The introduction of BCG vaccination to neonates in Northern Sweden, 1927–31

Re-analysis of historical data to understand the lower mortality among BCG-vaccinated children

Schaltz-Buchholzer, Frederik; Kjær Sørensen, Marcus; Benn, Christine Stabell; Aaby, Peter

Published in:
Vaccine

DOI:
10.1016/j.vaccine.2021.06.006

Publication date:
2022

Document version:
Accepted manuscript

ABSTRACT

Background: Following the introduction of oral Bacille Calmette-Guérin (BCG) a century ago, Albert Calmette suggested that BCG both provided protection against death from tuberculosis (TB) and other causes. The findings were not pursued. Today, there is considerable evidence that intradermal BCG have beneficial *non-specific effects* (NSEs). We re-analyzed data from BCG's introduction 1927-1931 in Sweden hypothesizing that BCG reduced infectious deaths.

Methods: In three papers on BCG, the progress of BCG vaccination rollout and effects on the child mortality in Norrbotten was sequentially updated. BCG was provided free of charge to newborns in the highly TB-prevalent region Norrbotten. We excluded deaths from congenital conditions and analyzed cause-specific post-neonatal mortality by vaccination status. Due to apparent differences in effects during the study periods, post-hoc, effects were assessed overall and separately in 2 periods (1927-1929, 1930-1931).

Results: TB households were slightly more likely to accept vaccination; much fewer sick newborns and those with congenital problems were vaccinated. BCG coverage was 28.3% (5,659/20,012); 8.7% (1,746/20,012) died. Excluding congenital disease deaths, the BCG/unvaccinated Risk Ratio (RR) of post-neonatal childhood death was 0.53 (0.45-0.62). BCG was associated with 80% (49-92%) reduced mortality from TB in both periods. From 1927-29, BCG appeared to protect strongly against deaths from all diseases, including the non-infectious, RR=0.09 (0.02-0.36), presumably reflecting non-vaccination of sick children. From 1930-1931, there was only a modest protection against non-infectious deaths, RR=0.92 (0.49-1.70), indicating less bias (p=0.004 for same effect). During 1930-1931, BCG

was associated with reductions in non-TB infectious deaths (RR=0.75 (0.58-0.97)). 2/3 of those deaths were caused by respiratory infection, against which the BCG/unvaccinated RR was 0.61 (0.43-0.84). Other causes of death were less frequent and provided no clear pattern, except that BCG was associated with more deaths from meningitis, RR=6.85 (2.20-21.37).

Conclusion: Healthy vaccinee bias, particularly in 1927-1929, resulted in strongly beneficial overall BCG effects. However, the 1930-1931 data provided some support that BCG both protected against TB deaths and from respiratory infections.

INTRODUCTION

Bacille Calmette-Guérin (BCG) will celebrate 100 years of use as a vaccine against tuberculosis (TB) in 2021 [1,2]. Many high-income countries stopped the use of BCG several decades ago due to low prevalence of TB, but TB persists as an epidemic disease in low-income countries associated with marked morbidity and mortality and the TB research community is working hard to develop a new and more effective TB vaccine. The future use of BCG may therefore depend on whether BCG, aside from providing some protection against TB, also has beneficial effects against non-TB infections, what has been called beneficial *non-specific effects* (NSEs) [1]. A series of observational studies and randomized controlled trials indicate that BCG has marked effects on overall mortality and morbidity [3–6]; a WHO-commissioned systematic review reported that BCG vaccination is associated with a 50% reduction in all-cause mortality[7]. In the first decade (1920s-1930s) after the introduction of BCG, the vaccine was distributed from France to several laboratories around the world and administered to nearly 1 million infants [8]. In 1929-1930, however, the BCG strain used in Lübeck, Germany, was contaminated with human TB causing 72 child deaths and many more TB infestations [8]. Presumably to counter the BCG skepticism that followed the Lübeck disaster, Albert Calmette (**Figure 1**) published a report with the Royal Society of Medicine to assure that BCG was safe and could not revert to a virulent form of TB [8]. The focus in the 1920s was on providing BCG to those who could benefit the most from vaccination: newborns living in TB-infected families. Calmette noted in his article: "*The general mortality of 8,075 vaccinated children exposed to tuberculous infection, aged from one month to one year, controlled by 114 dispensaries, has been 4.6%, whereas in non-vaccinated children of the same age, living under similar conditions, it is at least 16%, and*

often exceeds 25%." [8] Thus, Calmette suggested a 4-fold difference in mortality between vaccinated and unvaccinated infants and he continued: *"Can it be that tuberculous infection plays a more important part in infant mortality than we have supposed? (…) Or does the harbouring of BCG, followed by its digestion and elimination, confer on the organism a special aptitude to resist those other infections which are so frequent in young children?"* [8]

Hence, Calmette formulated already in 1931, the question which may now determine BCG's future: *Does BCG have beneficial effects against non-TB infections?* Calmette referred to a series of similar reports that he had received from Romania, Sweden, Belgium, Holland, Spain, Greece, USA, Canada, and Uruguay. "*In Roumania, where more than 80,000 have now been vaccinated, the general mortality since 1927 has been 50% less in the vaccinated than in the non-vaccinated. In Sweden, 4,009 infants were vaccinated in the province of North Bothnia alone between September 1927, and May 1, 1930; 8,342 have not been vaccinated, serving as controls. The general mortality has been 2.3% in the vaccinated, 9.5% in the non-vaccinated*" [8]. Again, there appeared to be a 4-fold difference in mortality between vaccinated and unvaccinated infants.

These studies did usually not have clearly defined control groups and they mostly focused on deaths from TB. But were the effects on mortality so large that this would indicate that BCG had detectable beneficial NSEs already when introduced, preventing more than just the TB deaths?

Justification: The historical data from Sweden report mortality data by cause of death but was not analyzed using modern statistical methods. The data represents the first community introduction of BCG, at a time when other childhood vaccines were not in

common use and there was a heavy TB burden. Hence, the specific and non-specific effects of BCG can be assessed over a longer age range without interference from other vaccines and the vaccine was administered orally rather than by the intradermal route used today. Having the limitations of this observational historic dataset in mind, which was published in French and is not commonly available online, we therefore re-analyzed the data from Norrbotten (North Bothnia) [9–11] to make this historical data accessible to a broader audience and assess whether indications of non-specific effects of BCG are detectable in this early data.

METHODS

Data sources

The introduction of BCG in the northernmost district in Sweden, Norrbotten, was initiated by the physician Carl Näslund in September 1927 in a project sponsored by the Swedish National Anti-tuberculosis Society. Näslund wrote three papers on BCG which sequentially updated the progress of BCG vaccination and the child mortality in Norrbotten [9–11]. For the present analysis, only the original data reported in Näslund's papers was available. Calmette's statements regarding data from Sweden [8] were based on Näslund's first report, which was first reported at a TB congress in 1930 [9], and the total dataset was later provided in a final report covering the period from September 1927 to December 1931 [11]. We extracted data from the original publications and calculated 1930-31 data as the difference between the total 1927-31 data set [11] and the data reported for 1927-29 [9].

Intervention and target population

Oral BCG was provided to newborns within 5 days of birth by physicians or nurses. Vaccinated children were listed in a special register which also had information on parents and other family members. The register had precise information on the health of family members, possible sources of TB in the family or the environment, and on hygienic and economic conditions of the family. Follow-up information was also noted in this register [10].

There is no information on which BCG strain was used, but presumably it was the same as used by Calmette. The vaccine was produced according to Calmette's specifications and new batches of the vaccine were distributed every week to the dispensaries across the region for oral administration within 5 days of birth. Calmette recommended 3 doses of oral BCG provided with 2-day intervals [8]; however, Näslund did not mention whether three doses were used in Norrbotten [9–11]. BCG vaccination was voluntary and offered to all newborns irrespective of whether the family had TB cases or not. Social and health conditions were registered within the program and healthy neonates were eligible for vaccination; neonates deemed frail and those suspected of congenital illness were not vaccinated.

Control group

Infants that were unvaccinated (due to frailty, logistic difficulty in providing BCG within 5 days of birth, choice not to be vaccinated) served as controls.

Follow-up period

Since the children were recruited at birth and the study started in the end of 1927 and the follow-up was ongoing until 1931, no child was followed longer than four years (see **Table 1**). According to Näslund, vaccinated and unvaccinated children were monitored and

followed as thoroughly as possible and the mortality data provided was compiled using extracts from the Swedish Central Statistical Office Mortality Registry [11]. It is not described whether Näslund assessed the quality of the cause of death data.

Outcomes

Due to the policy of providing BCG within 5 days of birth, the historic mortality data is available in the following age groups: 0-5 days after birth, neonatal period (0-30 days), post-neonatal infant period (1-12 months), and for 1-, 2- and 3-year-old children. In most analyses, Näslund excluded deaths that occurred before 5 days of age because there had not been time for such infants to be vaccinated shortly after birth. Furthermore, deaths occurring during the first month of life were excluded because he believed it would take a month to develop an immune response against TB and that mortality in the first month of life could therefore not have been affected by BCG [10,11]. Finally, congenital deaths were excluded since congenital weakness had been an exclusion criteria for the vaccinators.

We therefore examined the deaths overall and by cause of death between 1 and 48 months of age with exclusion of the congenital deaths.

Statistical analyses

The original reports listed mortality numbers among vaccinated versus unvaccinated children with no statistical assessment of the respective mortality rate ratios in the two groups. The historical reports thus simply provides percentages to be assessed and interpreted by the reader. Applying more modern statistical methods to the historical data, we assessed the BCG vaccinated vs. unvaccinated mortality risk overall and stratified by causes of death and age group using Fisher's 2-sided exact tests, providing Risk Ratios (RRs).

To address whether the possible biases affecting the selection for vaccination might have changed over time, we conducted post hoc analyses to address whether the BCG effect was different in the 1927-1929 and 1930-1931 periods.

The data was not organized and prepared for a modern survival analysis. For example, no child was censored because it had moved or was lost to follow-up. Hence, the denominator was the total number of children that had entered the study. There was no published data on sex of the children.

All analyses were conducted using Stata16 (Stata Corp, College Station, Texas) and reported with 95% Confidence Intervals (CIs).

RESULTS

Summary of the historical data published by Näslund

A total of 20,012 newborns were included in the cohort. According to Näslund, the program did not vaccinate children, who, at birth, were sick or weak [10]. Hence, the approach suggest healthy vaccinee bias. While the specific data was not provided, Näslund claimed, however, to have identified no major differences between vaccinated and unvaccinated children with respect to hygiene, social, economic conditions, and nutritional practices (breastfeeding). Families with TB cases were slightly more likely to have their children vaccinated than families without TB cases. In Näslund's view, nothing prevented a comparison of the vaccinated and unvaccinated children to study the protective effect of BCG against TB [10].

The BCG coverage was 27% in 1928, 38% in 1929, 27% in 1930, and 20% in 1931 for an overall coverage of 28% (5,659/20,012) [11]. The decline in coverage during 1930-31 was caused by the Lübeck disaster [11]. Näslund stated, without providing specific numbers, that during the last 6 months of 1931 and the beginning of 1932, the population regained confidence in BCG, and the BCG coverage rose again [11]**.**

The crude overall mortality was 8.7% (1,746/20,012) from birth to the end of 1931; 3.7% (211/5,659) among BCG-vaccinated infants and 10.7% (1,535/14,353) among the unvaccinated, nearly a 3-fold difference (**Table 1**).

Causes of death were presented by age group (**Table 1, Figure 2**). The cause was unknown for 21% (361/1,746) of the deaths, the percentage being similar for unvaccinated (21%, 319/1,535) and vaccinated children (20%, 42/211). A very large share of the deaths, 28% (484/1,746), were classified as *congenital debility* (**Table 1**). Furthermore, non-infectious causes, a designation not further specified, amounted to 9% (160/1,746) of the deaths [11].

Only 4% (69/1,746) of deaths were classified as being due to TB and Näslund reiterated that there may well have been more undiagnosed TB deaths, since autopsies were not done [9–11]. A further 4% were due to *spasmophilia* (71/1,746), which most likely meant convulsions. Näslund grouped diphtheria, erysipelas, measles, scarlet fever, and sepsis together as one group representing 3% (51/1,746) of all deaths that could therefore not be further subdivided. In some analyses, we have grouped pneumonia, bronchitis, influenza, and whooping cough as “respiratory infections”, which amounted to 25% (437/1,746) of all deaths. The last two groups were meningitis representing 2% (29/1746) and gastrointestinal infections representing 5% (84/1,746).

Novel analysis of the mortality data

Näslund conducted several subgroup analyses to see how certain exclusions affected the difference in mortality between BCG-vaccinated and unvaccinated children. Mimicking these steps by excluding all deaths from congenital causes, the 1-48-month mortality risk was 3.0% (170/5,618) for BCG-vaccinated and 5.8% (783/13,601) for unvaccinated children, nearly a two-fold difference in mortality (**Table 2**). From 1-12 months, the all-cause mortality risk was 2.4% (132/5,620) among BCG recipients versus 4.6% (626/13,605) for the unvaccinated, the BCG/unvaccinated RR being 0.51 (0.43-0.62) (**Table 2**). Between 1 to 4 years, the BCG/unvaccinated RR was 0.57 (0.40-0.81); the combined BCG/unvaccinated RR was thus 0.53 (0.45-0.62) from 1 month to 48 months of age.

Effects of BCG against death from TB

From 1-48-months, there were a total of 64 deaths from TB (BCG: 5, unvaccinated: 59). BCG vaccination was associated with reduced mortality from TB in both infancy and childhood, the overall reduction between 1-48 months of age being 80% (49-92%) (**Table 2**).

Effects of BCG against death from non-TB infections and non-infectious causes

BCG vaccination was associated with increased risk of death from meningitis between 1-48-months, the RR being 2.24 (1.05-4.76) (**Table 3**). For other infections, however, there was a protective effect. BCG-vaccinated children had 44% (28-56%) lower risk of death from respiratory infections, 63% (23-83%) for gastrointestinal infections, 42% (-12 to 70%) for convulsions, and 58% (-7 to 84%) for the small group of other infections. The effect of meningitis differed significantly ($p<0.002$) from the effect on other infections. Overall, the reduction in the mortality risk from non-TB infections between 1-48 months of age was 42%

(28-53%). Hence, the effect of BCG differed significantly between TB and non-TB infections (test of interaction, p=0.03). However, there was also a 52% (18-72%) reduction in death from non-infectious diseases which may suggest selection bias favoring the BCG-vaccinated children (**Table 2**).

The 1927-1929 and the 1930-1931 data: post hoc analysis

We present the data from 1927-1929 [9] in Table 4 and from 1930-1931 [11] in Table 5 and Figure 3. Due to the non-vaccination of frail children, BCG vaccination was associated with a very low risk of deaths from congenital conditions in both periods. The vaccine efficacy against death from TB was similar in the two periods. However, we noted that the effect on non-infectious diseases was modified by period; in the first report covering 1927-29, BCG was associated with a RR of 0.09 (0.02-0.36) for death from non-infectious diseases (**Table 4**) [9], whereas the same RR was 0.92 (0.49-1.70) in the second period from 1930-1931 (test of interaction, p=0.004) (**Table 5**) [11]. The RR of death from non-TB infectious diseases also changed from 0.32 (0.23-0.45) in the first period to 0.75 (0.58-0.97) in 1930-1931 (test of interaction, p<0.001). Respiratory deaths constituted 60% (168/279) and 63% (225/357) of the infectious disease deaths in the two periods. The RR for death from respiratory infection changed from 0.40 (0.27-0.60) in the first period to 0.61 (0.43-0.84) in the second period (test of interaction, p=0.11). For the smaller groups of infections, i.e. convulsions, gastrointestinal, meningitis and other infections, BCG was beneficial for all in the first period (**Table 4**) but less so in the second period (**Table 5**). In the second period, BCG vaccination was associated with a strong increase in the risk of death from meningitis (**Table 5**). Even if we assume that convulsions might have been misclassified cases of meningitis, there would

still be an increased risk of death associated with BCG vaccination, the RR being 1.97 (1.06-3.67).

DISCUSSION

Main findings

Oral BCG was associated with reduced risk of death from TB and from non-TB infections, particularly respiratory infections, but not from meningitis. The estimated effect of BCG on respiratory and other non-TB infections differed by period and was less pronounced in the last period where there may have been less healthy vaccinee bias, as judged by the effect on non-infectious deaths.

Strengths and weaknesses

The Norrbotten data is from a period with a high all-cause mortality due to infectious diseases. To our knowledge, no other detailed analyses of the disease-specific effects associated with the community introduction of BCG has been presented from any country. There appear to have been no other vaccine provided to the youngest children, so it has been possible to track both specific and non-specific effects related to BCG over an extended age range.

BCG was associated with reduced risk of non-TB infectious diseases, except meningitis, both during infancy and between 1-4 years of age, when the selection biases occurring shortly after birth would be anticipated to have a less pronounced effect.

We had only the data reported in Näslund's papers, providing no possibility of confirming the accuracy of the data or the cause of death classifications. The deaths with unknown

cause had similar distribution as the infectious deaths, so the lack of some causes of death has probably simply reduced the power of the study.

Even though Näslund noted no hindrance for comparisons of vaccinated and unvaccinated children [10], the study was likely confounded because most children excluded due to congenital problems were in the unvaccinated group [10]. In the first period (**Table 4**), non-infectious deaths occurred mostly among the unvaccinated. In the second period, however, there was little difference in the risk of non-infectious death for vaccinated and unvaccinated children and the protective efficacy for all other infectious diseases was also reduced (**Table 6**). Hence, it seems that *healthy vaccinee bias* was more pronounced in the first period (1927-1929).

Näslund did not note the difference between the two periods and provided no information that recruitment practices changed, except that acceptance went down after the Lübeck disaster.

Results of observational studies like Näslund's are often dismissed since they are assumed to be determined mainly by biases and confounding. However, several trends in Näslund's data from the second period are difficult to reconcile with *healthy vaccinee bias* being the main cause of the much lower mortality of BCG-vaccinated children. First, TB-infected families were more likely to get vaccinated. This appears unlikely to be consistent with families with lower mortality having preferentially had their infants BCG-vaccinated, since TB-infested families presumably were poorer and had worse socioeconomic conditions. However, there may have been a positive selection bias among the non-TB infected families. Second, in 1930-1931, BCG had little effect on non-infectious diseases; if healthier families

preferentially had their infants vaccinated, then BCG-vaccinated children should also have had a lower risk of deaths from non-infectious diseases. Perhaps the Lübeck disaster preferentially caused BCG vaccine hesitancy among the wealthier, better informed families. Third, meningitis deaths were significantly increased among the BCG-vaccinated, an effect different from all other infectious causes of death (**Table 3 and Table 5**).

Hence, though bias most likely occurred with respect to who were BCG-vaccinated, it is difficult to understand the totality of data unless it is assumed that BCG provided substantial protection against TB and also some non-specific protection against respiratory infections.

Näslund's interpretation

Näslund was not in doubt that BCG protected against death from TB, even though autopsies were not made, and he recommended in each report that the vaccination program ought to be continued [9–11]. However, Näslund struggled to understand the almost 3-fold difference in mortality between vaccinated and unvaccinated children. Though he did not directly make use of the concepts, he attempted to evaluate whether bias or confounding could explain why BCG vaccination was associated with much lower mortality than being unvaccinated. Though he provided no data in support of the conclusions, Näslund noted that there were no differences in hygienic, social, economic conditions and nutritional practices for the families of vaccinated and unvaccinated children in the data which had been collected by the TB control program. The only difference he emphasized was that slightly more families with TB accepted to have their child vaccinated.

Like Calmette, he speculated that BCG could have prevented other infectious diseases.

In the process, he stated: "*One might of course be tempted to find an explanation for this lower mortality of vaccinated children in the idea that the BCG vaccine provokes a* ***non-specific immunity.***"

But he also went on to say *"If this were the case, the deaths caused by the different infectious diseases should be relatively more numerous among the unvaccinated children than among the vaccinated children. This was not the case, however, and Table IV [****Table 1****] makes it perfectly clear."* [11]

Apparently, Näslund analyzed the data as percentages of all deaths among the vaccinated and unvaccinated children and not as RRs between the two groups. From that perspective, it is correct that the infectious deaths between 1-48 months of age continued to be as numerous among the BCG-vaccinated, being 65% (116/178), versus 59% (520/885) among the unvaccinated children (**Table 2**). But he did not compare the "risk" of vaccinated and unvaccinated persons.

As a possible explanation, Näslund suggested that maybe the parents of vaccinated children were more careful in caring for their children [10]. However, Näslund ended his last report from 1932 [11] by stating "*None of the hypotheses that we have just presented therefore offer a certain and objective basis for specifying the causes of the relatively low mortality of children vaccinated in Norrbotten. However, certain indications prove that BCG vaccination may have contributed to this.*" [11] Unfortunately, he provided no further analysis of the effects of BCG on child survival in Norrbotten.

Consistency with other findings

A few years later in 1935, the Institute Pasteur started a trial of three doses of oral BCG at birth versus no BCG with alternate allocation based on number in the civil registration system in Algiers [12,13]. Infant mortality was 21%, but the reduction in infant mortality in the BCG-vaccinated group was only 3% (-2 to 7%). The analysis was by intention-to-treat so many children in the "vaccinated" group had actually died before the public health nurses had time to visit and vaccinate the newborns. However, after BCG revaccinations at 1 and 3 years of age, the reduction in all-cause mortality between 1 and 4 years of age was 22% (17-27%).

In terms of protection against TB, previous studies have reported protective efficacies of BCG ranging from 0-80% and that the efficacy is dependent on an Equatorial gradient, being higher the further away from the Equator, possibly due to fewer environmental mycobacteria [14]. The TB attack rates for vaccinated versus unvaccinated infants in Norrbotten indicates that BCG had a protective efficacy of around 80%, which would be consistent with the hypothesis of more enhanced effects of BCG against TB further from the Equator.

It is difficult to compare Näslund's study with other studies of the potential NSEs of BCG, partly because BCG was administered orally and partly because more recent studies of BCG have mainly focused on the first 4-6 weeks of life, because BCG provided at birth is followed by a series of other childhood vaccines provided shortly after the first month of life. A meta-analysis of three RCTs from Guinea-Bissau providing BCG-Denmark to healthy low-weight newborns at hospital discharge reported a 38% reduction in neonatal mortality[3]. An analysis of pediatric ward admissions within the same cohort revealed that BCG especially

reduced the risk of death from septicemia [4]. A study from India using BCG-Russia, however, found no effect on neonatal mortality [15]. A meta-analysis of 6 historical trials reported that BCG was associated with a 25% (6-41%) reduction in non-TB deaths not caused by violence and accidents, when compared to controls [16]. Furthermore, numerous observational studies have found BCG to be associated with beneficial effects on non-TB deaths in both low-income and high-income countries [7,17–19].

With respect to specific disease effects, a recent RCT from Uganda showed that BCG-Denmark-at-birth was associated with a 29% reduction in non-TB infections [6]; most of this effect was related to respiratory infections [1]. The same pattern with a particularly beneficial effect for respiratory infections has been seen in other studies [3,20].

Interpretation

Numerous studies have now indicated that certain strains of BCG are associated with substantial NSEs that reduce the all-cause mortality risk and BCG has been shown to induce protection against bacteria, viruses and parasites [21–23].

Judged by modern standards, Näslund's study had many flaws; the selection for BCG vaccination was not well-described and there was no statistical control for potential confounding factors. Still, the data from particularly 1930-1931 suggests that oral BCG had substantial effects on both the risk of death from TB and respiratory infections. Hence, oral BCG had presumably also beneficial NSEs, but with a peculiar negative effect for meningitis

Calmette suggested that data from several countries indicated 3 to 4-fold differences in mortality between vaccinated and unvaccinated children, but this would have been for children exposed to TB in the home. Näslund´s community data suggested rather a 2-fold

difference in the mortality for infectious diseases. Though selection bias occurred with respect to who were BCG-vaccinated in the first days of life, it would be difficult to construct a bias and confounding pattern which would explain the observed varying effects of BCG for different causes of death. The data, on the other hand, is compatible with BCG providing protection against TB and some non-specific protection against respiratory infections. The signal with increased mortality from meningitis has not been reported elsewhere but may merit further attention in future studies.

Näslund wrote no further papers about BCG after his 1932 report [11]. Calmette died shortly after in 1933. Hence, the beneficial (and potential deleterious) NSEs of BCG were not pursued.

CONCLUSION

Our analysis yielded some support that BCG both protected against TB deaths and from respiratory infections when it was introduced in northern Sweden. The combined epidemiological and immunological data documenting BCG's beneficial NSEs have major implications for vaccination programs in both developed and developing countries, since we have not fully exploited the beneficial NSEs of BCG for public health. It is urgent that this potential for preventing non-TB infections is prioritized. Interestingly, the COVID-19 pandemic has raised the interest in the broad beneficial immune effects associated with live vaccines and whether BCG can provide protection against COVID-19 is thus being broadly investigated in >40 trials [24,25]. The centenary of BCG is therefore likely to be celebrated with many more studies of the vaccine's beneficial NSEs.

Authors' contributions

PAA conceived the idea of reviewing historical data and initiated a review of the historical studies, which were procured in different archives. PAA conducted the first analysis of Näslund's data and FSB further analyzed the historical data for his PhD dissertation and wrote the first draft of the present paper, which was critically reviewed by CSB, FS, MKS and PAA. All authors approved the final manuscript.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE OF INTERESTS

Funders did not have any influence on the study design, data collection, analysis, interpretation, writing or decision to submit the present paper for publication. None of the authors have any conflict of interest to declare.

REFERENCES

1. Aaby P, Benn CS. BCG: new life for a centenarian vaccine. Lancet Infect Dis **2021**;

2. Benn CS, Fisker AB, Rieckmann A, Sørup S, Aaby P. Vaccinology: time to change the paradigm? Lancet Infect Dis **2020**; 20:e274–e283.

3. Biering-Sørensen S, Aaby P, Lund N, et al. Early BCG-Denmark and Neonatal Mortality Among Infants Weighing <2500 g: A Randomized Controlled Trial. Clin Infect Dis **2017**; 65:1183–1190.

4. Schaltz-Buchholzer F, Biering-Sørensen S, Lund N, et al. Early BCG Vaccination, Hospitalizations, and Hospital Deaths: Analysis of a Secondary Outcome in 3 Randomized Trials from Guinea-Bissau. J Infect Dis **2019**; 219:624–632.

5. Benn CS, Roth A, Garly M-L, et al. BCG scarring and improved child survival: a combined analysis of studies of BCG scarring. J Intern Med **2020**; 288:614–624.

6. Prentice S, Nassanga B, Webb EL, et al. BCG-induced non-specific effects on heterologous infectious disease in Ugandan neonates: an investigator-blind randomised controlled trial. Lancet Infect Dis **2021**; 0. Available at: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30653-8/abstract. Accessed 22 February 2021.

7. Higgins JPT, Soares-Weiser K, López-López JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ **2016**; 355:i5170.

8. Calmette A. Preventive Vaccination Against Tuberculosis with BCG. Proc R Soc Med **1931**; 24:1481–1490.

9. Näslund C. Experiences sur la vaccination BCG dans la province Norrbotten (La Bothnie du Nord). In: L'Union Internationale Contre la Tuberculose. VIIème Conférence de l'Union internationale contre la tuberculose, Oslo, 12-15 août 1930. Oslo: A.W. Brøggersboktrykkeri a/s, 1931. Pages 100-107.

10. Näslund C. Expérience de vaccination par le BCG dans la province du Norrbotten (Suède). Revue de la Tuberculose 1931;12(5):617-636.

11. Näslund C. Resultats des experiences de vaccination par le BCG poursuivies dans le Norrbotten (Suède) (Septembre 1927–Décembre 1931). Vaccin Prev Tuberc Rapp Doc Paris Inst Pasteur **1932**;

12. Sergent E, Catanei A, Ducros-Rougebrief H. Prèmunition antituberculeuse par le BCG. Campagne porsuivie depuis 1935 sur 21.244 nouveau-nés vaccines et 20.063 non vaccines. Arch L'Institut Pasteur D'Algerie 32, 1–8, 1954.

13. Benn CS, Fisker AB, Whittle HC, Aaby P. Revaccination with Live Attenuated Vaccines Confer Additional Beneficial Nonspecific Effects on Overall Survival: A Review. EBioMedicine **2016**; 10:312–317.

14. Mangtani P, Abubakar I, Ariti C, et al. Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials. Clin Infect Dis **2014**; 58:470–480.

15. Jayaraman K, Adhisivam B, Nallasivan S, et al. Two Randomized Trials of the Effect of the Russian Strain of Bacillus Calmette-Guerin Alone or With Oral Polio Vaccine on Neonatal Mortality in Infants Weighing <2000 g in India. Pediatr Infect Dis J **2019**; 38:198–202.

16. Shann F. The non-specific effects of vaccines. Arch Dis Child **2010**; 95:662–667.

17. Rieckmann A, Villumsen M, Sørup S, et al. Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971–2010. Int J Epidemiol **2017**; 46:695–705.

18. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. BMJ **2000**; 321:1435–1438.

19. Schaltz-Buchholzer F, Berendsen M, Roth A, et al. BCG skin reactions by 2 months of age are associated with better survival in infancy: a prospective observational study from Guinea-Bissau. BMJ Glob Health **2020**; 5.

20. Giamarellos-Bourboulis EJ, Tsilika M, Moorlag S, et al. Activate: Randomized Clinical Trial of BCG Vaccination against Infection in the Elderly. Cell **2020**; 183:315-323.e9.

21. Berendsen ML, Gijzel SW van, Smits J, et al. BCG vaccination is associated with reduced malaria prevalence in children under the age of 5 years in sub-Saharan Africa. BMJ Glob Health **2019**; 4:e001862.

22. Arts RJW, Moorlag SJCFM, Novakovic B, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe **2018**; 23:89-100.e5.

23. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. Proc Natl Acad Sci U S A **2012**; 109:17537–17542.

24. Madsen AMR, Schaltz-Buchholzer F, Benfield T, et al. Using BCG vaccine to enhance non-specific protection of health care workers during the COVID-19 pandemic: A structured summary of a study protocol for a randomised controlled trial in Denmark. Trials **2020**; 21:799.

25. Ten Doesschate T, Moorlag SJCFM, van der Vaart TW, et al. Two Randomized Controlled Trials of Bacillus Calmette-Guérin Vaccination to reduce absenteeism among health care workers and hospital admission by elderly persons during the COVID-19 pandemic: A structured summary of the study protocols for two randomised controlled trials. Trials **2020**; 21:481.

Table 1. Causes of death by BCG vaccination status and period of follow-up.

Cause of death	Total deaths (birth to 4 years of age n (%)		Neonatal deaths n (%)		Infant deaths between 1-12 months (%)		Deaths between 1 to 4 years of age n (%)		Deaths from 1 month to 4 years of age n (%)	
	BCG (n=5,659)	No BCG (n=14,353)	BCG (n=5,659)	No BCG (n=14,353)	BCG (n=5,626)	No BCG (n=13,703)	BCG (n=5,488)	No BCG (12,979)	BCG (n=5,626)	No BCG (n=13,703)
Tuberculosis	5 (0.1%)	64 (0.4%)	0 (0.0%)	5 (0.0%)	2 (0.0%)	23 (0.2%)	3 (0.1%)	36 (0.3%)	5 (0.1%)	59 (0.4%)
Meningitis	13 (0.2%)	16 (0.1%)	0 (0.0%)	2 (0.0%)	5 (0.1%)	10 (0.1%)	8 (0.1%)	4 (0.0%)	13 (0.2%)	14 (0.1%)
Pneumonia	35 (0.6%)	153 (1.1%)	3 (0.1%)	16 (0.1%)	24 (0.4%)	105 (0.8%)	8 (0.1%)	32 (0.2%)	32 (0.6%)	137 (1.0%)
Bronchitis	23 (0.4%)	92 (0.6%)	2 (0.0%)	16 (0.1%)	16 (0.3%)	64 (0.5%)	5 (0.1%)	12 (0.1%)	21 (0.4%)	76 (0.6%)
Influenza	12 (0.2%)	54 (0.4%)	2 (0.0%)	4 (0.0%)	8 (0.1%)	39 (0.3%)	2 (0.0%)	11 (0.1%)	10 (0.2%)	50 (0.4%)
Pertussis	11 (0.2%)	57 (0.4%)	0 (0.0%)	1 (0.0%)	10 (0.2%)	48 (0.4%)	1 (0.0%)	8 (0.1%)	11 (0.2%)	56 (0.4%)
Diphtheria, measles, scarlet fever, erysipelas, or sepsis	9 (0.2%)	42 (0.3%)	4 (0.1%)	13 (0.1%)	4 (0.1%)	19 (0.1%)	1 (0.0%)	10 (0.1%)	5 (0.1%)	29 (0.2%)
Gastrointestinal infections	10 (0.2%)	74 (0.6%)	2 (0.0%)	21 (0.1%)	8 (0.1%)	49 (0.4%)	0 (0.0%)	4 (0.0%)	8 (0.1%)	53 (0.5%)
Spasmophilia (Convulsions)	11 (0.2%)	60 (0.4%)	0 (0.0%)	14 (0.1%)	10 (0.2%)	39 (0.3%)	1 (0.0%)	7 (0.1%)	11 (0.2%)	46 (0.3%)
Congenital conditions	22 (0.4%)	462 (3.2%)	14 (0.2%)	360 (2.5%)	6 (0.1%)	98 (0.7%)	2 (0.0%)	4 (0.0%)	8 (0.1%)	102 (0.7%)
Non-infectious diseases	18 (0.3%)	142 (0.9%)	2 (0.0%)	61 (0.4%)	12 (0.2%)	68 (0.4%)	4 (0.1%)	13 (0.1%)	16 (0.3%)	81 (0.5%)
Cause unknown	42 (0.7%)	319 (2.2%)	4 (0.1%)	137 (1.0%)	33 (0.6%)	162 (1.2%)	5 (0.1%)	20 (0.2%)	38 (0.7%)	182 (1.3%)
Total	211 (3.7%)	1535 (10.7%)	33 (0.6%)	650 (4.5%)	138 (2.5%)	724 (5.3%)	40 (0.7%)	161 (1.2%)	178 (3.2%)	885 (6.5%)

Table 2. Risk of death from major death cause categories by BCG vaccination status and period of follow-up.

	Neonatal deaths n (%)		Infant deaths Infant deaths between 1-12months n (%)		Deaths between 1 to 4 years of age n (%)		Deaths between 1 to 48 months of age n (%)	
Cause of death	BCG (n=5,659)	No BCG (n=14,353)	BCG (n=5,626)	No BCG (n=13,703)	BCG (n=5,488)	No BCG (12,979)	BCG (n=5,626)	No BCG (n=13,703)
Tuberculosis (TB)	0 (0.0%)	5 (0.0%)	2 (0.0%)	23 (0.2%)	3 (0.1%)	36 (0.3%)	5 (0.1%)	59 (0.4%)
BCG/unvaccinated RR	NA		0.21 (0.05-0.90)		0.20 (0.06-0.64)		0.20 (0.08-0.51)	
Non-TB infections	13 (0.2%)	87 (0.6%)	85 (1.5%)	373 (2.7%)	26 (0.5%)	88 (0.7%)	111 (2.0%)	461 (3.4%)
BCG/unvaccinated RR	0.38 (0.21-0.68)		0.56 (0.44-0.70)		0.70 (0.45-1.08)		0.58 (0.47-0.72)	
Non-infectious diseases	2 (0.0%)	61 (0.4%)	12 (0.2%)	68 (0.5%)	4 (0.1%)	13 (0.1%)	16 (0.3%)	81 (0.6%)
BCG/unvaccinated RR	0.08 (0.02-0.34)		0.43 (0.23-0.79)		0.73 (0.24-2.23)		0.48 (0.28-0.82)	
Unknown death cause	4 (0.1%)	137 (1.0%)	33 (0.6%)	162 (1.2%)	5 (0.1%)	20 (0.2%)	38 (0.7%)	182 (1.3%)
BCG/unvaccinated RR	0.07 (0.03-0.20)		0.50 (0.34-0.72)		0.59 (0.22-1.57)		0.51 (0.36-0.72)	
All causes of death[1]	19 (0.3%)	290 (2.0%)	132 (2.3%)	626 (4.6%)	38 (0.7%)	157 (1.2%)	170 (3.0%)	783 (5.7%)
BCG/unvaccinated RR	0.17 (0.10-0.26)		0.51 (0.43-0.62)		0.57 (0.40-0.81)		0.53 (0.45-0.62)	
Congenital conditions	14 (0.2%)	360 (2.5%)	6 (0.1%)	98 (0.7%)	2 (0.0%)	4 (0.0%)	8 (0.1%)	102 (0.7%)
BCG/unvaccinated RR	0.10 (0.06-0.17)		0.15 (0.07-0.34)		1.18 (0.22-6.45)		0.19 (0.09-0.39)	

Note: Deaths from other causes are censored in each subgroup. Abbreviations: BCG, Bacille Calmette-Guérin; RR, Risk Ratio; TB, Tuberculosis.

[1] Excluding death caused by congenital conditions.

Table 3. Risk of death from different infectious diseases by BCG vaccination status and period of follow-up.

	Neonatal deaths n (%)		Infant deaths Infant deaths between 1-12months n (%)		Deaths between 1 to 4 years of age n (%)		Deaths from 1 month to 4 years of age n (%)	
Cause of death	BCG (n=5,659)	No BCG (n=14,353)	BCG (n=5,626)	No BCG (n=13,703)	BCG (n=5,488)	No BCG (12,979)	BCG (n=5,626)	No BCG (n=13,703)
Tuberculosis	0 (0.0%)	5 (0.0%)	2 (0.0%)	23 (0.2%)	3 (0.1%)	36 (0.3%)	5 (0.1%)	59 (0.4%)
BCG/unvaccinated RR	NA		0.21 (0.05-0.90)		0.20 (0.06-0.64)		0.20 (0.08-0.51)	
Non-TB infections	13 (0.2%)	87 (0.6%)	85 (1.5%)	373 (2.7%)	26 (0.5%)	88 (0.7%)	111 (2.0%)	461 (3.4%)
BCG/unvaccinated RR	0.38 (0.21-0.68)		0.56 (0.44-0.70)		0.70 (0.45-1.08)		0.58 (0.47-0.72)	
Of which								
Respiratory infections[1]	7 (0.1%)	37 (0.3%)	58 (1.0%)	256 (1.9%)	16 (0.3%)	63 (0.5%)	74 (1.3%)	319 (2.3%)
BCG/unvaccinated RR	0.48 (0.21-1.08)		0.55 (0.42-0.73)		0.60 (0.35-1.04)		0.56 (0.44-0.72)	
Convulsions	0 (0.0%)	14 (0.1%)	10 (0.2%)	39 (0.3%)	1 (0.0%)	7 (0.1%)	11 (0.2%)	46 (0.3%)
BCG/unvaccinated RR	NA		0.62 (0.31-1.25)		0.34 (0.04-2.75)		0.58 (0.30-1.12)	
Gastrointestinal infections	2 (0.0%)	21 (0.1%)	8 (0.1%)	49 (0.4%)	0 (0.0%)	4 (0.0%)	8 (0.1%)	53 (0.4%)
BCG/unvaccinated RR	0.24 (0.06-1.03)		0.40 (0.19-0.84)		NA		0.37 (0.17-0.77)	
Other infections[2]	4 (0.1%)	13 (0.1%)	4 (0.1%)	19 (0.1%)	1 (0.0%)	10 (0.1%)	5 (0.1%)	29 (0.2%)
BCG/unvaccinated RR	0.78 (0.25-2.39)		0.51 (0.17-1.51)		0.24 (0.03-1.85)		0.42 (0.16-1.07)	
Meningitis	0 (0%)	2 (0.0%)	5 (0.1%)	10 (0.1%)	8 (0.1%)	4 (0.0%)	13 (0.2%)	14 (0.1%)
BCG/unvaccinated RR	NA		1.22 (0.42-3.56)		4.73 (1.42-15.70)		2.24 (1.05-4.76)	
Infectious diseases total	13 (0.2%)	92 (0.6%)	87 (1.5%)	396 (2.9%)	29 (0.5%)	124 (1.0%)	116 (2.1%)	520 (3.8%)
BCG/unvaccinated RR	0.36 (0.20-0.64)		0.54 (0.43-0.67)		0.55 (0.37-0.83)		0.54 (0.44-0.66)	

Note: Deaths from other causes are censored in each subgroup. Abbreviations: BCG, Bacille Calmette-Guérin; RR, Risk Ratio.

[1] Pneumonia, bronchitis, influenza, or whooping cough. [2] Diphtheria, erysipelas, measles, scarlet fever, or sepsis.

Table 4. Risk of death from different infectious diseases by BCG vaccination status and period of follow-up – 1927-1929 [4]

	Neonatal deaths n (%)		Infant deaths Infant deaths between 1-12 months n (%)		Deaths between 1 to 2 years of age n (%)		Deaths from 1 month to 2 years of age n (%)	
Cause of death	BCG (n=3,377)	No BCG (n=6,932)	BCG (n=3,364)	No BCG (n=6,605)	BCG (n=1,533)	No BCG (3,542)	BCG (n=3,364)	No BCG (n=6,605)
Tuberculosis	0 (0.0%)	4 (0.1%)	0 (0.0%)	4 (0.1%)	1 (0.1%)	9 (0.3%)	1 (0.0%)	13 (0.2%)
BCG/unvaccinated RR	NA		NA		0.26 (0.03-2.02)		0.17 (0.02-1.29)	
Respiratory infections[1]	2 (0.1%)	15 (0.2%)	25 (0.7%)	119 (1.8%)	3 (0.2%)	21 (0.6%)	28 (0.8%)	140 (2.1%)
BCG/unvaccinated RR	0.27 (0.06-1.20)		0.41 (0.26-0.63)		0.33 (0.10-1.11)		0.40 (0.27-0.60)	
Convulsions	0 (0.0%)	10 (0.1%)	5 (0.1%)	22 (0.3%)	0 (0.0%)	4 (0.1%)	5 (0.1%)	26 (0.4%)
BCG/unvaccinated RR	NA		0.45 (0.17-1.18)		NA		0.38 (0.15-1.00)	
Gastrointestinal infections	0 (0.0%)	13 (0.2%)	2 (0.1%)	34 (0.5%)	0 (0.0%)	3 (0.1%)	2 (0.1%)	37 (0.6%)
BCG/unvaccinated RR	NA		0.12 (0.03-0.48)		NA		0.11 (0.03-0.45)	
Other infections[2]	1 (0.0%)	8 (0.1%)	1 (0.0%)	12 (0.2%)	0 (0.0%)	3 (0.1%)	1 (0.0%)	15 (0.2%)
BCG/unvaccinated RR	0.26 (0.03-2.05)		0.16 (0.02-1.26)		NA		0.13 (0.02-1.02)	
Meningitis	0 (0.0%)	1 (0.0%)	1 (0.0%)	8 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.0%)	10 (0.2%)
BCG/unvaccinated RR	NA		0.25 (0.03-1.96)		NA		0.20 (0.03-1.58)	
All infectious diseases	3 (0.1%)	51 (0.7%)	34 (1.0%)	199 (3.0%)	4 (0.3%)	42 (1.2%)	38 (1.1%)	241 (3.6%)
BCG/unvaccinated RR	0.12 (0.04-0.39)		0.34 (0.23-0.48)		0.22 (0.08-0.61)		0.32 (0.23-0.45)	
Congenital conditions	8 (0.2%)	190 (2.7%)	3 (0.1%)	49 (0.7%)	0 (0.0%)	3 (0.1%)	3 (0.1%)	52 (0.8%)
BCG/unvaccinated RR	0.09 (0.04-0.18)		0.12 (0.04-0.39)		NA		0.11 (0.04-0.37)	
Non-infectious	0 (0.0%)	18 (0.3%)	2 (0.1%)	41 (0.6%)	0 (0.0%)	4 (0.1%)	2 (0.1%)	45 (0.7%)
BCG/unvaccinated RR	NA		0.10 (0.02-0.40)		NA		0.09 (0.02-0.36)	
Unknown death cause	2 (0.1%)	68 (1.0%)	21 (0.6%)	77 (1.2%)	0 (0.0%	6 (0.2%)	21 (0.6%)	83 (1.3%)
BCG/unvaccinated RR	0.06 (0.01-0.25)		0.54 (0.33-0.87)		NA		0.50 (0.31-0.81)	

Note: The population and deaths are based on the figures reported in the first report (3). The 1-2 year population has been calculated as the number of children born in 1927-1929 minus neonatal and infant deaths and minus the number of children still under one year of age by the end of 1929 (3, Table II). Deaths from other causes are censored in each subgroup. Abbreviations: BCG, Bacille Calmette-Guérin; RR, Risk Ratio.

[1] Pneumonia, bronchitis, influenza, or whooping cough. [2] Diphtheria, erysipelas, measles, scarlet fever, or sepsis.

Table 5. Risk of death from different infectious diseases by BCG vaccination status and period of follow-up – 1930-31 [6]

	Neonatal deaths n (%)		Infant deaths between 1-12 months n (%)		Deaths between 1 to 4 years of age n (%)		Deaths from 1 month to 4 years of age n (%)	
Cause of death	BCG (n=2,430)	No BCG (n=7,646)	BCG (n=4,033)	No BCG (n=9,795)	BCG (n=4,392)	No BCG (9,554)	BCG (n=4,033)	No BCG (n=9,795)
Tuberculosis	0 (0.0%)	1 (0.0%)	2 (0.0%)	19 (0.2%)	2 (0.0%)	27 (0.3%)	4 (0.1%)	46 (0.5%)
BCG/unvaccinated RR	NA		0.26 (0.06-1.10)		0.16 (0.04-0.68)		0.20 (0.07-0.58)	
Respiratory infections[1]	5 (0.2%)	22 (0.3%)	33 (0.8%)	137 (1.4%)	13 (0.3%)	42 (0.4%)	46 (1.1%)	179 (1.8%)
BCG/unvaccinated RR	0.72 (0.27-1.89)		0.59 (0.40-0.85)		0.67 (0.36-1.25)		0.61 (0.43-0.84)	
Convulsions	0 (0.0%)	4 (0.1%)	5 (0.1%)	17 (0.2%)	1 (0.0%)	3 (0.0%)	6 (0.1%)	20 (0.2%)
BCG/unvaccinated RR	NA		0.71 (0.26-1.93)		0.73 (0.08-6.97)		0.72 (0.29-1.78)	
Gastrointestinal infections	2 (0.1%)	8 (0.1%)	6 (0.1%)	15 (0.2%)	0 (0.0%)	1 (0.0%)	6 (0.1%)	16 (0.2%)
BCG/unvaccinated RR	0.79 (0.17-3.70)		0.97 (0.38-2.50)		NA		0.91 (0.36-2.31)	
Other infections[2]	3 (0.1%)	5 (0.1%)	3 (0.1%)	7 (0.1%)	1 (0.0%)	7 (0.1%)	4 (0.1%)	14 (0.1%)
BCG/unvaccinated RR	1.89 (0.45-7.89)		1.04 (0.27-4.02)		0.31 (0.04-2.53)		0.66 (0.22-2.00)	
Meningitis	0 (0.0%)	1 (0.0%)	4 (0.1%)	2 (0.0%)	8 (0.2%)	2 (0.0%)	12 (0.3%)	4 (0.0%)
BCG/unvaccinated RR	NA		4.86 (0.89-26.51)		8.70 (1.85-40.95)		6.85 (2.20-21.37)	
All infectious diseases	10 (0.4%)	41 (0.5%)	53 (1.3%)	197 (2.0%)	25 (0.6%)	82 (0.9%)	78 (1.9%)	279 (2.8%)
BCG/unvaccinated RR	0.77 (0.39-1.53)		0.65 (0.48-0.88)		0.66 (0.42-1.04)		0.66 (0.51-0.84)	
Congenital	6 (0.2%)	170 (2.2%)	3 (0.1%)	49 (0.5%)	2 (0.0%)	1 (0.0%)	5 (0.1%)	50 (0.5%)
BCG/unvaccinated RR	0.11 (0.05-0.25)		0.15 (0.05-0.48)		4.35 (0.39-47.97)		0.24 (0.10-0.60)	
Non-infectious	2 (0.1%)	43 (0.6%)	10 (0.2%)	27 (0.3%)	4 (0.1%)	9 (0.1%)	14 (0.3%)	36 (0.4%)
BCG/unvaccinated RR	0.15 (0.04-0.60)		0.90 (0.44-1.86)		0.97 (0.30-3.14)		0.92 (0.49-1.70)	
Unknown death cause	2 (0.1%)	69 (0.9%)	12 (0.3%)	85 (0.9%)	5 (0.1%)	14 (0.1%)	17 (0.4%)	99 (1.0%)
BCG/unvaccinated RR	0.09 (0.02-0.37)		0.34 (0.19-0.63)		0.78 (0.28-2.16)		0.41 (0.24-0.68)	

Notes: The population and deaths are based on first and third reports (3,5). The neonatal group was the children born in 1930-1931 (N=9,703) as well as 1/12 of the children born in 1929 and who survived to January 1, 1930 (373) (3, Table II). The post-neonatal infants were calculated as the children born in 1930-1931 who survived the first month of life (N=9,360) as well as the children born in 1929 and who survived to January 1, 1930 (N=4,468) (3, Table II). The children at risk at 1-4 years of age were calculated as children born in 1927-1929 and who survived to January 1, 1930 (N=9,484) (3, Tables II and VI), and 50% of the children born in 1930-1931 and did not die in infancy would reach the age of one year (4,462). Hence, given no more specific information, we have assumed that the births and follow-up for children born in 1930-1931 was equally distributed between 1930 and 1931.

1 **Table 6. Overview of key publications and key results from 1 month to 4 years of age.**

	BCG/Control Risk Ratio		
Follow-up period (Ref.)	Tuberculosis	Infectious diseases other than tuberculosis	Non-infectious diseases
1927-29 [4]	0.17 (0.02-1.29)	0.32 (0.23-0.45)	0.09 (0.02-0.36)
1930-31	0.20 (0.07-0.58)	0.75 (0.58-0.97)	0.92 (0.49-1.70)
Combined 1927-31 [6]	0.20 (0.08-0.51)	0.58 (0.47-0.72)	0.48 (0.28-0.82)