Effect of BCG vaccination against tuberculosis infection in Young immigrants: a systematic review and meta-analysis

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Abstract: This study aimed to review the effect of BCG vaccination against TB infection in young immigrants. We performed a systematic review and meta-analysis to determine whether the BCG vaccination is effective against TB infection among immigrant children and young adults. We also examined whether past living history in high-risk areas or countries would impact the effectiveness of BCG vaccination.

*Keywords: BCG vaccination, tuberculosis infection, immigrants, meta-analysis*

1. Introduction

Tuberculosis (TB) is a disease affecting the lung caused by Mycobacterium tuberculosis (M. Tuberculosis) infection[2]. It is one of the leading causes of death worldwide and its long incubation period (2-5 years) makes screening at early stages difficult. Centers for Disease Control and Prevention (CDC) reported that infants and young children are more likely to develop severe forms of TB[3]. Research showed that people from countries with a high prevalence of TB would have a higher risk of getting TB infection than those from countries with a low prevalence of TB, and they are the main population of immigrants[1]. Those two factors make young immigrants a high-risk group for TB and the main resource for importing TB cases from countries with a low prevalence of TB. So, it is important to have effective preventive measures, such as vaccines, to lower the rate of TB infection among young immigrants to prevent worldwide TB outbreaks. As the only vaccine to avoid Tuberculosis infection now, the Bacille Calmette-Guérin (BCG) vaccine is recommended in most countries[3]. Previous studies showed that the BCG vaccination could decrease the risk of meningitis and miliary TB in children by 80%[1].

Currently, there are two main tests to distinguish whether subjects are infected by Tuberculosis germs. One is the tuberculin skin test (TST)[6], and the other is T cell based interferon γ release assays (IGRA)[6]. Compared with TST, IGRA has advantages in its more accurate positive result. However, TST would be preferred to lower the cost of TB infection screening in mid-and-low income countries.

2. Methods

2.1. Search strategy and inclusion criteria
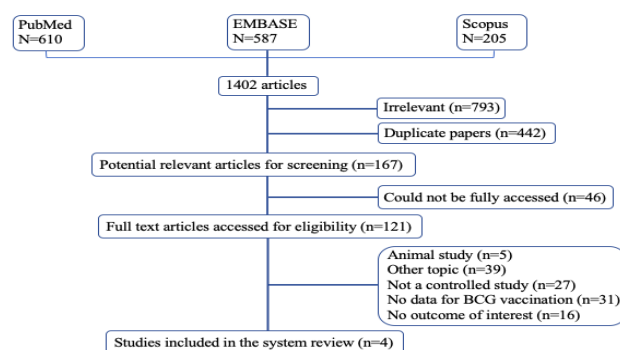
Note. BCG infection or infection was defined as positive results of either TST or IGRA test though tested people did not have symptoms of active TB. Latent TB was also included. Young adults were defined as people whose ages were from 18 to 30 years olds. Children were defined as people whose

ages were from 0 to 17 years olds.

Figure 1: Study selection for meta analysis of the effect of BCG vaccination against Tuberculosis infection in young immigrants

We searched in the following databases: PubMed (2007 until December 2021), EMBASE (2007 until December 2021) and MeSH (2007 until December 2021). Finding articles were reviewed to determine whether they were suitable for this meta-analysis or not. Related articles and articles in reference lists of articles found by the database searches were also reviewed. We selected 167 articles for abstract review based on title review and re-duplication. After filtering 46 articles that could not be fully accessed, 121 articles remained for further analysis. Finally, 4 articles (included 4 studies) were selected for this meta-analysis (Figure 1).

2.2 Characters of included studies

The meta-analysis included studies of children who immigrated from countries other than countries where studies were located, born in immigrant families, and were refugees. Four selected studies were in Germany, Greece, Sweden and Malaysia. Formal BCG vaccination records or BCG scar were accepted to confirm BCG vaccination status for children and adolescents in studies (Table 1).

Table 1: Characteristics of studies included in meta analysis of the effect of BCG vaccination against Tuberculosis infection in young immigrants

Author/year	Country	Study period (Y)	Study Setting	Sample Size	Age group (years)	Quality rating*
Mueller-Hermelink 2018[4]	Germany	September 2015 to November 2016	Asylum seeking children	986	3 months to 15 years	Moderate
Son 2018[7]	Korea	January 2011 to May 2016	Children who would immigrate to America	1687	2 years to 14 years	Low
Trollfors 2021[9]	Sweden	2010 to 2018	Young immigrants	1404	0 months to 17 years	High
Wong 2020[10]	Malaysia	April 2018 to April 2019	Refugee children	430	3 years to 17 years	High

* Newcastle-Ottawa scale rating: High (>66.6%), Moderate (33.3%-66.6%), Low (<33.3%)

2.3. Primary analysis

The primary analysis with 4 studies and 3939 participants found the overall risk ratio was 0.43 (95% confidence interval 36% to 50%), indicating 57% protective rate of BCG vaccines to prevent tuberculosis infection in the vaccinated group compared with the unvaccinated group. The heterogeneity was high (I^2=91%, P<0.00001) between each study (Figure 2).

Figure 2: Protection against Tuberculosis infection as determined by interferon γ release assay (IGRA) or tuberculin skin test (TST) in young immigrants vaccinated with BCG or not.

2.4. Subgroup analysis

The statistics from 4 studies showed TB infection cases and rates among young immigrants with their BCG vaccination rate. The BCG vaccination rate for all studies was moderate, in the range of 50% to 75%. Table 2 and Figure 3 showed that more people moved from countries with a low-risk level of TB would get BCG vaccinated than those who moved from areas with a high-risk level of TB ($|r|<0$, [r=Pearson correlation: no correlation ($|r|<0$), low ($0.1<|r|<0.3$), medium ($0.3<|r|<0.5$), high ($0.5<|r|<1.0$)]). And the infection rate of TB for people who came from mid-low TB risk areas would be lower than those from high TB risk areas ($|r|=0.424$).

Table 2: Characteristics related to the possibility of Tuberculosis infections for young immigrants

Country of Arrival	TB Risk Level of Country of Origin	Sample Size	BCG vaccinated rate	TB infection cases	TB infection rate
Malaysia10	High risk	367	66.0%	52	14.2%
	Mid-low risk	57		3	5.3%
Germany4	High risk	968	57.6%	66	6.8%
Sweden9	High risk	1404	72.0%	239	17.0%
Korea7	High risk	115	75.2%	28	24.3%
	Mid-low risk	1549		63	4.1%
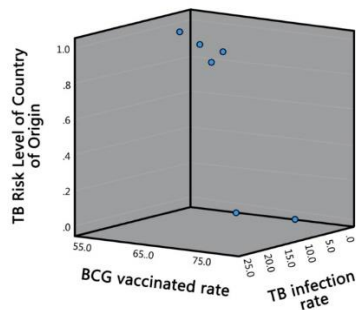
Correlations

		TB Risk Level of Country of Origin	BCG vaccinated rate	TB infection rate
TB Risk Level of Country of Origin	Pearson Correlation	1	-.219	.707
	Sig. (2-tailed)		.676	.116
	Sum of Squares and Cross-products	1.333	-3.867	14.500
	Covariance	.267	-.773	2.900
	N	6	6	6
BCG vaccinated rate	Pearson Correlation	-.219	1	.424
	Sig. (2-tailed)	.676		.402
	Sum of Squares and Cross-products	-3.867	233.173	114.960
	Covariance	-.773	46.635	22.992
	N	6	6	6
TB infection rate	Pearson Correlation	.707	.424	1
	Sig. (2-tailed)	.116	.402	
	Sum of Squares and Cross-products	14.500	114.960	315.455
	Covariance	2.900	22.992	63.091
	N	6	6	6

Figure 3: The correlation between characteristics related to the possibility of Tuberculosis infections for young immigrants

3. Discussion

This systematic review and meta-analysis aimed to test if BCG vaccination could protect young people, especially young immigrants, against tuberculosis infection and reinforced recent research on this topic. Previous research done in Indonesia (a high-prevalence country) showed that BCG protection against TB infection was around 48% among examined young children (95% confidence interval 19% to 67%)[8]. Another research done in Greece (a low-prevalence country) represented that BCG protection against TB infection was around 19% among examined young children (95% confidence interval 8% to 29%)[8]. Research results showed that BCG vaccines would help protect adolescents from TB infections. Scientists indicated that immigrating from foreign countries would be a risk factor for young children infected by TB[8]. Statistics included in this review showed that young immigrants from countries with low TB risk levels would have higher BCG vaccination rates and lower infection rates than those with high TB risk levels[5]. The relationship between the effectiveness of BCG vaccines and the immigration history of young immigrants could be concluded from this meta-analysis, which would improve future TB control.

Findings from this meta-analysis would provide several important public health points for governments to prevent TB infections. We find that the BCG vaccine effectively prevents TB infections among young immigrants. Immigrants with BCG vaccination records would lower infection rates than those without vaccination records. It shows that preventive therapy is effective. Also, it shows that the pre-screening process before young immigrants leave their home countries is essential for immigrant countries. Though young children rarely infect other people, there is still a risk for governments to accept young immigrants with TB infections.

However, the result of this meta-analysis should be treated with caution. Several limitations occur during the analysis process. Data would not be considered complete, and the analysis only includes data from 4 countries. It could not represent every situation in the world. Also, the described data doesn't show participants' history of TB infection. It means that the exposure of some young immigrants would be different, which would possibly make them more easily susceptible to being affected by TB. Moreover, the travel routes of young immigrants are not clearly included in the research, so it is hard to control that every participant would experience the same situation, such as the contact history with TB infectors and the travel history in places that gather with TB infectors.

4. Conclusion

This meta-analysis includes 4 research from different countries globally, which mainly focuses on young immigrant groups. The result shows that BCG vaccines would effectively prevent young immigrants from getting TB infection. Immigrants from high TB risk areas have a lower BCG vaccination rate than those from mid-low TB risk areas. It represents that the policy of putting prevention first would be helpful to solve the problem of TB infections in young children around the world, especially immigrants, to decrease the possibility of imported TB cases.

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