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

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Background: Severe combined immunodeficiency (SCID) is a syndrome characterized by profound T-cell deficiency. BCG vaccine is contraindicated in patients with SCID. Because most countries encourage BCG vaccination at birth, a high percentage of patients with SCID are vaccinated before their immune defect is detected.

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Objectives: We sought to describe the complications and risks associated with BCG vaccination in patients with SCID.
Methods: An extensive standardized questionnaire evaluating complications, therapeutics, and outcomes regarding BCG vaccination in patients given a diagnosis of SCID was widely distributed. Summary statistics and association analysis was performed.
Results: Data on 349 BCG-vaccinated patients with SCID from 28 centers in 17 countries were analyzed. Fifty-one percent of the patients had BCG-associated 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 ($P = .006$) and death caused by BCG-associated complications ($P < .0001$). The odds of experiencing complications among patients with T-cell numbers of 250/μL or less at diagnosis was 2.1 times higher (95% CI, 1.4-3.4 times higher; $P = .001$) than among those with T-cell numbers of greater than 250/μL. BCG-associated complications were reported in 2 of 78 patients who received antimycobacterial therapy while asymptomatic, and no deaths caused by BCG-associated complications occurred in this group. In contrast, 46 BCG-associated deaths were reported among 160 patients treated with antimycobacterial therapy for a symptomatic BCG infection ($P < .0001$).
Conclusions: BCG vaccine has a very high rate of complications in patients with SCID, which increase morbidity and mortality rates. Until safer and more efficient antituberculosis vaccines become available, delay in BCG vaccination should be considered to protect highly vulnerable populations from preventable complications. (J Allergy Clin Immunol 2014;133:1134-41.)

Key words: *Primary immunodeficiency, severe combined immunodeficiency, vaccine, BCG, mycobacteria, newborn screening, hematopoietic stem cell transplant, immune reconstitution syndrome*

Tuberculosis is a major global health problem. In 1993, the World Health Organization (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 more than 4 billion doses applied, the live attenuated *Mycobacterium bovis* BCG vaccine has been a part of efforts to control tuberculosis and remains one of the most widely used of all current vaccines worldwide. Since the 1960s, it has been administered routinely in the majority of countries, and currently, approximately 120 million persons, mostly newborns, are vaccinated every year through national childhood immunization programs. The BCG vaccine has a documented protective effect against meningitis and disseminated tuberculosis 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 effect of BCG vaccination on transmission of *M tuberculosis* is therefore limited (reviewed in Plotkin et al[1] and the Global Tuberculosis Report, 2012, WHO, http://www.who.int/tb/publications/global_report/gtbr12_main.pdf).

Abbreviations used
HSCT: Hematopoietic stem cell transplantation
IL2RG: IL-2 receptor γ
IRS: Immune reconstitution syndrome
MAT: Multidrug antimycobacterial therapy
RAG: Recombination-activating gene
SCID: Severe combined immunodeficiency
WHO: World Health Organization

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 (SCID) includes a heterogeneous group of genetic conditions characterized by profound deficiencies in T-cell (and in some types B-cell, natural killer cell, or both) 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 (eg, IL-2 receptor γ *[IL2RG]* and *IL7RA*), antigen receptor processing (eg, recombination-activating gene 1 *[RAG1]*, *RAG2*, and *CD3D*), or nucleotide processing (eg, adenosine deaminase *[ADA]*) cause this fatal childhood condition, unless immune reconstitution can be accomplished.[4] However, it should be noted that patients with severe manifestations of other syndromic conditions might have clinical signs and symptoms consistent with SCID.[5] BCG, as other live attenuated vaccines, is absolutely contraindicated in patients with SCID (as reviewed by Plotkin et al[1] and the Centers for Disease Control and Prevention[6] and the 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, patients with SCID 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 given a diagnosis of SCID, the most severe form of primary immunodeficiency diseases.

METHODS

An extensive standardized questionnaire evaluating diagnostics, therapeutics, and outcomes concerning BCG-vaccinated patients with SCID was developed by an *ad hoc* scientific interest group (the "BCG infection in SCID patients interest group"; N.R., G.D., B.N., and S.D.R.; see Table E1 in this article's Online Repository at www.jacionline.org). The questionnaire was widely distributed to primary immunodeficiency patients/caregivers through professional organizations (the European Society for Immunodeficiencies, Latin American Society for Immunodeficiencies, and Clinical Immunology Society), patient advocacy groups (the Jeffrey Modell Foundation), 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 were collected between April 2010 and March 2012.

Data relevant to (1) SCID diagnosis, treatment, immune reconstitution, and outcome, as well as (2) BCG vaccination and (3) BCG-associated complication diagnosis, treatment, and outcome was analyzed. For the purposes of this multicenter international retrospective study, we analyzed patients given diagnoses of SCID at the participating centers based on the clinical and laboratory findings of recurrent/severe infections and/or failure

TABLE I. BCG-vaccinated patients with SCID: distribution and HSCT

Country (centers)*	Universal BCG vaccination at birth†	BCG-vaccinated patients with SCID (n = 349)	HSCT‡ (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)§	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

*A total of 821 patients were given diagnoses of SCID in these centers, including 349 who were BCG vaccinated and reported for the current study.
†For recent changes or individualized BCG vaccination policies in different countries, please refer to http://www.bcgatlas.org/.
‡Other forms of SCID treatment (eg, gene therapy, 3 patients; enzyme replacement, 2 patients; or thymus transplantation, 1 patient) are also included in this category.
§National Center Database of Primary Immunodeficiencies, which collects data from 13 centers in the Czech Republic.

to thrive, severe T-cell lymphopenia (in the absence of a condition consistent with Omenn syndrome or maternal engraftment), and/or severe functional T-cell defects. BCG-associated complications were defined based on clinical, microbiological, and/or histopathologic 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 pathologic manifestations that were attributed to an excessive and/or dysregulated immune response to BCG as a consequence of improvement in immune status were associated with a diagnosis of immune reconstitution syndrome (IRS).[8] Deaths caused by BCG-associated complications, as well as all-cause mortality, were analyzed as outcome variables. BCG-associated deaths were defined as cases in which the primary cause of death was strongly associated with BCG-associated complications, as determined by the clinical care team. Continuous variables were compared by using the Kruskal-Wallis test. The Fisher 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 by 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 .05 were considered statistically significant. Data analyses were performed with SAS software (version 9.3; SAS Institute, 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 might not be representative of the entire SCID population. Because of the limitations of data collection, we used the midpoint of the reported time interval of BCG vaccination and hematopoietic stem cell transplantation (HSCT) in the time-to-event analysis. Additional variability and bias might be introduced by using this *ad hoc* method.

RESULTS

Population demographics

A total of 821 patients were given diagnoses of SCID in the 28 participating centers from 17 different countries, 349 of whom were BCG vaccinated (42%) and analyzed in this retrospective study (Table I). When the analysis was restricted to countries with mandatory at-birth BCG vaccination policies, the rate of BCG-vaccinated patients with SCID increased 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 (Fig 1, *A*). The specific type of SCID diagnosis was determined in 159 (46%) patients and not defined in the remainder of the cohort. *IL2RG* deficiency was the most frequently reported, followed by defects in *RAG1*/*RAG2*, *ADA*, MHC class II deficiency, *IL7RA*, Artemis *(DCLRE1C)*, Janus kinase 3 *(JAK3)*, purine nucleoside phosphorylase *(PNP)*, zeta chain–associated protein of 70 kDa *(ZAP70)*, and Cernunnos *(NHEJ1)*. We cannot formally exclude that among the patients with no specific SCID type defined, some could have been affected by other known primary immunodeficiency diseases presenting with an SCID-like phenotype of severe T-cell lymphopenia and/or severe functional T-cell defects and increased susceptibility to mycobacterial diseases (eg, Mendelian susceptibility to mycobacterial disease–associated genetic defects).

BCG vaccination

Age at vaccination was determined in 345 of 349 patients with SCID. The majority (258/345 [75%]) were vaccinated within the first month of life (<1 week, 204 patients; 1-2 weeks, 6 patients; and 3-4 weeks, 48 patients), whereas the remainder (87/345) were vaccinated later (1-3 months, 74 patients; 4-6 months, 8 patients; 7-12 months, 3 patients; and >12 months, 2 patients). BCG vaccine was administrated on the deltoid area in all patients: 301 intradermally, 38 subcutaneously, and 10 in an undetermined manner. The vaccine strain was reported in 252 patients: Danish, 88 patients; Moreau, 66 patients; Pasteur, 32 patients; Glaxo, 29 patients; Tokyo, 19 patients; and Russia, 18 patients.

BCG-associated complications

BCG-associated complications are described in Fig 1, *B* to *F*. After BCG vaccination, 177 (51%) patients with SCID had complications: 59 (17%) localized and 118 (34%) disseminated, a 400- and 33,000-fold increase, respectively, over the general population. Age at onset of BCG-associated complications was determined in 158 patients: less than 1 month in 8 patients, 1 to 3 months in 33 patients, 4 to 6 months in 67 patients, 7 to 12 months in 34 patients, and greater than 12 months in 16 patients. Among patients presenting with disseminated complications, involvement of the extraregional 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 patients with disseminated complications, whereas positive blood culture results were even more uncommon (n = 1 [1% of patients with disseminated complications]).

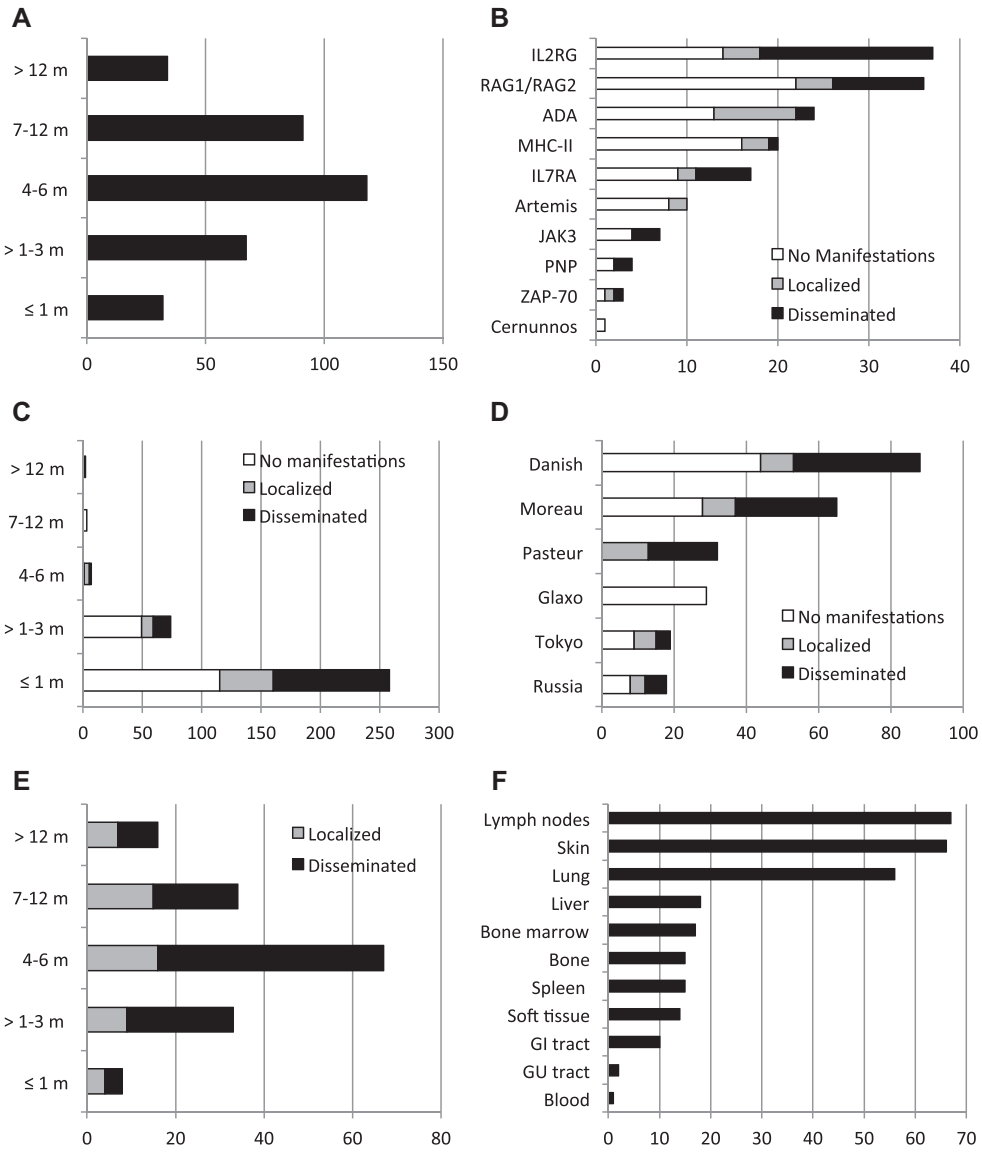

FIG 1. BCG-vaccinated patients with SCID: epidemiologic characteristics. **A,** Age at SCID diagnosis. **B,** SCID diagnosis and BCG-associated complications (no manifestations or localized or disseminated complications). **C,** Age at BCG vaccination and BCG-associated complications (no manifestations or localized or disseminated complications) distribution. **D,** BCG vaccine strain and BCG-associated complications (no manifestations or localized or disseminated complications). **E,** Age at onset of BCG-associated complications (localized or disseminated complications). **F,** Site of involvement of disseminated BCG-associated complications. *GI*, Gastrointestinal; *GU*, genitourinary. *X-axis*, number of patients.

The median absolute T-cell number at the time of SCID diagnosis in patients with localized or disseminated BCG-associated complications was significantly lower than that in patients without BCG-associated complications ($P = .003$, Table II). Logistic regression analysis showed that the odds of experiencing BCG-associated complications among patients with SCID with T-cell numbers of 250/μL or less at diagnosis was 2.1 times higher (95% CI, 1.4-3.4 time higher; $P = .001$) than that among those with T-cell numbers of greater than 250/μL, and the difference remained significant after adjusting for the age at BCG vaccination. Patients with and without BCG-associated complications were not significantly different in either B-cell or natural killer cell numbers.

Two hundred thirty-eight (68%) patients received antimycobacterial treatment after receiving a diagnosis of SCID. At the time of treatment initiation, 78 (22%) were asymptomatic in terms of BCG-associated complications, and 160 (46%) were symptomatic (53 with localized and 107 with disseminated manifestations).

Among asymptomatic antimycobacterial agent–treated patients who underwent HSCT (n = 64), 49 (77%) received multidrug antimycobacterial therapy (MAT), whereas 10 (16%) were treated with isoniazid monotherapy (no information on 5 patients). MAT included isoniazid plus rifampicin–based treatment in 49 (77%) patients, 18 of them (28%) having 1 or more additional drugs. The enteral route was preferred in 94% of these

TABLE II. BCG-vaccinated patients with SCID: statistical analysis

Age at BCG vaccination			
	BCG vaccination at ≤1 mo	BCG vaccination at >1 mo	*P* value
Sex, no. (%)			
Female	88 (34.8)	40 (46)	NS
Male	165 (65.2)	47 (54	
Age at SCID diagnosis (mo), median (range)	5 (0.5-48)	6 (0.5-100)	NS
BCG-associated complications, no. (%)			
No manifestations	115 (44.6)	54 (62.1)	.006
Loc/Diss manifest	143 (55.4)	33 (37.9)	
Age at HSCT (mo), median (range)	7 (0.5-75)	8 (0.5-107)	NS
Mortality in BCG-SCID			
BCG-rel, no. (%)	45 (18)	0 (0)	<.0001
Overall, no. (%)	132 (52.8)	38 (43.7)	NS

Median lymphocytes at SCID diagnosis			
	No manifestations	Localized or disseminated	
T cells/μL (25th-75th percentile)	197 (14-942)	49 (5-343)	.003
B cells/μL (25th-75th percentile)	103 (5-640)	140 (11-710)	NS
NK cells/μL (25th-75th percentile)	160 (38-410)	100 (19-366)	NS

BCG-rel, Death related to BCG-associated complications; *Loc/Diss manifest*, localized or disseminated manifestations of BCG-associated complications; *NK*, natural killer; *No manifestations*, no manifestations of BCG-associated complications; *NS*, not significant.

patients. No significant differences between monotherapy and MAT were detected when death caused by BCG-associated complications was compared ($P = .99$). By the time of data analysis, 63% of these patients were alive (median follow-up, 57 months; range, 4-126 months). Among symptomatic patients receiving antimycobacterial treatment and undergoing HSCT (n = 76), 64 (82%) were treated with MAT, whereas 4 (5%) were treated with isoniazid monotherapy (no information on 8 patients). MAT included isoniazid plus rifampicin–based treatment in 61 (80%) patients, 47 (62%) of them having 1 or more drugs added to the scheme. Eighty-four percent of these patients were treated through the enteral route, and 11% were treated through 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 months).

BCG-associated complications were reported in 3% (2/64) of asymptomatic patients receiving antimycobacterial treatment and undergoing HSCT. Antimycobacterial 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 antimycobacterial treatment: 32% for less than 3 months, 15% for 4 to 6 months, 21% for 7 to 12 months, and 32% for more than a year.

No deaths related to BCG-associated complications were reported among BCG-asymptomatic treated patients with SCID, whereas 46 deaths caused by BCG occurred among BCG-symptomatic treated patients (7 in patients who underwent HSCT and 39 in patients who did not, including 45 patients with disseminated complications and 1 patient with localized disease; $P < .0001$). 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 ($P = .09$).

One hundred eleven BCG-vaccinated patients with SCID (32%; 96 of them presenting with no manifestations and 15 symptomatic, including 9 with disseminated and 6 with localized complications) did not receive antimycobacterial treatment after SCID diagnosis. Forty-five (40%) of these patients underwent HSCT (32 asymptomatic and 13 symptomatic, including 8 with disseminated and 5 with localized complications), 15 of them received antimycobacterial treatment after HSCT (3 asymptomatic and 8 with disseminated and 4 with localized manifestations), 28 of them (63%) are alive, and no deaths caused by BCG-associated complications were reported (median follow-up, 46 months; range, 0-187 months). Of the remaining 66 patients (60%, 64 were asymptomatic and 2 were symptomatic, including 1 with disseminated and 1 with localized complications) who did not undergo HSCT by the time of data analysis, 22 (33%) were alive, and only 1 BCG-associated death was reported in this group (presenting with disseminated disease). Interestingly, survival rates for patients who did not receive pre-HSCT antimycobacterial treatment (27/45) was not statistically different from those in patients who received antimycobacterial treatment and underwent HSCT (94/139, $P = .47$).

Age at BCG vaccination showed a significant association with BCG-associated 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-associated complications (disseminated or localized) compared with patients vaccinated after 1 month of age ($P = .006$). Moreover, the odds of having BCG-associated complications among those vaccinated within the first month of life were 2.03 times higher than those vaccinated after the age of 1 month (odds ratio, 2.03; 95% CI, 1.24-3.35). A log-rank test comparing time to death caused by BCG-associated complications in patients vaccinated within or after 1 month of age also identified significant differences between these 2 groups ($P < .0001$, Fig 2). Moreover, survival analysis comparing time to death within 24 months of age before HSCT for patients vaccinated early versus late showed that the hazard of death was 2.12 times higher for those receiving early vaccination (95% CI, 1.12-3.89; Fig 2). These results strongly suggested that early BCG vaccination (≤1 month) is associated with increased BCG-associated complications and subsequent death associated with those complications.

SCID treatment

Of the 349 BCG-vaccinated patients with SCID, 190 (54%) underwent HSCT (n = 184) or another form of SCID-specific treatment (eg, gene therapy [n = 3], enzyme replacement [n = 2], or thymus transplantation [n = 1]). The median age at HSCT was 7.5 months (range, 0.5-107 months). No significant differences in T-cell engraftment were detected between patients receiving early (≤1 month) versus late (>1 month) BCG vaccination or among patients undergoing transplantations without or with BCG-associated complications (localized or disseminated). No significant differences in the proportion of death caused by

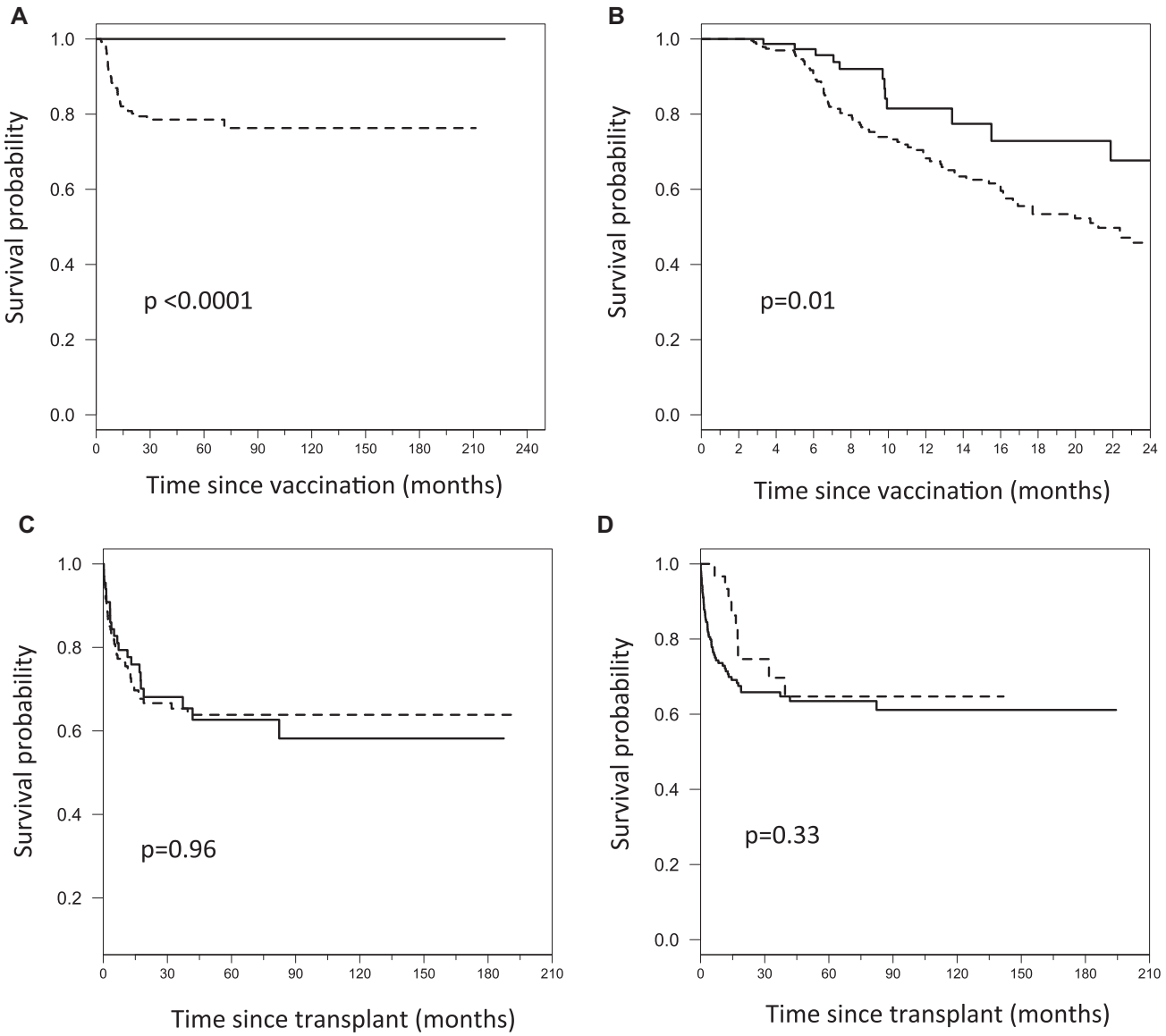

FIG 2. Time-to-event analysis by age at BCG vaccination and age at HSCT. **A,** Kaplan-Meier curves for the time from vaccination to death caused by BCG-associated complications comparing early (≤1 month of age, *dashed line*) versus late (>1 month of age, *solid line*) vaccination ($P < .0001$). **B,** 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*) versus late (>1 month of age, *solid line*) vaccination ($P = .01$). **C,** Kaplan-Meier curves for time from HSCT to death comparing early (≤1 month of age, *dashed line*) versus late (>1 month of age, *solid line*) vaccination ($P = .96$). **D,** Kaplan-Meier curves for the time from HSCT to death comparing early (≤3 months of age, *dashed line*) versus late (>3 months of age, *solid line*) transplantation ($P = .33$).

BCG-associated complications were detected either among patients receiving matched related, matched unrelated, mismatched related, or mismatched unrelated forms of HSCT ($P = .97$). However, death caused by BCG-associated complications was still more frequent among patients receiving early vaccination compared with those vaccinated later ($P = .049$). Death caused by BCG-associated complications was also significantly more frequent among patients undergoing HSCT with localized or disseminated BCG-associated complications versus those with no manifestations ($P = .006$). When all-cause mortality was compared among patients receiving HSCT, no significant difference was detected between patients receiving early versus late BCG vaccination ($P = .96$), implying that after HSCT, the age at BCG vaccination has no significant effect on survival rates (Fig 2). Finally, although we did not find significant differences in post-HSCT survival between early (≤3 months) and late (>3 months) HSCT ($P = .33$), the difference between these 2 groups within the first 12 months after transplantation was statistically significant ($P = .01$, Fig 2).

Of 190 patients who underwent HSCT or another form of SCID treatment, 55 (29%) had IRS (33 with disseminated disease, 14 with localized complications, and 8 with no manifestations). Most patients (57%) presented with these manifestations within a month of HSCT. IRS prevalence was also analyzed in different

subsets of patients: those receiving antimycobacterial treatment while BCG asymptomatic had significantly less of this complication (5/64) compared with either BCG-symptomatic antimycobacterial-treated patients (33/81, $P < .0001$) or non-treated patients (17/45, $P = .0003$).

DISCUSSION

The prevalence of BCG-associated complications in the general population can vary widely depending on the reporting country and the vaccine strain used. However, reports of 1 in 2,500 vaccinees presenting with localized BCG-associated complications and 1 in 100,000 presenting with disseminated complications represent a fair estimate of the prevalence of such complications.[1,9] When focused exclusively on patients given a diagnosis of SCID, the prevalence of BCG-associated complications has been estimated to be higher than in the general population,[10-12] although a definitive effect 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-associated complications are more prevalent in patients with SCID than in the general population. On the basis of our observations, one in every 2 BCG-vaccinated patients with SCID had BCG-associated manifestations, two thirds in the form of disseminated complications (an approximate 33,000-fold increased compared with the general population) and the other third in the form of localized complications (an approximate 400-fold increase). Our analysis found 2 individual variables to significantly correlate with this increased prevalence of BCG-associated complications: the total number of T cells at the time of SCID diagnosis and the patient's age at the time of BCG vaccination. Although patients with SCID presenting with higher T-cell numbers were underrepresented among those with BCG-associated 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 to be a strong predictor for BCG-associated 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 caused by vaccine-associated complications. Age at BCG vaccination was independent of other variables, including BCG strain, vaccination route, or type of SCID diagnosed. Less clear than the association between age of vaccination and complications are the mechanism or mechanisms underlying this finding. All patients with SCID, independent of their underlying genetic defect, share a defective adaptive immune response. Therefore the relative maturity of the innate immune arm involved with controlling mycobacterial infections could by hypothesized as a factor altering the balance toward controlling or not controlling BCG.[13,14] Equally 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 given diagnoses of SCID within the first 6 months of life. Until safer and more efficient forms of antituberculosis vaccines become available,[17] delaying BCG vaccination beyond 1 month of age is likely to have a favorable effect in this highly vulnerable population, as well as other susceptible neonates (eg, HIV-positive infants).[18] Moreover, delaying BCG vaccination would also benefit the clinical effect of neonatal SCID screening, preventing application of an absolutely contraindicated vaccine before 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, 2 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 decrease in coverage and the 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 diphtheria-pertussis-tetanus vaccine (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, the incidence of BCG-preventable mycobacterial diseases within the first 6 months of life is extremely uncommon. Literature on pediatric tuberculous meningitis, a BCG vaccine–preventable disease, shows that the mean age of presentation for this life-threatening disease is 23 to 49 months, although a few cases have been described during the first 6 months of life, whereas the medians span from 12 to 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 and highly vulnerable immunodeficient patients.

As expected, the major intervention affecting survival in this cohort of BCG-vaccinated patients with SCID was providing immunologic reconstitution by means of HSCT. Interestingly, a subset of patients who did not receive any antimycobacterial treatment but underwent HSCT did not have any BCG-associated complications or IRS (27/190). This outcome might suggest that HSCT by itself could 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 class II deficiency, 2 *IL2RG*, 1 *JAK3*, 1 Artemis *(DCLRE1C)*, 1 *PNP*, 1 *IL7RA*, and 1 Cernunnos *(NHEJ1)*; median T-cell numbers, 250/μL; median age at HSCT, 7 months), higher maturity of innate immunity, residual acquired immunity, or other unidentified disease modifiers.

We observed that patients with SCID started on antimycobacterial therapy while BCG-asymptomatic had significantly fewer BCG-associated complications before HSCT, as well as less IRS after HSCT and decreased mortality caused by BCG-associated complications. The rationale for this approach is to control an infection involving the known inoculation of 37,500 to 3,200,000 live mycobacteria in a highly susceptible host.[28] However, we recognize that our data do not provide definitive proof of benefit for pre-emptive antimycobacterial therapy because of

confounding factors associated with this type of retrospective study. Still, in the setting of commonly used prophylactic therapy in patients with SCID (eg, immunoglobulin replacement and antimicrobial agents), it seems entirely appropriate to consider early initiation of antimycobacterial therapy at the time of SCID diagnosis. If this strategy is chosen, it is less clear which antimycobacterial scheme would be most effective.

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

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Clinical implications: Delaying BCG vaccination until after 1 month of age should diminish BCG-associated complications in patients with SCID and should not adversely affect BCG-preventable disease.

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