.

BHP covers a random sample of villages/towns in each region, but the regional sample is not weighted according to the region's population. BHP HDSS cover all regions, which comprise of one urban region and nine rural regions. All estimates were computed by region. The regional estimates were weighted according to the sample representation of the total population in the region according to data from the WHO/UNICEF Joint Reporting Forms.

1.2.2 BCG coverage

The coverage was estimated as daily BCG vaccination coverage until 365 days of life (Figure 1) using information collected in the year following the coverage age, e.g. BCG coverage at day 1 was estimated using vaccination information obtained between day 1 and day 366. Only those with assessed vaccination status in the relevant period contributed to the BCG coverage estimate at a certain age. BCG is typically not provided after 1 year of age, and we thus assumed that the BCG coverage was constant from 1 year of age. Using known prior contact with a health facility

(reported to be born at a health facility or registration of other vaccines according to the vaccination card); we calculated the potential BCG coverage by age in the non-restrictive scenario, if all children were vaccinated at their first registered contact with a health facility.

1.2.3 Meta-analysis of BCG studies

To assess the effect of BCG on all-cause mortality, we conducted a meta-analysis of all studies assessing the effect of BCG versus no BCG in Guinea-Bissau. We identified six published studies¹⁻⁶, and one manuscript under preparation⁷. Of the six studies, three were randomised trials conducted in low-weight infants, where children were randomised to BCG-at-birth or the usually delayed BCG. We used the effect of BCG in the neonatal period, since few children in the control group had received BCG at this age⁶. BCG-at-birth was associated with 72% lower mortality in trial I (Hazard Ratio (HR): 0.28 (0.06-1.37)⁵; 45% lower mortality in trial II (HR:0.55 (0.34-0.89)⁴, 11% of children in the control group had received BCG at 28 days); and 30% lower mortality in trial III (HR: 0.70 (0.47-1.04)⁶, 17% of children in the control group had received BCG at 28 days). The four other studies included in the meta-analysis were observational studies, one of which was conducted in low-weight children². All observational studies compared mortality of BCG-vaccinated children with mortality of BCG-unvaccinated children^{1-3 7}. In the meta-analysis, BCG was associated with 42% (19-58%) lower all-cause mortality (Figure 3).

1.2.4 Vaccination costs

We obtained costs of BCG vaccines, syringes, safety boxes and freight from the national department of the Expanded Programme on Immunizations (EPI) [personal communication: Carlitos Bale, Director of the Expanded Programme on Immunization in Guinea-Bissau] (Table 1). We assumed that there would be no other additional costs related with disregarding the vial-opening policy. We thus assumed that the extra time spent by health staff to perform BCG vaccination would correspond to the time used explaining the mothers to return for vaccination another day and providing the vaccine to the majority of these children on a later occasion.

Currently a vial of BCG is opened if 10-12 children are present for vaccination. We therefore assumed 50% wastage of BCG vaccine in the baseline scenario. When disregarding the restrictive vial-opening policy, a vial of BCG should be opened even if only one child is present. We therefore assumed 95% wastage of BCG when disregarding the vial-opening policy (non-restrictive scenario). In both scenarios, we assumed 5% wastage of syringes and safety boxes.

1.2.5 Household costs of seeking BCG

We have previously estimated the household costs of seeking BCG vaccination in rural Guinea-Bissau to 1.89 USD (2016 value) per BCG vaccinated child⁸. Using the World Bank Consumer Price Index (CPI)⁹, we updated this value to 1.92 USD in 2017 values. We found that mothers on average went to the health facility 1.26 times before succeeding getting their child vaccinated⁸. Children born in health facilities can be BCG-vaccinated without actively seeking BCG-vaccination. We therefore estimated the proportion of children born in health facilities, and the proportion of these vaccinated at birth according to BHP data, and applied these proportions to the WHO/UNICEF 2017-birth cohort estimate (Table 3). For all children not vaccinated at birth, we assumed that their mother would seek vaccination 1.26 times in order to get the child vaccinated in the restrictive scenario. In the non-restrictive scenario, we assumed that children born in health facilities would be vaccinated at birth and that all children would be vaccinated at the first contact with a health facility. Thus, mothers would bring their child for BCG vaccination only once.

We did not have corresponding information for the urban population, and we therefore used the household costs of seeking BCG vaccination obtained in the rural area for the whole population.

1.2.6 Costs of hospital admissions

Using data from the rural HDSS¹⁰ and from the National Hospital Simão Mendes¹¹, we assessed the median number of bed days for all-cause hospital admissions of children less than 5 years old. In both settings, the median number of bed days per hospital admission was 5 days.

We have estimated the cost incurred by the health system per hospital bed day as 14.92 USD in a micro-costing study from Guinea-Bissau in 2014¹², corresponding to a 2017-value of 15.58 USD using the World Bank CPI⁹. Hospital admissions are free for all children below 5 years of age in Guinea-Bissau¹³. We therefore assumed that the costs incurred by the household per hospital bed day only consisted of the value of the mothers' time spent. We have previously estimated the value of a mother's time per day to 2.80 USD¹⁴ (2.98 2017-USD) based on a regression model by Knight and colleagues estimating average monthly earnings in 2011¹⁵.

1.3 Details on TB estimates

1.3.1 Calculation of Case Fatality Ratio (CFR)

We calculated the Case Fatality Ratio (CFR) for TB mortality by dividing the total number of TB deaths in children aged 0 to 4 years with the total number of TB cases among children aged 0 to 4 years.

2. Details on model and model equations

In the baseline analysis, we assumed that the female and male estimates had a correlation factor of 1.0 for TB incidence, and TB mortality. We furthermore assumed that BHP mortality estimates by age had a correlation factor of 1.0. To assess the impact of these correlations, we ran a sensitivity analysis assuming that the estimates were not correlated.

2.1 TB deaths model with equations

The percentage change in TB deaths, $pTBD$, was calculated based on the estimated number of TB deaths in the non-restrictive scenario with no restrictive vial-opening policy, $nTBD_{non-restrictive}$, and the number of TB deaths in the current baseline situation, $nTBD_{baseline}$ (Equation 1). The baseline scenario was calibrated to the 2016 Global Burden of Disease (GBD) estimate of paediatric TB deaths using the daily risk of TB death in children aged 0-4 years (Equation 2):

$$pTBD = ((nTBD_{non-restrictive} - nTBD_{baseline}) / nTBD_{baseline}) \times 100 \quad \text{Equation 1}$$

$$nTBD_{baseline} = \sum_{t=0}^{t=1826} n_t \times R_{TB0-4} \quad \text{Equation 2}$$

Where n_t was the sum of children alive at age t , and R_{TB0-4} was the daily risk of TB death in children aged 0-4. The daily risk of TB death is the risk per person per day. The population at risk was adjusted for all-cause deaths on a daily basis; assuming BCG had no effect on all-cause mortality.

We estimated the number of TB deaths in children aged 0-4 in the non-restrictive scenario using:

$$nTBD_{non-restrictive} = (\sum_{t=0}^{t=1826} V_t \times RV_{TB0-4}) + (\sum_{t=0}^{t=182} U_t \times RU_{TB0-4}) \quad \text{Equation 3}$$

Where V_t was the number of BCG-vaccinated children at time t , RV_{TB0-4} was the daily individual risk of TB death in BCG-vaccinated children aged 0-4, U_t was the number of BCG-unvaccinated children at time t , and RU_{TB0-4} was the daily risk of TB death in BCG-unvaccinated children aged 0-4.

The individual daily risk of TB death in unvaccinated children, RU_{TB0-4} , was estimated using

$$nTBD_{non-restrictive} = (\sum_{t=0}^{t=182} V_t \times RU_{TB0-4} \times RR) + (\sum_{t=0}^{t=1826} U_t \times RU_{TB0-4})$$

$$RU_{TB0-4} = \frac{nTBD_{non-restrictive}}{(\sum_{t=0}^{t=182} V_t \times RR_{TB}) + (\sum_{t=0}^{t=1826} U_t)} \quad \text{Equation 4}$$

Where RR was the risk-ratio of TB death in BCG-vaccinated children compared with BCG-unvaccinated children.

The individual daily risk of TB death among BCG-vaccinated children, RV_{TB0-4} , was calculated using

$$RV_{TB0-4} = RR \times RU_{TB0-4} \quad \text{Equation 5}$$

We estimated the number of TB deaths at time t in the non-restrictive scenario for BCG-vaccinated ($nTBDv_{tNR}$) and BCG-unvaccinated children ($nTBDu_{tNR}$), respectively:

$$nTBDv_{tNR} = RV_{TB0-4} \times V_{tNR} \quad \text{Equation 6}$$

$$nTBDu_{tNR} = RU_{TB0-4} \times U_{tNR} \quad \text{Equation 7}$$

Where RV_{TB0-4} was the daily individual risk of TB death among BCG-vaccinated children aged 0-4 (calculated based on the baseline scenario – Equation 5), V_{tNR} was the number of BCG-vaccinated children at time t in the non-restrictive scenario, RU_{TB0-4} was the daily individual risk of TB death among BCG-unvaccinated children aged 0-4 (calculated based on the baseline scenario – Equation 4), and U_{tNR} was the number of BCG-unvaccinated children at time t in the non-restrictive scenario.

We then calculated the total number of TB deaths in children aged 0-4 in the non-restrictive scenario.

$$nTBD_{non-restricti} = \sum_{t=0}^{t=1826} nTBDv_{tNR} + \sum_{t=0}^{t=1826} nTBDu_{tNR} \quad \text{Equation 8}$$

Using the case-fatality ratio, CFR , we estimated the number of TB cases:

$$nTB_{0-4} = nTBD_{non-restrict} / CFR \quad \text{Equation 9}$$

2.2 All-cause deaths model with equations

The effect of disregarding the restrictive BCG vial-opening policy on all-cause deaths was estimated using the same approach as for TB deaths, but with minor adjustments as we had more precise data for all-cause deaths allowing for age-specific mortality estimates (Table 1).

The percentage change in all-cause deaths, $pACD$, was calculated based on number of all-cause deaths in the non-restrictive scenario, $nACD_{non-restrict}$, and the number of all-cause deaths in the baseline scenario, $nACD_{baseline}$. In the baseline scenario, we used paediatric mortality estimates obtained from the Bandim Health Project 2012-2017 (Appendix 1.2.1), using the daily risk of all-cause death per person at age t .

$$pACD = ((nACD_{non-restrict} - nACD_{baseline}) / nACD_{baseline}) \times 100 \quad \text{Equation 10}$$

$$nACD_t = n_t \times R_t \quad \text{Equation 11}$$

Where n_t was the sum of children alive at age t , and R_t was the daily risk of all-cause death at age t .

Leading to the total number of all-cause deaths in children aged 0-4, $nACD_{0-4baseline}$:

$$nACD_{0-4baseline} = \sum_{t=0}^{t=182} nACD_{tbaseline} \quad \text{Equation 12}$$

We estimated the number of all-cause deaths at age t in the non-restrictive scenario using:

$$nACD_t = (V_t \times RV_{Act}) + (U_t \times RU_{Act}) \quad \text{Equation 13}$$

Where V_t was the number of BCG-vaccinated children at time t , RV_{Act} was the daily individual risk of all-cause death in BCG-vaccinated children at age t , U_t was the number of BCG-unvaccinated children at time t , and RU_{Act} was the daily risk of all-cause death in BCG-unvaccinated children at age t .

Given $RV_{Act} = RU_{Act} \times RR_{AC}$, the individual daily risk of all-cause death in unvaccinated children at age t , RU_{Act} , was estimated using

$$nACD_t = (V_t \times RU_{Act} \times RR_{AC}) + (U_t \times RU_{Act})$$

$$RU_{Act} = \frac{nACD_t}{(V_t \times RR_{AC}) + (U_t)} \quad \text{Equation 14}$$

Where RR_{AC} was the risk-ratio of all-cause death in BCG-vaccinated children compared with BCG-unvaccinated children.

The individual daily risk of all-cause death at time t among BCG-vaccinated children, RV_{Act} , was calculated using

$$RV_{Act} = RR_{AC} \times RU_{Act} \quad \text{Equation 15}$$

We estimated the number of all-cause deaths at time t in the non-restrictive scenario for BCG-vaccinated ($nACD_{vNR}$) and BCG-unvaccinated children ($nACD_{uNR}$), respectively:

$$nACD_{vNR} = RV_{Act} \times V_{tNR} \quad \text{Equation 16}$$

$$nACD_{uNR} = RU_{Act} \times U_{tNR} \quad \text{Equation 17}$$

Where RV_{Act} was the daily individual risk of all-cause death at time t among BCG-vaccinated children (calculated based on the baseline scenario – Equation 15), V_{tNR} was the number of BCG-vaccinated children at time t in the non-restrictive

scenario, RU_{ACt} was the daily individual risk of all-cause death at time t among BCG-unvaccinated children (calculated based on the baseline scenario – Equation 14), and U_{INR} was the number of BCG-unvaccinated children at time t in the non-restrictive scenario.

We then calculated the total number of all-cause deaths in children aged 0-4 in the non-restrictive scenario.

$$nACD_{0-4} = \sum_{t=0}^{t=1826} nACDv_t + \sum_{t=0}^{t=1826} nACDu_t \quad \text{Equation 18}$$

2.3 All-cause hospital admission model with equations

The daily age-specific risk of all-cause hospital admission (risk of all-cause hospital admission per person per day) was estimated using the BHP age-stratified hospital admission data (Methods explained in Appendix 1.2.1). Based on the daily risk of all-cause hospital admission and the meta-estimate of the effect of BCG on all-cause hospital admission (Appendix 1.2.1), we calculated the daily risk of all-cause hospital admission in BCG-vaccinated and BCG-unvaccinated children, respectively.

The daily risk of all-cause hospital admission was applied to the WHO/UNICEF birth cohort estimate of 2017 [personal communication: Carlitos Bale, Director of the Vaccination Programme in Guinea-Bissau]. We calculated the percentage change in all-cause hospital admission, $pACH$, based on number of all-cause hospital admissions in the non-restrictive scenario, $nACH_{non-restrictive}$, and the number of all-cause hospital admissions in the baseline scenario, $nACH_{baseline}$. We used paediatric hospital admissions estimates obtained from the BHP surveillance data in 2012-2017 (Appendix 1.2.1) to obtain the daily risk of all-cause hospital admission at age t .

$$pACH = ((nACH_{non-restrictive} - nACH_{baseline})/nACH_{baseline}) \times 100 \quad \text{Equation 19}$$

$$nACH_t = n_t \times R_{ACHt} \quad \text{Equation 20}$$

Where n_t was the sum of children alive at age t , and R_{ACHt} was the daily risk of all-cause hospital admission at age t .

Leading to the total number of all-cause hospital admissions in children aged 0-4, $nACH_{0-4baseline}$:

$$nACH_{0-4baseline} = \sum_{t=0}^{t=1826} nACH_{tbaseline} \quad \text{Equation 21}$$

We estimated the number of all-cause hospital admissions at age t in the non-restrictive scenario using:

$$nACH_t = V_t \times RV_{ACHt} + U_t \times RU_{ACHt} \quad \text{Equation 22}$$

Where V_t was the number of BCG-vaccinated children at time t , RV_{ACHt} was the daily individual risk of all-cause hospital admission in BCG-vaccinated children at age t , U_t was the number of BCG-unvaccinated children at time t , and RU_{ACHt} was the daily risk of all-cause hospital admission in BCG-unvaccinated children at age t .

The individual daily risk of all-cause hospital admission in unvaccinated children at age t , RU_{ACHt} , was estimated using

$$nACH_t = (V_t \times RU_{ACHt} \times RR_{ACH}) + (U_t \times RU_{ACHt})$$

$$RU_{ACHt} = \frac{nACH_t}{(V_t \times RR_{ACH}) + (U_t)} \quad \text{Equation 23}$$

Where RR_{ACH} was the risk-ratio of all-cause hospital admission in BCG-vaccinated children compared with BCG-unvaccinated children.

The individual daily risk of all-cause hospital admission at time t among BCG-vaccinated children, RV_{ACHt} , was calculated using

$$RV_{ACHt} = RR_{ACH} \times RU_{ACHt} \quad \text{Equation 24}$$

We estimated the number of all-cause hospital admissions at time t in the non-restrictive scenario for BCG-vaccinated ($nACHv_{tNR}$) and BCG-unvaccinated children ($nACHu_{tNR}$), respectively:

$$nACHv_{tNR} = RV_{ACHt} \times V_{ta} \quad \text{Equation 25}$$

$$nACHu_{tNR} = RU_{ACHt} \times U_{ta} \quad \text{Equation 26}$$

Where RV_{ACHt} was the daily individual risk of all-cause hospital admission at time t among BCG-vaccinated children (calculated based on the baseline scenario – Equation 24), V_{tNR} was the number of BCG-vaccinated children at time t in the non-restrictive scenario, RU_{ACHt} was the daily individual risk of all-cause hospital admission at time t among BCG-unvaccinated children (calculated based on the baseline scenario – Equation 23), and U_{tNR} was the number of BCG-unvaccinated children at time t in the non-restrictive scenario.

We then calculated the total number of all-cause hospital admissions in children aged 0-4 in the non-restrictive scenario.

$$nACH_{0-4} = \sum_{t=0}^{t=182} nACHv_t + \sum_{t=0}^{t=1826} nACHu_t \quad \text{Equation 27}$$

2.4 Details on incremental costs and cost-effectiveness of disregarding the restrictive vial-opening policy with equations

We estimated the vaccine costs in each scenario based on the number of children vaccinated by 12 months of age, $nBCG_{12}$, the vaccine wastage factor, WF , and the price per dose including freight costs, $price_{BCG}$:

$$vaccine_{costs} = nBCG_{12} \times WF \times price_{BCG} \quad \text{Equation 28}$$

The wastage factor was based on the vaccine wastage assumed in each scenario. In the baseline scenario, we assumed 50% vaccine wastage corresponding to a wastage factor of 2. In the non-restrictive scenario, we assumed 95% vaccine wastage corresponding to a wastage factor of 20. In sensitivity analyses, we adjusted the wastage factors in the baseline scenario to 35%, 40%, 45%, 55% and 60% respectively, and wastage factors in the non-restrictive scenario to 70%, 75%, 80%, 85% and 90%, respectively.

We calculated the injection supply costs as a summation of the costs of application syringe costs, mixing syringe costs and safety box cost:

$$injection\ supply_{costs} = application\ syringe_{costs} + mixing\ syringe_{costs} + safety\ box_{costs}$$

Equation 29

For each item, we calculated the costs by multiplying the number of items used by the item unit price including freight:

$$cost_{item} = n_{item} \times price_{item} \quad \text{Equation 30}$$

Number of items used were calculated by equations 31-33 assuming 5% wastage of each item, resulting in a wastage factor of 1.05:

$$n_{app.syr} = nBCG_{12} \times WF \quad \text{Equation 31}$$

$$n_{mix.syr} = \frac{nBCG_{12} \times WF_{BCG}}{vial\ size} \times WF_{mix.syr} \quad \text{Equation 32}$$

$$n_{safety\ box} = \frac{n_{app.syr} + n_{mix.syr}}{safety\ box\ capacity} \times WF_{safety\ box} \quad \text{Equation 33}$$

Where vial size was assumed to be 20 dose vials and safety box capacity was assumed to be 100 syringes as used in previous analyses¹⁴.

We calculated the incremental costs of averted/additional TB hospital admissions and all-cause hospital admissions:

$$costs_{hosp} = n_{hosp} \times n_{bedday} \times (cost_{bedday} + cost_{mother}) \quad \text{Equation 34}$$

Where n_{hosp} was the number of additional admissions (if negative, number of averted admissions) in the non-restrictive scenario, n_{bedday} was 60 days for TB hospital admissions and 5 days for all-cause hospital admissions, $cost_{bedday}$ was the cost incurred by the health system per bed day and $cost_{mother}$ was the cost incurred by the household per bed day.

We calculated the household costs of seeking BCG vaccination. The number of children vaccinated at birth in the baseline scenario was estimated based on the proportion of children born in health facilities multiplied by the proportion of these vaccinated at birth. In the non-restrictive scenario, it was assumed that all children born in health facilities were vaccinated at birth.

$$n_{noBCG} = n_{total} - n_{total} \times p_{HF} \times p_{BCG} \quad \text{Equation 35}$$

Where n_{total} was the birth cohort of 2017, p_{HF} was the proportion born in health facilities and p_{BCG} was the proportion of children vaccinated at birth in the health facility, and n_{noBCG} was the number of children not BCG vaccinated at birth, and for whom the mother should seek vaccination. As we have previously found that mothers on average bring their child for vaccination 1.26 times before obtaining BCG vaccination at cost of USD 1.92 per time, we used this information to calculate the household costs of seeking BCG vaccination in each scenario:

$$HHcost_{BCG} = n_{noBCG} \times 1.26 \times 1.92 \text{ USD} \quad \text{Equation 36}$$

The incremental household costs of seeking BCG when disregarding the restrictive vial-opening policy was obtained by subtracting the household costs in the restrictive scenario from the household costs in the non-restrictive scenario.

We summed the incremental vaccination costs, the incremental hospital admission costs and incremental household costs of seeking BCG vaccination, and obtained the total incremental costs of disregarding the restrictive vial-opening policy.

To obtain an estimate of the cost-effectiveness of disregarding the restrictive vial-opening policy, we initially calculated life years gained (LYG) from disregarding the restrictive vial-opening policy accounting for TB-specific and all-cause effects of BCG vaccine.

Using the estimated number of TB deaths, $nTBD$, and all-cause deaths, $nACD$, averted, and the World Bank estimate of a life expectancy, LE , of 57 years at birth in Guinea-Bissau in 2017¹⁶, we calculated the number of LYG per year accounting for TB-specific, LYG_{yTB} , and all-cause effects, LYG_{yAC} , respectively:

$$LYG_{yTB} = nTBD_y \times (LE - y) \quad \text{Equation 37}$$

$$LYG_{yAC} = nACD_y \times (LE - y) \quad \text{Equation 38}$$

We calculated the number of LYG per year for the first 5 years of age, where y was the age, by multiplying the number of TB deaths/all-cause deaths averted per year of age by the remaining life expectancy.

In the base case analysis, we discounted x (future LYG, future costs, and future deaths) by 3% per year as recommended by WHO¹⁷:

$$x_{disc} = \frac{x}{(1+0.03)^{year}} \quad \text{Equation 39}$$

The incremental cost-effectiveness ratio (ICER) of disregarding the restrictive vial opening policy was calculated accounting for TB-specific and all-cause effects, respectively, using the same approach, described by equation 40-43:

$$ICER_{LYG} = \frac{\text{Total incremental costs}}{LYG_{non-restrictiv}} \quad \text{Equation 40}$$

$$ICER_{LYGdisc} = \frac{\text{Total incremental costs}}{LYGdisc_{non-restrict}} \quad \text{Equation 41}$$

$$ICER_{Daverted} = \frac{\text{Total incremental costs}}{Daverted_{non-restrict}} \quad \text{Equation 42}$$

$$ICER_{Daverteddisc} = \frac{\text{Total incremental costs}}{Daverted_{non-restrictivedisc}} \quad \text{Equation 43}$$

2.5 Details on TB model assuming all-or-nothing BCG vaccine efficacy

As a sensitivity analyses, we changed the model structure from assuming leaky BCG vaccine efficacy to a model structure assuming all-or-nothing BCG vaccine efficacy, as in the original model developed by Roy and colleagues¹⁸.

We calculated the absolute and percentage change in number of TB deaths per birth cohort during the first 5 years of life in the non-restrictive scenario compared with the baseline scenario. The percentage change in TB deaths, $pTBD_{AN}$, was calculated based on number of TB deaths in the non-restrictive scenario, $nTBD_{ANnon-restricti}$, and the number of

TB deaths in the baseline scenario, $nTBD_{ANbaseline}$. As in the main analysis, the baseline scenario was calibrated to the 2016 Global Burden of Disease estimates¹⁹ of paediatric TB deaths using the daily risk of TB death in unprotected children aged 0-4.

$$pTBD_{AN} = ((nTBD_{ANnon-restr} - nTBD_{ANbaseline}) / nTBD_{ANbaseline}) \times 100$$

Equation 44

The number of paediatric TB deaths per birth cohort in the first 5 years of life ($nTBD_{AN}$) was estimated to be:

$$nTBD_{AN} = \sum_{t=0}^{t=1826} nUP_t \times R_{0-4}$$

Equation 45

Where t was the age in days; nUP_t was the number of unprotected children at age t ; R_{0-4} was the daily individual risk of TB death in unprotected children aged 0-4 years.

The number of unprotected children at age t (nUP_t) was estimated to be the number of unvaccinated children at age t plus the number of vaccinated children with insufficient immune response to prevent TB death at age t :

$$nUP_t = U_t + (V_t \times (1 - VE))$$

Equation 46

Where U_t was the number of unvaccinated children at age t , V_t was the number of vaccinated children at age t , and VE was the vaccine efficacy (proportion), and:

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

Equation 47

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

Equation 48

$$VE = 1 - RR_{TB}$$

Equation 49

Where, BC was the annual number of live births in Guinea-Bissau in 2017, D_t was the number of all-cause deaths at age t , Cov_t was the proportion of BCG-vaccinated children at t , and RR_{TB} was the rate ratio of TB deaths in BCG-vaccinated children compared with BCG-unvaccinated children.

The daily individual risk of TB death in unprotected children aged 0-4 years (R_{0-4}) was:

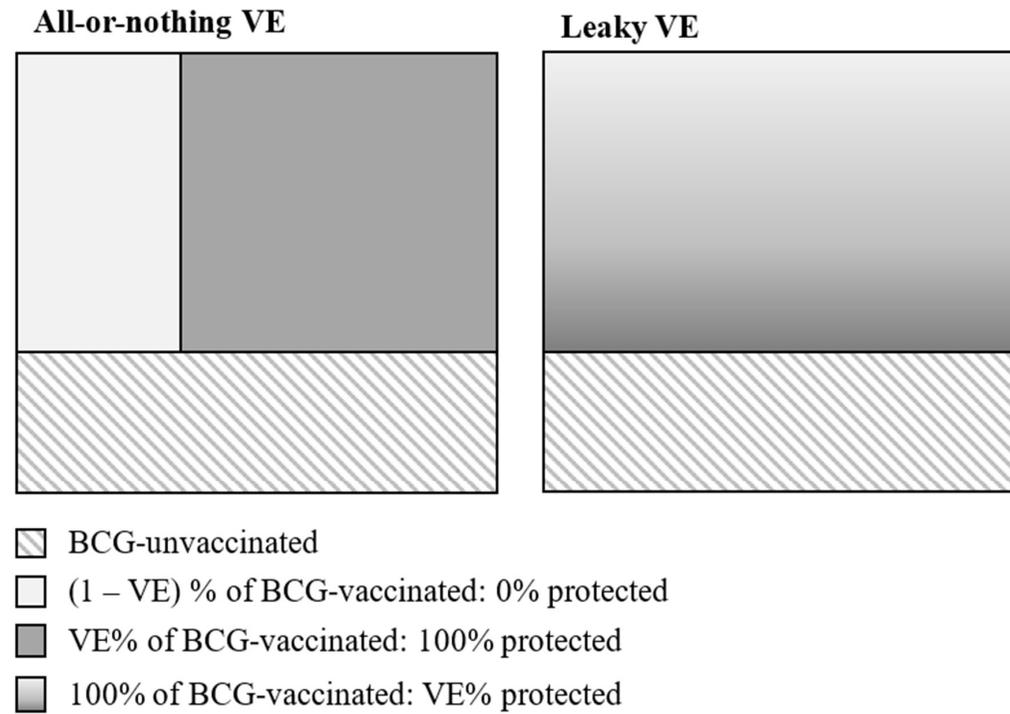
$$R_{0-4} = Mort_{0-4} / \sum n_{0-4}$$

Equation 50

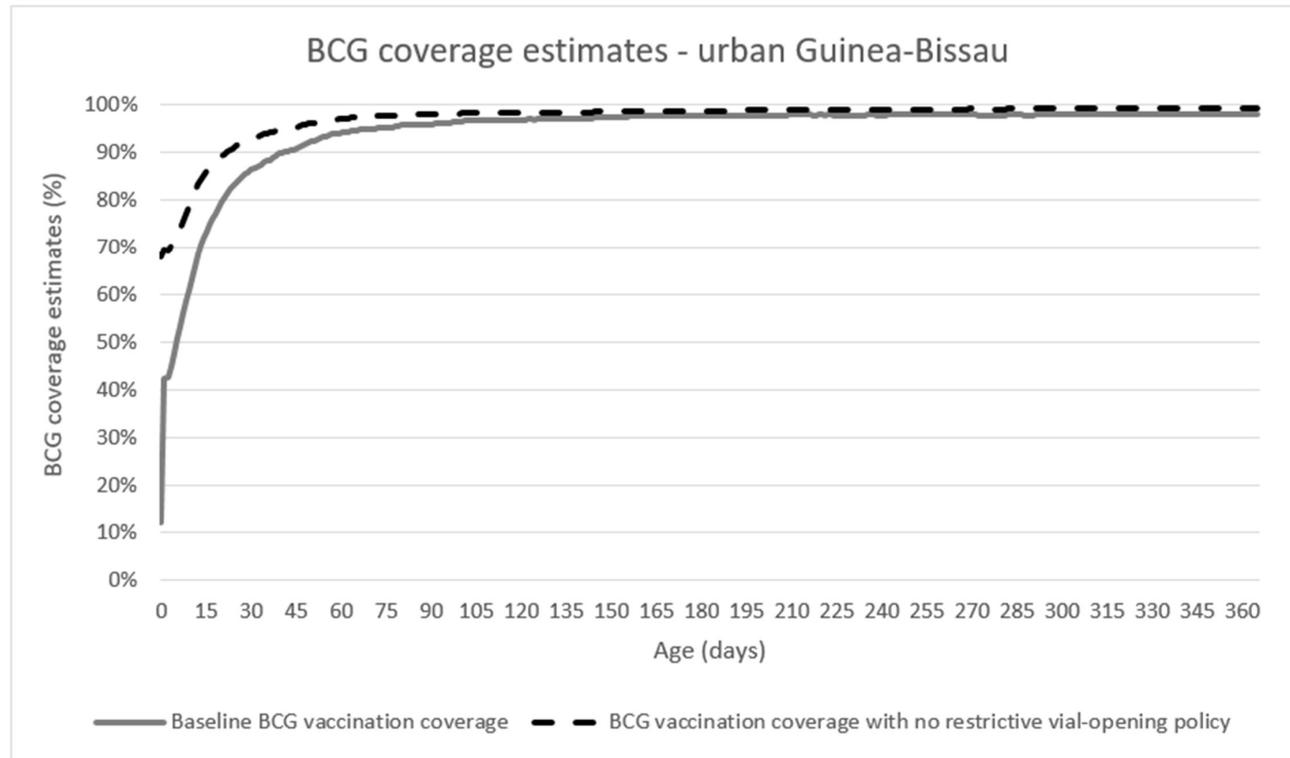
Where $Mort_{0-4}$ was the number of TB deaths in each age group, and $\sum n_{0-4}$ was the sum of unprotected person days.

3. Supplementary Figures and tables

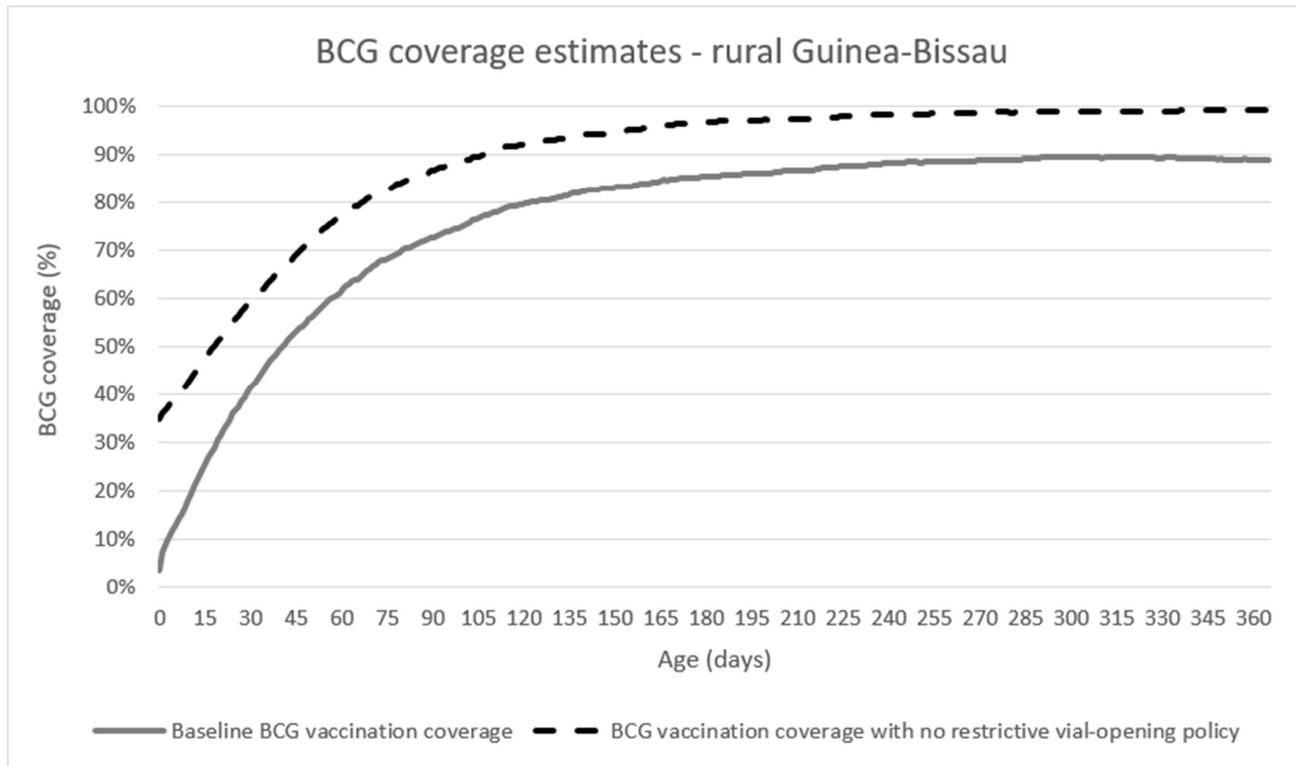
3.1 All-or-nothing and leaky vaccine efficacy



3.2 BCG coverage estimates in urban Guinea-Bissau in the baseline scenario and the non-restrictive scenario



3.3 BCG coverage estimates in rural Guinea-Bissau in the baseline scenario and the non-restrictive scenario



3.4 Cost-effectiveness analyses of disregarding the restrictive BCG vial-opening policy by urban and rural population

	URBAN POPULATION		RURAL POPULATION	
	Restrictive (baseline) scenario	Non-restrictive scenario	Restrictive (baseline) scenario	Non-restrictive scenario
Birth population of 2017	19,018	19,018	50,194	50,194
Total number of children born in health facilities	12,791	12,791	20,563	20,563
Number of children BCG-vaccinated at birth	7,987	12,791	5,119	20,563
Number of children not BCG-vaccinated at birth	11,031	6,227	45,075	29,631
BCG coverage at 12 months of age	98 %	99 %	89 %	99 %
Total household costs of seeking BCG vaccination*	26,626 USD	11,929 USD	108,803 USD	56,765 USD
Total BCG vaccine costs*	7,621 USD	77,008 USD	18,257 USD	203,330 USD
Total Injection supply costs	1,136 USD	1,828 USD	2,722 USD	4,826 USD
TB-specific effects only	Median (95% Uncertainty Range)	Median (95% Uncertainty Range)	Median (95% Uncertainty Range)	Median (95% Uncertainty Range)
Total number of paediatric TB deaths	8 (3 to 22)	8 (3 to 21)	26 (10 to 69)	21 (8 to 57)
Total LYG		11 (0 to 47)		225 (9 to 943)
Total LYG discounted		5 (0 to 23)		109 (4 to 458)
Total number of paediatric TB hospital admissions	11	11	36	30
Total costs of TB hospital admissions	12,638 USD	12,314 USD	39,740 USD	33,218 USD
Total costs of TB hospital admissions discounted	11,589 USD	11,288 USD	36,506 USD	30,512 USD
Incremental costs of disregarding the restrictive vial-opening policy (including vaccination costs, household costs and costs averted by TB hospital admissions)		55,058 USD		128,618 USD
Incremental costs of disregarding the restrictive vial-opening policy - discounted		55,081 USD		129,147 USD

ICER per LYG (USD)		2,473 (423 to 23,733)		252 (36 to 2,649)
ICER per LYG discounted (USD)		5,115 (876 to 49,049)		524 (77 to 5,455)
ICER per TB death averted (USD)		137,307 (23,493 to 1,317,677)		13,898 (2,002 to 146,002)
ICER per TB death averted discounted (USD)		147,732 (25,315 to 1,416,715)		15,272 (2,245 to 159,037)
All-cause effects				
Total number of all-cause deaths	1,071 (897 to 1,302)	961 (795 to 1,180)	3,787 (3,303 to 4,386)	3,467 (2,992 to 4,048)
Total LYG by averted all-cause deaths		6,345 (2,704 to 9,810)		17,922 (7,005 to 29,622)
Total LYG by averted all-cause deaths - discounted		3,023 (1,288 to 4,674)		8,650 (3,360 to 14,230)
Total number of all-cause hospital admissions	1,806	1,816	4,004	4,012
Total costs of all-cause hospital admissions	167,510 USD	168,459 USD	371,471 USD	372,135 USD
Total costs of all-cause hospital admissions discounted	155,588 USD	156,468 USD	342,545 USD	343,138 USD
Incremental costs of disregarding the restrictive vial-opening policy (including vaccination costs, household costs and costs averted by hospital admissions)		56,331 USD		135,805 USD
Incremental costs of disregarding the restrictive vial-opening policy - discounted		56,262 USD		135,734 USD
ICER per LYG (USD)		5 (3 to 11)		4 (2 to 10)
ICER per LYG discounted (USD)		10 (6 to 23)		8 (4 to 20)
ICER per all-cause death averted (USD)		273 (168 to 635)		210 (113 to 542)
ICER per all-cause death averted discounted (USD)		280 (173 to 653)		221 (120 to 567)

USD: US Dollar 2017 value, LYG: Life year gained, ICER: Incremental cost-effectiveness ratio

* The urban population constitutes 27% of the birth population, and the rural population constitutes 73% of the birth population.

3.5 Main results of disregarding the restrictive vial-opening policy with and without assumed correlation of mortality estimates and TB incidence estimates

	Baseline scenario	Non-restrictive scenario	Absolute change	Percentage change
TB-specific effects	Median (95% Uncertainty Range)	Median (95% Uncertainty Range)	Median (95% Uncertainty Range)	Median (95% Uncertainty Range)
Total number of paediatric TB deaths ¹	33 (13 to 89)	29 (11 to 79)	-4 (-15 to 0)	-11.0% (-28.8% to -0.5%)
Total number of paediatric TB deaths - assuming no correlations ²	35 (18 to 74)	31 (15 to 66)	-4 (-13 to 0)	-11.0% (-28.8% to -0.5%)
All-cause effects				
Total number of all-cause deaths ³	4,820 (4,309 to 5,425)	4,429 (3,920 to 5,028)	-392 (-624 to -158)	-8.1% (-12.7% to -3.3%)
Total number of all-cause deaths - assuming no correlations ²	4,833 (4,632 to 5,041)	4,440 (4,155 to 4,743)	-394 (-615 to -160)	-8.1% (-12.7% to -3.3%)

¹ Assuming perfect correlation between male and female TB incidence, and perfect correlation between male and female TB mortality

² Assuming no correlations between data input

³ Assuming perfect correlation between all-cause mortality by age

3.6 Tables of base case incremental cost-effectiveness ratios (ICERs) in USD by varying vaccine wastage assumptions

Table 3.6.1 ICERs in USD per discounted LYG by averted TB deaths

	70% VW in non-restrictive scenario	75% VW in non-restrictive scenario	80% VW in non-restrictive scenario	85% VW in non-restrictive scenario	90% VW in non-restrictive scenario	95% VW in non-restrictive scenario
35% VW in restrictive scenario	-448	-352	-209	30	507	1,938
40% VW in restrictive scenario	-465	-369	-226	12	489	1,920
45% VW in restrictive scenario	-485	-390	-247	-8	469	1,901
50% VW in restrictive scenario	-509	-414	-271	-32	445	1,876
55% VW in restrictive scenario	-539	-444	-301	-62	415	1,846
60% VW in restrictive scenario	-577	-481	-338	-99	378	1,809

VW: Vaccine wastage assumption. Assumptions used for the main analysis are marked in grey colour.

Table 3.6.2 ICERs in USD per discounted TB death averted

	70% VW in non-restrictive scenario	75% VW in non-restrictive scenario	80% VW in non-restrictive scenario	85% VW in non-restrictive scenario	90% VW in non-restrictive scenario	95% VW in non-restrictive scenario
35% VW in restrictive scenario	-13,038	-10,259	-6,089	860	14,758	56,453
40% VW in restrictive scenario	-13,539	-10,760	-6,590	359	14,257	55,952
45% VW in restrictive scenario	-14,132	-11,352	-7,182	-233	13,665	55,359
50% VW in restrictive scenario	-14,842	-12,062	-7,893	-944	12,954	54,649
55% VW in restrictive scenario	-15,710	-12,931	-8,761	-1,812	12,086	53,781
60% VW in restrictive scenario	-16,796	-14,016	-9,847	-2,898	11,000	52,695

VW: Vaccine wastage assumption. Assumptions used for the main analysis are marked in grey colour.

Table 3.6.3 ICERs in USD per discounted LYG by averted all-cause deaths

	70% VW in non-restrictive scenario	75% VW in non-restrictive scenario	80% VW in non-restrictive scenario	85% VW in non-restrictive scenario	90% VW in non-restrictive scenario	95% VW in non-restrictive scenario
35% VW in restrictive scenario	-4	-3	-1	1	5	19
40% VW in restrictive scenario	-4	-3	-1	1	5	18
45% VW in restrictive scenario	-4	-3	-2	1	5	18
50% VW in restrictive scenario	-4	-3	-2	0	5	18
55% VW in restrictive scenario	-4	-3	-2	0	4	18

60% VW in restrictive scenario	-5	-4	-3	0	4	17
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VW: Vaccine wastage assumption. Assumptions used for the main analysis are marked in grey colour.

Table 3.6.4 ICERs in USD per discounted all-cause death averted

	70% VW in non-restrictive scenario	75% VW in non-restrictive scenario	80% VW in non-restrictive scenario	85% VW in non-restrictive scenario	90% VW in non-restrictive scenario	95% VW in non-restrictive scenario
35% VW in restrictive scenario	-99	-74	-37	26	151	526
40% VW in restrictive scenario	-104	-79	-41	21	146	521
45% VW in restrictive scenario	-109	-84	-47	16	141	516
50% VW in restrictive scenario	-116	-91	-53	9	134	509
55% VW in restrictive scenario	-123	-98	-61	2	127	502
60% VW in restrictive scenario	-133	-108	-71	-8	117	492

VW: Vaccine wastage assumption. Assumptions used for the main analysis are marked in grey colour.

The results in table 3.6.1-3.6.4 are based on base-case analysis, and therefore differ from the main results, which are based on Monte Carlo simulations.

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