

Effectiveness of Bacillus Calmette-Guerin for Tuberculosis Prevention Among Chinese People: Systematic Review and Meta-analysis

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Abstract: *Background:* Our previous study showed that the protective effect of Bacillus Calmette-Guerin (BCG) declined with time, which is supported by a following study saying "BCG vaccination protection against tuberculosis varies between populations, to an extent that cannot be attributed to chance alone". *Objective:* To investigate BCG protective effect among Chinese people, so as to update the development and use of immunological agents. *Methods:* Systematic review was carried out: electronic databases searches, screening of identified studies based on inclusion and exclusion criteria, data extraction and meta-analysis were undertaken. *Results:* Initial search identified 3067 articles from four Chinese databases, after selection, 25 met the eligibility criteria among which 6 were cohort studies and 19 were case-control studies, with the total participant of 1311758 and 5169 respectively. None of the experimental studies such as randomized controlled trials (RCTs) were identified. The P value of Egger's test was 0.016 for cohort studies and 0.067 for case-control studies, which, together with funnel plot, indicated that the available evidences were at risk of publication bias. The pooled estimate of RR for cohort studies was 0.24, with 95% confidence interval (95%CI) (0.11, 0.52), and of OR for case-control studies it was 0.37 with 95%CI (0.31,0.45). *Conclusions:* The available evidence shows positive and definite effect of BCG in preventing TB among Chinese people but it should be supported by more studies to avoid publication bias risk. High quality studies are encouraged worldwide to update the development and use of immunological agents to cope with tuberculosis epidemiology.

Keywords: Bacillus Calmette-Guerin (BCG), China, Meta-analysis, Observational study, Systematic review, Tuberculosis (TB).

1. INTRODUCTION

The trends in estimated tuberculosis (TB) incidence rates among 22 high-burden countries from 1990 to 2012 showed different patterns, such as declining (e.g. China), stable (e.g. Pakistan) and ascending (e.g. South Africa) [1], which, to some extent, reflect the comprehensive results of various factors including TB prevention and treatment endeavor. In China, the Bacillus Calmette-Guerin (BCG) was approved as the immunological preparation of the National Immunization Program for TB prevention since foundation of P.R. China, and each newborn was to be inoculated with the first dose. How about the evidence of its protection efficacy? We carried out a prior study, including randomized/quasi-randomized controlled trails, showing that the 5 year and 10 year incidences of BCG were lower than that of the control in different settings worldwide, while the 15 year and 20 year incidence varied. Other researchers reported that BCG vaccination protection against TB varies between populations, to an extent that cannot be attributed to chance

alone [2]. How about the evidence after several decades' application of BCG in China? We therefore now report a new systematic review and meta-analysis of the evidence available to evaluate the effectiveness of BCG for TB prevention among Chinese people, to inform immunological agent development and use.

2. METHODS

2.1. Study Eligibility Criteria

The inclusion criteria: studies that investigated effectiveness of BCG for TB prevention, targeting at individual Chinese.

The exclusion criteria: studies without control group or the comparison was not blank.

2.2. Search Strategy

Chinese databases of CBM, CNKI, VIP and WANFANG were searched from creations till February 2014 using keywords of BCG and TB, without limitation of study design, and the references of eligible studies were also searched.

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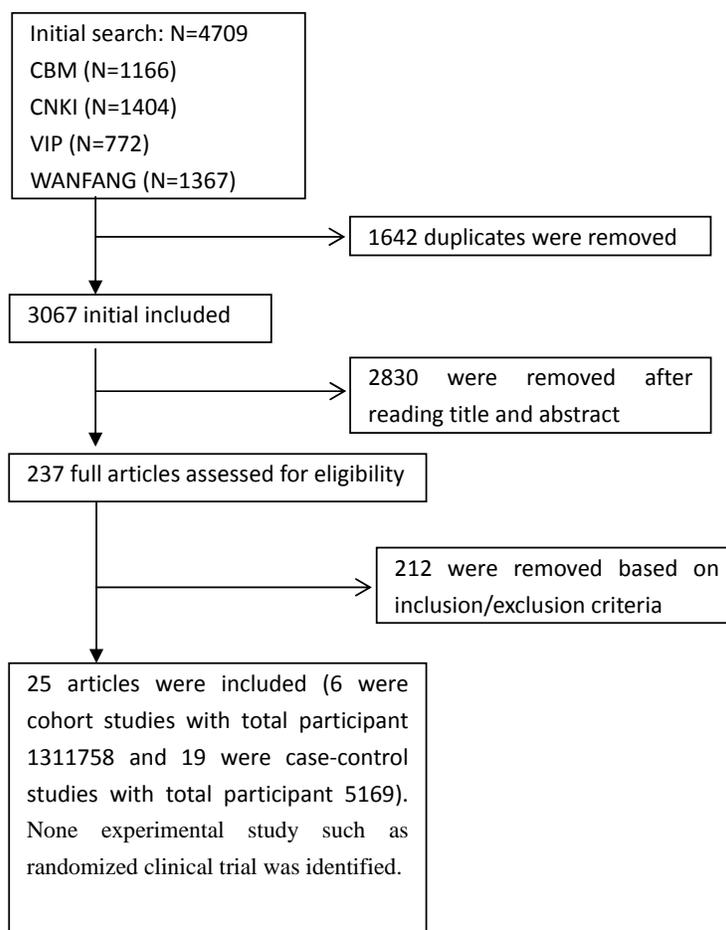


Fig. (1). Flow diagram of study searching and selection process.

2.3. Quality Assessment in Individual Studies

Two reviewers independently performed data extraction and quality assessment, disagreements were resolved by discussion. The Newcastle–Ottawa quality assessment scale (NOS) [3, 4] was used to evaluate the quality of included observational studies.

2.4. Risk of Publication Bias Evaluation

Software of Stata 12.0 was used to test publication bias. RevMan 5.2 was applied to draw the funnel plot.

2.5. Statistical Analysis

Statistical analysis was carried out using RevMan 5.2. All studies were grouped by study design, as prior protocol, to pool the whole effect. Heterogeneity was analyzed and the estimate was pooled for each level of the important heterogeneity factors. The fixed effect model was applied in groups without heterogeneity, and in the others (after analysis, heterogeneity existed yet) the random effect model was applied. Relative risk (RR) or odds ratio (OR) and their 95% confidence interval (95%CI) were used for binary variable. P values of less than 0.05 were considered as statistically significant for both heterogeneity test and the pooled estimates.

3. RESULTS

3.1. Description of Study Identification

The initial search identified 3067 articles, after title and abstract screening, 237 full-length papers were read carefully and 25 observational studies were included, among which 6 were cohort studies and 19 were case-control studies, none of the experimental studies such as RCTs were identified (Fig. 1).

3.2. Characteristics of Included Studies and Quality Assessment

Table 1 and Table 2 show the characteristics of cohort studies [5-10] and case-control studies [11-29] respectively.

The total sample size of six cohort studies is 1311758. The start time varied from year 1968 to 2002, with a span from 1 to 30 years. The ratio of prospective versus retrospective design is 1:1. The targeted population is children or teen-agers and three out of six studies targeted at meningial TB. The studies got a NOS score from 5 to 9 with an average of 6.3. The items on which studies did not perform generally well include “Selection of the unexposed cohort”, “Control for important factor or additional factor” and “Follow-up long enough for outcomes to occur”.

Table 1. Characteristics of the included cohort studies.

Study ID	Time	Setting	Design Type	Sample Size	Age Range	Average Age	Disease Type	NOS Score
Guo Chongzheng 1990	1985-1987	Gaoping county	Retrospective	93835	0-14	NA	Meningeal TB	9
Guo Jinwu 2006	1995-1996	Wuhan city	Prospective	5652	14-25 (college freshman)	18.5	TB	6
Hou Dongqing 2001	1968-1997	Zhuzhou city	Prospective	140852	0-14	NA	TB	6
Huang Lianzhang 1988	1980-1984	Yancheng city	Retrospective	1064175	1 and 7	NA	Meningeal TB	6
Li Zhigang 1998	1994-1996	Zhangjiakou city	Prospective	6981	17-20 (college freshman)	18.5	Pulmonary TB	6
Wu Xirong 2012	2002-2010	Peking city	Retrospective	263	0-17	5.5	Meningeal TB	5
Total/average				1311758				6.3

Table 2. Characteristics of the included case-control studies.

Study ID	Time	Setting/Population	n1:n2	Sample Size	Exposure Measurement	Age (Range or Mean)	Disease Type	NOS Score
Cui Xiwen 2007	2006	Kunshan city	1.05	190	History of BCG inoculation	20-60	Pulmonary TB	7
Feng Fumin 2006	2004-2005	Tangshan city	0.63	224	BCG scar	44.25	Pulmonary TB	6
Feng Fumin 2007	NA	Tangshan city	0.62	227	BCG scar	44.38	Pulmonary TB	7
Jiang Xuefeng 2008	2005-2007	Yinchuan city	0.67	298	History of BCG inoculation	NA(adult)	TB	7
Ji Chunmei 2006	2004	Tangshan city	1	248	BCG scar	47	Pulmonary TB	8
Li Shengtuan 1999	1992-1996	Troops	0.5	239	BCG scar	21.6	Pulmonary TB	8
Liu Wei 2003	2001-2002	Peking city	0.6	244	History of BCG inoculation	27	Pulmonary TB	5
Liu Wei 2006	2001-2004	Troops	0.59	374	History of BCG inoculation	NA(adult)	Pulmonary TB	6
Li Zijian 2001	1998-1999	Jinan city	1	324	BCG scar	19	TB	8
Ma Shixue 2005	2004	Tengzhou city	1	224	BCG scar	53.53	Pulmonary TB	7
Shi Qingming 2002	1999-2000	Hefei city	0.9	166	BCG scar	NA(undergraduate students)	Pulmonary TB	6
Wang Zhibin 2002	1998-2000	Southern part of China	0.5	414	History of BCG inoculation	18-52	TB	7

Table 2. contd...

Study ID	Time	Setting/Population	n1:n2	Sample Size	Exposure Measurement	Age (Range or Mean)	Disease Type	NOS Score
Wu Qirong 1991	1987	Liaoning province	0.23	326	History of BCG inoculation	0-14	Meningeal TB	7
Xiong Changhui 2012	2007-2008	Jiangxi province	0.33	160	BCG scar	0-14	Meningeal TB	8
Yang Jianan 2002	2000	China	0.5	306	BCG scar	NA	Pulmonary TB	8
YeWenkui 1991	1986-1988	Peking city	0.5	360	BCG scar	19-28	Infiltrative pulmonary TB	6
ZengNianhua 2001	1998-2000	South China	1	276	History of BCG inoculation	18-52	Pulmonary TB	8
ZhangXueqing 2009	2007-2008	Jining city	0.9	285	BCG scar	NA(young/middle-aged)	Pulmonary TB	7
ZhouYingyu 2003	1999-2000	Enterprise in Changde city	1	284	BCG scar	20-56	TB	7
Total/average				5169				7.0

NA: not available

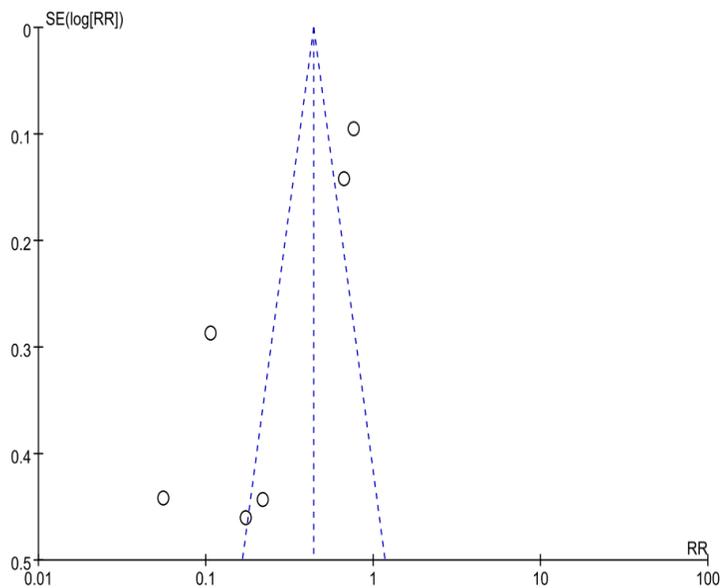


Fig. (2). Funnel plot for cohort studies.

The total sample size of case-control studies 5169. Most studies began in 1990s or later except for two (in 1980s). The targeted population is adult except for two targeted 0-14 years' children. Twelve out of nineteen studies targeted pulmonary TB. The studies got a NOS score from 5 to 8 with an average of 7.0. The items on which studies did not perform generally well include "Representativeness of cases", "Exposure assessment" and "Non-response rate".

4. PUBLICATION BIAS

Fig. (2) and Fig. (3) show respectively the funnel plot of cohort studies and of case-control studies, with P value of

Egger's test 0.016 and 0.067 respectively, implying that the symmetry is not good for both kind of study designs, especially for cohort study, and that the included studies are at risk of publication bias.

4.1. Effectiveness of BCG for TB Prevention

4.1.1. Cohort Study

Fig. (4) is the forest plot of BCG's prevention effect in cohort study. The overall effect (RR) for all is 0.24 with 95%CI (0.11, 0.52). The P value of heterogeneity test is far less than 0.05 with statistic I square of 95%, statistically

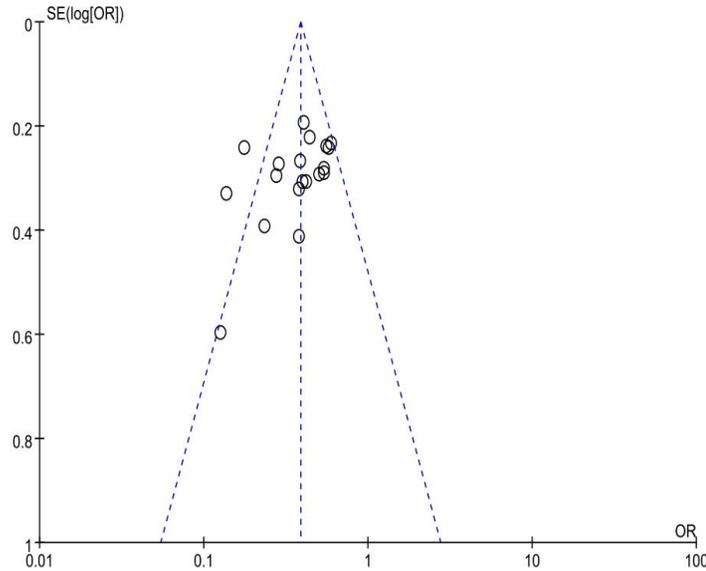


Fig. (3). Funnel plot for case-control studies.

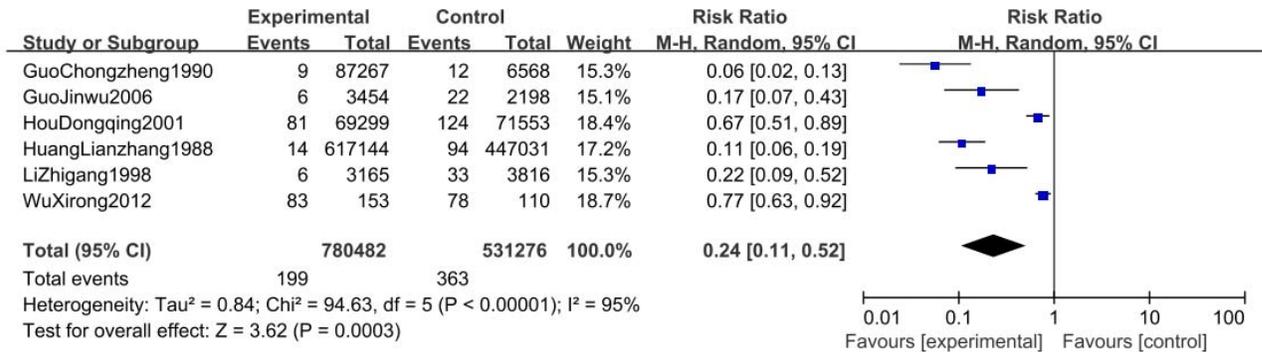


Fig. (4). The pooled estimate of BCG’s protection effect in cohort study.

implying heterogeneity among studies. We then explored the factors which might contribute to the heterogeneity and carried out analysis in each level of potential factors, as shown in Fig. (5), displaying great improvement of the heterogeneity. The pooled value is statistically significant for each level of the factor, with pooled point estimate of RR 0.20 for those aged elder than 14. And for children not elder than 14 years old, it is 0.10 for studies not later than 1990 and 0.71 for studies after 1990.

4.1.2. Case-control Study

Fig. (6) is the forest plot of BCG’s prevention effect in case-control study. The overall effect OR is 0.37 with 95%CI (0.31, 0.45). Similarly, the heterogeneity among studies is statistically significant, further analysis in Fig. (7) shows that the pooled point estimate of OR is 0.24, 95% CI (0.14, 0.40) for those aged not elder than 14 (the targeted disease type is TB meningitis for all). And for those aged elder than 14, it is 0.42 (0.37, 0.48) for those targeted at TB, and 0.14 (0.07, 0.26) for one study targeted at infiltrative pulmonary TB. The P value is less than 0.05 in all groups.

DISCUSSION

According to The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria [30, 31], the original studies included in this research are not of high quality at beginning (no RCTs are identified), however, it is reasonable to rate up the quality of the evidence, for the magnitude of pooled estimate of the effect is large enough: RR 0.24 for cohort studies and OR 0.37 for case-control studies. In addition, all the studies show consistent directions of BCG’s positive effects, both between cohort and case-control study design and among articles in each study design group. Although it is not the reason to weigh, but it is a sound basis not to decline the quality [32], as it suggests good agreement with the studies, given that it is not affected by publication bias. In publication bias topic, our analysis shows that the included studies are at risk that, how it will result in the pooled estimate? It is worth further investigation and more researches are encouraged.

Heterogeneity analysis indicated that the time might be a source of heterogeneity, and based on professional knowledge and supported by literatures, we set the threshold

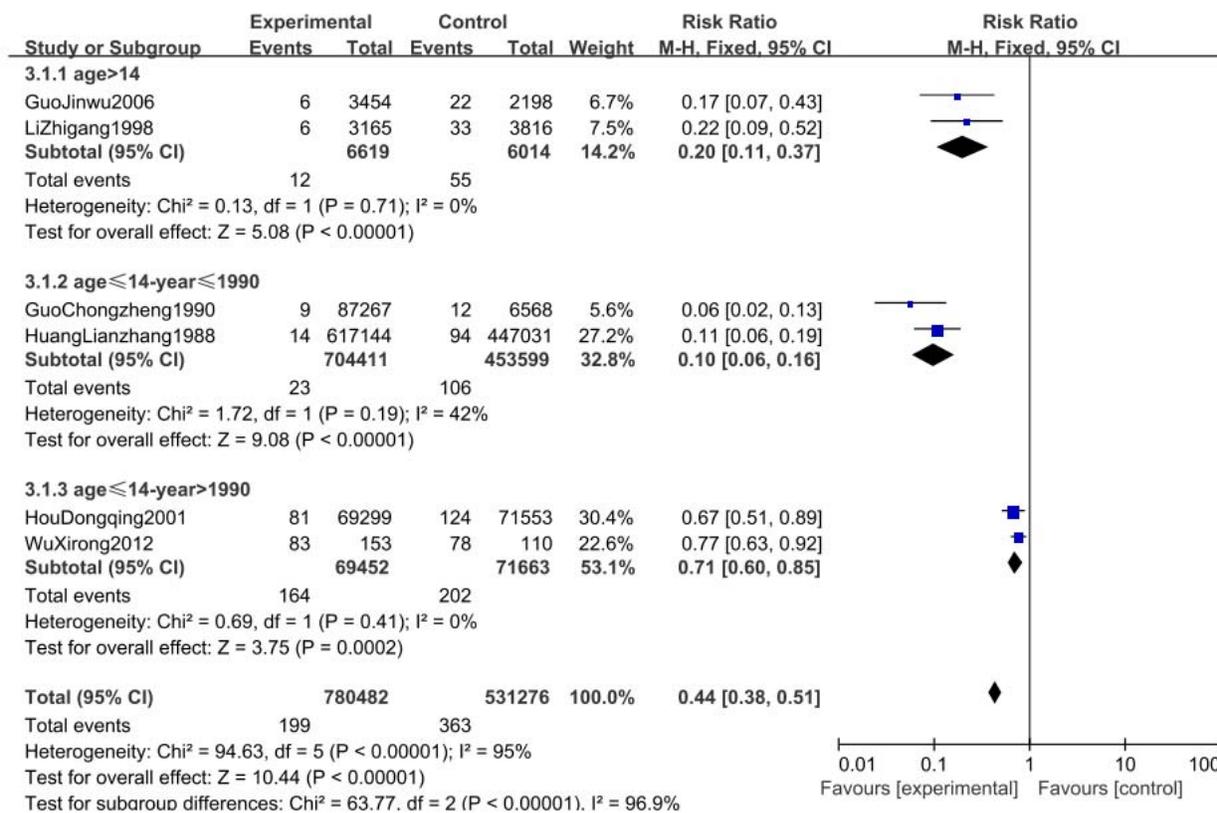


Fig. (5). The pooled estimate of BCG’s protection effect in cohort study in group.

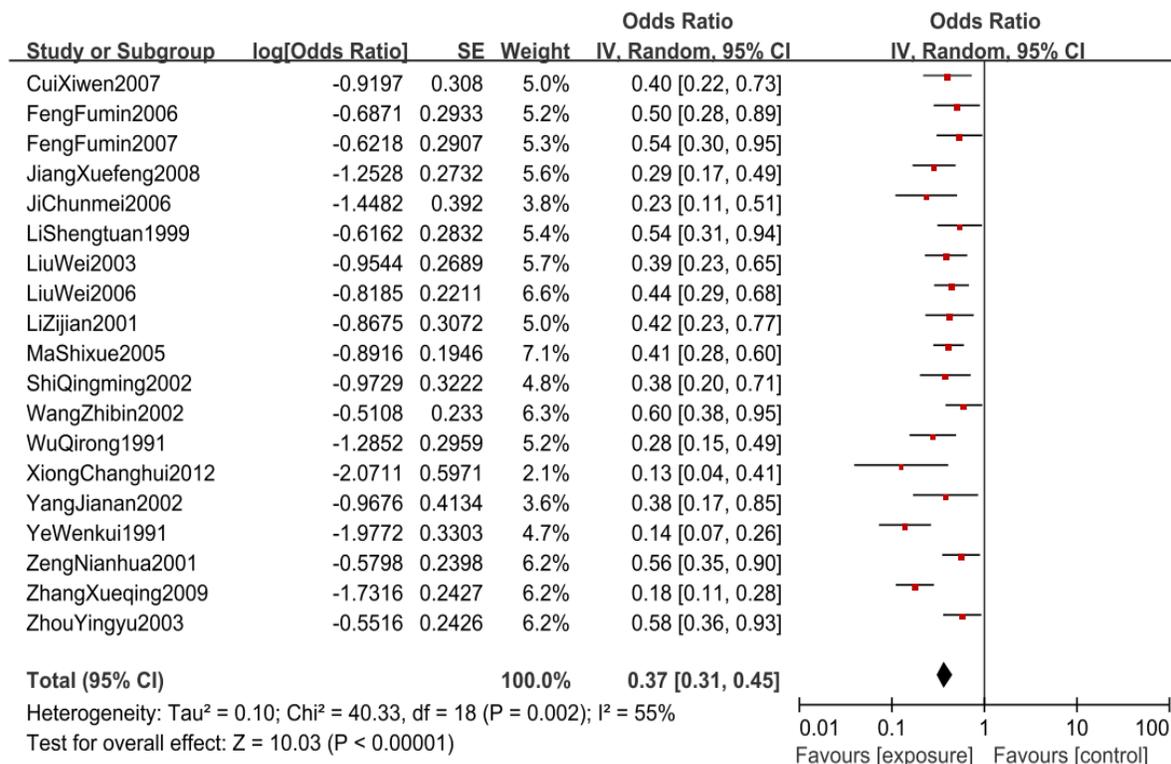


Fig. (6). The pooled estimate of BCG’s protection effect in case-control study.

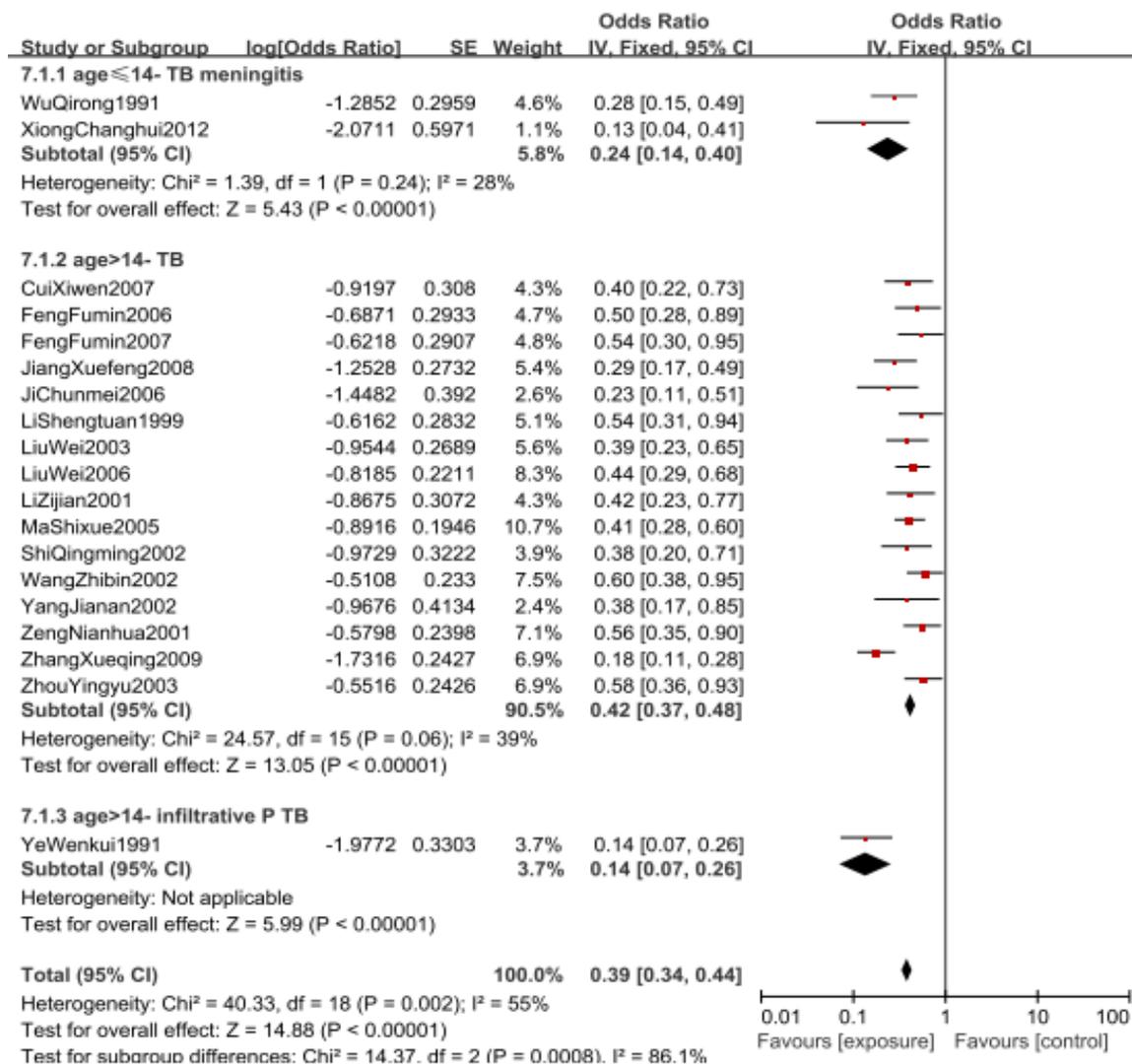


Fig. (7). The pooled estimate of BCG’s protection effect in case-control study in group.

of time as year 1990 for subgroup analysis, for the following reasons: Firstly, the change of BCG vaccination procedures: skin scratch method accounted for 20% and intradermal injections accounted for 80% in China in 1980s, and the latter had been fully adopted in 1990's [33]. The latter had a twice higher 16-week serum conversion rate than the former based on a survey of BCG vaccination procedure in China in the 1980's [34]. Secondly, The change of population coverage: sample survey of immunization coverage plan in China in 1983 to 1988 showed that: BCG vaccination rate for 12-24 month old children were 33.9%, 50.4%, 78.8%, 70%, 85.3%, 98.4% respectively, change of vaccination rate among population may affect immunity effects [35].

CONCLUSION

The available evidence shows positive and definite effect of BCG in preventing TB among Chinese people, while, it should be supported by more studies to avoid publication bias risk. High quality studies are encouraged worldwide to inform immunological agents development and use to cope with TB epidemiology.

CONFLICT OF INTEREST

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