Title

BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies.

Journal

Journal of Allergy and Clinical Immunology, 133(4)

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Publication Date

2014-04-01

DOI

10.1016/j.jaci.2014.02.028

Peer reviewed

Published in final edited form as:
J Allergy Clin Immunol. 2014 April ; 133(4): 1134–1141. doi:10.1016/j.jaci.2014.02.028.

BCG vaccination in SCID patients: complications, risks and vaccination policies

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Abstract

Background—SCID is a syndrome characterized by profound T cell deficiency. BCG vaccine is contraindicated in SCID patients. Because most countries encourage BCG vaccination at birth, a high percent of SCID patients are vaccinated before their immune defect is detected.

Objectives—To describe the complications and risks associated with BCG vaccination in SCID patients.

Methods—An extensive standardized questionnaire evaluating complications, therapeutics, and outcome regarding BCG in patients diagnosed with SCID was widely distributed. Summary statistics and association analysis was performed.

Results—Data on 349 BCG vaccinated SCID patients from 28 centers in 17 countries was analyzed. Fifty-one percent of the patients developed BCG complications, 34% disseminated and 17% localized (a 33,000 and 400 fold increase, respectively, over the general population). Patients receiving early vaccination (≤ 1 month) showed an increased prevalence of complications ($p=0.006$) and death due to BCG complications ($p<0.0001$). The odds of experiencing complications among patients with T cells ≤ 250/uL at diagnosis was 2.1 times higher (95% CI, 1.4-3.4; $p = 0.001$) than among those with T cells > 250/uL. BCG complications were reported in 2/78 patients who received anti-mycobacterial therapy while asymptomatic and no deaths due to BCG complications occurred in this group. In contrast 46 BCG-associated deaths were reported among 160 patients treated with anti-mycobacterial therapy for a symptomatic BCG infection ($p<0.0001$).

Conclusions—BCG vaccine has a very high rate of complications in SCID patients, which increase morbidity and mortality rates. Until safer and more efficient anti-tuberculosis vaccines become available, delay in BCG vaccination should be considered to protect highly vulnerable populations from preventable complications.

Keywords

primary immunodeficiency; SCID; vaccine; BCG; mycobacteria; new born screening; hematopoietic stem cell transplant; immune reconstitution syndrome

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The authors have no conflicts of interest to declare.

Introduction

Tuberculosis is a major global health problem. In 1993 the WHO declared the disease a global public health emergency and in 2011 one third of the world's population was thought to be infected with *Mycobacterium tuberculosis* with almost 9 million new cases diagnosed and 1.4 million deaths attributed to this organism. In recent years, most technologically advanced countries have managed to control— although not eradicate—tuberculosis. With over 4 billion doses applied, the live-attenuated *M. bovis* bacille Calmette – Guérin (BCG) vaccine has been a part of efforts to control tuberculosis and worldwide remains one of the most widely used of all current vaccines. Since the 1960s it has been given routinely in the majority of countries and currently approximately 120 million people -mostly newborns- are vaccinated every year through national childhood immunization programs. The BCG vaccine has a documented protective effect against meningitis and disseminated TB in children, however it does not prevent primary infection and, more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community. The impact of BCG vaccination on transmission of *M. tuberculosis* is therefore limited (reviewed in[1], and Global Tuberculosis Report, 2012, WHO, http://www.who.int/tb/publications/global_report/gtbr12_main.pdf).

Despite its long history and extensive use, there appears to be no other vaccine as controversial as BCG and its history contains aspects of folklore and superstition that often supersede facts in public health discussions and policy[1-3]

Severe combined immunodeficiency disease (SCID) includes a heterogeneous group of genetic conditions characterized by profound deficiencies of T (and in some types, B and/or NK cell) numbers and function. If untreated, infants with typical SCID succumb early in life from severe and recurrent infections. Mutations in different genes affecting cytokine signaling (e.g., *IL2RG*, and *IL7RA*), antigen receptor processing (e.g., *RAG1*, *RAG2*, and *CD3δ*) or nucleotide processing (e.g., adenosine deaminase –*ADA*-) cause this fatal childhood condition, unless immune reconstitution can be accomplished[4]. However, it should be noted that individuals with severe manifestations of other syndromic conditions may have clinical signs and symptoms consistent with SCID[5]. BCG, as other live-attenuated vaccines, is absolutely contraindicated in SCID patients (reviewed in[1,6], and Global Tuberculosis Report, 2012, World Health Organization, http://www.who.int/tb/publications/global_report/gtbr12_main.pdf). However, because it is usually administered at birth, SCID patients in most countries using BCG are vaccinated before their immune deficiency is diagnosed.

The aim of this study was to describe the complications and risks associated with BCG vaccination in patients diagnosed with SCID, the most severe form of primary immunodeficiency diseases.

Methods

An extensive standardized questionnaire evaluating diagnostic, therapeutic, and outcome concerning BCG–vaccinated SCID patients was developed by an *ad-hoc* scientific interest

group (i.e., “BCG infection in SCID patients interest group”; NR, GD, BN and SDR) (Supplemental material S1). The questionnaire was widely distributed to primary immunodeficiency patient-caregivers through professional organizations (ESID, LASID and CIS), patient advocate groups (JMF) and individually to other colleagues by members of the scientific interest group. All data for this retrospective study represented a 10-year cumulative experience for each reporting institution and was collected between April 2010 and March 2012.

Statistical analysis

Data relevant to: a) SCID diagnosis, treatment, immune-reconstitution and outcome; as well as b) BCG vaccination, and c) BCG complications diagnosis, treatment and outcome, was analyzed. For the purposes of this multicenter international retrospective study, we analyzed patients diagnosed with SCID at the participating centers based on the clinical and laboratory findings of recurrent/severe infections and/or failure to thrive, severe T cell lymphopenia (in the absence of a condition consistent with Omenn syndrome or maternal engrafment) and/or severe functional T cell defects. BCG complications were defined by clinical, microbiological and/or histopathology findings and were classified as localized (persistent lesions -ulcer, abscess, fistula, or lymphadenopathy- limited to the region of inoculation) or disseminated (evidence of infection distal to injection-site lesions, including positive blood or bone marrow cultures)[7]. Data entered by the referring centers detailing pathological manifestations that were attributed to an excessive and/or dysregulated immune response to BCG as a consequence of improvement in their immune status were diagnosed with immune reconstitution syndrome (IRS)[8]. Deaths due to BCG complications as well as all-cause mortality were analyzed as outcome variables. BCG-related deaths were defined as cases where the primary cause of death was strongly associated with BCG complications, as determined by the clinical care team. Continuous variables were compared using the Kruskal-Wallis test. Fisher's exact test was used to compare proportions. Logistic regression was used to evaluate the effects of covariates on a binary outcome variable. Kaplan-Meier curves were plotted and compared using the log-rank test. Cox regression was used to evaluate the effects of covariates in a time-to-event analysis. All P values are 2-sided, and P values of less than 0.05 were considered to be statistically significant. Data analyses were performed with SAS version 9.3 (SAS Institute Inc, Cary, NC).

As with any retrospective observational study of this nature, there are limitations that should be considered when interpreting the results. We acknowledge the possibility of diagnostic criteria discrepancies among the participating centers. Our analysis only included children who received BCG vaccinations, and these children may not be representative of the entire SCID population. Due to the limitation of data collection, we used the mid-point of the reported time interval of BCG vaccination and HSCT in the time-to-event analysis. we acknowledge the possibility of diagnostic criteria discrepancies among the participating centers. Additional variability and bias may be introduced by this ad-hoc method.

Results

Population demographics

A total of 821 patients were diagnosed with SCID in the 28 participating centers from 17 different countries, 349 of whom were BCG vaccinated (42%) and analyzed in this retrospective study (Table 1). When the analysis was restricted to countries with mandatory at birth BCG vaccination policies, the rate of BCG vaccinated SCID patients rose to 88%.

SCID diagnosis

SCID diagnosis was established in 9% of the patients before the age of 1 month, in 29% before 3 months, in 63% before 6 months, and in 90% before 1 year (Figure 1A). The specific type of SCID diagnosis was determined in 159 patients (46%), while not defined in the remainder of the cohort. Deficiency of IL2RG was the most frequently reported, followed by defects in RAG1/RAG2, ADA, MHC-II, IL7RA, Artemis, JAK3, PNP, ZAP-70, and Cernunnos. We cannot formally exclude that among the patients with no specific SCID type defined, some could have been affected by other known PIDDs presenting with a SCID-like phenotype of severe T cell lymphopenia and/or severe functional T cell defects, and increased susceptibility to mycobacterial diseases (e.g., Mendelian susceptibility to mycobacterial disease-associated genetic defects).

BCG vaccination

Age at vaccination was determined in 345 (of 349) SCID patients. The majority (258/345; 75%) were vaccinated within the first month of life (< 1 week: 204 patients; 1-2 weeks: 6; 3-4 weeks: 48); while the remainder (87/345) were vaccinated later (1-3 months: 74; 4-6 months: 8; 7-12 months: 3; and >12 months: 2). BCG vaccine was administrated on the deltoid area in all patients: 301 intradermally, 38 subcutaneously, and 10 not determined. The vaccine strain was reported in 252 individuals: Danish: 88; Moreau: 66; Pasteur: 32, Glaxo: 29; Tokyo: 19; and Russia: 18.

BCG complications (Figure 1B-F)

After BCG vaccination, 177 SCID patients (51%) developed complications: 59 localized (17%) and 118 disseminated (34%), a 400 and 33,000 fold increase, respectively, over the general population. Age at onset of BCG complications was determined in 158 patients: <1 month in 8 patients; 1-3 months in 33; 4-6 months in 67; 7-12 months in 34; and >12 months in 16 patients. Among patients presenting disseminated complications, involvement of extra-regional lymph nodes (n=67, 57%), skin (n=66, 56%) or lungs (n=55, 47%) was the most common clinical presentation; BCG infections compromising the liver (n=18, 15%), spleen and bones (n=15, 13% each) were reported less frequently. Isolation of *M. bovis* BCG from bone marrow was described in 14% (n=17) of disseminated patients, while positive blood cultures were even more uncommon (n=1, 1% of disseminated patients).

The median absolute T cell number at the time of SCID diagnosis in patients with localized or disseminated BCG complications was significantly lower than that in patients without BCG complications (p=0.003) (Table 2). Logistic regression analysis showed that the odds of experiencing BCG complications among SCID patients with T cells ≤ 250/uL at diagnosis

was 2.1 times higher (95% CI, 1.4-3.4; p = 0.001) than that among those with T cells > 250/uL, and the difference remained significant after adjusting for the age at BCG vaccination. Patients with and without BCG complications were not significantly different in either B cell or NK cell numbers.

Two hundred thirty-eight patients (68%) received anti-mycobacterial treatment after being diagnosed with SCID. At the time of treatment initiation 78 (22%) were asymptomatic in terms of BCG complications while 160 (46%) were symptomatic (53 with localized and 107 with disseminated manifestations).

Among asymptomatic anti-mycobacterial treated patients who underwent HSCT (n=64), 49 (77%) received MAT, while 10 (16%) were treated with INH monotherapy (no information on 5 patients). MAT included INH+RP- based treatment in 49 patients (77%), 18 of them (28%) having one or more additional drugs. The enteral route was preferred in 94% of these patients. No significant differences between monotherapy and MAT were detected when death due to BCG complications was compared (p=0.99). By the time of data analysis, 63% of these patients were alive (median follow up, 57 months; range 4-126). Among symptomatic patients receiving antimycobacterial treatment and undergoing HSCT (n=76), 64 (82%) were treated with MAT, while 4 (5%) were treated with INH monotherapy (no information on 8 patients). MAT included INH+RP-based treatment in 61 patients (80%), 47 of them (62%) getting one or more drugs added to the scheme. Eighty-four percent of these patients were treated through the enteral route and 11% using a mixed (enteral and parenteral) route. By the time of data analysis 70% of these patients were alive (median follow up, 45 months; range, 0-158)

BCG-associated complications were reported in 3% (2/64) of asymptomatic patients receiving anti-mycobacterial treatment and undergoing HSCT. Anti-mycobacterial treatment of already symptomatic patients undergoing HSCT resulted in complete clinical resolution of the infection in 30%, partial resolution in 46% and no resolution in 24%. After HSCT, 59% of the patients were kept on anti-mycobacterial treatment: 32% for less than 3m, 15% for 4-6m, 21% for 7-12m and 32% for more than a year.

No deaths related to BCG complications were reported among BCG-asymptomatic treated SCID patients, while 46 deaths due to BCG occurred among BCG-symptomatic treated patients (7 in patients who underwent HSCT, 39 in patients who did not; 45 patients with disseminated complications and 1 patient with localized disease) (p<0.0001). The median age of death for these patients (38 with reported data) was 6.8 months. When the analysis was restricted to patients undergoing HSCT, no deaths were reported among the asymptomatic treated group (0/64) and 7 deaths occurred among the 120 symptomatic treated patients (p=0.09).

One hundred and eleven BCG-vaccinated SCID patients (32%; 96 of them presenting with no manifestations, and 15 symptomatic included 9 with disseminated and 6 with localized complications) did not receive anti-mycobacterial treatment after SCID diagnosis. Forty-five of these patients (40%) underwent HSCT (32 asymptomatic and 13 symptomatic 8 with disseminated and 5 with localized complications), 15 of them received anti-mycobacterial

treatment post-HSCT (3 asymptomatic, 8 with disseminated and 4 with localized manifestations), 28 of them (63%) are alive and no deaths due to BCG complications were reported (median follow up, 46 months; range, 0-187). Of the remaining 66 patients (60%, 64 were asymptomatic and 2 were symptomatic, 1 disseminated and 1 localized) who did not undergo HSCT by the time of data analysis, 22 (33%) were alive and only 1 BCG-related death was reported in this group (presenting with disseminated disease). Interestingly, survival rates for patients who did not get pre-HSCT anti-mycobacterial treatment (27/45) was not statistically different from patients who received anti-mycobacterial treatment and underwent HSCT (94/139) (p=0.47).

Age at BCG vaccination showed a significant association with BCG complications independently of the type of SCID, the vaccine strain or the route of vaccination. Patients vaccinated within the first month of life showed an increased prevalence of BCG complications (disseminated or localized) compared to patients vaccinated after 1 month of age (p=0.006). Moreover, the odds of developing BCG complications among those vaccinated within the first month of life were 2.03 times higher than those vaccinated after the age of 1 month (OR=2.03; 95% CI, 1.24-3.35). A log-rank test comparing time to death due to BCG complications in patients vaccinated within or after 1 month of age also identified significant differences between these two groups (p<0.0001) (Figure2). Moreover, survival analysis comparing time to death within 24 months of age before HSCT for patients vaccinated early vs. late showed that the hazard of death was 2.12 times higher for those getting early vaccination (95% CI, 1.12-3.89) (Figure 2). These results strongly suggested that early BCG vaccination (≤1 month) is associated with increased BCG complications and subsequent death associated with those complications.

SCID treatment

Out of the 349 BCG-vaccinated SCID patients, 190 (54%) underwent HSCT (n=184) or other form of SCID-specific treatment (e.g., gene therapy [n=3], enzyme replacement [n=2], or thymus transplant [n=1]). The median age at HSCT was 7.5 months (range: 0.5- 107). No significant differences in T cell engraftment were detected between patients getting early (≤1 month) vs. late (>1 month) BCG vaccination, or among patients transplanted without or with BCG complications (localized or disseminated). No significant differences in the proportion of death due to BCG complications were detected either among patients getting matched related, matched unrelated, mismatched related, or mismatched unrelated forms of HSCT (p=0.97). However, death due to BCG complications was still more frequent among patients getting early vaccination compared to those vaccinated later (p=0.049). Death due to BCG complications was also significantly more frequent among patients undergoing HSCT with localized or disseminated BCG complications vs. those with no manifestations (p=0.006). When all-cause mortality was compared among HSCT patients, no significant difference was detected between patients getting early vs. late BCG vaccination (p=0.96), implying that after HSCT the age at BCG vaccination has no significant impact on survival rates (Figure 2). Finally, although we did not find significant differences in post-HSCT survival between early (≤3 months) and late (>3months) HSCT (p=0.33), the difference between these two groups within the first 12 months after transplant was statistically significant (p=0.01) (Figure 2).

Out of 190 patients who underwent HSCT or other form of SCID treatment, 55 (29%) developed Immune reconstitution syndrome (IRS) (33 with disseminated disease, 14 with localized complications and 8 with no manifestations). Most patients (57%) presented these manifestations within a month of HSCT. IRS prevalence was also analyzed in different subsets of patients: those receiving anti-mycobacterial treatment while BCG-asymptomatic had significantly less of this complication (5/64) compared to either BCG-symptomatic anti-mycobacterial-treated patients (33/81, $p<0.0001$) or non-treated patients (17/45, $p=0.0003$).

Discussion

Prevalence of BCG complications in the general population can vary widely depending on the reporting country and the vaccine strain utilized. However, reports of 1 in 2,500 vaccinees presenting with localized BCG complications and 1 in 100,000 developing disseminated complications represent a fair estimate of the prevalence of such complications[19]. When focused exclusively on patients diagnosed with SCID, the prevalence of BCG complications has been estimated to be higher than in the general population[10-12], although definitive impact has not previously been established.

The cumulative experience of 28 centers in 17 countries from Africa, the Americas, Asia, and Europe confirms that as expected BCG complications are more prevalent in SCID patients than in the general population. Based on our observations, one in every two BCG-vaccinated SCID patients developed BCG-associated manifestations, two-thirds in the form of disseminated complications (an approximate 33,000 fold increased compared to the general population) and the other one-third in the form of localized complications (an approximate 400 fold increase). Our analysis found two individual variables to significantly correlate with this increased prevalence of BCG complications: the total number of T cells at the time of SCID diagnosis, and the patient's age at BCG vaccination. While SCID patients presenting with higher T cell numbers were underrepresented among those developing BCG complications, these results should be cautiously interpreted. Maternal T cell engraftment was not systematically evaluated in most of the patients surveyed and patients presenting with Omenn syndrome and oligoclonal T cell expansion were not excluded from the analysis. Furthermore, detailed information on T cell functional studies were not part of the original survey and analysis. On the other hand, age at BCG vaccination appeared as a strong predictor for developing BCG complications, with patients vaccinated within the first month of life having a substantially higher risk, which in turn was also associated with an increased rate of death due to vaccine-associated complications. Age at BCG vaccination was independent of other variables including the BCG strain, the vaccination route or the type of SCID diagnosed. Less clear than the association between age of vaccination and complications, are the mechanism(s) underlying this finding. All SCID patients, independent of their underlying genetic defect, share a defective adaptive immune response. Therefore, relative maturity of the innate immune arm involved with controlling mycobacterial infections could by hypothesized as a factor altering the balance towards controlling or not controlling BCG[1314]. As relevant as determining the biological mechanism to explain this variability, is developing a strategy to intervene and improve the clinical outcome.

BCG vaccine has a worldwide coverage of 88% (http://apps.who.int/immunization_monitoring/en/globalsummary/GS_GLOProfile.pdf?CFID=6942726&CFTOKEN=73185195) and most of these vaccines are applied at birth (http://www.bcgatlas.org/). Similar to other large SCID series published[15,16], the majority of patients in our cohort (63%) were diagnosed with SCID within the first 6 months of life. Until safer and more efficient forms of anti-tuberculosis vaccines become available[17], delaying BCG vaccination beyond one month of age is likely to have a favorable impact in this highly vulnerable population, as well as other susceptible neonates (e.g., HIV positive infants)[18]. Moreover, delaying BCG vaccination would also benefit the clinical impact of neonatal SCID screening, preventing application of an absolutely contraindicated vaccine prior to establishing the diagnosis of SCID. This issue will become increasingly relevant as countries still encouraging early BCG vaccination start implementing neonatal SCID screening[19,20]. However, two major drawbacks could be foreseen in delaying BCG vaccination: the “missed opportunity” of vaccinating patients after birth based on the concept that there will be an associated decline in coverage, and the very low potential increased risk of BCG-preventable diseases during the “unprotected” intervals. WHO data (updated to July 12, 2012) demonstrated a BCG coverage of 89.2% for countries encouraging at birth vaccination policies, values that are very similar to the 89% coverage in the same countries for administration of the third dose of DPT (DPT3) typically given at 6 months of age. (http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tscoveragedtp3.htm). These data suggest there would be little or no decrease in coverage by delaying BCG vaccination. In addition, incidence of BCG-preventable mycobacterial diseases within the first 6 months of age is extremely uncommon. Literature on pediatric tuberculous meningitis, a BCG-preventable disease, shows that the mean age of presentation for this life threatening disease is 23-49 months, although a few cases have been described during the first 6 months of life while the medians span from 12-24 months of age[21-26]. The prospect of modifying BCG vaccination policies will certainly warrant extensive discussions balancing the needs of both the immunocompetent general population as well as the highly vulnerable immunodeficient patients.

As expected, the major intervention impacting survival in this cohort of BCG vaccinated SCID patients was providing immunologic reconstitution by HSCT. Interestingly, a subset of patients who did not receive any anti-mycobacterial treatment but underwent HSCT did not develop any BCG-associated complications or IRS (27/190). This outcome may suggest that HSCT by itself may suffice as an anti-BCG treatment, however other variables could have potentially influenced these results, including vaccine viability[27], SCID genotype (13 undefined SCIDs, 7 MHC II, 2 IL2RG, 1 JAK3, 1 Artemis, 1 PNP, 1 IL7RA and 1 Cernunnos; median T cells=250/uL, median age at HSCT=7 months), higher maturity of innate immunity, residual acquired immunity, or other unidentified disease modifiers.

We did observe that SCID patients started on anti-mycobacterial therapy while asymptomatic had significantly less BCG complications before HSCT, as well as less IRS after HSCT and decreased mortality due to BCG complications. The rationale for this approach is to control an infection involving the known inoculation of 37,500 to 3,200,000 live microorganisms in a susceptible host[28]. However, we recognize that our data does not provide definitive proof of benefit for pre-emptive anti-mycobacterial therapy because of

confounding factors associated with this type of retrospective study. Still, in the setting of commonly utilized prophylactic therapy in SCID (e.g., immunoglobulin replacement and antimicrobials), it seems entirely appropriate to consider early initiation of anti-mycobacterial therapy at SCID diagnosis. If this strategy is chosen, it is less clear as to which anti-mycobacterial scheme would be most effective.

In summary, our data strongly suggest that in SCID patients, early BCG vaccination and lower numbers of T cells at SCID diagnosis increase the probability of developing BCG complications. Furthermore, SCID patients presenting with BCG complications are at increased risk of dying due to this. Finally, the age at BCG vaccination had no significant influence on survival rates in SCID patients who received HSCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acknowledgments

We would like to thank all the patients, their families and the medical teams who took and take care of our patients; VT thanks the European Community's Seventh Framework Program FP7/2007-2013 under grant agreement no. 201549 (EUROPADnet HEALTH-F2-2008-201549) who supported his participation in this study. We also thank the IT Department of the Hospital Garrahan in Buenos Aires, Argentina, for generating a web site for the survey, and Dr. Klaus Warnatz for his help and support with the logistics of the survey.

Funding: This research was supported by the Intramural Research Program of the NIH, National Institute of Allergy and Infectious Disease.

Abbreviations

BCG	bacille Calmette – Guérin
CIS	Clinical Immunology Society

DPT	diphtheria-pertussis-tetanus vaccine
ESID	European Society for Immunodeficiencies
HSCT	hematopietic stem cell transplantation
INH	isoniazid
IRS	immune-reconstitution syndrome
JMF	Jeffrey Modell Foundation
LASID	Latin American Society for Immunodeficiencies
MAT	multidrug antimycobacterial therapy
RP	rifampicin
SCID	severe combined immunodeficiency
WHO	World Health Organization

References

1. Plotkin, SA.; Orenstein, WA.; Offit, PA. Vaccines. 6th ed.. Elsevier/Saunders; Edinburgh: 2013.
2. Comstock GW. The International Tuberculosis Campaign: a pioneering venture in mass vaccination and research. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Sep; 1994 19(3):528–540. [PubMed: 7811874]
3. Fine PE. Bacille Calmette-Guerin vaccines: a rough guide. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Jan; 1995 20(1):11–14. [PubMed: 7727635]
4. Buckley RH. Transplantation of hematopoietic stem cells in human severe combined immunodeficiency: longterm outcomes. Immunologic research. Apr; 2011 49(1-3):25–43. [PubMed: 21116871]
5. Al-Herz W, Bousfiha A, Casanova JL, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Frontiers in immunology. 2011; 2:54. [PubMed: 22566844]
6. General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control. Jan 28; 2011 60(2):1–64.
7. Talbot EA, Perkins MD, Silva SF, Frothingham R. Disseminated bacille Calmette-Guerin disease after vaccination: case report and review. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Jun; 1997 24(6):1139–1146. [PubMed: 9195072]
8. Gantzer A, Neven B, Picard C, et al. Severe cutaneous bacillus Calmette- Guerin infection in immunocompromised children: the relevance of skin biopsy. Journal of cutaneous pathology. Jan; 2013 40(1):30–37. [PubMed: 23157280]
9. Lotte A, Wasz-Hockert O, Poisson N, et al. Second IUATLD study on complications induced by intradermal BCG-vaccination. Bulletin of the International Union against Tuberculosis and Lung Disease. Jun; 1988 63(2):47–59. [PubMed: 3066422]
10. Romanus V, Fasth A, Tordai P, Wiholm BE. Adverse reactions in healthy and immunocompromised children under six years of age vaccinated with the Danish BCG vaccine, strain Copenhagen 1331: implications for the vaccination policy in Sweden. Acta Paediatr. Dec; 1993 82(12):1043–1052. [PubMed: 8155923]

11. Gonzalez B, Moreno S, Burdach R, et al. Clinical presentation of Bacillus Calmette-Guerin infections in patients with immunodeficiency syndromes. The Pediatric infectious disease journal. Apr; 1989 8(4):201–206. [PubMed: 2654859]
12. Yao CM, Han XH, Zhang YD, et al. Clinical characteristics and genetic profiles of 44 patients with severe combined immunodeficiency (SCID): report from Shanghai, China (2004-2011). Journal of clinical immunology. Apr; 2013 33(3):526–539. [PubMed: 23250629]
13. Sharma AA, Jen R, Butler A, Lavoie PM. The developing human preterm neonatal immune system: a case for more research in this area. Clin Immunol. Oct; 2012 145(1):61–68. [PubMed: 22926079]
14. Satwani P, Morris E, van de Ven C, Cairo MS. Dysregulation of expression of immunoregulatory and cytokine genes and its association with the immaturity in neonatal phagocytic and cellular immunity. Biology of the neonate. 2005; 88(3):214–227. [PubMed: 16210844]
15. Buckley RH, Schiff RI, Schiff SE, et al. Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. The Journal of pediatrics. Mar; 1997 130(3):378–387. [PubMed: 9063412]
16. Gennery AR, Slatter MA, Grandin L, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? The Journal of allergy and clinical immunology. Sep; 2010 126(3):602–610. e601–611. [PubMed: 20673987]
17. Parida SK, Kaufmann SH. Novel tuberculosis vaccines on the horizon. Current opinion in immunology. Jun; 2010 22(3):374–384. [PubMed: 20471231]
18. Koppel A, Leonardo-Guerrero J, Rives S, Paniagua-Torres N, Sparrow C, Beck-Sague CM. Immune reconstitution inflammatory syndrome due to Mycobacterium bovis Bacillus Calmette-Guerin in infants receiving highly active antiretroviral therapy: a call for universal perinatal rapid HIV testing prior to administration of BCG immunization of neonates. Journal of tropical pediatrics. Aug; 2010 56(4):280–283. [PubMed: 19952057]
19. Chien, Y-H.; Chiang, S-C.; Chang, K-L., et al. Incidence of severe combined immunodeficiency through newborn screening in a Chinese population.. Journal of the Formosan Medical Association. http://dx.doi.org/10.1016/j.jfma.2012.10.020. In press
20. Kanegae MPP, dos Santos AMN, Cavalcanti CM, Condino Neto A. Newborn screening for severe combined immunodeficiency. Revista Brasileira de Alergia e imunopatologia. Jan-Feb;2011 34(1): 1–7.
21. van Well GT, Paes BF, Terwee CB, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of South Africa. Pediatrics. 2009; 123(1):e1–8. [PubMed: 19367678]
22. Lee LV. Neurotuberculosis among Filipino children: an 11 years experience at the Philippine Children's Medical Center. Brain & development. Dec; 2000 22(8):469–474. [PubMed: 11111059]
23. Farinha NJ, Razali KA, Holzel H, Morgan G, Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. The Journal of infection. Jul; 2000 41(1):61–68. [PubMed: 10942642]
24. Yaramis A, Gurkan F, Elevli M, et al. Central nervous system tuberculosis in children: a review of 214 cases. Pediatrics. Nov.1998 102(5):E49. [PubMed: 9794979]
25. Doerr CA, Starke JR, Ong LT. Clinical and public health aspects of tuberculous meningitis in children. The Journal of pediatrics. Jul; 1995 127(1):27–33. [PubMed: 7608807]
26. Paganini H, Gonzalez F, Santander C, Casimir L, Berberian G, Rosanova MT. Tuberculous meningitis in children: clinical features and outcome in 40 cases. Scandinavian journal of infectious diseases. 2000; 32(1):41–45. [PubMed: 10716076]
27. Ho MM, Markey K, Rigsby P, et al. Report of an international collaborative study to establish the suitability of using modified ATP assay for viable count of BCG vaccine. Vaccine. Aug 26; 2008 26(36):4754–4757. [PubMed: 18586063]
28. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. B World Health Organ. 1990; 68(1):93–108.

Capsule summary

BCG immunization beyond 1 month of age diminishes vaccine-associated morbidity and mortality in patients diagnosed with SCID.

Clinical implications

Delaying BCG vaccination until after one month of age should diminish BCG-related complications in SCID patients and should not adversely impact BCG-preventable disease.

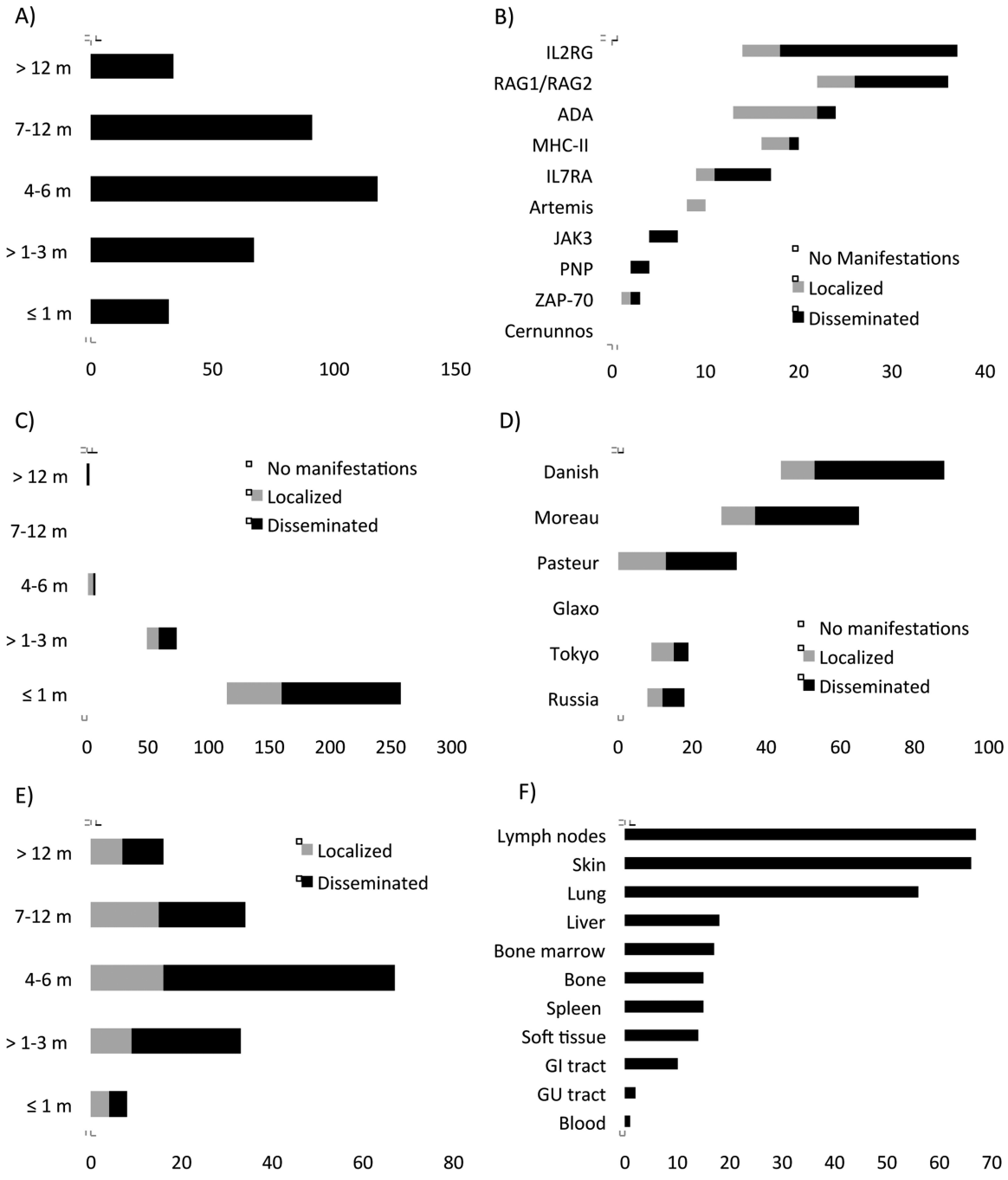

Figure 1.

BCG-vaccinated SCID patients, epidemiologic characteristics A) Age at SCID diagnosis; B) SCID diagnosis and BCG complications (No manifestations, Localized, Disseminated); C) Age at BCG vaccination and BCG complications (No manifestations, Localized, Disseminated) distribution; D) BCG vaccine strain and BCG complications (No manifestations, Localized, Disseminated); E) Age at onset of BCG complications (Localized, Disseminated); F) Site of involvement of Disseminated BCG complications. X axis, number of patients.

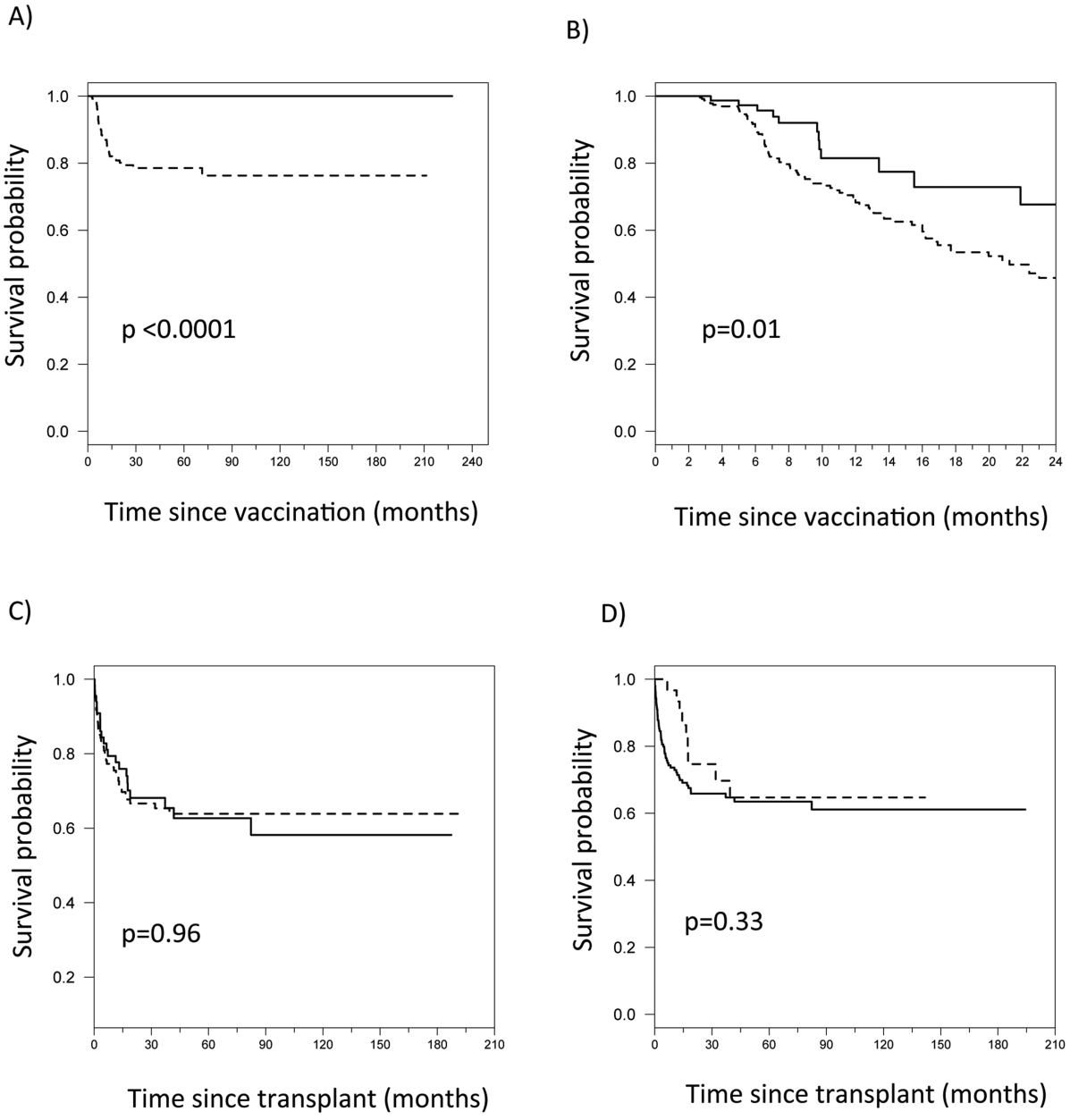

Figure 2.

Time-to-event analysis by age at BCG vaccination and age at HSCT. A) Kaplan-Meier curves for the time from vaccination to death due to BCG complications comparing early (≤ 1 month of age, dashed line) vs. late (> 1 month of age, solid line) vaccination ($p<0.0001$). B) Kaplan-Meier curves for the time from vaccination to death within 24 months of age before HSCT comparing early (≤ 1 month of age, dashed line) vs. late (>1 month of age, solid line) vaccination ($p=0.01$). C) Kaplan-Meier curves for the time from HSCT to death comparing early (≤ 1 month of age, dashed line) vs. late (> 1 month of age, solid line) vaccination ($p=0.96$). D) Kaplan-Meier curves for the time from HSCT to death comparing

early (≤ 3 months of age, dashed line) vs. late (> 3 months of age, solid line) transplant (p=0.33).

Table 1

BCG-vaccinated SCID patients, 523 distribution and HSCT

Country (centers)[1]	Universal BCG vaccination at birth[2]	BCG SCID pts. (n=349)	HSCT[3] (n=190)
Argentina (3)	Yes	10	6
Brazil (3)	Yes	58	24
Colombia (1)	Yes	6	1
Costa Rica (1)	Yes	10	6
Czech Republic (1)[4]	Yes	15	8
Egypt (1)	Yes	26	1
France (1)	No	44	44
Iran (1)	Yes	31	0
Japan (4)	No	6	6
Kuwait (1)	No	10	4
Mexico (2)	Yes	14	5
Oman (1)	Yes	4	2
Poland (1)	Yes	8	5
Portugal (1)	Yes	5	5
Russia (1)	Yes	8	0
Turkey (3)	No	40	27
United Kingdom (2)	No	54	46

[1] A total of 821 SCID patients were diagnosed in these centers, including 349 who were BCG vaccinated and reported for the current study

[2] For recent changes or individualized BCG vaccination policies in different countries, please refer to http://www.bcgatlas.org/

[3] HSCT, hematopoietic stem cell transplantation; other forms of SCID treatment (e.g., gene therapy -3 patients-, enzyme replacement -2 patients-, or -thymus transplant -1 patient-) are also included in this category.

[4] National Center Database of Primary Immunodeficiencies, which collects data from 13 centers in the Czech Republic.

Table 2

BCG-vaccinated SCID, statistical analysis

Age at BCG vaccination			
	BCG Vaccination ≤ 1 month	**BCG Vaccination > 1 month**	**P-value**
Gender, n (%)			
Female	88 (34.8)	40 (46))	NS
Male	165 (65.2)	47 (54	
Age at SCID Dx, Median (range)	5 months (0.5-48)	6 months (0.5-100)	NS
BCG Complications, n (%)			
No Manifestations	115 (44.57 %)	54 (62.07%)	0.006
Loc/Diss Manifest.	143 (55.43 %)	33 (37.93 %)	
Age at HSCT, Median (range)	7 months (0.5-75)	8 months (0.5-107)	NS
Mortality in BCG-SCID			
BCG-rel., n (%)	45 (18)	0 (0)	<0.0001
Overall, n (%)	132 (52.8)	38 (43.7)	NS

Median lymphocytes at SCID diagnosis			
	No Manifestations	**Localized or Disseminated**	
T cells/uL (pc 25-75)	197 (14-942)	49 (5-343)	0.003
B cells/uL (pc 25-75)	103 (5-640)	140 (11-710)	NS
NK cells/uL (pc 25-75)	160 (38-410)	100 (19-366)	NS

No manifestations, no manifestations of BCG complications; Loc/Diss Manifest, localized or disseminated manifestations of BCG complications; BCG-rel. mortality, death related to BCG complications; pc, percentile; NS, not significant.