

Effectiveness of bacillus Calmette–Guerin vaccination history on pulmonary tuberculosis symptoms

Safar Farajnia^a, Khalil Ansarin^b, Leyla Sahebi^{c,*}

^a Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

^b Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

^c Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Science, Tabriz, Iran

ARTICLE INFO

Keywords:

Mycobacterium tuberculosis
Vaccine effectiveness
Symptoms
Bacillus Calmette–Guerin
Pulmonary tuberculosis

ABSTRACT

Introduction: The aim of this study was to explore the effectiveness of BCG vaccination on the severity of clinical symptoms of pulmonary tuberculosis symptoms (PTb) in patients from the northwest and west of Iran.

Materials and methods: In a cross sectional study of 358 patients with a diagnosis of PTb, 11 clinical symptoms, including cough, chest pain, dyspnea, sputum, fever, hemoptysis, weight loss, loss of appetite, wheezing, weakness, and fatigue were checked and patients with a score of six or more were placed in the severe clinical symptoms group. BCG vaccination scar and clinical symptoms were examined and recorded.

Results: Of the subjects included in this study, 264 cases (73.7%) had no BCG vaccination scar. Comparison of the severity of clinical symptoms of PTb in patients with BCG vaccine history to those lacking vaccination history revealed lower symptom severity in patients who had been vaccinated (vaccine effectiveness = 95.5%; $p < 0.00001$)

Conclusion: The results of this study may imply that Adjusting for age sex and smoking status, BCG vaccination decreases the severity of clinical symptoms in patients with PTb. We suggest performing a retrospective cohort study on a larger population.

1. Introduction

Bacillus Calmette–Gurein (BCG) is remains the only vaccine used regularly to vaccinate against TB [1]. Reports on the effectiveness of BCG vaccine are controversial and its ability to protect individuals from TB is varied in different parts of the world [1–2]. In fact BCG does not always protect people from getting TB [3]. In a meta-analysis by Roy and et al. on 14 studies and 3855 participants, a protective efficacy of 19% against infection among vaccinated children after exposure compared with unvaccinated children was reported [4]. Some trials reported 60–80% protective efficacy against severe forms of pulmonary tuberculosis (PTb) (military and meningitis) in children. In addition, BCG vaccination protects against extra-pulmonary TB [5]. No information is available regarding the effectiveness of BCG on clinical symptoms of pulmonary tuberculosis symptoms (PTb). The aim of this study was to measure the amount of protection BCG offered in lessening the severity in Ptb patients

2. Materials and methods

In a 2014 cross sectional study, 358 patients with PTb were randomly selected for analysis from five border provinces of Iran including East and West Azerbaijan, Ardebil, Kermanshah, and Kurdistan. Sputum-positive PTb was defined by WHO in 2007 to be based on the presence of at least one acid fast bacilli (AFB+) in at least one sputum sample in countries with a well-functioning external quality assurance system [6].

2.1. Transporting and preparing cultures

Samples were cultured and the isolates were transported by TB laboratories in each province to the reference laboratory under standard conditions. After receiving the cultures, screening was performed to confirm the isolates as members of the Mycobacterium tuberculosis (MTB) complex. The complex was identified by culturing on a Löwenstein-Jensen (LJ) medium containing p-nitro benzoic acid where growth indicates the bacilli are not part of the MTB complex. The differentiation of MTB from other members of the MTB complex was

* Corresponding author.

E-mail address: sahebileila@yahoo.com (L. Sahebi).

<https://doi.org/10.1016/j.jctube.2019.100126>

identified based on a niacin and nitrate test [6–7].

2.2. Severe clinical symptom criteria and BCG scar

Criteria for identifying severe forms of TB are generally based on radiological signs and symptoms of disease [8–9]. In this study, chest X-ray data was not available, so we relied on the 11 TB clinical symptoms: cough, chest pain, dyspnea, sputum, fever, hemoptysis, weight loss, loss of appetite, wheezing, weakness, and fatigue. Positivity for each symptom was recorded as score of 1, whereas negative symptoms were recorded as 0, so that a score ranging from 0–11 was given to each patient. Patients with a score of six or more were placed in the severe clinical symptoms group. History of BCG vaccination was determined by a physician through checking for the presence of the typical BCG scar often left by the vaccine in the deltoid part of the upper arm

2.3. Demographic variables

Demographic data including age, gender (0: female, 1: male), and smoking status (0: No, 1: Yes) was obtained through a questionnaire. .

2.4. Statistical analyses

In a pilot study, the validity of the questionnaire was evaluated and its reliability was assessed using a statistical reliability test (Cronbach's alpha = 0.92). A multiple linear regression test was performed to assess the effect of BCG vaccination on the prevention of acute TB while controlling for age, sex and smoking. A significance level of 0.05 was considered using SPSS 20 software (SPSS Inc., Chicago, Ill, USA). Vaccine effectiveness (VE) was determined by using the formula, $VE = (1 - OR) \times 100$, where OR is the odds of vaccination history among patients with acute TB to odds of vaccination in non-acute TB patients [10]. Confidence interval was calculated at the 95% level.

2.5. Compliance with ethical standards

There were and continue to be no relationships or interests that can have direct or potential influence or impart bias on this work. The authors declare that they have no competing interests. This work is a section of a PhD thesis that has been approved by the regional ethics committee (code of 5/4/5375 in date of September 8, 2012) in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards in Tabriz University of Medical Science. The rights of all patients were regarded. All patients had the right to decide what, if any, identifiable data could be gathered, and to choose what to say during a study or interview. The researchers did not know the names of participants and participant identification was blinded.

3. Results

Based on the prevalence of the smear-positive PTb in five provinces, isolates were proportionally sampled from patients in East Azerbaijan (124 [34.6%]), Kermanshah (66 [18.4%]), West Azerbaijan (50 [14.0%]), Kurdistan (74 [20.7%]), and Ardabil (44 [12.3%]).

The age range of patients was six months to 96 years old, the mean age of MTB patients was 53.65 (SD = 23.0), and 164 (45.8%) of the patients were female. Of the 358 active MTB patients, 264 cases (73.7%) had no BCG vaccination scar. A total of 96 patients (26.8%) had no history of active smoking. Clinical symptoms of TB patients were distributed as follows: cough 161 cases (44.97%), chest pain 144 (40.22%), dyspnea 136 (37.99%), sputum 184 (51.4%), fever 136 (37.99%), hemoptysis 76 (21.23%), weight loss 172 (48.04%), loss of appetite 125 (34.92%), wheezing 132 (36.87%), weakness 134 (37.43%), and fatigue 108 patients (30.17%).

We used multiple linear regression models to examine the adjusted

Table 1

examine the associations between acute TB and BCG vaccination scar after controlling of age, gender, smoking habit and TB drug resistance by multiple linear regression.

Variables	Coefficients		Sig.
	B	Std. Error	
Age	−0.011	0.012	0.391
Gender (0 = Female, 1 = Male)	−1.287	0.434	0.004
Smoking habit(0 = No, 1 = Yes)	0.699	0.562	0.215
Any TB drug resistance (0 = No, 1 = Yes)	1.281	0.769	0.098
Vaccination scar (0 = No, 1 = Yes)	−2.572	0.622	0.000

associations between acute TB and BCG vaccination scar after controlling for age, gender, and smoking status. Interestingly, the probability of acute TB was significantly less among patients with a BCG vaccination scar compared to patients without vaccination history (P -value < 0.001) (Table 1).

We analyzed adjusted BCG VE based on PTb clinical symptoms. The BCG vaccine showed a strong preventive effect against acute TB (VE = 95.5%; 95% CI, 80.7%–98.9%), after controlling for age, gender, and smoking status. In addition, VE was significantly different in groups stratified by age in the 46–60-year-old group (95% CI, 17.8%–93.8%) and non-smokers (95% CI, 55.6%–92.2%) (Fig. 1).

4. Discussion

The BCG vaccine has been used in Iran since 1947. The *Pasteur 1173P2* strain was cultured in Iran for the first time in 1974 and 3 years after that, the first lyophilized BCG vaccine was produced [11]. Between 1980 and 2016, BCG vaccination coverage has increased from 7% to 99% in Iran [12], but there is no study regarding the effect of BCG vaccination on PTb symptoms.

Our study provided important findings on the effect of BCG vaccination on symptoms of PTb. The results indicated that the BCG vaccine had an overall effectiveness of 95.5% for the prevention of acute TB.

In cases where a vaccine does not fully protect the vaccinated person, vaccination still has a preventive effect on the development of severe types of disease in children [5]. So it is postulated that vaccination could be effective in relieving the symptoms of PTb in adults. The basis of BCG's protection in the prevention of TB is related to the antigenic similarity of the particular vaccine strain with prevalent wild infectious strains in the community. Results from a previous study of our group indicated that BCG vaccination induces higher immunity against certain MTB strains [13]. But determining how BCG vaccine affects the severity of TB symptoms is challenging.

TB is a chronic disease with multiple clinical symptoms that imposes a noticeable burden on society and disability in patients. The main finding of this study was the reduction of clinical symptoms of TB in patients who had a history of BCG vaccination. These findings could be key implications for its use in current immunization programs as well as in the future development of new and improved TB vaccines.

Although this was not a randomized control trial, our data are important since it is the first study indicating VE on acute TB development. Lack of patients and impossibility of investigating the role of BCG vaccination on radiological signs was a limitation. We suggest performing a retrospective cohort study on a larger population.

5. Conclusion

The results of the present study indicated that BCG vaccine shows an overall effectiveness of 95.5% in the prevention of acute TB.

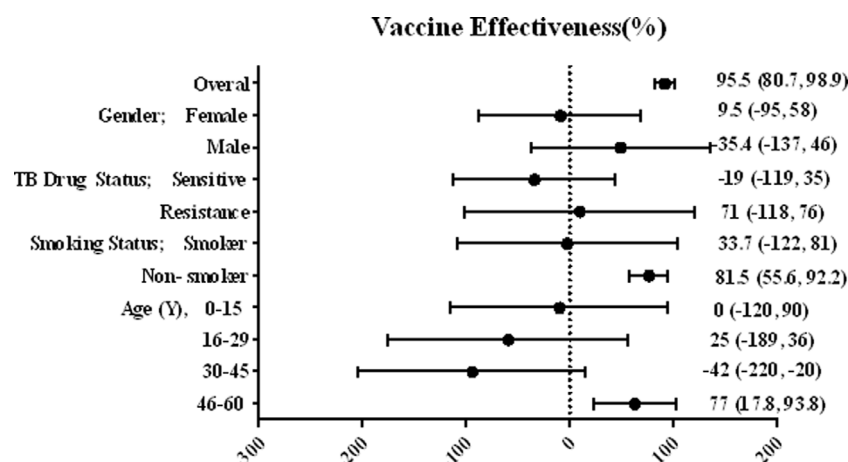


Fig. 1. Adjusted vaccine effectiveness $([1 - \text{Odds Ratio}] \times 100\%)$ overall and stratified by age, gender, smoking status and drug resistance status in Iranian TB patients.

Declaration of Competing Interest

The authors warrant, there is not any conflict interest, financial or otherwise. This is not a duplicate submission, such as, the work on which this paper is based has not already, been reported in a published article or in another paper that has been submitted or accepted for publication elsewhere in print or electronic media.

Acknowledgments

We wish to thank our colleagues in other countries who helped us search literature. Special thanks to Hasmic Margaryan (Armenia) and Dr. Amina Al Thawani (Iraq). Many thanks to Lesley Carson for her help in finalizing the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jctube.2019.100126](https://doi.org/10.1016/j.jctube.2019.100126).

References

- [1] Putera I, Pakasi TA, Syahmar I, Bramantyo AA, Karyadi E, Melani A, et al. Effectiveness of the Bacillus Calmette - Guérin vaccine in an Indonesian population with D543N NRAMP1 Polymorphism. *J Infect Dev Ctries* 2015;9(1):42–7. <https://doi.org/10.3855/Jidc.5047>.
- [2] Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA* 1994;271:698–702.
- [3] Davenne T., McShane H. Why don't we have an effective tuberculosis vaccine yet? *Expert Rev Vaccines*. 2016; 15(8): 1009–1013.
- [4] Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis. *BMJ* 2014;349:g4643. <https://doi.org/10.1136/bmj.g4643>.
- [5] Varaine F., Rich M. Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. Médecins Sans Frontières and Partners In Health. 2014 ISBN number: 2-90106498-96-3. Last Updated: 7 June 2017. Accessed July 16, 2019 from: http://refbooks.msf.org/msf_docs/en/tuberculosis/tuberculosis_en.pdf.
- [6] WHO. TB diagnostics and laboratory strengthening - WHO policy 2015. Last Update: 14 June 2015. Accessed July 16, 2019 from: https://www.who.int/tb/areas-of-work/laboratory/policy_sputum_smearpositive_tb_case/en/.
- [7] Van Soolingen D, Qian L, de Haas PE, Douglas JT, Traore H, Portals F, et al. Predominance of a single genotype of *Mycobacterium tuberculosis* in countries of East Asia. *J Clin Microbiol* 1995;33(12):3234–8.
- [8] Raina AH, Bhat A, Bhat FA, Chhangal KH, Dhobi GN, Koul PA, et al. Pulmonary tuberculosis presenting with acute respiratory distress syndrome (ARDS): a case report and review of literature. *Egypt J Chest Dis Tuberc* 2013;62(4):655–9.
- [9] Silva DR, Gazzana MB, Dalcin Pde T. Severe tuberculosis requiring ICU admission. *J Bras Pneumol* 2012;38(2):386–94. <https://doi.org/10.1590/S1806-37132012000300015>.
- [10] Weinberg CA, Szilagyi PG. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. *J Infect Dis* 2010;11:1607–10.
- [11] Fallah F, Abdolghafoorian H. The history of tuberculosis and bacillus Calmette–Guérin vaccine in Iran. *Arch Pediatr Infect Dis* 2015;3(1):20766.
- [12] WHO. WHO. Global Health Observatory data repository, full child immunization immunization coverage estimates by country(2016) last update 102018. Accessed 22 July 2019 from: <https://apps.who.int/gho/data/view.main.UHCIMMUNIZATIONv?lang=en>.
- [13] Sahebi L, Ansarin K, Hoffner S, Farajnia S, Seyyedi M, Khalili M, et al. Molecular epidemiology of *Mycobacterium tuberculosis* strains in the north-west and west of Iran. *Ann Med Health Sci Res* 2015;5(5):334–9.