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Interventions

Non-specific effects of BCG vaccination on morbidity among children in Greenland: a population-based cohort study

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Abstract

Background: The potential non-specific effects of BCG (Bacillus Calmette-Guérin) vaccination, with reported reduction of infectious disease morbidity among vaccinated children, in addition to the protective effect against tuberculosis (TB), are highly debated. In Greenland, BCG vaccination was introduced in 1955, but temporarily discontinued from 1991 to 1996 due to nationwide policy changes. Using the transient vaccination stop, we aimed to investigate possible non-specific effects of BCG vaccination by measuring nation-wide hospitalization rates due to infectious diseases other than TB among vaccinated and unvaccinated children.

Methods: A retrospective cohort study including all children born in Greenland aged 3 months to 3 years from 1989 to 2004. A personal identification number assigned at birth allowed for follow-up through national registers. Information on hospitalization due to infectious diseases was obtained from the Greenlandic inpatient register using ICD-8 and ICD-10 codes. Participants with notified TB were censored. Incidence rate ratios (IRR) were estimated using Poisson regression.

Results: Overall, 19 363 children, hereof 66% BCG-vaccinated, were followed for 44 065 person-years and had 2069 hospitalizations due to infectious diseases. IRRs of hospitalization in BCG-vaccinated as compared with BCG-unvaccinated children were 1.07 [95% confidence interval (CI) 0.96–1.20] for infectious diseases overall, and specifically 1.10 (95% CI 0.98–1.24) for respiratory tract infections. Among BCG-vaccinated children aged 3 to 11 months, the IRR of hospitalization due to infectious diseases was 1.00 (95% CI 0.84–1.19) as compared with BCG-unvaccinated children.

Conclusion: Our results do not support the hypothesis that neonatal BCG vaccination reduces morbidity in children caused by infectious diseases other than TB.

Key words: BCG, non-specific effects, prevention of infection

Key Messages

- Potential beneficial non-specific effects of vaccination with BCG on mortality and morbidity are highly debated and diverging results are reported among different child populations in different geographical regions.
- Our results do not support the hypothesis that neonatal BCG vaccination reduces morbidity from infectious diseases other than TB in children aged 3 months to 3 years.
- In Greenland, nationwide policy changes with a temporary complete stop and subsequent re-introduction of BCG vaccination, in combination with: a high burden of infectious diseases; a documented effect of BCG on TB incidence; and an Arctic environment free of non-tuberculosis mycobacteria believed to influence the effect of BCG vaccination; provides us with an ideal setting in which to study the non-specific effects of BCG vaccination.

Background

Since the 1950s, the BCG (Bacillus Calmette-Guérin) vaccine has been used to prevent tuberculosis (TB). The vaccine has a well-documented protective effect against disseminated TB and TB meningitis among children and is the most widely administered vaccine, with estimated global vaccine coverage of 85%.[1,2] A number of studies have suggested that BCG vaccination, in addition to its effect on TB, may decrease morbidity from other infectious diseases.[3,4] This effect is referred to as the heterologous or non-specific effect of the vaccine.[5] It is hypothesized that administering the live attenuated BCG vaccine to neonates improves the overall effect of their immune response towards pathogens unrelated to the *Mycobacterium tuberculosis* complex by inducing cross-reactivity of the adaptive immune system and by training the innate immune system through epigenetic reprogramming.[6]

Observational studies from West Africa have reported decreased incidences of acute lower respiratory infections (ALRI) and mortality among BCG-vaccinated children, especially in the early years of life, more than could be expected due to the effect against TB.[4,7,8] Two randomized controlled trials of BCG vaccination among low-birthweight children report an association between BCG vaccination and reduced mortality, the most recent proposing BCG vaccination as a mediator of comprehensive protection against infections, based on innate cytokine responses.[9,10]

In Greenland, the national childhood vaccination programme has included neonatal BCG vaccination since 1955.[11] However, due to a markedly reduced incidence of TB in the 1980s, the health authorities in Greenland discontinued BCG vaccination from 1991 through 1996.[12,13] This transient discontinuation, in combination with a high burden of infectious diseases in Greenland[14–18] and the fact that the Arctic climate provides an environment free of the non-tuberculosis mycobacteria (NTM) believed to influence the effect of BCG vaccination,[19] constitutes an ideal setting for a natural experiment in which to investigate specific and non-specific effects of BCG vaccination.

The purpose of this study was to determine possible non-specific effects of BCG vaccination by comparing nationwide hospitalization rates due to infectious diseases, other than TB, among cohorts of BCG-vaccinated and unvaccinated children aged 3 months to 3 years in Greenland.

Methods

Setting

Greenland is part of the Kingdom of Denmark and is governed by the Greenland Self-Government. During the study period, the average annual population was 55 902.[20] The majority of the population is Inuit (88%)[21] and 30% of the population live in the capital Nuuk, 56% in coastal towns and 13% in settlements.[22] All Greenlanders have universal and free access to the health care system, consisting of a central hospital in Nuuk, hospitals in 16 towns and nurse stations in settlements. All hospitals also serve the local settlements and provide both primary and secondary health care including hospital admissions.

National registers

At birth, all Greenlanders receive a personal identification number through the Civil Registration System (CRS), allowing individual follow-up through all national registers. The CRS provides information on sex, age, place of residence, ethnicity and mortality. Participants were considered Inuit if both parents were born in Greenland. Since 1987, all information on hospital admissions has been reported to the Greenlandic Inpatient Register (GLPR) and

Table 1. The National Childhood vaccination programme in Greenland up to the age of 3 years during the study period, according to vaccine and period

Vaccine	1987–90 (BCG-vaccinated)	1991–95 (BCG-unvaccinated)	1996 (BCG-unvaccinated)	1997–2001 (BCG-vaccinated)	2001–04 (BCG- vaccinated)
BCG	Neonatal	–	–	Neonatal	Neonatal
Pertussis	5, 9, 40 weeks	5, 9, 40 weeks	5, 9, 40 weeks		
DT-IPV[a]*	5, 6 and 15 months	5, 6 and 15 months	5, 6 and 15 months		
DTP-IPV[b]*				3, 5 and 12 months	3, 5 and 12 months
HiB[c]	–	–	3, 5 and 12 months	3, 5 and 12 months	3, 5 and 12 months
MMR[d]*	15 months	15 months	15 months	15 months	15 months
OPV[e]	2 years	2 years	2 years	2 years	–

Cells with (–) indicate that the vaccine is not given, empty cells indicate that the vaccine is given but in another combination of vaccines.
[a]Diphtheria, tetanus, inactivated polio vaccine.
[b]Diphtheria, tetanus, pertussis, inactivated polio vaccine.
[c]*Haemophilus influenzae* type B, was introduced 1996, delivery and coverage was irregular initially.
[d]Measles, mumps, rubella.
[e]Oral polio vaccine, was discontinued 1 July 2001.
*Compound vaccines.

includes information on, for example, discharge diagnosis and time of admission. The GLPR used the 8th Revision of the International Classification of Diseases (ICD-8) from 1987 and the 10th Revision (ICD-10) from 1994. Through the GLPR, data on hospitalizations were obtained and categorized as: all-cause morbidity (all diagnoses due to disease), infectious diseases and respiratory tract infections. Parasitic infections and post-infectious conditions were not classified as infectious diseases, but were included in all-cause morbidity. All hospitalizations of healthy children were excluded (e.g. codes for healthy live-born children and for healthy accompanying individuals). For specific ICD-8 and ICD-10 codes, see Supplementary Appendix, Table A1, available at *IJE* online.

Since 1955, TB has been mandatorily notifiable in Greenland, and information on TB was obtained through the TB notification system maintained by the National Board of Health.[23] Information on birthweight and place of delivery (hospital, nurse station, home) was obtained from the national birth register to which notification has been mandatory since 1990.

BCG vaccination

As part of the Greenlandic national childhood vaccination programme, BCG has been administered intradermally (0.05 ml *Mycobacterium bovis* BCG, Danish strain 1331) to neonates since 1955, with a brief discontinuation from 1991 through 1996.[24,25] The childhood vaccination programme is voluntary and free of charge. Coverage rates of neonatal BCG vaccination in the study period has been reported to be > 93%[11] and, specifically for East Greenland, coverage of 99% has been reported.[25] No catch-up vaccination was offered to the unvaccinated children, except in the West Greenland town of Maniitsoq.[11] In the present study we assumed all children born from 1 January 1991 to 31 December 1996 to be BCG-unvaccinated, an assumption which has been validated elsewhere.[11,25] During the study period, BCG vaccination was postponed for newborns with birthweight below 2000 g.[26]

Throughout the study period, the national childhood vaccination programme also included the following vaccines during the first 3 years after birth: pertussis, diphtheria, tetanus, inactivated polio, measles, mumps, rubella, oral polio (OPV) and *Haemophilus influenzae* type B. For timing of vaccinations and changes of the vaccination programme over time, see Table 1. Mandatory notification of vaccinations was introduced in 2000, reporting high vaccination coverage of > 80% (except for OPV).[27–29]

Study design

A cohort study was established, based exclusively on information from national registers. The main cohort consisted of all children born in Greenland and living in Greenland at least once between 3 months and 3 years of age during the period from 1 January 1989 to 31 December 2004. Follow-up began at 3 months of age to avoid transient misclassification of BCG vaccination status due to delayed vaccination and to avoid lack of hospitalization registration caused by delayed registration of the infant's CRS number. Children were followed until one of the following: death, age > 3 years, TB or end of follow-up (31 December 2004), whichever came first. Children were excluded from follow-up at time of emigration and reincluded if returning to Greenland. Children who emigrated before beginning of follow-up (age 3 months) without returning to Greenland before the age of 3 years never

entered follow-up. Furthermore, children were excluded from follow-up during hospitalization and the first 14 days following discharge after a hospital admission due to an infectious disease. To test whether findings for the main cohort were applicable also to the youngest children, an additional cohort of children aged 3 days to 3 months was established using similar definitions. Our cohort size was determined by the entire population of Greenland in certain birth cohorts.

Statistical analysis

The association between BCG vaccination and hospitalization was evaluated by incidence rate ratios (IRR) estimated by log-linear Poisson regression. The variance was estimated by a sandwich estimator, as the same child could contribute with several hospitalizations. As BCG vaccination status was defined by birth cohort, an analysis of BCG with adjustment for age and calendar period is an age-period-cohort analysis, i.e. additional assumptions were needed to allow for estimation. These assumptions were: the age effect is the same for all calendar periods and birth cohorts; the period effect can be described by a log-linear effect with an age-specific slope; and the only potential birth cohort effect is the possible BCG vaccination effect. More specifically, the regression included an age effect (3–11 months, 1 year, 2 years), a linear period effect (based on period in 1-year categories) in interaction with age, and a BCG vaccination effect (birth cohorts: 1989–90, 1997–2004). In addition, IRRs for vaccination were adjusted by sex, ethnicity and place of birth (so main effects for these variables were included). Whether age and sex modified the BCG vaccination effect was evaluated by including an interaction term. Similar analyses were performed with mortality as outcome (except in these analyses children were also at risk during hospitalization), and in extended cohorts including children aged 3 days to 5 years [in these analyses age was categorized as (3 days–3 months, 1 year, 2 years, 3 years, 4 years)]. All tests were based on the score test. All analyses were performed in SAS 9.4 using the GENMOD procedure.

Ethical considerations

The study was purely register-based and did not physically involve any children. The study was conducted in accordance with the Helsinki II declaration and was approved by the Research Ethics Committee for Health Science Research in Greenland (approval No. 2015-04) and the Danish Data Protection Agency. The Agency for Health and Prevention and the Greenlandic National Board of Health, respectively, gave permission to use the GLPR and the TB notification system.

Table 2. Demographic characteristics by BCG vaccination in a cohort of 19 363 children aged 3 months to 3 years and born in Greenland

	Unvaccinated		Vaccinated	
	N	(%)	*N*	(%)
All	6677	(34.5)	12 686	(65.5)
Sex				
Boys	3382	(50.7)	6432	(50.7)
Girls	3295	(49.3)	6254	(49.3)
Ethnicity				
Inuit	5499	(82.4)	10 463	(82.5)
Non-Inuit	314	(4.7)	594	(4.7)
Mixed	864	(12.9)	1629	(12.8)
Place of birth				
The capital, Nuuk	1383	(20.7)	2583	(20.4)
Town (excluding Nuuk)	3814	(57.2)	7356	(58.0)
Settlement	1470	(22.0)	2693	(21.2)
Unknown	10		54	
Birthweight				
< 2000 g	71	(1.1)	112	(1.3)
≥ 2000 g	6312	(98.9)	8487	(98.6)
Unknown*	294		4087	
Place of delivery				
Hospital	5180	(97.5)	6847	(98.6)
Nurse station	79	(1.5)	56	(0.8)
Home	56	(1.1)	42	(0.6)
Unknown*	1362		5741	

*The group of unknown is relatively larger for vaccinated children, as mandatory registration to the national birth register started in 1990.

Results

Overall, 19 363 children were included in the study and had 4316 hospitalizations during a total of 44 065 person-years (pyrs) of follow-up. Of all hospitalizations, 2069 were due to infectious diseases, and of these 1581 hospitalizations due to respiratory tract infections. Median time of follow-up was 2.75 years [interquartile range (IQR) 2.03-2.75]. During follow-up, 127 children died, 30 emigrated without return and 24 were diagnosed with TB. In Table 2, demographic characteristics for BCG-vaccinated and BCG-unvaccinated children are shown.

Among vaccinated children, the incidence rate (IR) of hospitalizations due to infectious diseases was 47.6 per 1000 pyrs [95% confidence interval (CI) 45.1-50.3] as compared with 45.9 per 1000 pyrs (95% CI 42.8-49.2) among unvaccinated children. Figure 1 shows the observed IR of hospitalizations due to infectious diseases each year during 1989–2004 in three age groups as point estimates, where the highest IRs were observed among the youngest children. Furthermore, Figure 1 shows the estimated trend in IR for each age group according to calendar year, allowing for a different level of IR for BCG-vaccinated and

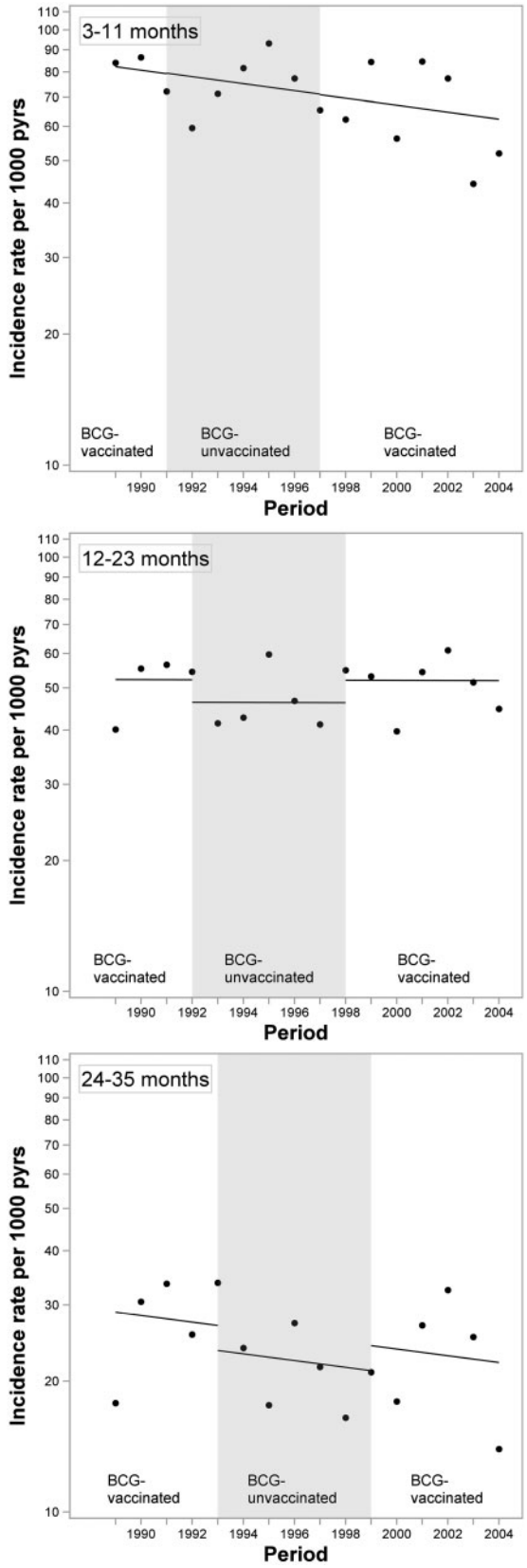

Figure 1. Observed incidence rate (IR) of hospitalisation due to infectious disease per 1000 person-years (pyrs) for each year during the study period (1989-2004) in three age groups (point estimates marked by •). The full drawn lines are estimated trends in IR according to calendar year allowing for a different level of IR for BCG-vaccinated and BCG-unvaccinated children (–). The white area within the graph is BCG-vaccinated children, the grey area within the graph is BCG-unvaccinated children. Dots representing years with both vaccinated and unvaccinated children are placed at the border between white and grey.

BCG-unvaccinated children. The estimated ratios between the different levels of IR for infectious diseases in vaccinated and unvaccinated children for the three age groups are shown in Table 3 as adjusted IRRs.

There were no differences between vaccinated and unvaccinated children overall or in any of the age groups: age 3–35 months [adjusted IRR 1.07 (95% CI 0.96-1.20)], age 3–11 months [adjusted IRR 1.00 (95% CI 0.84-1.19)], age 12–23 months [adjusted IRR 1.13 (95% CI 0.95-1.34)] and age 24–35 months [adjusted IRR 1.15 (95% CI 0.92-1.43)], $P_{\text{effect modification by age}} = 0.44$. The results were similar with adjustment for age in months and with no adjustment (data not shown).

Adjusted IRR estimates for hospitalizations due to infectious diseases among all children did not change when we excluded children with a birthweight below 2000 g [i.e. children who most likely had a delayed BCG vaccination [IRR 1.09 (95% CI 0.98-1.22)], or when only including participants born in East Greenland, where the vaccination assumption was validated and 99% followed the vaccination assumption[25] [IRR 1.12 (95% CI 0.88-1.42)]. Furthermore, no change was observed when censoring children who were offered catch-up vaccination in Maniitsoq in 1997 [IRR 1.09 (95% CI 0.97-1.21)], or when we only included children born in a hospital, i.e. excluding deliveries at home or at nurse stations, possibly leading to delayed BCG vaccination [IRR 1.05 (95% CI 0.85-1.31)]. The same lack of association between BCG vaccination and hospitalization was observed when grouping infectious diseases as respiratory tract infections [IRR 1.10 (95% CI 0.98-1.24)] and non-respiratory tract infections [IRR 0.93 (95% CI 0.74-1.16)] (Table 3). In addition, BCG vaccination was not associated with reduced risk of hospitalization due to non-infectious diseases [IRR = 0.94 (95% CI 0.84-1.05)] (Table 3). Last, there was no difference when comparing IRRs for boys [1.07 (95% CI 0.93-1.23)] with those for girls [1.08 (95% CI 0.93-1.26)], $P_{\text{effect modification by sex}} = 0.90$.

In mortality analysis, 127 children died during 44 198 pyrs of follow-up. BCG vaccination was not associated with reduced mortality [adjusted IRR 1.21 (95% CI 0.81-1.81)] (Table 4). In an additional cohort, including children aged 3 days to 3 months, 191 hospitalizations due to infectious diseases were observed during 3922 pyrs of follow-up. In this cohort we likewise found no difference in hospitalization due to infectious diseases among

Table 3. Events, Incidence Rate (IR) and Incidence Rate Ratio (IRR) of hospitalization by BCG vaccination according to age for different types of hospitalisation in a cohort of 19 363 children aged three months to three years and born in Greenland

	All Hospitalisations															
	All-cause morbidity				Infectious diseases									Non-infectious diseases		
					All			Respiratory tract infections			Non-respiratory tract infections					
Age	Pyrs	Events	IR*	IRR (95% CI)†	Events	IR*	IRR (95% CI)†	Events	IR*	IRR (95% CI)†	Events	IR*	IRR (95% CI)†	Events	IR*	IRR (95% CI)†
All																
Unvaccinated	17 493	1719	98.3	1 (ref)	803	45.9	1 (ref)	616	35.2	1 (ref)	204	11.7	1 (ref)	916	52.4	1 (ref)
Vaccinated	26 572	2597	97.7	1.00 (0.92-1.10)	1266	47.6	1.07 (0.96-1.20)	965	36.3	1.10 (0.98-1.24)	315	11.9	0.93 (0.74-1.16)	1331	50.1	0.94 (0.84-1.05)
3-11 months																
Unvaccinated	4923	740	150	1 (ref)	370	75.2	1 (ref)	295	59.9	1 (ref)	85	17.3	1 (ref)	370	75.2	1 (ref)
Vaccinated	7313	1037	142	0.95 (0.82-1.11)	518	70.8	1.00 (0.84-1.19)	400	54.7	1.01 (0.85-1.20)	121	16.5	0.88 (0.58-1.32)	519	71.0	0.90 (0.74-1.09)
12-23 months																
Unvaccinated	6352	615	96.8	1 (ref)	294	46.3	1 (ref)	220	34.6	1 (ref)	75	11.8	1 (ref)	321	50.5	1 (ref)
Vaccinated	9672	1003	104	1.07 (0.93-1.22)	504	52.1	1.13 (0.95-1.34)	386	39.9	1.19 (0.97-1.46)	121	12.5	0.91 (0.65-1.27)	499	51.6	1.01 (0.86-1.19)
24-35 months																
Unvaccinated	6218	364	58.5	1 (ref)	139	22.4	1 (ref)	101	16.2	1 (ref)	44	7.1	1 (ref)	225	36.2	1 (ref)
Vaccinated	9587	557	58.1	1.00 (0.86-1.16)	244	25.5	1.15 (0.92-1.43)	179	18.7	1.15 (0.88-1.50)	73	7.6	1.05 (0.70-1.56)	313	32.6	0.90 (0.74-1.10)

*IRs are per 1000 pyrs.

†IRRs are adjusted for age and period (with the assumption described in the method section) and sex, ethnicity and place of birth.

Table 4. Events, incidence rate (IR) and incidence rate ratio (IRR) of mortality by BCG vaccination according to age in a cohort of 19 363 children aged three months to three years and born in Greenland

		Mortality		
Age	Pyrs	Events	IR*	IRR (95% CI)†
All				
Unvaccinated	17 544	47	2.7	1 (ref)
Vaccinated	26 654	80	3.0	1.21 (0.80-1.82)
3-11 months				
Unvaccinated	4946	24	4.9	1 (ref)
Vaccinated	7347	52	7.1	1.61 (0.94-2.75)
12-23 months				
Unvaccinated	6371	17	2.7	1 (ref)
Vaccinated	9704	12	1.2	0.49 (0.24-1.01)
24-35 months				
Unvaccinated	6227	6	1.0	1 (ref)
Vaccinated	9603	16	1.7	1.75 (0.71-4.34)

*IRs are per 1000 pyrs.

†IRRs are adjusted for age and period (with the assumption described in the method section) and sex, ethnicity and place of birth.

vaccinated as compared with unvaccinated children [adjusted IRR 0.72 (95% CI 0.49-1.06)].

To compare our results with other studies, we also estimated the risk of hospitalization due to respiratory tract infections for children aged 3 days to 1 year [IRR 0.96 (95% 0.81-1.12)], children aged 3 days to 3 years [IRR 1.07 (95% 0.95-1.20)] and for children aged 3 days to 5 years [IRR 1.03 (95% 0.93-1.14)]; see Supplementary Appendix, figure A1, available at *IJE* online.

Discussion

In this population-based cohort study from Greenland, we did not find any protective effects of neonatal BCG vaccination on child morbidity when excluding TB, as measured by hospitalization rates due to infectious diseases among children aged less than 3 years. Specifically, we did not find any reduced risk of hospitalizations due to respiratory tract infections other than TB among BCG-vaccinated children. Additionally, neonatal BCG vaccination was not associated with any reduction in mortality rate among children between 3 months and 3 years of age.

The hypothesis that BCG vaccination may have non-specific effects is not new.[3] One of the first studies to show a protective effect of BCG vaccination on child mortality was a follow-up study among 8752 children in West Africa, carried out 15 years ago.[4] The finding was later confirmed in several observational studies[7,8] and in one randomized controlled trial among low-birthweight children,[10] although the effects were only confirmed among neonates,[10] on the incidence of ALRI,[8] and were more pronounced among girls as compared with boys.[8] Two recent observational studies, one from Spain and one from 37 low- and middle-income countries, found reductions in respiratory tract infections among BCG-vaccinated children aged 0–14 years of 41% and among children under the age of 5 years of 17–37%.[30,31] Most published studies on the subject report a positive non-specific effect of BCG vaccination on child morbidity and mortality. However, in contrast to this, the World Health Organization (WHO) published a systematic review in 2014 reporting great risk of bias in a number of the published studies, stating uncertainty towards the evidence on the effects of BCG vaccination on all-cause mortality.[3]

It is not clear why non-specific effects are observed in some studies and in some countries and not in others, including our study. Observational studies are prone to bias that may not be accounted for, and this goes for our study as well as for others. There are, however, some differences between conditions in Greenland and those of other countries, which make our results particularly interesting. Greenland, being a developed country, has high rates of a number of childhood infections including respiratory tract infections,[15] otitis media,[16] hepatitis,[17] TB[23] and invasive pneumococcal infections, comparable to developing countries.[18] However, unlike other countries with high TB incidence, the TB epidemic in Greenland is characterized by not being associated with HIV infection[14,32,33] or malnutrition.[1,34] Also, children in Greenland are not undernourished[35] and non-tuberculous mycobacteria (NTM) are rare or non-existing.[36] These factors are all known to influence both the immune system[37] and BCG vaccine effectiveness.[19] Possibly for these and other reasons, we previously demonstrated a clear protective effect of BCG vaccination against TB and *Mycobacterium tuberculosis* infection in Greenland,[25] a finding that has been difficult to clearly demonstrate in other populations including populations in tropical settings.[38] Thus, if BCG vaccination has non-specific protective effects against infections in general, we would a priori expect such effects to be measurable in the Greenlandic population. However, we did not observe such effects, either towards infections in general, or towards respiratory tract infections or towards mortality. Thus, we believe that we observe a more unbiased picture of the effects of BCG vaccination in Greenland as compared with other parts of the world. In addition, BCG vaccination in Greenland was given according to year of birth only, and was not influenced by individual factors. This could lead to bias, and we have previously shown that actual BCG vaccination status

corresponds well with year of birth in Greenland.[25] BCG vaccination is administered within 48 h of birth, except for children of low birthweight (1.3%) or on the rare occasion when a delivery does not take place at a hospital (1.6%); these children do however constitute a minority.

It has been discussed how non-specific effects of different vaccines might modify each other.[6,10,31] Our study evaluates non-specific effects of neonatal BCG vaccination in a real-life setting in a population of children aged 3 months to 3 years also exposed to other vaccines according to the Greenlandic childhood vaccination programme. During the study period, most of these vaccines were given at age 3 months or older. We therefore performed an additional analysis among children aged 3 days to 3 months. In this group, as shown in Results, we observed an IRR of 0.72 (95% CI 0.49-1.06), but the evaluation in this age group was low-powered.

Our study has a number of strengths. It was population based, relying exclusively on register information, minimizing selection bias. Greenland has a very high BCG vaccine coverage, minimizing misclassification of the exposure. The nationwide discontinuation of BCG vaccination offers the best possible randomization of the exposure in a setting where real-time randomization of BCG would be unethical. The GLPR was validated in 2011; this report documented a stable reporting rate, high register completeness and accuracy regarding, for example, respiratory diseases, asthma/allergies and viral diseases from 1987 to 2009.[39] It may be argued that we only included morbidity leading to hospitalizations and not morbidity leading to outpatient treatment, which prevents us from estimating the association between BCG vaccination and outpatient morbidity. Trained physicians make diagnoses; however, inpatient diagnoses are determined after longer observation time and/or use of diagnostic tests, as compared with outcomes based on surveys, self-reported symptoms and outpatient diagnoses, which also provides our study with high outcome specificity. We do not consider it likely that possible non-specific effects of BCG vaccination would be observed only for outpatient morbidity and not for inpatient morbidity. We performed a number of sensitivity analyses and found no effect modification by age or sex, and no effect of excluding children at risk of delayed BCG vaccination. Furthermore, our results were not affected by adjustment. Thus, we do not believe that bias or confounding would explain the lack of association between BCG and infectious morbidity found in the present study.

However, since the specific effects of BCG vaccination against *Mtb* infection and TB have been convincingly documented in this TB high-endemic setting, BCG vaccination is still important for public health in Greenland in prevention of *Mtb* infection and TB.

In conclusion, among children in Greenland aged 3 months to 3 years we did not observe any reduced risk of hospitalization due to all-cause morbidity, infectious diseases or mortality among BCG-vaccinated children as compared with BCG-unvaccinated children. Consequently this study does not support the hypothesis that neonatal BCG vaccination carries non-specific effects reducing morbidity in children caused by infectious diseases other than TB.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author Contributions

All authors made substantial contributions to the acquisition, analysis and interpretation of the data, and drafting, revising and approving the final version of the paper, and all agreed to be accountable for all aspects of the work.

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