

Neonatal Bacille Calmette-Guerin Vaccination and Type 1 Diabetes

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Type 1 diabetes is a genetic disorder that is associated with the early development of autoimmunity against islet β -cells (1). The a priori genetically determined risk for type 1 diabetes is modified by mostly unknown environmental factors that are thought to contribute to the increasing incidences of childhood diabetes in the last decade. Changes in exposure to environment are also discussed as a potential means to reduce the incidence of type 1 diabetes. Adjuvant therapy that includes vaccinations with agents such as Bacille Calmette-Guerin (BCG), for example, have been proposed as beneficial modifiers of the immune system that can reduce the incidence of autoimmune diabetes in animal models (2). In humans, there have also been sporadic reports of preserving β -cell function when BCG vaccination is administered soon after diabetes onset (3), and it has been suggested that BCG vaccination early in childhood could reduce the incidence of type 1 diabetes. Hence, there is substantial interest in whether immunostimulation with BCG could be used as a primary, secondary, or tertiary vaccination strategy for type 1 diabetes.

RESEARCH DESIGN AND METHODS

Vaccination with BCG in the first weeks after birth was practiced in Germany until 1998. Approximately 25% of children received vaccination, which was given as a single injection. Between 1989 and 2000, we recruited newborn children of parents with type 1

diabetes living in Germany into a prospective study (4) that examined the development of islet autoimmunity and type 1 diabetes. Islet autoantibodies (antibodies to insulin, GAD, and insulinoma-associated protein 2) were measured at age 9 months and age 2, 5, 8, and 11 years. Children were prospectively monitored for the development of type 1 diabetes, which was diagnosed using World Health Organization criteria. As part of the study, pediatrician-validated vaccination records were collected for participating children. All families gave written informed consent to participate in the study, which was approved by the ethical committee of Bavaria, Germany (Bayerische Landesärztekammer Nr. 95357). A total of 1,237 newborn children were recruited between 1989 and 1998 and followed for islet autoantibodies and diabetes (Fig. 1A). Validated vaccination records were obtained in 839 of these children: 206 were vaccinated with BCG before age 3 months (median vaccination age 5 days [interquartile range 3–16]), another 10 were vaccinated after age 3 months, and 623 received no vaccination. A further 373 children were recruited after 1998 and were not vaccinated with BCG. Ninety children developed persistent islet autoantibodies (positive for at least one autoantibody on two occasions), including 55 who developed persistent multiple islet autoantibodies. Twenty-six islet autoantibody-positive children and no autoantibody-negative children developed type 1 diabetes. The cumulative fre-

quencies of islet autoantibodies and type 1 diabetes were determined using life table analysis, with follow-up calculated from birth until the age of the first positive sample or last negative sample (4). Follow-up to diabetes was calculated from birth to onset or last contact or from first antibody positivity to diabetes onset or last contact. Comparisons between BCG-vaccinated and nonvaccinated groups were performed using the log-rank test for autoantibody and diabetes development; the Mann-Whitney *U* test for total vaccination events, breast-feeding duration, autoantibody number, and titer; and Fisher's exact test for HLA genotype distribution and demographic data. Case subjects with missing vaccination data were not included in comparisons.

RESULTS— The cumulative risks for developing islet autoantibodies by age 2 or 5 years were unaffected by BCG vaccination in the first 3 months of life (Fig. 1B). Risks were 5.9% (95% CI 2.6–9.2) by age 5 years in vaccinated children and 7.1% (5.3–8.9) in nonvaccinated children for the development of any islet autoantibody ($P = 0.30$) and 4.9% (1.9–7.9) vs. 5.2% (3.7–6.7) for the development of multiple islet autoantibodies ($P = 0.91$). Although BCG vaccination did not affect autoantibody development, it modified the rate of progression to type 1 diabetes in autoantibody-positive children (Fig. 1C). The overall diabetes risk in BCG-vaccinated children was 2.5% by age 5 years compared with 1.2% in nonvaccinated children ($P = 0.28$). Progression to type 1 diabetes in BCG-vaccinated autoantibody-positive children (54% by age 5 years from antibody detection [95% CI 23–85]) was significantly faster than in nonvaccinated children (27% [13–40]; $P = 0.03$) and remained significant when the analysis was restricted to children with multiple islet autoantibodies (74 vs. 37%; $P = 0.05$). Accelerated progression to type 1 diabetes was particularly evident in children who developed islet autoantibodies by age 2 years (75% within 5 years in BCG-vaccinated [95% CI 45–99] vs. 31% in nonvaccinated [15–47] children;

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Abbreviations: BCG, Bacille Calmette-Guerin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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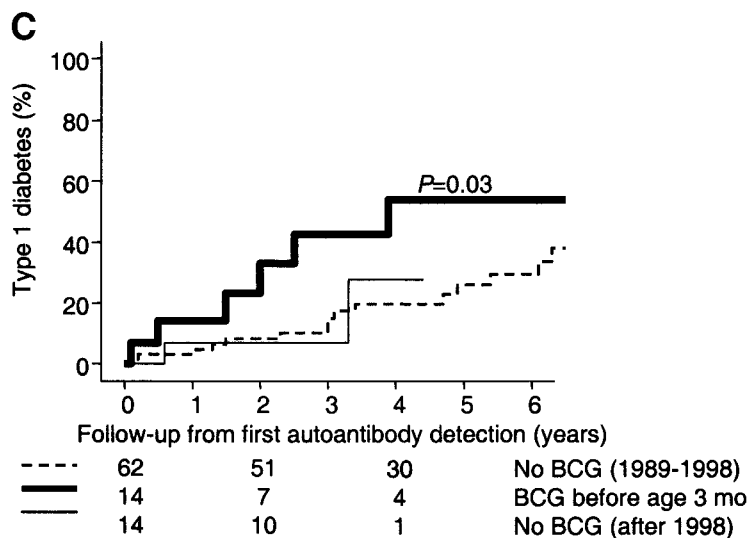
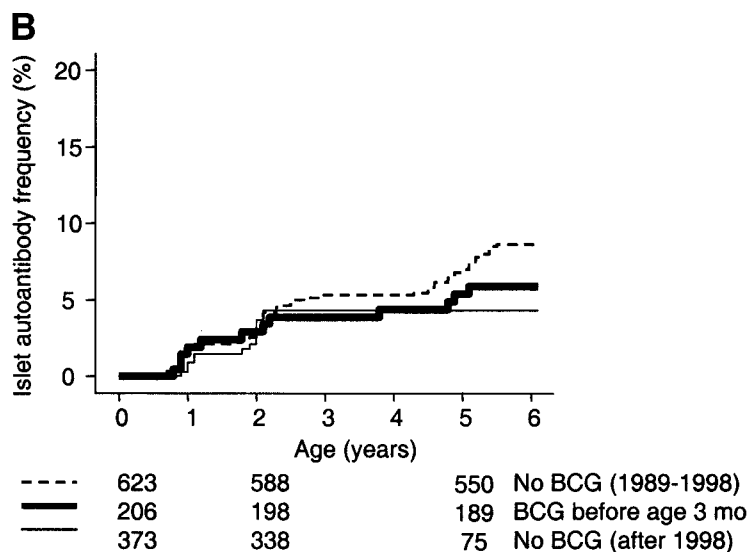
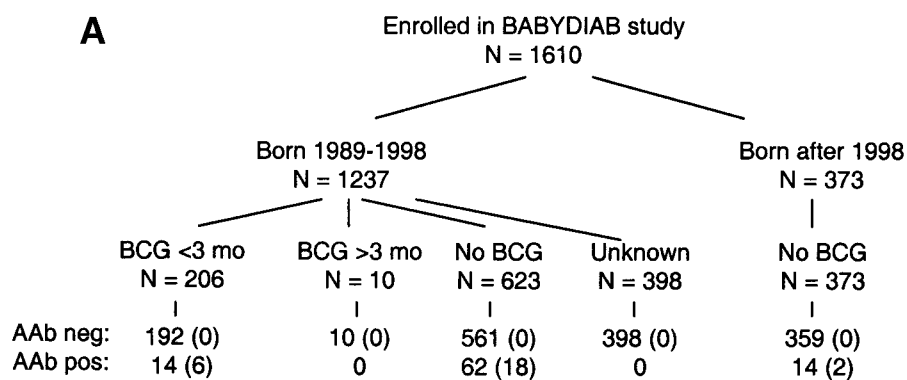


Figure 1—A. Recruitment, BCG vaccination, islet autoantibody, and type 1 diabetes status in the BABYDIAB Study cohort. The numbers of islet autoantibody–negative (AAb neg) and positive (AAb pos) children and the number of children who have developed type 1 diabetes (given in parentheses) are shown for each of the BCG vaccination subgroups. Cumulative islet autoantibody frequency (B) and progression to type 1 diabetes (C) after developing islet autoantibodies with respect to BCG vaccination status in the BABYDIAB cohort. Children are categorized as having received BCG vaccination before age 3 months (thick solid line), not receiving BCG vaccination and born between 1989 and 1998 (broken line), and no BCG vaccination and born after 1998 (thin solid line). Islet autoantibody–positive children who received BCG vaccination before age 3 months progressed to type 1 diabetes significantly faster than islet autoantibody children who were recruited during BCG vaccination years 1989–1998 but were not vaccinated ($P = 0.03$).

$P = 0.005$). Moreover, among the 26 children who developed type 1 diabetes, the age of onset was significantly younger in children who had BCG vaccination (median age 2.8 years [range 1.3–6]) than in children who were not vaccinated (me-

dian age 5 years [range 1.4–9.9]; $P = 0.04$). There were no significant differences between BCG-vaccinated and nonvaccinated autoantibody-positive children with respect to the total number of vaccination events, the reported infant feeding habits, the pro-

portion with the high-risk HLA DR3/4 or DR4/4 genotypes, islet autoantibody number or titer, and demographics (sex of child, sex of parent with type 1 diabetes, and residence: former East Germany versus former West Germany) that might confound the

observed rapid disease progression in BCG-vaccinated children (data not shown).

CONCLUSIONS— No evidence was found that BCG vaccination could prevent against β -cell-damaging processes leading to type 1 diabetes in genetically at-risk children. The findings do not suggest that BCG vaccination will affect the overall incidence of type 1 diabetes, a conclusion that is consistent with that of retrospective case-control studies in Canada and Sweden (5,6). Unlike previous studies, we were able to study disease progression rates. Although numbers progressing to diabetes are small, our study suggests that neonatal BCG vaccination may accelerate progression from autoimmunity to diabetes. BCG vaccination has relatively strong immunostimulatory effects, as evidenced by inflammation and

enlargement of lymph nodes around the site of injection, which could explain a possible disease acceleration. Our findings do not support the use of the immunostimulatory effects of neonatal BCG vaccination to prevent type 1 diabetes.

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