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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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 studies[1-6], and one manuscript under preparation[7]. 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 age[6]. 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 children[2]. 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 child[8]. 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 vaccinated[8]. 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 HDSS[10] and from the National Hospital Simão Mendes[11], 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 2014[12], corresponding to a 2017-value of 15.58 USD using the World Bank CPI[9]. Hospital admissions are free for all children below 5 years of age in Guinea-Bissau[13]. 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 USD[14] (2.98 2017-USD) based on a regression model by Knight and colleagues estimating average monthly earnings in 2011[15].

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):

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

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

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:

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

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

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

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

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

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

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:

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

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

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, $nACD_{non-restri}$, 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 ($nACDv_{tNR}$) and BCG-unvaccinated children ($nACDu_{tNR}$), respectively:

$$nACDv_{tNR} = RV_{ACt} \times V_{tNR} \quad \text{Equation 16}$$

$$nACDu_{tNR} = RU_{ACt} \times U_{tNR} \quad \text{Equation 17}$$

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_{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 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, $nACH_{non-restric}$, 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:

$$injection\ supply_{costs} = application\ syringe_{costs} + mixing\ syringe_{costs} + safety\ box_{costs} \quad \text{Equation 29}$$

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 analyses[14].

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

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

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:

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

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 2017[16], 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 WHO[17]:

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

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:

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

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

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

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

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 colleagues[18]. 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 estimates[19] 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:

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

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

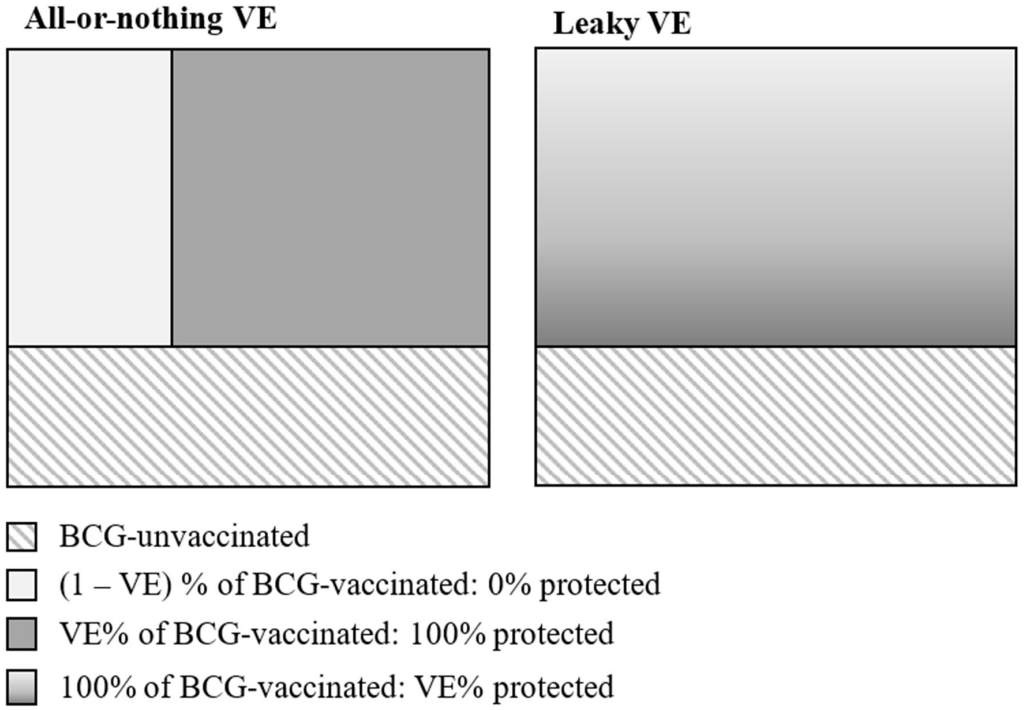
The daily individual risk of TB death in unprotected children aged 0-4 years (R_{0-4}) was:

$$R_{0-4} = Mort_{0-4}/\sum n_{0-4}$$ Equation 50

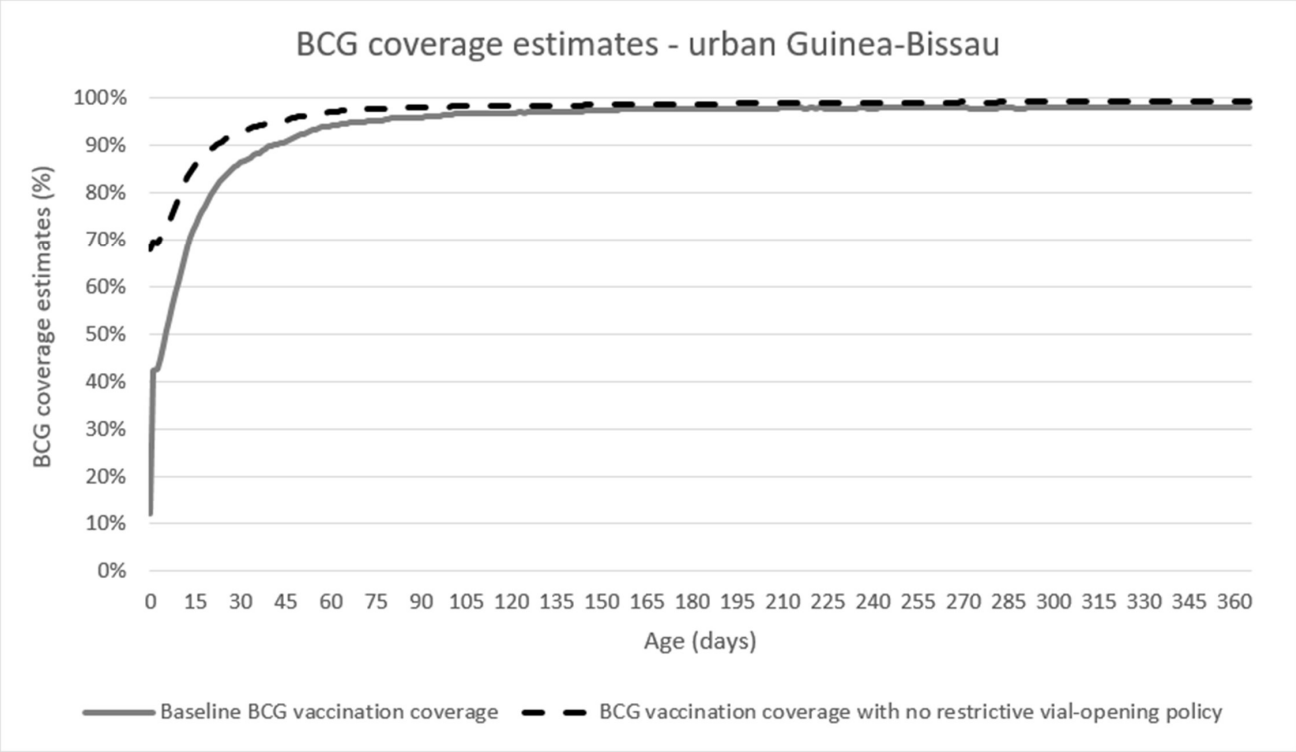
Where $Mort_{0-4}$ was the number of TB deaths in each age group, and $\sum n_{0-4}$ was the sum of unprotected person days.

3. Supplementary Figures and tables

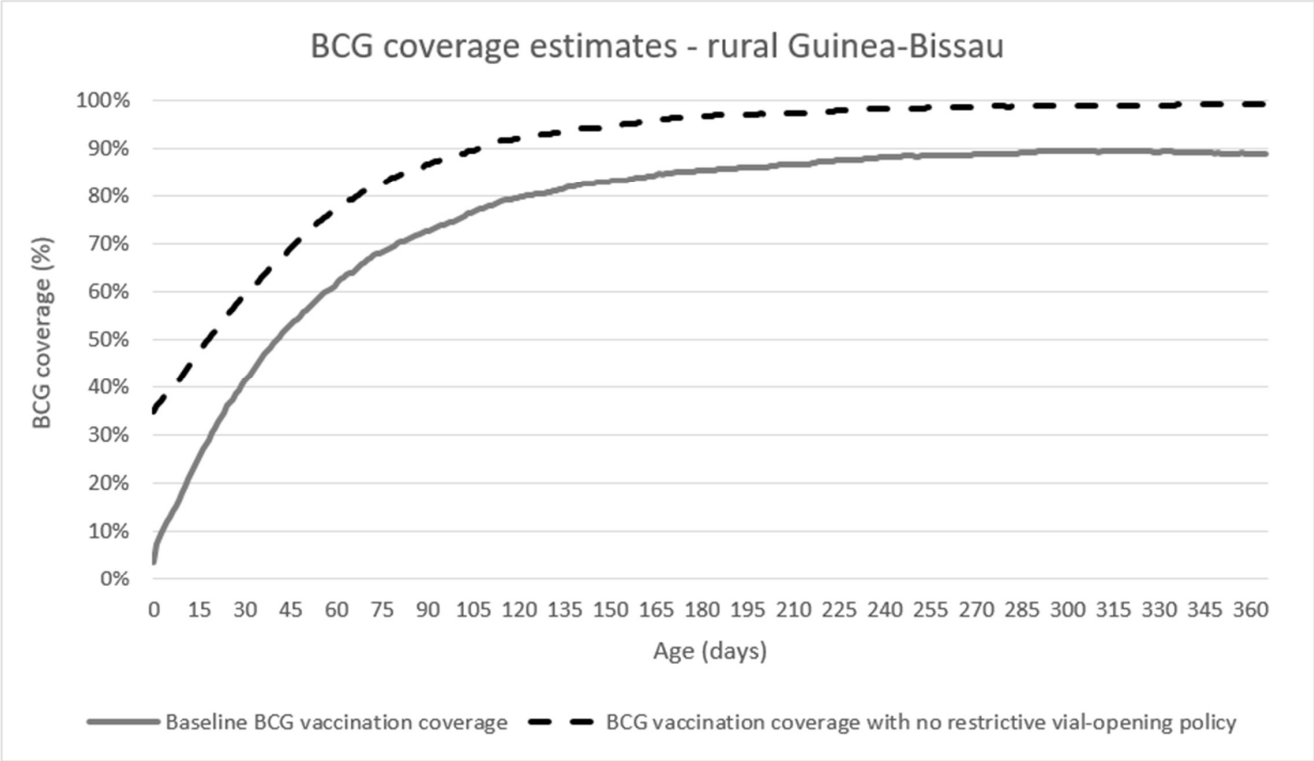
3.1 All-or-nothing and leaky vaccine efficacy



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

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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