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Chrystelle Kiang Date

Bacillus Calmette-Guérin (BCG) Vaccine and Adult Mortality in Two Prospective Cohort Studies

By

Chrystelle Kiang
Master of Public Health

Epidemiology

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KM Venkat Narayan, MD, MSc, MBA
Committee Chair

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Chrystelle Kiang

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Massachusetts Institute of Technology
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Faculty Thesis Advisor: KM Venkat Narayan, MD, MSc, MBA

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2019

ABSTRACT

Bacillus Calmette-Guérin (BCG) Vaccine and Adult Mortality in Two Prospective Cohort Studies

By Chrystelle Kiang

Background There is evidence of beneficial non-specific effects of live-attenuated vaccines, including Bacillus Calmette-Guérin (BCG) for tuberculosis, primarily in child mortality. The aim of this study is to examine whether this association remains consistent in adulthood in women in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II).

Methods These are two prospective cohort studies of women followed from 1984 to 2014 in NHS and from 1991 to 2015 in NHS II. Vaccination status was self-reported at baseline and death obtained by post office, next-of-kin, and/ or via systematic searches of state records and National Death Index.

Results Of the 87,699 women included in NHS, 13% had received the BCG vaccine and of the 93,514 in NHS, 2% received it. There was no association of mortality by vaccination status in either cohort. In NHS, there were 25,224 total deaths and the adjusted hazard ratio (HR) and 95% confidence interval (95% CI) of all-cause mortality was 1.04 (95% CI: 0.99 – 1.08). In NHS II, there were 2,591 total deaths and the HR was 1.01 (95% CI: 0.79 – 1.30). These findings were consistent when participants were subset by race and by type of death (cardiovascular, cancer, or other).

Conclusions Adult mortality was independent of BCG vaccine status, contrary to what is seen in child mortality. BCG vaccine may not provide non-specific benefits in adulthood.

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BACKGROUND

There are two commonly used types of vaccines, live and inactivated. Live vaccines, also referred to as live-attenuated or attenuated, contain a weakened form of the living microbe which can replicate in humans but cannot cause disease. They differ from inactivated vaccines, which contain the killed microbe and confer a weaker immune response than live vaccines. There is some evidence that live-attenuated vaccines, including Bacille Calmette-Guérin (BCG) for tuberculosis (TB) and oral polio vaccine, have non-specific effects and are associated with increased childhood survival (1)(2). In addition to the epidemiologic associations, there is a plausible immunologic mechanism by trained immunity (3)(4)(5).

Most of evidence regarding BCG is based on vaccination during infanthood and mortality in childhood. Non-specific mortality in the case of BCG is defined as death by causes other than TB. In systematic reviews, the association has been found in various cohorts of children (2). Clinical trials have shown BCG vaccines for infants to be inversely associated with mortality (6)(7). In 2014, the World Health Organization called for further research of non-specific effects of vaccines on childhood mortality (8). In 2016, Rieckmann et al. looked at mortality in a cohort of children in Denmark among children with BCG vaccine, vaccinia (for smallpox), both, or neither and found an adjusted hazard ratio of 0.58 (95% confidence interval: 0.39 - 0.85) for BCG vaccine in a cohort of children in Denmark (9).

There is less research of adult mortality as the main outcome, leaving a gap of knowledge about the effect of BCG on mortality beyond childhood. The association has been investigated in adults in Guinea-Bissau based on scars left by the BCG vaccine

(mortality ratio of 0.56, 95% CI: 0.24-1.32) but the authors note the potential for exposure misclassification, as the vaccinia vaccine also results in a scar, and survivor bias (10). Adult survival has also been examined among people with melanoma, with better survival for those previously vaccinated for BCG than those who were not (HR 0.69, 95% CI 0.49-0.98) (11). It is unclear if this lack of research is because of the expected duration of immune benefit or due to lack of longitudinal data in a population with an adequate prevalence of BCG vaccine to observe mortality.

BCG is not part of the current routine vaccine schedule in the United States (US) with the exception of children who live with adults who have untreated TB, and healthcare workers who work with patients with high percentage of certain resistant strains of TB (12). Although BCG vaccine is not mandatory in the US, there is motivation to examine the association in adults further in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) cohorts. The cohorts are comprised of registered nurses across 17 states, who are more likely to have the BCG vaccine as healthcare workers, and we have high quality follow up data on their mortality and comorbidities. The long-term effects of BCG vaccine must be understood to better inform future vaccine recommendations.

METHODS

Hypothesis

Based on current body of literature, we will investigate the association between BCG vaccination and all-cause mortality in a prospective cohort.

Study Population

The study population consists of two cohorts of women from the Nurses' Health Study and Nurses' Health Study II. NHS was started in 1976 with 121,700 registered nurses aged 30 to 55, but baseline for this analysis is 1986. NHS II is comprised of 116,429 nurses aged 30-55 in baseline year of 1989. Person-time was counted when women received the vaccine or turned 35, when they were no longer eligible to receive the BCG vaccine. Participants completed questionnaires by mail at enrollment and follow up every other year after with demographic and medical information, covering the time in between. The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Exposure and Covariate Assessment

BCG status was assessed with response to a question asked to each cohort. For NHS this was asked in 1992 with the question "Your TB skin test since 1985?" and answer choices given as "Pos", "Neg", "Not done", and "BCG prior to 1985". There was a follow-up question to ascertain date of seroconversion: "If ever positive, conversion date:" with answer choices of "Before 1985", "1985+", and "Never positive". In NHS II, this was asked in 1993 with the question "Your TB skin test since 1989?" and answer choices given as "Pos", "Neg", "Not done", and "BCG prior to 1989". The same follow up question was asked, "If ever positive, conversion date:" with answer choices of "Before

1989", "1989+" or "Never positive". Participants with missing or contradicting answers, such as answering 'Negative' to the first question but providing a conversion date earlier than the test year, were excluded. Covariate information was obtained from bi-annual questionnaires. This was updated self-reported information on age, weight, smoking status, menopause status, family medical history, and diseases including hypertension and diabetes. Body mass index (BMI) was calculated from these reports as kg/m^2. The covariates included were based on variables known to be associated with mortality.

Outcome Assessment

The outcome of interest was death from any cause. Mortality data for both cohorts was obtained by notification of death upon return of questionnaire, either by the post office or from next-of-kin, and/ or via systematic searches of state records and National Death Index (13). Only confirmed cause of deaths are used from medical record review, next-of-kin, or death certificate information. Cause of death was classified according to the eighth and ninth revisions of the International Classification of Diseases (ICD), which were used to group related deaths. Cardiovascular disease (CVD) included but was not limited to ischemic heart disease, stroke, rheumatic fever, and sudden death. 'Other' deaths were categorized as deaths not caused by CVD or cancer, the two leading causes of death.

Statistical Analysis

Participants were followed from the date of return of the baseline questionnaire to the date of death or the end of follow up, which was in June 2014 for NHS and June 2015 for NHS II. These dates were used to calculate individual person-time. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95%

confidence intervals of mortality by vaccination status. The time scale in the regression model was in two-year intervals, given the frequency of questionnaire returns, and the model was stratified by age in years. The multivariable analysis adjusted for self-reported race, smoking status, and BMI. Cohorts were analyzed at separately given their differences in participant make up, in geographic location and age at baseline. Variables stratified by common cutoffs: BMI of ≤ 25 kg/m^2 or > 25 kg/m^2, smoking as ever or never smoked, and race/ ethnicity as white or not. All statistical tests were 2-sided and performed using SAS version 9.2 for UNIX (SAS Institute Inc).

RESULTS

Baseline characteristics for both cohorts are shown in Table 1. The prevalence of BCG vaccine varied between cohorts with 13% in NHS and 2% in NHS II. Within cohorts, the vaccinated and unvaccinated groups were similar in BMI, smoking status, hypertension, hypercholesterolemia, and menopause status. At baseline, the average age in the NHS cohort is 52, much older than the average of 34 in NHS II. Within cohorts, the ages between vaccination groups were similar. In NHS, the vaccinated group is younger than the unvaccinated (51 and 52, respectively), while in NHS II the vaccinated group is older (36 and 34). Regardless of vaccine status, about 70% of women in NHS were post-menopausal, a much greater proportion than the 2% in NHS II. This follows with the difference in average age between cohorts. Most participants identified as white, with a similar proportion of white women in NHS between unvaccinated and vaccinated groups (94% and 93%, respectively). However, these proportions differed in NHS II where 94% of the unvaccinated group was white while 72% of the vaccinated group was white.

After exclusions, the NHS cohort consisted of 87,699 women and NHS II of 93,514 women. Among women in NHS, there were 25,224 deaths over 2,258,597 person-years and among women in NHS II, there were 2,591 deaths over 2,406,940 person-years. Adjusting for baseline differences, there was no association found between BCG vaccination and risk of mortality. In comparing all-cause mortality in those who received BCG vaccine to those who did not, the adjusted hazard ratio in NHS was 1.03 (95% CI: 0.99 – 1.08) and NHS II was 1.01 (95% CI: 0.79 – 1.28). This finding was consistent among white and non-white participants. In white participants, the adjusted

HR in NHS was 1.04 (95% CI: 0.99 – 1.08) and 0.92 (95% CI: 0.69 – 1.22) in NHS II. Among non-white participants, the adjusted HR in NHS was 1.02 (95% CI: 0.87 – 1.20) and in NHS II, 1.11 (95% CI: 0.71 – 1.73).

When examined by type of death, there were no meaningful associations between BCG vaccine and mortality when adjusted for race, smoking, and BMI, seen in Table 3. In NHS, the majority of deaths were due to diseases not related to cardiovascular diseases (CVD) or cancers, with 12,006 deaths due to other causes, including 8 related to tuberculosis. Cancer was the next leading cause of death, followed by CVD. For tuberculosis alone, the HR was 1.47 (95% CI: 0.62 – 3.02) but this represented a very small number of total deaths (<0.5%). The HRs for deaths due to cancer and other causes were 1.03 (95% CI: 1.00 – 1.05) and 0.99 (95% CI: 0.98 – 1.01). There was a slightly elevated hazard in NHS for those with the BCG vaccine and CVD deaths, with an HR of 1.04 (95% CI: 1.02– 1.07). In NHS II, the leading cause of death was due to cancer, followed by other, then CVD. There was only one death was related to tuberculosis. There were no significant associations in NHS II by cause of death, with HRs for deaths related to CVD, cancer, and other causes were 0.79 (95% CI: 0.59 – 1.06), 1.03 (95% CI: 1.00 – 1.05), 1.37 (95% CI: 0.62 – 3.02).

DISCUSSION

Overall, BCG vaccination was not associated with a change in mortality in these cohorts. This was consistent for most causes of death across both cohorts, with the exception of CVD deaths in NHS. There was a slight increase in CVD deaths for women with the BCG vaccine (HR: 1.04, 95% CI: 1.02– 1.07). However, the model used only adjusted for race, smoking, and BMI, so the association may be confounded.

The strength of this analysis lies in the long follow-up in a sample size with validated covariates and mortality data. The large number of deaths in both cohorts in both the vaccinated and unvaccinated groups allowed for precision in estimating the hazard ratio of the association and provided capacity to look at various causes of death. These cohorts have proven to be a reliable data source for epidemiologic research.

Perhaps the most important limiting factor in this analysis is in the lack of age at vaccination, as previous research is based on confirmed childhood vaccination. The participants may have received the vaccine up to age 35, as per standard recommendation for healthcare professionals. To avoid counting immortal person-time, only women who were over the age of 35 were included in the study, who were no longer eligible to receive the vaccine. If there is a difference based on age of vaccination, it is not possible to identify in these cohorts.

There are some potential sources of bias that were not addressed analytically. Although a small amount had conflicting answers for the questionnaire, there is possibility for misclassification of vaccination status. There may also be some survivor bias, as the unvaccinated participants would have to live to age of 35 to even be included in the study. There may be some unmeasured confounding by other vaccines,

as previous research has found that if DTP is given along with BCG, mortality risk may increase based on the chronologic order they were administered (2). However, that may also be limited to childhood mortality and we did not have other vaccination history.

Because follow up begins in adulthood, we didn't calculate non-specific mortality, meaning deaths by causes other than TB, as that would definitely be affected by survival bias. Given the small number of deaths by TB observed in our cohorts, our estimates for non-specific mortality would be similar to all-cause anyway.

Future Directions

These results do not directly conflict with previous research, as there is no association rather than an increase or decrease in risk. This study only follows for adult mortality while previous research looked at childhood mortality. There remains a gap of knowledge in the time between childhood and adulthood. A similar analysis could be strengthened if age of vaccination is obtained, with confirmed childhood vaccination and follow-up through adulthood. This design would be ideal to address survival bias and confirm the longevity of the non-specific effects of BCG. Nonetheless, these results provide confidence in the continuation of phasing out BCG from the routine vaccine schedule.

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TABLES

Table 1. Age-adjusted baseline characteristics of study population by vaccination status.

	NHS (1982)		NHS II (1989)	
	No BCG	BCG	No BCG	BCG
n	76,094	11,605	90,691	2,161
Age, years	52.5 (7.3)	51.4 (5.9)	34.4 (4.7)	36.5 (4.4)
Body mass index, kg/m^2	25.3 (4.8)	25.4 (4.8)	24.1 (5.0)	23.6 (4.9)
Smoker, %	20	21	13	11
White, %	94	93	94	72
Postmenopausal, %	55	53	2	2
Family history of diabetes, %	24	24	15	17
Hypertension, %	7	7	5	5
Diabetes, %	1	1	1	1
Hypercholesterolemia, %	3	3	11	11

Values shown as means (standard deviation) for continuous variables, percentages for categorical variables, standardized to age distribution of study population.

Table 2. Hazard ratio (95% confidence interval) of all-cause mortality by vaccination status, for each cohort.

	No BCG	BCG	95% CI
NHS			
Age-adjusted	1.00 (ref)	1.01	(0.97, 1.05)
Fully adjusted	1.00 (ref)	1.03	(0.99, 1.08)
NHS II			
Age-adjusted	1.00 (ref)	1.03	(0.81, 1.29)
Fully adjusted	1.00 (ref)	1.01	(0.79, 1.28)

Table 3. Hazard ratio (95% confidence interval) of all-cause mortality by vaccination status, subset by race/ ethnicity for each cohort.

	White			Non-white		
	No BCG	BCG	(95% CI)	No BCG	BCG	(95% CI)
NHS						
Age-adjusted	1.00 (ref)	1.01	(0.97, 1.05)	1 (ref)	1.03	(0.88, 1.21)
Fully adjusted	1.00 (ref)	1.04	(0.99, 1.08)	1 (ref)	1.02	(0.87, 1.20)
NHS II						
Age-adjusted	1.00 (ref)	0.97	(0.65, 1.46)	1 (ref)	1.35	(0.68, 2.68)
Fully adjusted	1.00 (ref)	0.98	(0.65, 1.47)	1 (ref)	1.89	(0.93, 3.84)

Table 4. Hazard ratio (95% confidence interval) of specific cause of death by vaccination status for each cohort.

	n	No BCG	BCG	95% CI
NHS				
Total deaths	25,224	1.00 (ref)	1.03	(0.99, 1.08)
CVD	5,005	1.00 (ref)	1.04	(1.02, 1.07)
Cancer	8,213	1.00 (ref)	1.03	(1.00, 1.05)
Other	12,006	1.00 (ref)	0.99	(0.98, 1.00)
TB	8	1.00 (ref)	1.37	(0.62, 3.02)
NHS II				
Total deaths	2,591	1.00 (ref)	1.01	(0.79, 1.28)
CVD	263	1.00 (ref)	0.90	(0.56, 1.43)
Cancer	1,193	1.00 (ref)	0.80	(1.63, 1.00)
Other	1,135	1.00 (ref)	1.16	(0.97, 1.37)
TB*	1	-	-	-

CVD: Cardiovascular disease. Other is deaths not related to cardiovascular disease or cancers, and include tuberculosis (TB).

* There were not enough deaths due to tuberculosis in NHS cohort to obtain HR.