Vaccine 37 (2019) 6510–6517

Contents lists available at ScienceDirect

Vaccine

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

BCG vaccine and leprosy household contacts: Protective effect and probability to becoming sick during follow-up

Rafaela Resende Gomes [a], Douglas Eulálio Antunes [a,b,*], Diogo Fernandes dos Santos [a,b], Elaine Fávaro Pípi Sabino [a,b], Dulcinéia Bernardes Oliveira [a], Isabela Maria Bernardes Goulart [a,b]

[a] National Reference Center for Sanitary Dermatology and Leprosy, Clinics Hospital, Federal University of Uberlandia, Uberlandia, MG 38.413-018, Brazil
[b] Postgraduate Program in Health Sciences, School of Medicine, Federal University of Uberlandia, Uberlandia, MG 38400-902, Brazil

ARTICLE INFO

Article history:
Received 3 January 2019
Received in revised form 4 August 2019
Accepted 27 August 2019
Available online 6 September 2019

Keywords:
Leprosy
Bacillus Calmette-Guérin vaccine
Household contacts
Survival curve
Relative risk

ABSTRACT

Background: Immunoprophylaxis with Bacillus Calmette–Guérin (BCG) vaccine is still the most effective intervention in the prevention of leprosy among household contacts (HHCs) of leprosy patients.
Methods: A retrospective cohort study using data of 5.061 HHCs for a period of 16 years (follow-up of 7 years per leprosy HHCs), evaluating the occurrence of disease as the main outcome and the presence or absence of BCG scars verified at the first evaluation. Statistical analyzes were performed using the relative risk, hazard ratio and survival curves by Kaplan-Meier test.
Results: A total of 92 contacts sickened, of which 41.3% (38/92) in the first year and 58.7% (54/92) in the course of the other years of follow-up. Of those who became sick, 62% (57/92) developed borderline tuberculoid (BT). The additional protective effect occurred for those who had 2 BCG scars at the first follow-up assessment (Relative Risk: 0.41; p = 0.007) when compared to those not previously exposed to the vaccine. The number of BCG scars examined at the first assessment (t_0 = time zero) affected the occurrence of the outcome evidenced by the difference in survival curves throughout the follow-up (Log Rank, p = 0.041; Breslow, p = 0.012; Tarone-Ware, p = 0.020). Leprosy HHCs with 0 BCG scar at time zero (t_0) have a shorter survival time (average time of 22 months between t_0 and outcome) when compared to those with 2 BCG scars (average time of 36 months between t_0 and outcome).
Conclusions: Vaccination of healthy individuals without signs and symptoms of leprosy is extremely important because BCG vaccine has an additional protective effect in those cases with 2 BCG scars throughout follow-up. Reducing the risk of leprosy HHCs becoming sick depends on preventive actions such as immunoprophylaxis and index cases treatment.

1. Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (*M. leprae*), which affects the skin and especially the peripheral nerves causing neural lesions and consequently physical disabilities [1]. It was estimated worldwide that the number of new cases of leprosy detected in 2017 reached 210.671 cases, with India (126.164 cases) and Brazil (26.875 cases) occupying first and second places in number of new cases respectively [2].

The aerial route has been identified as the main means of transmission of the disease as reported in studies involving DNA analysis of nasal conchae biopsies, nasal swab samples and serology of households contacts of leprosy. Therefore, the aerial route is the main way of bacillus transmission, which favors the persistence of the disease in the epidemiological context [3].

In this scenario, leprosy HHCs are the group most likely to become sick, presenting a risk from 5 to 8 times greater in relation to non-contacts of leprosy [4]. Although there is no specific vaccine for this disease, BCG, a vaccine developed to prevent pulmonary tuberculosis, has shown a protective effect against leprosy, as explained in several studies [5–7].

The protective effects of BCG in preventing leprosy ranged from 26 to 41% in experimental studies, with small differences between paucibacillary (62%) and multibacillary (76%) forms, whereas in the prevention of pulmonary tuberculosis this effect reaches 83% [8].

Due to the high protective effect of the BCG vaccine against tuberculosis and leprosy, the World Health Organization (WHO) advocates in countries with a high incidence of these diseases, a single dose of BCG vaccine that should be administered to healthy

* Corresponding author at: National Reference Center for Sanitary Dermatology and Leprosy (CREDESH/HC/UFU), Av. Aspirante Mega, 77, Bairro Jaragua, Uberlandia, MG CEP: 38.413-018, Brazil.
E-mail address: credsh@hc.ufu.br (D.E. Antunes).

https://doi.org/10.1016/j.vaccine.2019.08.067
0264-410X/

neonates to prevent severe forms of both diseases [9]. Selective vaccination strategies for risk groups, as leprosy HHCs, are adopted by several countries with a high number of new cases such as Brazil [10].

Thus, the Brazilian Ministry of Health has recommended several actions to prevent leprosy, such as, household contacts surveillance, health professionals advices and BCG vaccine. BCG vaccination is conditioned by the presence of clinical signs of the disease, hence, if the HHCs do not present skin lesions or symptoms suggestive of nerve damage associated with absence of vaccine scar or have only one scar, one dose of intradermal BCG must be administered. On the other hand, if the HHCs have two vacine scars, must not be administered the vaccine [11].

Household contacts surveillance is the main strategy for controlling leprosy, including activities such as anamnesis, dermatoneurological evaluation, collecting of biolological material to realization of laboratory tests (serology and blood PCR). The aim of HHCs surveillance is following asymptomatic cases without clinical signs and laboratory alterations, providing immunoprophylaxis with the BCG vaccine [7,12].

This study aims to demonstrate the protective effect of the BCG vaccine and the probability of becoming sick during the follow-up of leprosy HHCs by means of survival curves.

2. Methods

2.1. Sample and study design

A retrospective cohort study, that used data of 5.061 leprosy HHCs, encompassing a period of 16 years, which took place at National Reference Center for Sanitary Dermatology and Leprosy (CREDESH) of the Clinical Hospital (HC) located at the Federal University of Uberlandia.

2.2. Definition criteria for leprosy contacts

HHCs were defined as persons who live or have lived in the same dwelling as a patient with leprosy in the last 5 years before the leprosy diagnosis [3].

2.3. Follow-up time

In this study, time zero (t_0) corresponded to the first evaluation of leprosy contacts and individual follow-up was completed after 7 years of annual evaluation. The main outcome of this study was the presence of sick individuals among leprosy HHCs diagnosed during the follow-up period.

2.4. Clinical evaluation and screening tests

Household contacts for leprosy were evaluated annually for 7 years and submitted to screening tests such as: dermatoneurological evaluation; inspection of the deltoid region for the presence and number of BCG scars; collection of biological samples for the analysis of anti-PGL-I IgM serology (Enzyme-linked immunosorbent assay – ELISA) and extraction of blood DNA for Real-Time Quantitative Polymerase Chain Reaction (RT qPCR).

2.5. Eligible criteria for routine diagnostic tests

The presence of signs and symptoms such as skin lesions with decreased sensation to touch, temperature, or pain; muscle weakness, numbness in the hands, arms, feet, and legs associated with neural thickening and/or anti-PGL-I positive serology and/or Positive blood DNA for *M. leprae*.

2.6. Diagnostic criteria for leprosy in household contacts

Household contacts eligible for routine diagnostic examinations were submitted to medical evaluation; sensory evaluation; skin biopsy; dermal smear (Bacilloscopy and PCR) and electroneuromyography. After complete clinical, epidemiological and laboratory evaluation, contacts were diagnosed and classified as sick according to the Ridley and Jopling criteria [13]. Diagnostic criteria were considered: clinical changes confirmed by specialists aided by tests such as skin biopsy; dermal smear bacilloscopy; electroneuromyography with alterations compatible with leprosy neuropathy, in addition to serology and qPCR of peripheral blood. Clinical and laboratory diagnosis depends on the interpretation of all tests together. It is emphasized that, patients classified clinically as borderline tuberculoid with up to five lesions and negative results for all complementary diagnostic tests were classified as BT/PB. However, patients classified clinically as borderline tuberculoid with more than five lesions and one or more positive results for complementary diagnostic tests were classified as BT/MB.

2.7. Inclusion and exclusion criteria

Cases of relapse previously treated were excluded, even if they have became HHCs of another index case. It was excluded those diagnosed clinically with leprosy in the first evaluation, as well as, cases diagnosed with other comorbidities such as: metabolic neuropathies (diabetes), mechanical trauma associated neuropathies; infectious diseases (cutaneous leishmaniasis, tuberculosis, Chagas disease, among others) and immunological and rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and others).

It was Included in the study leprosy HHCs who became sick during the 7 years of follow-up. All HHCs were diagnosed with leprosy by leprologists according to the clinical, immunological and histological criteria of Ridley and Jopling [13].

2.8. Variables of the study

The variables associated to the outcome were: number of BCG scars; year whose the leprosy HHCs became sick; the clinical form of HHCs; operational classification; sex; age group and the clinical form of their index cases. It was calculated the relative risk, hazard ratio, mean and median between t_0 and time to outcome, and difference among survival curves related to several variables.

2.9. Sample size

By means of data from a pilot study, of our Reference Center of Leprosy involving sample contacts from previous years, the sample size was calculated using the G-Power 3.1.9.2 software. For the purpose of calculation, the binomial test was used for two independent groups whose proportion of patients in the groups with scar and without BCG scar were 0.03 and 0.05 respectively. The alpha error probability was 0.05, test power of 0.90 and the allocation ratio (N2/N1) was equal to 1. The total sample size was 4168. However, we included 5016 contacts in the study in view of the losses included in the inclusion and exclusion criteria.

2.10. Statistical analysis

Binomial test was used to show that there was no difference between the proportions of individuals who became sick during the first year of follow-up and after this period of time. The relative risk and hazard ratio were calculated to verify the risk or protective effect of BCG on leprosy HHCs with 1 or 2 vaccine scars. The Kaplan-Meier method was performed to compare survival curves

for different factors such as a number of BCG scars at time zero, gender, age group and clinical form of the index cases. The Log Rank, Breslow, and Tarone-Ware tests were used to verify if there was a difference between survival curves in all leprosy HHCs follow-up periods. Statistical Package for Social Sciences (SPSS) v.22 software (IBM Corp., Armonk, NY, USA) was used for all statistical analyzes. A significance level of 0.05 ($\alpha = 5\%$; bilateral) was considered for all analyzes.

2.11. Ethical considerations

This study was approved by the Research Ethics Commitee of the Federal University of Uberlandia – Brazil (960.735/2014). The written informed consent was obtained, respecting the rights of the participants.

3. Results

3.1. Clinical and epidemiological characterizations

A total of 5.061 leprosy HHCs were examined for annual follow-up of 7 years per patient, whose data from 1998 to 2014 registered 117 individuals who became sick during this period. However, 17.1% (20/117) of these HHCs have already been sick in the first evaluation and 4.3% (5/117) were cases of relapse, therefore, they were excluded, remaining 92 sick HHCs, representing 1.82% (92/5036) of those evaluated during 16 years of data collecting (Supplementary Table 1).

Among those 92 HHCs that developed leprosy during follow-up, 62% (57/92) developed the borderline tuberculoid (BT) form, whose BT/paucibacillary (PB) represented 41.4% (38/92) and the BT/multibacillary (MB) 20.6% (19/92) followed by the clinical form tuberculoid leprosy (TT) with 13% (12/92), prevailing, hence, PB 64.1% (59/92) operational classification (Table 1). The majority of the leprosy HHCs who became sick were female, constituing 63% (58/92) of the sample, and the most frequent age groups were those from 20 to 39 (30.4%; 28/92) and from 40 to 59 years (39.1%; 36/92) (Table 1). By means of binomial test, it was showed that there was no difference between the proportions of individuals who became sick during the first year of follow-up and after this period of time (Table 1).

The Table 2 shows the clinical form and operational classification of the index cases of the leprosy HHCs who became sick, predominating the lepromatous leprosy (LL) form that represented 52.2% (48/92) and, consequently, the MB operational classification reached 82.6% (76/92) of the total of index cases.

3.2. Relative risk of leprosy HHCs to becoming sick

Of the leprosy HHCs that became sick, 41.3% (38/92) had a BCG scar inspected at the first assessment, followed by 10.9% (10/92) of those with 2 scars. Otherwise, 47.8% (44/92) of contacts who became sick had no BCG vaccine scar (Table 3). According to Table 4, although not significant, the relative risk of 0.81 ($p = 0.175$) demonstrated that BCG vaccine resulted in a possible protective factor for those exposed to 1 dose of BCG vaccine when compared to those not previously exposed to BCG vaccine (Table 4). Additional protective effect could be observed when the relative risk for those who had 2 BCG vaccines at the first follow-up assessment was 0.41 ($p = 0.007$) when compared to those not previously exposed to the vaccine.

3.3. Survival curves, hazard ratios and time-to-event for sick HHCs of leprosy

In order to verify whether the outcome, among the cases that became ill during follow-up, was influenced by factors such as number of BCG scars in the first evaluation, gender, age and clinical form of the index cases, we compared the curves of survival for each event that could influence the outcome of the disease over an individual follow-up of 7 years. Fig. 1 shows 3 survival curves for those with 0, 1 or 2 BCG scars in the first evaluation. In the first year, it is observed that the shortest survival belongs to the group that did not present any BCG scar, since 78.3% (34/44) of the individuals became ill in the first year, followed by those who presented 1 scar 64, 1% (24/38). On the other hand, cases with 2 scars had the longest survival in the first year of follow-up with only 36.7% (3/10) of the cases becoming sick in this period. Therefore, the presence of two BCG scars is associated with a better

Table 1
Clinical and epidemiological characteristics of leprosy households contacts that became sick during 7 years of follow-up.[a]

Variables		Became sick during the Fisrt year		Became sick after the first year of Follow-up		Total		Binomial test
		N°	%	N°	%	N	%	p-value
Clinical Form	I	5	5.4	3	3.3	8	8.7	*0.267*
	TT	3	3.3	9	9.8	12	13	*0.346*
	BT	25	27.2	32	34.8	57	62	*0.663*
	BB	5	5.4	5	5.4	10	10.9	*0.735*
	BL	0	0	2	2.2	2	2.2	*0.509*
	LL	0	0	3	3.3	3	3.3	*0.264*
Operational Classification	PB	23	25	36	39.1	59	64.1	*0.659*
	MB	15	16.3	18	19.6	33	35.9	*0.659*
Sex	Male	14	15.2	20	21.7	34	37	*1.000*
	Female	24	26.1	34	37	58	63	*1.000*
Age Group	0–19	4	4.3	7	7.6	11	12	*0.758*
	20–39	10	10.9	18	19.6	28	30.4	*0.500*
	40–59	17	18.5	19	20.7	36	39.1	*0.391*
	≥60	7	7.6	10	10.9	17	18.5	*1.000*
	Total	38	41.3	54	58.7	92	100	

Abbreviations: BB: borderline-borderline; BL: borderline-lepromatous; BT: borderline-tuberculoid; I: indeterminate; LL: lepromatous-lepromatous; MB: multibacillary; PB: paucibacillary; TT: tuberculoide.

[a] The table shows the clinical form, operational classification, sex and age group of leprosy contacts who became sick during and after the first year of follow-up. The statistical difference between the proportions in each column was verified by the binomial test.

Table 2
Clinical form and operational classification of the index cases of leprosy households contacts.[a]

Clinical Form of the index cases	Operational Classification					
	PB		MB		Total	
	N°	%	N°	%	N°	%
I	0	0	0	0	0	0
TT	6	6.5	0	0	6	7
BT	10	10.9	7	7.6	17	18
BB	0	0	13	14.1	13	14
BL	0	0	8	8.7	8	9
LL	0	0	48	52.2	48	52
Total	16	17.4	76	82.6	92	100

Abbreviations: BB: borderline-borderline; BL: borderline-lepromatous; BT: borderline-tuberculoid; I: indeterminate; LL: lepromatous-lepromatous; MB: multibacillary; PB: paucibacillary; TT: tuberculoid.
[a] The table shows the proportion of index cases of leprosy contacts by clinical form and operational classification.

Table 3
Number of BCG scars in the first evaluation and clinical form of leprosy households contacts that became sick during 7 years of follow-up.[a]

Clinical Form	Number of BCG Scars in the First Evaluation						Total	
	0		1		2			
	n°	%	n°	%	n°	%	n°	%
I	0	0	6	6.5	3	3.3	9	9.8
TT	5	5.4	5	5.4	2	2.2	12	13.0
BT	26	28.3	23	25.0	4	4.3	53	57.6
BB	8	8.7	4	4.3	0	0.0	12	13.0
BL	1	1.1	0	0.0	1	1.1	2	2.2
LL	4	4.3	0	0.0	0	0.0	4	4.3
Total	44	47.8	38	41.3	10	10.9	92	100

Abbreviations: BB: borderline-borderline; BL: borderline-lepromatous; BT: borderline-tuberculoid; I: indeterminate; LL: lepromatous-lepromatous; TT: tuberculoid.
[a] The table shows the percentage of leprosy households contacts according to clinical form and the number of BCG scars found in the first evaluation.

Table 4
Relative risk between leprosy HHCs who became sick and healthy leprosy HHCs according to the number of BCG scars inspected in the first assessment.[a]

BCG Scars in the first evaluation	Leprosy HHCs who become sick		Healthy Leprosy HHCs		Total		Relative Risk	Confidence Interval (95%)	p-value
	n°	%	n°	%	n°	%			
0	45	1.1	1762	42.5	1807	43.6	0.81	0.5447–1.218	0.175
1	47	1.1	2290	55.3	2337	56.4			
Total	**92**	2.2	**4052**	97.8	**4144**	100			
0	45	1.7	1762	65.3	1807	67.0	0.41	0.2016–0.8319	0.007
2	9	0.3	883	32.7	892	33.0			
Total	**54**	2.0	**2645**	98.0	**2699**	100			

Abbreviations: HHCs: Household contacts.
[a] Table shows relative risk in leprosy contacts group who became sick compared to contacts who did not develop leprosy during 7 years of follow-up. The factor analyzed was the number of BCG scars as a protection or risk factor for those with 1 or 2 scars in the first evaluation compared to those with no BCG scars.

prognosis compared to the other groups. Survival curves in the 3 groups (number of BCG scars in the first evaluation) had a significant difference in all follow-up periods, indicating that this factor predominantly influences the outcome of leprosy intradomiciliary contact (Log Rank, $p = 0.041$; Breslow, $p = 0.012$; Tarone-Ware, $p = 0.020$) (Fig. 1). Still in Fig. 1, it is noted that after 3 years of follow-up there was no difference between the survival curves of those with 0 or 1 BCG scars in the first evaluation.

The hazard ratio of 3 (0.63/0.21) was found by comparing those leprosy HHCs with 0 BCG scars to those with 2 vaccine scars, keeping the same factors such as: year that became sick (first year), sex (female), age group (from 20 to 39) and index case (lepromatous leprosy). Such information means that the chance of survival of an individual with 2 BCG scars, in the first year of follow-up, is 3 times higher than in cases with no one BCG scar. However, the chance of survival in the first year for a leprosy HHCs with 1 BCG scar will be 1.6 (0.35/0.21) times higher than that with 0 vaccine scar (hazard ratio) keeping the same criteria for sex, range age and case index previously reported.

Regarding the mean and median time between time zero (t_0) and time to outcome, it was observed that in those cases with 0 BCG scars, the average time was 1.91 years (1.15–2.67) or 22 months (median was 1 year) (supplementary Table 2). In those individuals with 1 BCG scar, the mean time to outcome was 1.97 years (1.47–2.47) or 23 months and a median of 1 year. However, cases with 2 BCG scars had an average of 3 years (2.26–3.8) or 36 months to get sick after the beginning of follow-up and a median time of 2 years (supplementary Table 2).

Comparison of survival curves in relation to gender, according to Fig. 2, shows that this factor was not crucial in determining the outcome of disease over the course of follow-up, because the curves overlap and show no significant difference between mean and median times (Log Rank, $p = 0.764$; Breslow, $p = 0.931$; Tarone-Ware, $p = 0.862$). Regarding the age group (Fig. 3), although

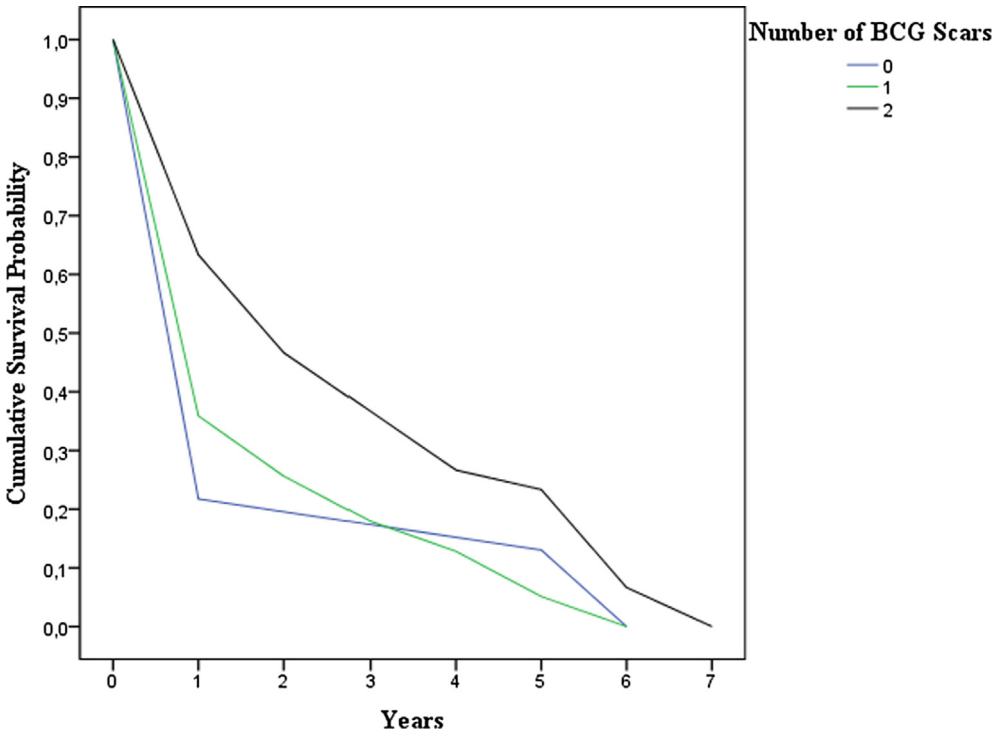

Fig. 1. Survival curve (Kaplan-Meier) of 92 leprosy HHCs that became sick during the annual follow-up for 7 years divided into 3 groups according to the number of BCG scars variable (verified in the first assessment – t_0). The comparison among 3 cumulative survival probability curves presented significative difference along all the time of follow-up (Log Rank, p = 0.041; Breslow, p = 0.012; Tarone-Ware, p = 0.020).

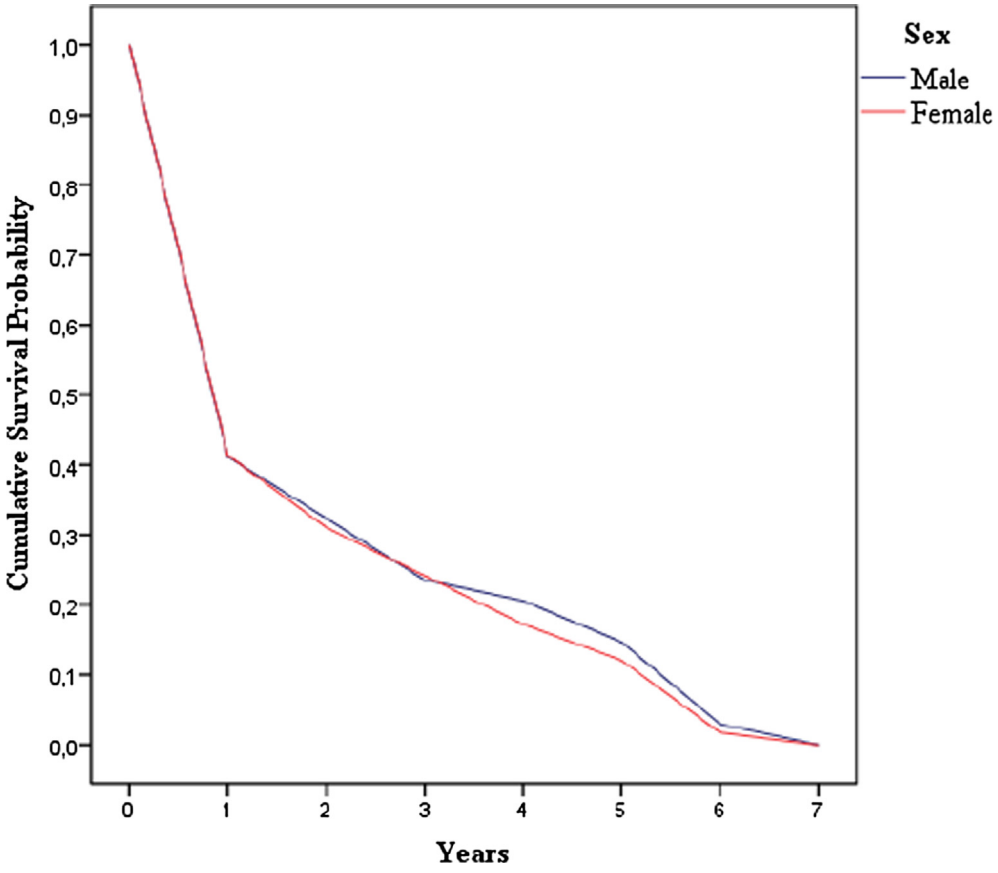

Fig. 2. Survival curve (Kaplan-Meier) of 92 leprosy HHCs that became sick during the annual follow-up for 7 years divided into 2 groups according to the sex variable. The comparison between 2 cumulative survival probability curves presented no significative difference along all the time of follow-up (Log Rank, p = 0.764; Breslow, p = 0.931; Tarone-Ware, p = 0.862).

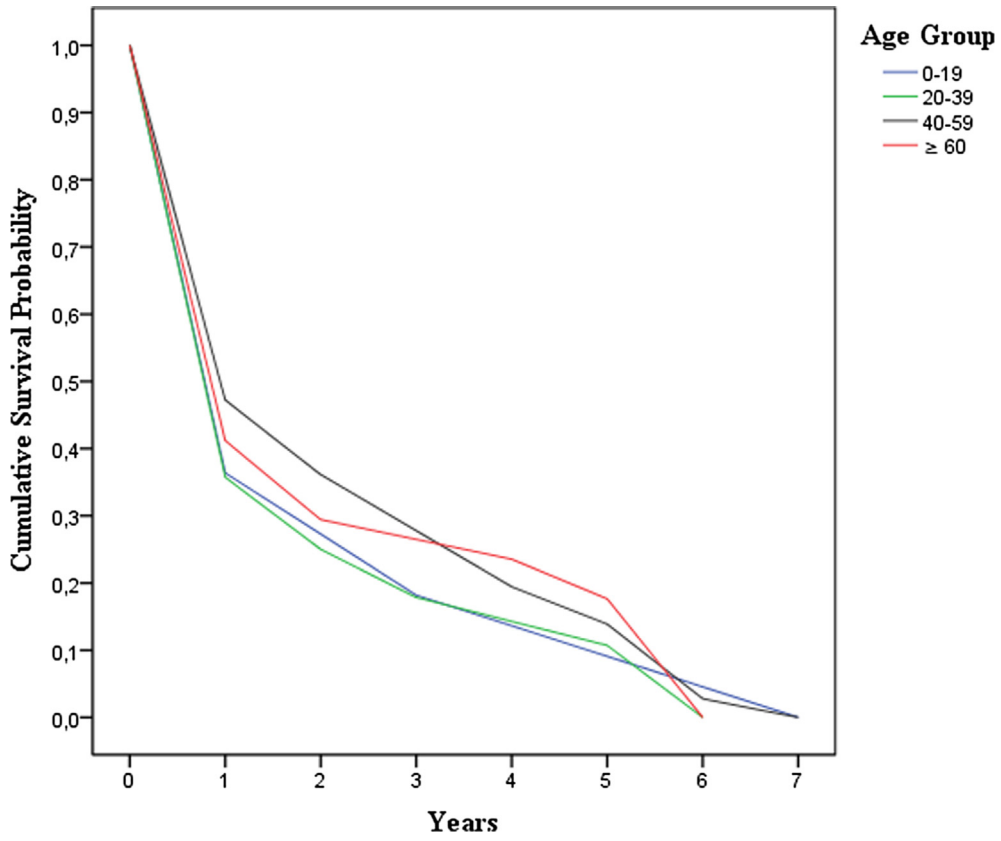

Fig. 3. Survival curve (Kaplan-Meier) of 92 leprosy HHCs that became sick during the annual follow-up for 7 years divided into 4 groups according to the Age Group variable. The comparison among 4 cumulative survival probability curves presented no significative difference along all the time of follow-up (Log Rank, p = 0.843; Breslow, p = 0.807; Tarone-Ware, p = 0.819).

groups between 0 and 19 years old and those between 20 and 39 years had shorter survival (curves with rapid decline), there was no significant difference between the mean time to disease occurrence. in these age groups (Log Rank, p = 0.843; Breslow, p = 0.807; Tarone-Ware, p = 0.819).

Similarly, when the groups were analyzed according to the clinical form of the index cases, the survival curves showed no difference between the mean and median times for illness (supplementary Table 2), demonstrating that this factor was not determinant in the occurrence of the disease (Log Rank, p = 0.981; Breslow, p = 0.928; Tarone-Ware, p = 0.971) (Fig. 4).

4. Discussion

It was observed in our study that most of leprosy HHCs sickened at the first year of follow-up, after administration of intradermal BCG vaccine, what may be a result of boosted cell-mediated immunity by homologues of *Mycobacterium leprae* antigens in BCG, promoting the recovering of immune system, that begins recognizes the antigens of this bacteria, revealing subclinical forms of the disease [14,15].

The clinical form BT/PB and, consequently, PB operational classification, were predominant in the contacts who became sick, since strategies and actions that compose the annual follow-up of this patients are associated to the use of laboratory tests, such as anti-PGL-I serology and RT qPCR of whole blood, both for detection of *M. leprae*, have collaborated for early diagnoses of the disease [16,17].

The higher frequency of female among the contacts who sickened may be associated with a higher demand for health services by individuals of this sex when compared to male, due to women are more concerned with health and body aesthetics [18]. In our study, the largest part of those leprosy HHCs who sickened were in the age group over 20 years, as opposed to results of other researches, whose largest number of leprosy HHCs were aged less than 15 years [19,20]. This contradiction can be explained by the differences between countries and endemic regions, since the high detection of leprosy in children under 15 reveals the persistence in the transmission of bacillus and the difficulties in the control of the disease by public health programs [21].

Previous researches have reported similar results to the index cases of this present study, regarding the predominance of the operational classification and clinical form, pointing out that the clinical form with the greatest potential for dissemination of the disease is LL, due to the high bacilloscopic indexes of these patients [16,22].

Several studies have demonstrated the protective effect of BCG vaccine by means of association measures, therefore, these effects agree with our findings that after dermatoneurological evaluation, the largest proportion of individuals who sickened had no one BCG scar [23,5,24]. Our findings demonstrated that a single scar of BCG promoted considerable protection against leprosy, and the addition of another scar (the presence of a second BCG scar) offered additional protection against the disease consonant to studies that showed similar results [25,26]. In the present study, the number of BCG scars at t_0 was the main factor that influenced the survival/protection of those individuals who became sick over a 7-year individual follow-up. The presence of 2 BCG scars in the first evaluation allowed longer time between t_0 and outcome in this group and, therefore, longer survival/protection as observed in other studies [27].

Agreeing with previously quoted, the implementation of immunoprophylaxis with intradermal BCG up to complete two

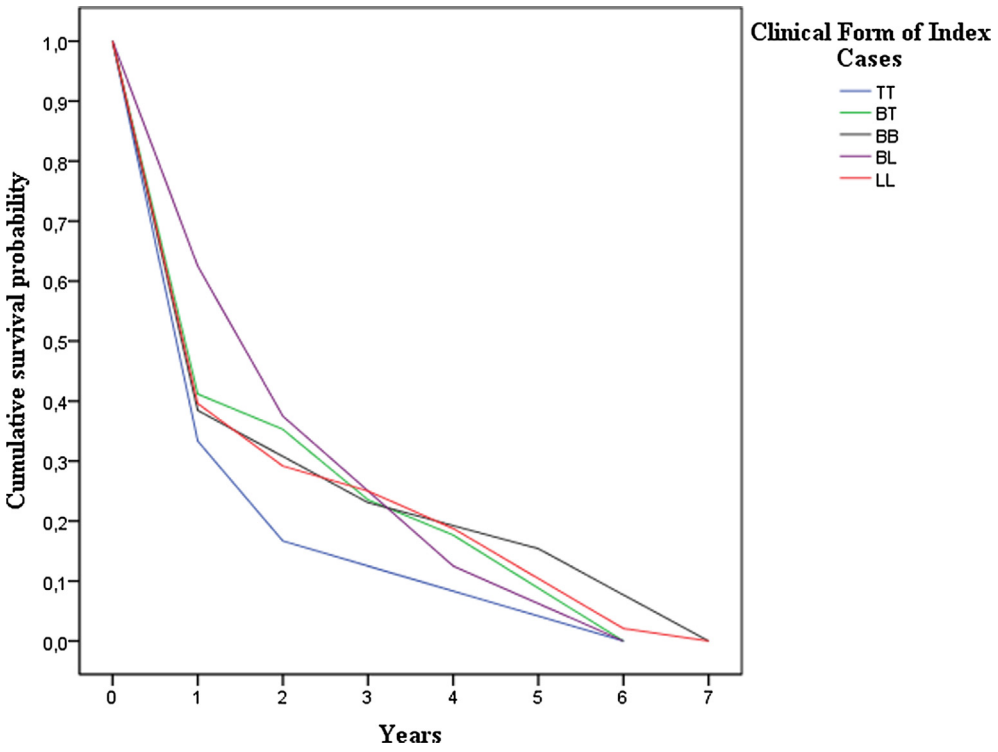

Fig. 4. Survival curve (Kaplan-Meier) of 92 leprosy HHCs that became sick during the annual follow-up for 7 years divided into 5 groups according to the Clinical Form of Index Cases variable. The comparison among 5 cumulative survival probability curves presented no significative difference along all the time of follow-up (Log Rank, p = 0.981; Breslow, p = 0.928; Tarone-Ware, p = 0.971).

doses of this vaccine was evidenced by several studies that this strategy reduces the risk of disease significantly [28,29].

While the other studies evaluated association measures unrelated to the time of outcome, such as odds ratio, relative risk and prevalence ratio, the present study verified the hazard ratio for the first year of follow-up. Hazard ratio is a measure of how rapidly the event of interest occurs which can be interpreted as the relative risk of the occurrence of the event as a function of time. Our study showed that the chance of survival/protection in those cases with 2 BCG scars in the first evaluation was 3 times higher when compared to those with 0 vaccine scars, keeping fixed factors such as sex, age group and clinical form of the index cases. In other words, such information indicates that within 1 year, individuals with 0 BCG scars become ill 3 times faster than those with 2 vaccine scars [19,30,31]. The factors sex, age and clinical form of the index cases did not influence the survival or probability of occurrence of the outcome in leprosy HHCs, since the survival curves for these attributes did not present significant difference. These findings are in line with a previous study that stratifying variables such as sex, age group and clinical form did not find a protective effect related to these factors in leprosy HHCs [32].

It should be emphasized that contact surveillance actions allow prevention and control of the disease, besides early diagnosis, since, after the diagnosis of the index case, its contacts will be monitored annually and advised to return to the health unit for clinical investigation and laboratory if signs and symptoms of the disease arise [33].

5. Conclusion

Our results allow us to conclude that administration of 2 BCG vaccines in healthy leprosy HHCs is extremely important, considering that the high number of contacts who sickened were characterized by the absence of BCG scar in the first evaluation. Besides of it, survival curve proved that 2 BCG scars provide an additional protective effect against the disease. Therefore, the reduction in the risk for the disease over years of follow-up is a result of surveillance actions of the leprosy HHCs, with emphasis on immunoprophylaxis, in addition to the treatment of index cases and multiprofessional teamwork leading to the control of leprosy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are grateful for the leprosy patients who participated in this research, as well as, the entire assistance and laboratory team of the Center for Sanitary Dermatology and Leprosy (CREDESH).

Funding sources

This work was supported by CNPq [Grant numbers, CNPq-465669/2014-0] and FAPEMIG, [Grant numbers, FAPEMIG-CBB-APQ-03613-17]. We declare that the funding sources had no involvement for the conduct of the research and/or preparation of the article.

References

[1] Sasaki S, Takeshita F, Okuda K, Ishii N. Mycobacterium leprae and leprosy: a compendium. Microbiol Immunol 2001;45:729–36. https://doi.org/10.1111/j.1348-0421.2001.tb01308.x.

[2] WHO. Global leprosy update, 2017. Wkly Epidemiol. N°35. 93, 2017. pp. 444-56.

[3] Araujo S, Freitas LO, Goulart LR, Goulart IM. Molecular evidence for the aerial route of infection of mycobacterium leprae and the role of asymptomatic carriers in the persistence of leprosy. Clinical Infectious Diseases: Official Publ

Infect Diseases Soc Am 2016;63(11):1412–20. https://doi.org/10.1093/cid/ciw570.
[4] Fine PE, Sterne JA, Ponnighaus JM, Bliss L, Saui J, Chihana A, et al. Household and dwelling contact as risk factors for leprosy in northern Malawi. Am J Epidemiol 1997;146(1):91–102.
[5] Duppre NC, Camacho LA, da Cunha SS, Struchiner CJ, Sales AM, Nery JA, et al. Effectiveness of BCG vaccination among leprosy contacts: a cohort study. Trans R Soc Trop Med Hyg 2008;102(7):631–8. https://doi.org/10.1016/j.trstmh.2008.04.015.
[6] Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. Expert Rev Vacc 2010;9(2):209–22. https://doi.org/10.1586/erv.09.161.
[7] Goulart IM, Bernardes Souza DO, Marques CR, Pimenta VL, Goncalves MA, Goulart LR. Risk and protective factors for leprosy development determined by epidemiological surveillance of household contacts. Clin Vacc Immunol: CVI 2008;15:101–5. https://doi.org/10.1128/CVI.00372-07.
[8] Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. Lancet 1995;346:1339–45. https://doi.org/10.5555/uri:pii:S0140673695923489.
[9] Setia MS, Steinmaus C, Ho CS, Rutherford GW. The role of BCG in prevention of leprosy: a meta-analysis. Lancet Infect Dis 2006;6:162–70. https://doi.org/10.1016/S1473-3099(06)70412-1.
[10] World Health O. BCG vaccine: WHO position paper, February 2018-Recommendations. Vaccine 2018;36:3408–10. https://doi.org/10.1016/j.vaccine.2018.03.009.
[11] Gillini L, Cooreman E, Wood T, Pemmaraju VR, Saunderson P. Global practices in regard to implementation of preventive measures for leprosy. PLoS NeglTrop Dis 2017;11:. https://doi.org/10.1371/journal.pntd.0005399e0005399.
[12] Shen JP, Gupte MD, Jiang C, Manickam P, Yu MW, Li WZ. Trends of case detection and other indicators of leprosy in China during 1985–2002. Chin Med Sci J Chung-kuo i hsueh k'o hsueh tsa chih 2005;20:77–82.
[13] Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. Int J Leprosy Mycobact Diseases: Off Organ Int Leprosy Assoc 1966;34:255–73.
[14] Richardus RA, Butlin CR, Alam K, Kundu K, Geluk A, Richardus JH. Clinical manifestations of leprosy after BCG vaccination: an observational study in Bangladesh. Vaccine 2015;33:1562–7. https://doi.org/10.1016/j.vaccine.2015.02.017.
[15] Texier L, Maleville J, Geniaux M, Gauthier O, Delaunay MM. Lepromatous leprosy after BCG vaccination. Medicina cutanea ibero-latino-americana 1975;3:381–2.
[16] Bazan-Furini R, Motta AC, Simao JC, Tarquinio DC, Marques Jr W, Barbosa MH, et al. Early detection of leprosy by examination of household contacts, determination of serum anti-PGL-1 antibodies and consanguinity. Mem Inst Oswaldo Cruz 2011;106:536–40. https://doi.org/10.1590/S0074-02762011000500003.
[17] Martinez AN, Talhari C, Moraes MO, Talhari S. PCR-based techniques for leprosy diagnosis: from the laboratory to the clinic. PLoS NeglTrop Dis 2014;8:. https://doi.org/10.1371/journal.pntd.0002655e2655.
[18] Le Grand A. Women and leprosy: a review. Lepr Rev 1997;68:203–11.
[19] Muliyil J, Nelson KE, Diamond EL. Effect of BCG on the risk of leprosy in an endemic area: a case control study. Int J Leprosy Mycobacterial Diseases: Official Organ Int Leprosy Assoc 1991;59:229–36.
[20] Zodpey SP, Bansod BS, Shrikhande SN, Maldhure BR, Kulkarni SW. Protective effect of Bacillus Calmette Guerin (BCG) against leprosy: a population-based case-control study in Nagpur, India. Leprosy Rev 1999;70:287–94.
[21] Oliveira MB, Diniz LM. Leprosy among children under 15 years of age: literature review. Anais brasileiros de dermatologia 2016;91(2):196–203. https://doi.org/10.1590/abd1806-4841.20163661.
[22] Araujo S, Rezende MM, Sousa DC, Rosa MR, Santos DC, Goulart LR, et al. Risk-benefit assessment of Bacillus Calmette-Guerin vaccination, anti-phenolic glycolipid I serology, and Mitsuda test response: 10-year follow-up of household contacts of leprosy patients. Rev Soc Bras Med Trop 2015;48:739–45. https://doi.org/10.1590/0037-8682-0245-2015.
[23] Zodpey SP, Ambadekar NN, Thakur A. Effectiveness of Bacillus Calmette Guerin (BCG) vaccination in the prevention of leprosy: a population-based case-control study in Yavatmal District, India. Public Health 2005;119:209–16. https://doi.org/10.1016/j.puhe.2004.04.007.
[24] Kerr-Pontes LR, Barreto ML, Evangelista CM, Rodrigues LC, Heukelbach J, Feldmeier H. Socioeconomic, environmental, and behavioural risk factors for leprosy in North-east Brazil: results of a case-control study. Int J Epidemiol 2006;35:994–1000.
[25] Convit J, Sampson C, Zuniga M, Smith PG, Plata J, Silva J, et al. Immunoprophylactic trial with combined Mycobacterium leprae/BCG vaccine against leprosy: preliminary results. Lancet 1992;339(8791):446–50. https://doi.org/10.1093/jie/dyl072.
[26] Duthie MS, Gillis TP, Reed SG. Advances and hurdles on the way toward a leprosy vaccine. Human Vaccines 2011;7:1172–83. https://doi.org/10.4161/hv.7.11.16848.
[27] Anjum V, Vijayakumaran P. Presence of an index case in households of newly registered leprosy patients: experience from a leprosy referral centre in South India. Lepr Rev 2015;86:383–6.
[28] Romero-Montoya M, Beltran-Alzate JC, Cardona-Castro N. Evaluation and monitoring of mycobacterium leprae transmission in household contacts of patients with Hansen's disease in Colombia. PLoS NeglTrop Dis 2017;11:. https://doi.org/10.1371/journal.pntd.0005325e0005325.
[29] Rodrigues LC, Kerr-Pontes LR, Frietas MV, Barreto ML. Long lasting BCG protection against leprosy. Vaccine 2007;25:6842–4. https://doi.org/10.1016/j.vaccine.2007.07.032.
[30] Orege PA, Fine PE, Lucas SB, Obura M, Okelo C, Okuku P. Case-control study of BCG vaccination as a risk factor for leprosy and tuberculosis in western Kenya. Int J Leprosy Other Mycobacterial Diseases: Official Organ Int Leprosy Assoc 1993;61:542–9.
[31] Altman DG, Bland JM. Time to event (survival) data. BMJ 1998;317:468–9.
[32] Lombardi C, Pedrazzani ES, Pedrazzani JC, Filho PF, Zicker F. Protective efficacy of BCG against leprosy in Sao Paulo. Bull Pan Am Health Organ 1996;30:24–30.
[33] Hacker Mde A, Duppre NC, Nery JA, Sales AM, Sarno EN. Characteristics of leprosy diagnosed through the surveillance of contacts: a comparison with index cases in Rio de Janeiro, 1987–2010. Mem Inst Oswaldo Cruz 2012;107 (Suppl 1):49–54. https://doi.org/10.1590/s0074-02762012000900009.