Tuberculosis in Vaccinated versus Unvaccinated Children with BCG Vaccine in Niamey: Epidemiological, Diagnostic and Outcome Aspects

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Doi: 10.19044/esipreprint.9.2022.p208

Approved: 17 September 2022
Posted: 19 September 2022

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Cite As:
Aboubacar S., Alido S., Moumouni K., Djafar M.A., Moumouni G., Assiatou G.I.M., Abasse M.O., Boubacar M.S., Habiba I.A., Nafissatou N. & Ibrahim G.T. (2022). *Tuberculosis in Vaccinated versus Unvaccinated Children with BCG Vaccine in Niamey: Epidemiological, Diagnostic and Outcome Aspects.* ESI Preprints.
https://doi.org/10.19044/esipreprint.9.2022.p208

Abstract

Introduction: Tuberculosis remains a public health problem worldwide. The BCG vaccination is one of response means. The objective of this work was to study impact of BCG vaccination on morbidity and mortality related to childhood tuberculosis in Niamey. **Patients and methods:** It was a multicenter prospective and comparative study from January to September 2017 in two-referral hospital centers of Niamey and the National Anti-Tuberculosis Center. The study population consisted exhaustively of children aged 0 to 15 years old suffering from tuberculosis. Epidemiological, diagnostic and evolving aspects in vaccinated and unvaccinated children were studied. Statistical tests used were Pearson's Chi² and Fisher's exact test ($p < 0.05$). **Results:** Ninety-one children were studied. The BCG vaccination rate was 60.4%. The mean age of children was 6 years 11 months [3 months-15 years]. Children under 2 years of age were less affected (11%) in vaccinated children than in unvaccinated children (3.2%). No association was found between duration of tuberculosis signs ($p = 0.37$), expression of tuberculin skin test ($p = 0.43$), and the children's BCG vaccination status. On the other hand, there was a significant link between vaccination status and the results of microscopic examination of sputum or gastric fluid ($p = 0.02$), occurrence of complications ($p = 0.014$) and death risk ($p = 0.003$). **Conclusion:** This study shows that children's BCG vaccination status interferes with some aspects of tuberculosis. Therefore, fighting against tuberculosis must be intensified, through combination of many strategies including vaccination.

Keywords: BCG vaccination; Children; Tuberculosis; Niger

Introduction

Tuberculosis is the most common specific bacterial disease and still remains a global public health problem, especially in developing countries, due to its morbidity and mortality. In 2015, according to WHO estimates, at least one million children contracted tuberculosis each year worldwide (O.M.S., 2016). In Niger, overall incidence is 95 cases per 100.000 habitants (PNLT, 2017). Control of tuberculosis in children is traditionally based on early diagnosis and treatment of pulmonary tuberculosis, identification of contacts and vaccination with BCG vaccine (O.M.S., 2016). The objective of this study was to investigate impact of BCG vaccine on tuberculosis morbidity and mortality in children.

Patients and methods

Type, period and setting of the study

This was a prospective multicenter and comparative study from January to September 2017 at two referral hospital centers of Niamey (national hospital of Niamey and Amirou Diallo national hospital), and the National Anti-Tuberculosis Center in Niger.

Study population

All children aged 0 to 15 years with all forms of tuberculosis were included. Children with sickle cell disease and who living with HIV/AIDS were excluded. Variables studied were BCG vaccination status, children age, diagnostic and evolving aspects.

Diagnostic criteria

Diagnosis of tuberculosis was suspected in children who had a long-lasting fever with night sweats, an altered general state of with asthenia, anorexia and weight loss. The diagnostic suspicion was supported by paraclinical criteria which are a tuberculin intradermal reaction test (IDRT) ≥10 mm, an accelerated sedimentation rate (≥ 20 mm at the first hour), exudative character and hyperlymphocytosis of the effusions (ascites and pleurisy), or histology of the adenopathies showing granulomatous lymphadenitis with caseous necrosis. Radiologically, it was presence of suspicious parenchymal opacities such as miliaria, caverns, or alveolo-interstitial opacities. And finally, therapeutic criteria which consisted of well-conducted antituberculosis treatment according to national protocol of tuberculosis management. In some cases, diagnosis is confirmed by the positivity of miscroscopic examination (sputum, gastric fluid).

Data analysis

Data analysis was performed using Epi-Info7 version 7.2.1 software. The relationship between categorical variables was estimated using Pearson's Chi^2 test and Fisher exact test ($p < 0.05$). Risk quantification was done by estimating the Odds Ratio (OR) and its confidence interval (CI) to 95%.

Results

Children characteristics

Ninety-eight cases of tuberculosis were collected during the study period. Four cases of HIV/AIDS infection and 3 cases of sickle cell disease were excluded. A total of 91 patients was studied. BCG vaccination rate was 60.4%. The mean age of children was 6 years 11 months [3 months-15 years]. Children under 2 years of age were less affected (11%) in vaccinated children than in unvaccinated children (3.2%).

Diagnostic aspects

The table 1 represents diagnostic aspects of tuberculosis. The mean duration of signs before admission was 40 days [21 to 120 days], with no relationship to BCG vaccination status (p=0.37). Tuberculin skin test (TST) was positive in 41.6% of vaccinated children versus 29.6% of unvaccinated children (p=0.43). Sputum or gastric fluid microscopic examination was done in 54.9% of patients. It was positive in 13.2% of vaccinated children versus 2.2% of unvaccinated children (OR=4.53; CI [1.05-31.70], p=0.02). Extrapulmonary localization was more frequent in vaccinated children (39.6%) than in unvaccinated children (29.6%), but there was no relationship (p=0.35).

Table 1. Link between diagnostic aspects and BCG vaccination status

	BCG Vaccination				
Variables	Yes N (%)	No N (%)	OR	CI	P
Duration of signs (days)					
≤30	29 (31.9)	20 (22)	0.89	[0.37-2.09]	0.37
>30	26 (28.6)	16(17.5)			
Result of TST					
Positive	38 (41.7)	27 (29.6)	1.12	[0. 24-4.83]	0.43
Negative	5 (5.5)	4 (4.4)			
Microscopic examination					
Positive	12 (13.2)	2(2.2)	4.53	[1.05-31.70]	0.02
Négative	23 (25.2)	13(14.3)			
Localization					
Pulmonary	19 (20.9)	9(9.9)	0.83	[0.33-2.06]	0.35
Extrapulmonary	36(39.6)	27(29.6)			

Therapeutic and evolving aspects

All patients were treated according to the therapeutic regime for new cases according to national protocol for management of tuberculosis. Evolution was more favorable in vaccinated children (55%) than in unvaccinated children (28.6%). The difference was significant (OR=3.78; CI [1.17-13.43], p=0.01). Complications such as bronchopulmonary sequelae were less frequent in vaccinated children (4.4%) than in unvaccinated children (6.6%), without relationship (p=0.08). Death was observed in 1.1% of vaccinated patients versus 7.7% of unvaccinated (OR=12.69; CI [1.84-300.81], p=0.003).

Discussion

Based on results observed, it was an interaction between BCG vaccination and TB morbidity and mortality in children. Mainly study limitation was related to small sample size.

Children under the age of two years were the least affected, with no relationship to age groups. This could be explained by the role of breastfeeding in this age group (Randriatsarafara and *al.* 2014). Vaccination coverage was 60.4%. Similar result was reported by Soumana and *al.* (2016) and Randrianambinina and *al.* (2015) with 65.5% of children vaccinated with BCG vaccine each one. However, they are lower than those reported by Randriatsarafara and *al.* (2014) and Ba and *al.* (2015) who found 82.5% and 84.5% of vaccinated patients respectively. In Niger, BCG vaccination is systematically given to children from birth. The low vaccination rate reported in this study could be explained by that children with TB often came from poor families with limited access to health services.

Average duration of signs of tuberculosis before admission was not related to the child's vaccination status. Long diagnostic delay observed could be explained by ignorance of signs of the disease, but also by beliefs of parents. Many of whom were still trying traditional treatment before consultation. IDRT expression was not associated with the BCG vaccination status. The same finding was made by Tinsa and *al.* (2009). However, Seddon and *al.* (2016) found a significant difference in IDRT results according to age group. In his study, vaccinated children under 5 years of age were more likely to have a positive TST than who were not vaccinated. An influence of vaccination on microscopic results was found in this study. Vaccinated children tending to have positive microscopic sputum or gastric fluid examination. Vaccination status of children did not influence pulmonary or extra-pulmonary localization of tuberculosis. No cases of tubercular meningitis were observed, but two cases of miliary tuberculosis were found. Most authors have shown that BCG vaccination protects against the severe forms of tuberculosis (disseminated forms and neuro-meningeal forms) in children (Valin and *al.* (2012), Schmiedel and *al.* (2015), Abubakar and *al.* (2013), Bourdin et *al.* (2006)). However, in the series of Sfaihi and *al.* (2019), BCG vaccination did not protect children from tuberculosis. In this case, the presence of one of severe forms in vaccinated children could be explained by low organism immune capacities or an massive contamination.
Tuberculosis course was more favorable in vaccinated children than in unvaccinated children. A significant association was found between vaccination status and mortality. Unvaccinated children had more death risk from tuberculosis than vaccinated children. Harris and *al.* (2016) demonstrated a death risk from tuberculosis of 151 per 100,000 for children not protected by BCG vaccine. Other studies and meta-analyses have

reported increased mortality in group of children not vaccinated with BCG vaccine (Favorov and *al.* (2012), Schmiedel and *al.* (2015), Abubakar and *al.* (2013), Moran and et *al.* (2010)). Grare and *al.* (2010) reported that in Swedish, Czech and German experiences, cessation of routine vaccination was associated with a real but limited increase of tuberculosis incidence in children. However, despite these observations, BCG vaccination recommendations should be made on local epidemiological factors.

Conclusion

This study shows that BCG vaccination status of children interferes with some aspects of tuberculosis. Vaccination status of children is related to occurrence of complications and risk of death. Thus, fighting against tuberculosis must be intensified through a combination of several strategies, such as vaccination, active screening and adequate case management, and promotion of research for new vaccines, diagnostics and therapeutics.

Conflict of interest: None

Authors contributions: SA and MOA and GIMA designed research protocol; IAH, NN, and MSB collected the data; SA, KM, and SA participated wrote the manuscript; and MAD, GM, and GTI proofread and edited final document.

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