Vaccine 34 (2016) 4586–4593

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Different effects of BCG strains – A natural experiment evaluating the impact of the Danish and the Russian BCG strains on morbidity and scar formation in Guinea-Bissau

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ARTICLE INFO

Article history:
Received 9 April 2016
Received in revised form 4 July 2016
Accepted 15 July 2016
Available online 1 August 2016

Keywords:
Non-specific/heterologous effects of vaccines
BCG vaccine
BCG strain
BCG scar
Child morbidity

ABSTRACT

Background: Different Bacillus Calmette-Guerin (BCG) vaccine strains may have different non-specific effects. We assessed the effect of two BCG strains (Danish and Russian) on childhood morbidity and BCG scarification in Guinea-Bissau.

Methods: During 2011–2013, infants in the Bandim Health Project's urban study area received the Danish or Russian BCG in a natural experiment. Health center consultations were registered at point of care and scar status and size at age 4½ months. We assessed the effect of strain on consultation rates between vaccination and age 45 days in Cox proportional hazards models. Scar prevalence and size were compared using binomial regression and ranksum tests.

Results: Among 1206 children, 18% received Danish BCG ($n = 215$) and 82% Russian BCG ($n = 991$). The adjusted hazard ratio (aHR) for consultations was 0.94 (95% CI 0.60–1.46) for Danish BCG compared with Russian BCG. Girls vaccinated with Danish BCG tended to have lower consultation rates compared with girls vaccinated with Russian BCG (aHR 0.56 (0.25–1.24)), whereas the effect was opposite for boys (aHR 1.24 (0.74–2.11)), $p = 0.09$. Children vaccinated with Danish BCG were more likely to develop a scar (97%) than children vaccinated with Russian BCG (87%), the relative risk (RR) being 1.11 (1.06–1.16). The effect was stronger in girls, and BCG scar size was larger among infants vaccinated with the Danish strain.

Conclusion: BCG strain influences scar prevalence and scar size, and may have sex differential effects on morbidity. BCG strains are currently used interchangeably, but BCG scarring has been linked to subsequent survival. Hence, more research into the health effects of different BCG strains is warranted. Small adjustments of BCG production could potentially lower childhood morbidity and mortality at low cost.

1. Introduction

Bacillus Calmette-Guerin (BCG) vaccine is recommended at birth in low income countries to protect against tuberculosis (TB). Estimates of the protection of the BCG vaccine against TB infections vary between 0% and 80% [1,2]. The current vaccine strains are all descendants from the original mycobacterium bovis isolate from 1921, and subsequent passages under different laboratory conditions have resulted in the different BCG strains [3]. Studies have indicated that different strains of BCG provide various mycobacterial specific protection [4–7]. There is no global consensus of which strain is optimal for general use; the following vaccines have been prequalified by WHO and are being used interchangeably: BCG Denmark (Danish 1331, Statens Serum Institut), BCG Chennai (Danish 1331, GreenSignal Bio Pharma Limited), BCG Russia (Moscow, Serum Institute of India), BCG Bulgaria (Sophia, BB-NCIPD Ltd) and BCG Japan (Tokyo, Japan BCG Laboratory) [8].

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http://dx.doi.org/10.1016/j.vaccine.2016.07.022
0264-410X/

Observational studies and randomized controlled trials (RCT) have shown that BCG vaccines, besides protecting against TB, also have strong beneficial non-specific effects (NSE), reducing all-cause mortality by more than can be explained by preventing TB [9–15]. This is possibly due to a general stimulation of the innate immune system enhancing protection against unrelated bacterial infections such as pneumonia and septicemia [14–19].

A good marker of BCG's NSE seems to be BCG scarification. Among BCG vaccinated children, children with a scar following BCG vaccination have lower morbidity and better survival rates than children without a scar [10,12,17,20]. To a large extent, reacting to BCG vaccination with a scar depends on a good BCG vaccination technique [17,21], however a number of studies suggest that the BCG strain may also be important for scar development [4,21].

Guinea-Bissau's Expanded Programme on Immunization (EPI) procures BCG vaccines through UNICEF. From 2010 to 2014 the EPI programme in Guinea-Bissau used the Russian strain. At the same time, the Bandim Health Project (BHP) used the Danish strain in a trial of administering BCG at birth to low birth weight (<2500 g, LBW) infants at three public health centers in Bissau city [22]. Left over doses of trial BCG vaccines, were used to vaccinate normal birth weight (NBW) infants (birthweight $\geqslant$ 2500 g) who presented for BCG vaccination on the same day. On other days, when no LBW children were present, NBW children received the Russian strain. This created a "natural experiment" among NBW children and the opportunity to compare the effect of different BCG strains in an unbiased manner.

The aim of the present study was to compare the effect of the Danish and the Russian BCG strains on overall morbidity and scar formation among NBW infants BCG vaccinated at three health centers in Bissau.

2. Methods

2.1. Setting

This study was conducted in the capital of Guinea-Bissau, Bissau city, where the BHP has maintained a Health and Demographic Surveillance system (HDSS) since 1978. The BHP covers the residential areas of Bandim, Belem, Mindara, and Cuntum, home to approximately 102,000 inhabitants. All households within this area are visited every month to register new pregnancies and births, and all children are assigned a unique ID number facilitating linkage between BHP databases.

There are three health centers in the BHP study area: Bandim, Cuntum and Belem. All health center visits for vaccinations and consultations are registered by BHP assistants. Free consultations are provided for study area children. Infants presenting for BCG vaccination have a questionnaire completed with basic information on the infant and mother, including ID number, sex, weight, age, date, and the batch numbers of the vaccine.

2.2. BCG vaccination policy and the natural experiment

BCG and oral polio vaccine (OPV) are recommended to NBW children at birth. Children born at the main hospital Simão Mendes (HNSM) are BCG vaccinated at daily vaccination sessions at the hospital's maternity ward, while children born at smaller hospitals, health centers, or at home, mainly seek vaccinations at health centers. Infants are vaccinated intradermally on the upper left deltoid region with 0.05 ml reconstituted BCG. As one vial of BCG contains 20 infant doses which should be used within 6 h, health centers have specific days for administering BCG in order to avoid vaccine wastage.

Due to enrolment in two BCG trials, BHP provided the Danish strain for all BCG vaccinations at the three health centers in the BHP study area until December 2011 [22,23]. From December 2011 until September 2013, LBW children were still randomized to receive Danish BCG at birth or wait until they had gained weight (national practice) [22]. Hence, Danish BCG strain was the vaccine given to NBW children at the health centers if a LBW child was present, while NBW children presenting for BCG vaccination on other days received the Russian strain. Thus, the strain of vaccine given to our study population of NBW infants was coincidental, depending on a single LBW infant's presence and subsequent randomization to BCG at birth.

2.3. Outcome measures

2.3.1. Morbidity

Pentavalent (Diphtheria-Tetanus-Pertussis, Hepatitis B and *Haemophilus influenzae* type b) vaccine is officially recommended at age 6 weeks, but at the health centers the vaccine is given from age 45 days. To avoid interference from non-specific effects of the pentavalent vaccine, morbidity was assessed as health center consultations between the time of BCG vaccination and 45 days of age. The BHP registers all medical consultations at the pediatric ward of HNSM and at the three health centers in the study area.

2.3.2. Scar assessment

A subset of children participated in an early measles vaccination trial (www.clinicaltrials.gov: NCT01644721). In this trial, children aged 4½ months, residing in the study area were invited for a health check at one of the three health centers and then randomized to receive an early measles vaccine or wait until 9 months of age. At the health check-up, the BHP assistants noted if the child had a BCG scar, and if so, they measured the scar size with a transparent ruler. Scar size was defined as the average of two perpendicular diameters, as done in previous studies [17,24].

2.4. Inclusion and exclusion criteria

NBW children living within the study area were included in the present study if BCG vaccinated at one of the three health centers during the study period. Children were excluded if they had missing information on BCG batch number or were vaccinated after 45 days of age.

For the analysis of scar prevalence, all children who had their arm assessed for presence of a BCG scar at enrolment into the early measles vaccination were eligible.

2.5. Statistical analysis

Baseline characteristics according to BCG strain were compared using Chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Consultation hazard ratios were estimated in Cox proportional-hazards models using time since BCG vaccination as the underlying time scale. Children entered the analysis on the date of BCG vaccination and were followed until age 45 days, death or migration out of the study area whichever came first. Our model allowed multiple events, however, if a child was registered with several consultations on the same day (mainly due to referrals) this counted as a single event.

We adjusted the estimates for baseline imbalances; sex, season of vaccination (rainy season (June–November) vs. dry season (December–May)) and health center (Bandim, Belem, Cuntum). Furthermore, all background variables were included one by one in the Cox proportional hazards model to examine how much each variable changed the unadjusted hazard ratio, keeping variables