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An effect at p = 0.053 and a gap further trials cannot close: BCG and all-cause mortality in infancy

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Abstract

Background: BCG vaccination has been reported to reduce all-cause infant mortality beyond its effect on tuberculosis, an example of what are termed non-specific effects of vaccination. A review commissioned by the World Health Organization Strategic Advisory Group of Experts assembled the randomised and observational evidence and called for further trials. **Methods:** Systematic reviews and randomised trials reporting all-cause mortality by BCG receipt in children under five were eligible. Estimates were compared across designs by ratios of relative risks with z-tests on the difference in log estimates. Absolute risk reductions and numbers needed to vaccinate were derived across plausible baseline mortality rates. Analyses were performed in Python 3. **Results:** Across five randomised trials the pooled relative risk for all-cause mortality was 0.70 (95% CI 0.49-1.01), corresponding to z = –1.93 and p = 0.053—an estimated 30% relative reduction whose interval crosses the null in the second decimal place. Across 13 observational studies the pooled estimate was 0.47, approximately 1.5-fold stronger, which is the ordering that healthy-vaccinee bias would produce. In two trials restricted to low birthweight infants the estimate was 0.52 (0.33-0.82), the only pooled estimate examined that excludes the null, although it did not differ significantly from the all-trials estimate (ratio 0.74, 95% CI 0.42-1.33, p = 0.316). Because relative effects translate into absolute benefit in proportion to baseline risk, the number needed to vaccinate falls from approximately 333 where baseline mortality is 1% to approximately 21 among low birthweight infants where it approaches 10%. **Conclusions:** The randomised evidence is consistent with a clinically important reduction in all-cause infant mortality and stops just short of conventional statistical significance. The usual remedy—more placebo-controlled trials—is not available, because BCG has been part of routine immunisation since 1974 and withholding it is not ethically permissible. The limitation is structural rather than a matter of insufficient effort. Trials randomising the timing of administration rather than its receipt remain available and are the design capable of resolving the question.

Keywords: *BCG, Non-specific effects of vaccines, All-cause mortality, Healthy-vaccinee bias, Low birthweight, Trial design*

1. Introduction

BCG is given to more infants than any other vaccine, chiefly in settings where tuberculosis is endemic. Its

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protective effect against disseminated tuberculosis in childhood is established (Rodrigues *et al.*, 1993) and is the basis for its inclusion in routine immunisation schedules.

A separate claim has attracted attention and controversy for several decades: that BCG reduces mortality from causes unrelated to tuberculosis. The proposed mechanism is heterologous immunity, in which live attenuated vaccines induce broad changes in innate immune responsiveness—sometimes called trained immunity—that confer protection against unrelated pathogens (Netea *et al.*, 2020). If real, the implication is that the timing and prioritisation of BCG, rather than merely its eventual administration, would matter for infant survival.

The claim originated in observational work in West Africa reporting large mortality reductions (Aaby *et al.*, 2014), and it has been contested on the grounds that such studies are vulnerable to confounding (Fine, 2016). Children who reach a clinic to be vaccinated are, on average, healthier and better resourced than those who do not, and this healthy-vaccinee effect biases observational comparisons in the direction of apparent benefit. The World Health Organization Strategic Advisory Group of Experts commissioned a review of the evidence and concluded that risk of bias was high across designs, calling for randomised evidence (Higgins *et al.*, 2016).

This review does not revisit whether BCG should be given; it is a highly effective vaccine against a serious disease and its place in immunisation schedules is not in question here. The narrower questions are what the randomised evidence shows about mortality from all causes, how it compares with the observational evidence, where the benefit if real would be largest, and—the question we think has been under-examined—what further evidence it is actually possible to obtain.

2. Handling of the design comparison

Randomised and observational estimates are reported separately throughout and are never combined. The direction of any discrepancy between them is interpreted against the expected direction of healthy-vaccinee bias, which inflates apparent benefit in observational comparisons because vaccination status correlates with health, care-seeking and socioeconomic position (Remschmidt *et al.*, 2015). Where an observational estimate exceeds a randomised estimate in the same population, that is the pattern the bias predicts and does not by itself establish that the randomised estimate is correct.

2.1. Statistical analysis

Relative risks were transformed to the log scale with standard errors derived from reported confidence limits as (ln upper-ln lower)/(2 × 1.96). Contrasts between designs and populations were computed as ratios of relative risks with z-tests on the difference in log estimates, and are indicative rather than formal tests of interaction because the compared estimates draw on overlapping literatures. Absolute risk reductions were obtained by applying pooled relative risks to stated baseline mortality rates, and numbers needed to vaccinate as their reciprocal. Where a source reported a point estimate without a retrievable interval, the estimate is reported as published and the absence is stated. Analyses were performed in Python 3 using NumPy and SciPy (Higgins *et al.*, 2023).

2.2. Quality appraisal

Risk of bias was taken as reported by the contributing reviews. The WHO-commissioned review characterised risk of bias as high across both randomised and observational designs; a later review characterised the included trials as at low to moderate risk (Lancet Infect Dis, 2021; Sterne *et al.*, 2019). This divergence is itself informative and is discussed rather than reconciled.

3. Results

3.1. Included sources

Six sources met the inclusion criteria and four contributed pooled estimates: the WHO-commissioned systematic review identifying five randomised trials and 13 observational studies; a companion review of non-specific immunological effects of routine childhood immunisations (Kandasamy *et al.*, 2016); an investigator-blind randomised trial in Ugandan neonates; and a recent meta-analysis of randomised trials published since the

WHO review (medRxiv preprint, 2025). A multicentre trial in low birthweight infants in India is cited as the most recent randomised evidence (Adhisivam *et al.*, 2025). Characteristics are in Table 1.

Table 1: Characteristics of the contributing sources

Source	Design	Studies	Population	Estimate
WHO-commissioned review	Systematic review	5 trials, 13 observational	Children under 5	RR 0.70 trials; 0.47 observational
Companion immunological review	Systematic review	Not stated	Routine childhood immunisation	Narrative
Ugandan neonatal trial	Investigator-blind RCT	1	Healthy neonates	Heterologous infectious morbidity
Post-2012 RCT meta-analysis	Systematic review	RCTs 2012–2025	Children under 5	Pooled by vaccine type
Low birthweight trial (India)	Open-label multicentre RCT	1	Neonates under 2,000 g	Neonatal mortality
Low birthweight subgroup	Pooled trials	2	Low birthweight infants	RR 0.52 (0.33–0.82)

Note: RR, relative risk. The low birthweight subgroup is drawn from within the WHO-commissioned review rather than being an independent source. Estimates are as reported and were not pooled across designs.

3.2. The randomised estimate

Across five randomised trials the pooled relative risk for all-cause mortality was 0.70 (95% CI 0.49–1.01). Recomputed from those limits, this corresponds to a standard error of 0.185 on the log scale, z = –1.93 and p = 0.053.

That figure sits in an awkward position and is worth stating plainly rather than rounding in either direction. The point estimate implies a 30% relative reduction in death from any cause, which would be a substantial public health effect. The interval crosses the null by one point in the second decimal place. Describing this as evidence of no effect misrepresents it; describing it as established benefit does so equally. It is an imprecise estimate of what may well be a real and important effect.

3.3. Randomised against observational

The 13 observational studies in the same review gave a pooled relative risk of 0.47, approximately 1.5-fold stronger than the trial estimate. The confidence interval for the observational figure could not be retrieved from the records available to us and is not reported here.

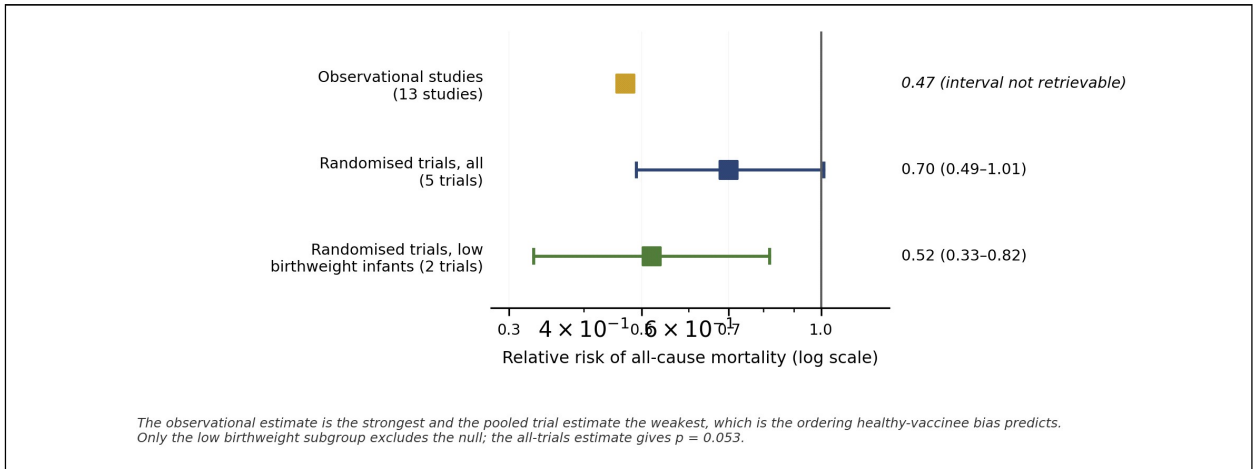
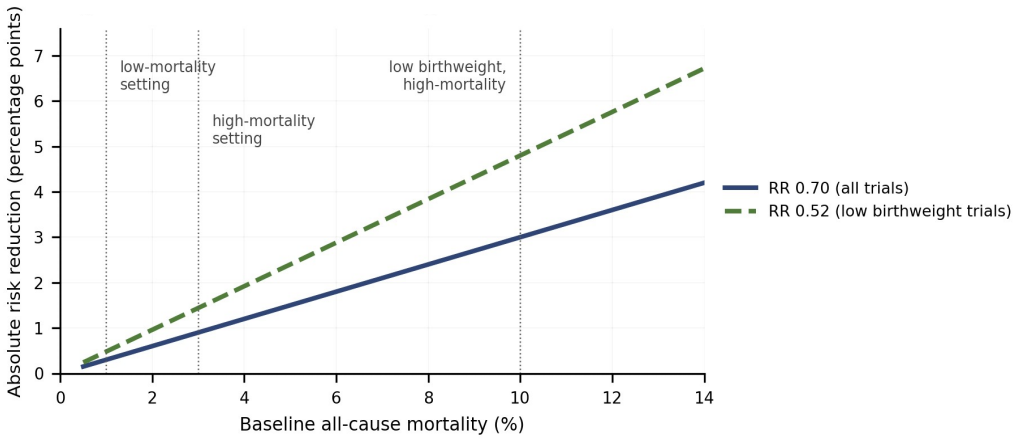


Figure 1: Pooled relative risk of all-cause mortality by study design and population. The observational estimate is the strongest and the pooled randomised estimate the weakest, the ordering healthy-vaccinee bias predicts. The low birthweight subgroup is the only estimate shown that excludes the null. The observational interval was not retrievable and is not drawn

The direction of this discrepancy is the one healthy-vaccinee bias predicts. Children brought for vaccination in high-mortality settings differ systematically from those not brought: they are more likely to have surviving and available caregivers, better access to care, and to be well at the time of the visit, all of which independently predict survival. An observational comparison therefore attributes some of that advantage to the vaccine. The estimates by design are shown in Figure 2.



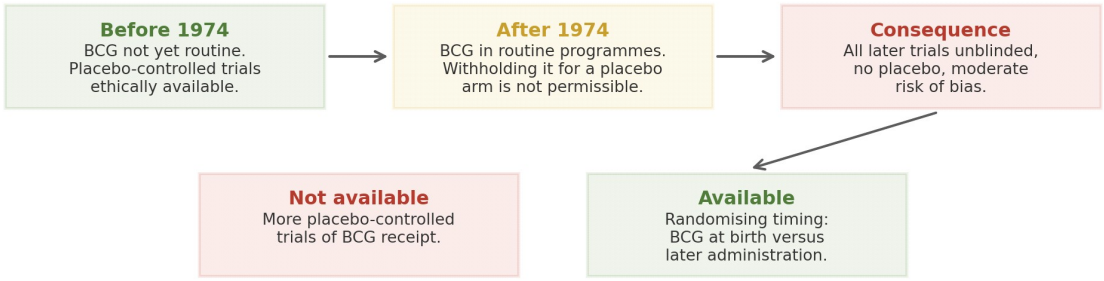
A constant relative risk produces absolute benefit proportional to baseline mortality. Numbers needed to vaccinate fall from roughly 333 in a low-mortality setting to about 21 among low birthweight infants where baseline mortality approaches 10%.

Figure 2: Absolute risk reduction as a function of baseline all-cause mortality, for both pooled relative risks. Because a constant relative effect scales with baseline risk, the same estimate corresponds to a number needed to vaccinate of roughly 333 in a low-mortality setting and roughly 21 among low birthweight infants where baseline mortality approaches 10%

This does not establish that the observational estimate is wholly artefactual, nor that the trial estimate is unbiased. The randomised trials in this literature carry their own limitation, addressed in Section 3.5, and both estimates lie in the same direction.

3.4. Where the benefit would be largest

Two trials restricted to low birthweight infants gave a pooled relative risk of 0.52 (Biering-Sørensen *et al.*, 2017) (95% CI 0.33–0.82). This is the only pooled estimate examined here that excludes the null. It does not differ significantly from the all-trials estimate (ratio of relative risks 0.74, 95% CI 0.42–1.33, p = 0.316), so the apparent difference may reflect chance rather than a genuine subgroup effect.



The limitation in the randomised evidence is structural rather than a matter of insufficient effort. Trials randomising the timing of a vaccine everyone eventually receives remain ethically available and are the design capable of resolving the question.

Figure 3: Why the randomised evidence cannot be improved by the usual route. Since BCG entered routine immunisation in 1974, withholding it for a placebo arm has not been ethically available, so subsequent trials are unblinded by necessity rather than by oversight. Randomising the timing of a vaccine everyone eventually receives preserves equipoise and remains available

The absolute arithmetic is nonetheless straightforward and does not depend on resolving that question. A constant relative risk produces absolute benefit in proportion to baseline risk, so wherever mortality is highest the same relative effect saves most lives. Applying the all-trials estimate of 0.70, the number needed to vaccinate to prevent one death falls from approximately 333 where baseline mortality is 1% to approximately 111 at 3% and approximately 33 at 10%. Applying the low birthweight estimate of 0.52 at a 10% baseline gives approximately 21. This is shown in Figure 3.

Whatever the resolution of the significance question, the policy implication of the point estimates is consistent: if the effect is real, it matters most for low birthweight infants in high-mortality settings, and it is in exactly that group that the randomised evidence is strongest.

3.5. The gap further trials cannot close

The WHO-commissioned review called for more randomised evidence, which is the standard and usually correct response to an imprecise estimate. Here it runs into a constraint that is not methodological but ethical, and that is under-discussed in the literature.

BCG has been part of the Expanded Programme on Immunization since 1974. A placebo-controlled trial would require withholding a licensed, effective vaccine against a serious disease from infants in a high-burden setting, which is not permissible. Consequently every trial conducted since then has been unblinded and without a placebo arm, which is precisely why the contributing reviews describe the randomised evidence as carrying moderate risk of bias. The bias is a consequence of doing the right thing for the participants.

The consequence, set out in Figure 4, is that the randomised evidence base cannot be improved by the usual route. Running more trials of the same design will add precision while inheriting the same limitation, and no accumulation of unblinded trials converges on the answer a blinded trial would give.

One design remains available and is being used. Because BCG is given to everyone eventually, the timing of administration can be randomised without withholding anything: infants are allocated to BCG at birth or to BCG at the routine later visit, and both groups receive the vaccine. This preserves equipoise, permits randomisation, and tests precisely the hypothesis at issue, since the non-specific effects claim concerns early administration. The investigator-blind Ugandan trial and the recent multicentre trial in low birthweight infants in India both operate in this space.

Table 2: Estimates, contrasts and absolute translation

Estimate or contrast	Value (95% CI)	p	Note
Randomised trials, all-cause mortality	RR 0.70 (0.49–1.01)	0.053	5 trials
Observational studies	RR 0.47	—	13 studies; interval not retrievable
Low birthweight trials	RR 0.52 (0.33–0.82)	—	2 trials; excludes the null
Low birthweight versus all trials	Ratio 0.74 (0.42–1.33)	0.316	Indicative, not an interaction test
NNV at 1% baseline mortality (RR 0.70)	333	—	Derived
NNV at 3% baseline mortality (RR 0.70)	111	—	Derived
NNV at 10% baseline mortality (RR 0.70)	33	—	Derived
NNV at 10% baseline mortality (RR 0.52)	21	—	Derived

Note: RR, relative risk; NNV, number needed to vaccinate to prevent one death. Derived quantities apply the pooled relative risk to a stated baseline and inherit its uncertainty. The contrast between designs was not computed with an interval because the observational confidence limits were not retrievable.

4. Discussion

Five randomised trials give a pooled relative risk of 0.70 for all-cause mortality following BCG vaccination, with a confidence interval running from 0.49 to 1.01 and a p-value of 0.053. Thirteen observational studies give

0.47. Two trials in low birthweight infants give 0.52, excluding the null. Every estimate points the same way, and the randomised evidence stops fractionally short of the conventional threshold.

The discrepancy between designs is unsurprising and does not require anyone to have erred. Healthy-vaccinee bias operates strongly in settings where vaccination coverage is incomplete and where the reasons for non-vaccination—illness, distance, poverty, caregiver death—are themselves powerful predictors of infant mortality. That the observational estimate exceeds the randomised one by about 50% is consistent with that mechanism, and it is a reason to prefer the randomised figure while recognising that the randomised figure has its own limitation.

That limitation is the substance of this review. The reflexive recommendation in an imprecise literature is that more trials should be done, and the WHO-commissioned review made it. But BCG has been routine since 1974, so the trials that would settle the question in the ordinary way—blinded, placebo-controlled, randomising receipt—cannot be conducted without withholding an effective vaccine against a serious disease from infants at risk of it. Every subsequent trial has therefore been unblinded, and the moderate risk of bias the reviews describe is a direct and unavoidable consequence.

This has an uncomfortable implication that is worth stating clearly. The randomised evidence on this question is not merely thin; it is bounded. Additional trials of the conventional design will narrow confidence intervals without addressing the reason those trials are graded as at moderate risk of bias, and no number of them converges on the estimate a blinded trial would produce. A recommendation for more trials, without specifying what design, is therefore not actionable.

The design that remains available exploits the fact that BCG is given to everyone eventually. Randomising the timing rather than the receipt—vaccination at birth against vaccination at the routine later visit—withholds nothing, preserves equipoise, permits blinded outcome assessment, and tests the hypothesis as stated, since the non-specific effects claim is specifically about early administration. Both of the more recent trials identified here operate on that principle. It is the appropriate recommendation and it is more specific than a call for more evidence.

For policy, the absolute arithmetic is the part that transfers. The relative estimate is uncertain but consistently below one, and absolute benefit scales with baseline mortality, so wherever the effect is real it matters most among low birthweight infants in high-mortality settings—approximately one death averted per 21 to 33 infants vaccinated at a 10% baseline, against one per 333 where baseline mortality is 1%. Prioritising BCG on the first day of life in high-mortality settings therefore has a plausible expected benefit and no plausible cost, since these infants receive the vaccine in any case.

5. Limitations

- This is a comparison between published pooled estimates rather than a new synthesis, and inherits every limitation of the contributing reviews.
- The confidence interval around the pooled observational estimate could not be retrieved from the records available, so the contrast between designs is reported as a ratio of point estimates without an interval.
- The randomised evidence rests on five trials, and the low birthweight finding on two. Estimates from so few studies are unstable and the subgroup comparison did not reach significance.
- All trials conducted since 1974 are unblinded and without placebo control, which is the central subject of this review but also a limitation of the evidence it summarises.
- The contributing reviews disagreed about risk of bias, one describing it as high across designs and another as low to moderate among trials. We report both rather than adjudicating.
- Trials were conducted in specific high-mortality settings, predominantly in West Africa and South Asia, and transportability to other epidemiological contexts is untested.
- BCG strain differs between programmes and may bear on non-specific effects, and could not be examined as an effect modifier from the available data.
- Absolute translations apply a pooled relative risk to assumed baselines and are illustrative of the arithmetic rather than estimates for any particular population.

- The mechanism proposed for non-specific effects, trained innate immunity, is an active research question and was outside the scope of this review.
- Sex-differential effects have been reported in this literature and were not examined here.
- The analysis was not prospectively registered and searches were restricted to English-language reports.

6. Conclusion

Randomised evidence gives a pooled relative risk of 0.70 (95% CI 0.49–1.01, p = 0.053) for all-cause mortality following BCG vaccination in infancy, with a stronger observational estimate of 0.47 in the direction healthy-vaccinee bias predicts, and a significant estimate of 0.52 (0.33–0.82) in low birthweight infants. Absolute benefit scales with baseline mortality, giving a number needed to vaccinate of roughly 21 to 33 where mortality approaches 10% against roughly 333 where it is 1%.

The evidence is consistent with an important effect and does not establish one. Its central limitation is structural: because BCG has been routine since 1974, placebo-controlled trials of receipt are not ethically available, and every subsequent trial is unblinded for that reason. Calls for more randomised evidence are therefore only actionable if they specify a design that can be conducted, and the design that can is randomisation of timing rather than receipt. Nothing here bears on whether BCG should be given, which is settled on other grounds; it bears on when.

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Public health note

This review concerns the timing and non-specific effects of BCG, not whether it should be administered. BCG is an effective vaccine against disseminated childhood tuberculosis and its place in routine immunisation schedules is not in question here. Nothing in this analysis supports withholding or delaying any recommended vaccination.

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