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Commentary: BCG has no beneficial non-specific effects on Greenland. An answer to the wrong question?

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Our group has spearheaded research into the 'non-specific effects' of vaccines in West Africa. Many observational studies and lately randomized trials have shown that BCG lowers all-cause mortality, particularly from septicaemia and respiratory infections.[1,2] These beneficial non-specific effects are seen as long as BCG is the most recent vaccine.[1–3] For this reason, a WHO-commissioned review of the non-specific effects of vaccines specifically selected results for the shortest period of follow-up, and where possible with censoring for subsequent vaccines.[4] In a meta-analysis of the included studies, BCG versus no BCG was associated with a 47% [95% confidence interval (CI) = 28-60%] reduction in all-cause mortality. The other live vaccine under review, measles vaccine, was likewise associated with large reductions in mortality; in contrast, most studies suggested that the non-live diphtheria-tetanus-pertussis (DTP) vaccine was associated with increased all-cause mortality. In 2014, WHO recommended further research into the potential non-specific effects of vaccines.[5]

Haahr *et al.* used a transient or temporary discontinuation of neonatal BCG vaccination from 1991 to 1996 in Greenland to compare BCG-vaccinated and BCG-unvaccinated birth cohorts with respect to infectious disease hospitalizations (the vast majority being due to respiratory infections) up to 3 years of age. They assumed that the only potential birth cohort effect was the possible BCG effect.[6] This may not be correct; there were changes in the timing of subsequent non-live vaccines, which were also associated with birth cohort.[6] Nonetheless, from 3 days to 3 months when BCG was the dominating vaccine, having received neonatal BCG was associated with a 28% (95% CI = -6-51%) reduction in the risk of infectious disease hospitalizations,[6] corroborating the findings from the WHO review. Haahr *et al.* did however not emphasize this result; instead they focused on the period from 3 months to 3 years of age.[6] What is studied in this age group is not the effect of neonatal BCG versus no BCG, but the effect of receiving first neonatal BCG and then non-live vaccines versus receiving non-live vaccines only. In this period, BCG was associated with a 7% (-4-20%) increased risk of infectious disease hospitalisation[6] (test for similar BCG effect between 0-3 months and 3-35 months, $P = 0.05$) (Table 1).

The findings from Greenland are similar to the findings from a recent cohort study in Finland using hospital admission data from before and after neonatal BCG vaccination was stopped in 2006.[7] The incidence rate ratio for hospital-treated pneumonia for BCG-vaccinated children was 0.73 (95% CI = 0.55-0.96) from birth and up to 3 months (before non-live vaccines were provided), versus 1.04 (0.89-1.20) from 3-12 months (test for interaction 0.03).[7] The findings are also similar to the results of a recent randomized trial in Denmark where the incidence rate ratio for GP visits for suspected infection was 0.88 (95% CI = 0.79-0.98) from birth to 3 months (again emphasizing the period before non-live vaccines were given), versus 1.03 (0.97-1.09) from 3-13 months (test for interaction 0.01).[8] The tendency for an age-differential effect of BCG was also seen for parental-reported infection, strongest for parent-reported fever [0.78 (0.52-1.03) before versus 1.05 (0.95-1.16) after 3 months] and pneumonia [0.50 (0.17-1.46) versus 1.26 (0.99-1.60)].[8] Thus, in the three studies from high-income settings, which have data on the effect of neonatal BCG on infectious diseases from birth to 3 months and from 3 months onwards, there are striking similarities: the effect of BCG was beneficial in the first months, but this effect disappeared after the children received non-live vaccines.

Table 1. The effect of neonatal BCG versus no neonatal BCG vaccination on infectious disease morbidity from birth to 3 months and from 3 months onwards

Study country	Health outcome	Young age group Comparing BCG versus no BCG	Older age group Comparing BCG then non-live vaccines versus non-live vaccines	Interaction test for similar neonatal BCG effect in young and older age group
Greenland[6]	Hospital admission for infectious diseases	0.72 (0.49-1.06) (3 days-< 3 months)	1.07 (0.96-1.20) (3-35 months)	0.05
Finland[7]	Hospital-treated primary pneumonia	0.73 (0.55-0.96) (0-< 3 months)	1.04 (0.89-1.20) (3-12 months)	0.03
Denmark[8]	GP visits due to suspected infectious disease	0.88 (0.79-0.98) (0-< 3 months)	1.03 (0.97-1.09) (3-13 months)	0.01
	Parent-reported infectious disease	0.87 (0.72-1.05) (0-< 3 months)	1.02 (0.97-1.07) (3-13 months)	0.09

Recent immunological studies have shed light on the immunological effects of BCG, demonstrating its ability to induce epigenetic modifications at the monocyte level, leading to generally increased innate immunity,[9] which again translates into better protection against heterologous pathogens and into increased immune responses to subsequent vaccines.[10] These immunological effects may explain the observation that neonatal BCG could reduce the risk of infection in the first months after BCG vaccination. They may also explain why the effect disappears after non-live vaccines are given; non-live vaccines have been associated with negative non-specific effects on health,[11] and receiving BCG before could potentially amplify these negative non-specific effects and be worse than receiving only the non-live vaccines.[3] Thus, the findings from Greenland seem to fit very well into the broader picture. Unfortunately, this conclusion is not emphasized.

First, the results from 0-3 months are only presented as a non-significant sensitivity analysis. Haahr *et al.* justify the exclusion of the 0-3 month period 'to avoid transient misclassification of BCG vaccination due to delayed vaccination and to avoid lack of hospitalisation registration caused by delayed registration of the infant's CRS [Civil Registration System] number'. However, elsewhere in the paper they mention that 'BCG vaccination is administered within 48 hours of birth, except for children of low birth weight (1.3%) or on the rare occasion when a delivery does not take place at a hospital (1.6%)'[6], making it clear that transient misclassification of BCG should not be a problem, and the authors have previously published that the CRS is updated weekly.[12] Thus, there appears to be no strong need to exclude the most relevant follow-up period and only present the results as a sensitivity analysis.

Second, when finding no beneficial effect on hospital admissions in the 3-35 months age group, the authors conclude that 'this study does not support the hypothesis that neonatal BCG vaccination carries non-specific effects reducing morbidity'. Thus, the paper gives the impression of having refuted neonatal BCG having beneficial non-specific effects—while actually refuting something else, namely that neonatal BCG has beneficial non-specific effects after non-live vaccines have been given. In fact, the most relevant analysis from 0-3 months of age, as well as the reversal of the BCG effect from 0-3 months to 3-35 months in study by Haahr *et al.*, both support that BCG does more than prevent tuberculosis.

Unfortunately, it is not rare to dismiss a hypothesis by using different exposures or outcomes or different methodologies from those used to formulate the hypothesis. WHO has previously commissioned studies to test our findings on negative non-specific effects of DTP vaccine. These studies claimed to have found no negative effect of DTP. However, it was later recognized that most studies used a flawed methodology with survival bias,[13] or they had given BCG together with DTP. Thus, the studies did not answer whether DTP had a negative non-specific effect.

The recent WHO review concluded that the non-specific effects of vaccines warrant further study and that it is important to involve many researchers.[5] However, as illustrated by the present example, it is very important that all researchers test the relevant hypotheses using the appropriate methodology. In this case, the relevant questions are whether BCG reduces infection until a non-live vaccine is given, and whether the effect changes after administration of non-live vaccines. In Greenland, Finland and Denmark, it appears that neonatal BCG does reduce infection in the first months of life, but may be associated with slightly increased risk of infection after administration of non-live vaccines.

Conflict of interest: We and the authors of the Haahr *et al.* paper come from the same institution.

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