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Role of dormancy survival regulator and resuscitation-promoting factors antigens in differentiating between active and latent tuberculosis: a systematic review and meta-analysis

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Abstract

Background Dormancy survival regulator (DosR) and resuscitation-promoting factor (Rpf) antigens of *Mycobacterium tuberculosis* are activated during dormant phase of tuberculosis (TB). This study evaluates the differential immunogenicity potentials of DosR and Rpf antigens in individuals with latent tuberculosis infection (LTBI) and active TB patients.

Methods After a literature search in electronic databases, studies were selected by following precise eligibility criteria. Outcomes were synthesized systematically, and meta-analyses were performed to estimate standardized mean differences (SMDs) in interferon-gamma (IFNγ) levels, and IFNγ positive immune cells between individuals with LTBI and active TB patients.

Results Twenty-six studies (1278 individuals with LTBI and 1189 active TB patients) were included. DosR antigens Rv0569 (Standardized mean difference; SMD 2.44 [95%CI: 1.21, 3.66]; $p < 0.0001$), Rv1733c (SMD 0.60 [95%CI: 0.14, 1.07]; $p = 0.011$), Rv1735c (SMD 1.16 [95%CI: 0.44, 1.88]; $p = 0.002$), Rv1737c (SMD 1.26 [95%CI: 0.59, 1.92]; $p < 0.0001$), Rv2029c (SMD 0.89 [95%CI: 0.35, 1.42]; $p = 0.002$), RV2626c (SMD 1.24 [95%CI: 0.45, 2.02); $p = 0.002$), and Rv2628 (SMD 0.65 [95%CI: 0.38, 0.91]; $p < 0.0001$) and Rpf antigens Rv0867c (SMD 1.33 [95%CI: 0.48, 2.18]; $p = 0.002$), Rv1009 (SMD 0.65 [95%CI: 0.05, 1.25]; $p = 0.034$), and Rv2450c (SMD 1.54 [95%CI: 0.92, 2.16]; $p < 0.0001$) elicited higher IFNγ levels in individuals with LTBI in comparison with active TB patients. IFNγ-positive immunoresponsive cells were significantly higher in individuals with LTBI than in active TB patients for antigens Rv1733c (SMD 1.02 [95%CI: 0.15, 1.88]; $p = 0.021$), Rv2029c (SMD 0.57 [95%CI: 0.05, 1.09]; $p = 0.031$), and Rv2628 [SMD 0.38 [95%CI: 0.15, 0.61]; $p = 0.001$).

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Conclusion DosR antigens Rv0569, Rv1733c, Rv1735c, Rv1737c, RV2626c, Rv2628, and Rv2029c, and Rpf antigens Rv0867c, Rv1009, and Rv2450c are found to elicit immune responses differently in individuals with LTBI and active TB patients.

Keywords Dormancy, Resuscitation, Antigen, Laten, Active, Tuberculosis

Background

Tuberculosis (TB) is a preventable and curable bacterial infectious disease caused by *Mycobacterium tuberculosis* (Mtb) which affects mostly the lungs. Globally, over 10 million people have TB and over a million die from this disease each year. Men are affected more than women and children (https://www.who.int//news-room/fact-sheets/detail/tuberculosis). Main source of infection is aerosols discharged into air upon coughing by the active TB patients. In the USA, incidence of active TB during the year 2022 was 2.5 cases per 100,000 persons [1] which increased to 2.9 cases per 100,000 in 2023 [2]. The incidence rate of active TB in China was 58 cases per 100,000 individuals in 2019 which has declined from 130 cases per 100,000 individuals in 1990. In China, the cure rate has improved to about 93% in recent years [3]. Neonatal Bacillus Calmette Guerin (BCG) vaccination has good efficacy against disseminated and pulmonary TB in young children, but a late-stage vaccination yields variable efficacy against pulmonary TB in adults. However, when it is efficacious, it provides long-term protection [4].

An important characteristic of Mtb is its ability to persist for long time in host in asymptomatic form as latent tuberculosis infection (LTBI) without being affected by fully functional immune system [5]. It is estimated that about a quarter of the world population has LTBI. Approximately 5–15% of individuals with LTBI develop active TB within two to five years whereas in rest of individuals immune system either eliminates the infection or a persistent immune response prevents active TB from appearing. Individuals with HIV infection, cancer, coronavirus disease, or diabetes, as well as those undergoing immunosuppressive therapy or kidney transplant, infants, and smokers are at a higher risk of transformation of LTBI to active TB [6, 7]. Such data emphasize the need to focus on LTBI diagnosis for devising fruitful TB control strategies.

Currently, WHO recommends tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) for the diagnosis of LTBI. In TST, a subcutaneous injection of old tuberculin or purified protein derivative is performed to examine immune response against the antigen. An induration reaction of >15 mm within 48–72 h indicates past or current infection. However, TST is constrained by its inability to differentiate between LTBI and active TB, cross reactivity with non-tuberculous mycobacteria (NTM), and false positivity with BCG vaccine. Newly developed methods such as the Diaskintest, C-Tb skin test, and EC test attempt to address the false-positivity of TST for BCG and NTM. Diaskintest, developed by Generium, Russia, is an intradermal injection of a recombinant protein obtained from genetically modified *Escherichia coli* (*E. coli*). The presence of redness or induration indicates reaction which is examined 48–72 h after injection. C-Tb is also a dermal test based on Mtb ESAT-6 and CFP10 antigens (Statens Serum Institute, Copenhagen, Denmark) whereas the EC test uses a fusion protein recombinant of ESAT-6 and CFP-10 *E. coli* antigens (Zhifei Longcom Biologic Pharmacy Company, China). Furthermore, IGRAs such as the T-cell spot of TB assay (T-SPOT-TB), QuantiFERON-TB Gold In-Tube, QuantiFERON-TB Gold-Plus, LIASON QuantiFERON-TB Gold, and LIOFeron TB/LTBI are modern methods which attempt to overcome some of the drawbacks of TST [8, 9]. However, none of these tests can differentiate between LTBI and active TB.

Interferon-gamma (IFNγ) is an important cytokine involved in protective immunity against TB. The ability of Mtb antigens to induce IFNγ is an important response to identify their antigenicity. Mtb downregulates most of its genes in stressful environments whereas some of its genes are activated in response to stressors such as hypoxia. There are at least 48 genes which are regulated by a dormancy survival regulator (DosR) regulon. DosR encoded gene products are termed "latency antigens" which are expressed differentially in individuals with LTBI and active TB patients. Additionally, resuscitation-promoting factors (Rpfs) is another class of five Mtb antigens which promote transition from dormancy to active disease and are recognized preferentially by the IFNγ producing cells of individuals with LTBI [10]. Such antigens may have potential to help in discriminating individuals with LTBI from active TB patients.

A previous systematic review of various classes of Mtb antigens observed that many latency antigens behave differently in individuals with LTBI and active TB [11]. In literature, several studies can be found that have quantified the immune responses against Mtb antigens to evaluate their abilities of distinguishing LTBI and active TB [12–14]. However, in literature there is no study to report a pooled analysis of the immunogenicity outcomes of DosR or Rpf antigens commonly implicated for their potential to differentiate stages of TB. The aim of the present study was to systematically review studies that evaluated the immunogenic roles of DosR and Rpf

antigens in individuals with LTBI and active TB patients and to perform meta-analyses of statistical indices estimating the significance of differences in IFNγ levels and IFNγ-positive immune cells between these groups.

Methods

This study was performed by following PRISMA guidelines.

Eligibility criteria

Inclusion criteria were: a study (a) evaluated the immunogenic roles of DosR and/or Rpf antigen/s in individuals with LTBI and active TB patients; (b) measured IFNγ levels, IFNγ producing immune cells, or antibody levels; and (c) reported statistical outcomes indicative of the significance of difference in immunogenicity between these groups. Exclusion criteria were: a study (a) evaluated the role of DosR and/or Rpf antigens in individuals with either LTBI or active TB but not in both; (b) reported the outcomes of household contacts of active TB patients or community members without LTBI information; (c) reported relevant outcomes in HIV-positive individuals; (d) reported data that could not be used in the meta-analysis; and (e) published outcomes as congress abstract.

Literature search

Research articles reporting relevant studies were searched in Google Scholar, and PubMed search engines using subject specific keywords. Primary string was "latent OR active AND tuberculosis OR Mycobacterium tuberculosis AND antigens AND dormancy AND resuscitation" In secondary combinations, several other keywords were used with primary string including "dormancy survival regulator", "DosR", "resuscitation promotion factor", "Rpf", "immune response", "CD4 T cells", and "interferon". Detailed search strategy is given in Appendix S1. At completion of the literature search, reference lists of all selected articles were also screened to strengthen the search. Literature search encompassed original research articles published in English before April 2024.

Data analysis

Demographic data, study conduct, antigen identity, and outcomes including the differences in IFNγ levels, IFNγ-positive immune cells, and antibodies (IgA/IgG) levels between individuals with LTBI and active TB patients were extracted from tabular or graphic contents of research articles and were organized in datasheets. The quality of the included studies was assessed using NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. A Gantt chart was drawn to show the significance of antigens in revealing differences between LTBI and active TB reported by individual studies. Meta-analyses of standardized mean differences (SMDs) were performed to seek the significance of difference between LTBI and active TB in IFNγ levels, IFNγ-positive immune cells, and/or IgA/IgG levels. The statistical index to measure heterogeneity was I^2. The I^2 is a measure of between-studies inconsistency in the outcomes which portray the proportion of observed variance attributable to differences in true effect sizes that cannot be due to sampling error alone. Meta-analyses were conducted with Stata software (Stata Corporation, College Station, Texas, USA).

Results

Twenty-six studies [13, 15–39] were included in the meta-analysis (Fig. 1; Table S1). These studies reported the outcomes of 1278 individuals with LTBI and 1189 active TB patients. The age of individuals with LTBI was 39.0 years [95% confidence interval (CI): 34.8, 43.3] whereas the age of individuals with active TB was 39.6 years [95% CI: 34.1, 45.2]. The proportion of females was 47% [95% CI: 41, 53] in LTBI group and 31% [95% CI: 22, 40] in active TB group. The quality of the included studies was generally good (Table S2).

A total of 42 antigens were evaluated in these studies. Among these, Rv2029c was the most evaluated antigen (10 studies), followed by the Rv2628 (8 studies), Rv0867c, and Rv1733c (7 studies each), Rv1737c (6 studies), Rv2031c, and 2389c (5 studies each), Rv2028c, and Rv2627c (4 studies each), Rv1009c, Rv1738, Rv2450c, and Rv2626c (3 studies each), Rv0081, Rv0569, Rv1735c, Rv1884c, Rv1996, Rv2003c, Rv2004c, Rv2005c, Rv2007c, Rv2030, 2659c, and Rv3407 (2 studies each), and Rv0079, Rv0080, Rv0140, Rv0570, Rv1734, Rv1813c, Rv2006, Rv2032, Rv2034, Rv2624, Rv2660c, Rv3127, Rv3128c, Rv3129, Rv3133c, Rv3131c, and Rv3353 (1 study each). 37 antigens belonged to DosR regulon and 5 belonged to Rpf class. A visual presentation of these antigens and their significance in revealing differences between LTBI and active TB as observed by individual studies is given in Fig. 2.

The majority of antigens belonging to DosR regulon including Rv0569 (SMD 2.435 [95% CI: 1.213, 3.656]; $p<0.0001$), Rv1733c (SMD 0.604 [95% CI: 0.136, 1.072]; $p=0.011$), Rv1735c (SMD 1.157 [95% CI: 0.436, 1.879]; $p=0.002$), Rv1737c (SMD 1.256 [95% CI: 0.593, 1.920]; $p<0.0001$), Rv2029c (SMD 0.890 [95% CI: 0.352, 1.423]; $p=0.002$), RV2626c (SMD 1.238 [0.455, 2.020); $p=0.002$), and Rv2628 (SMD 0.645 [95% CI: 0.384, 0.966]; $p<0.0001$) elicited higher IFNγ levels in individuals with LTBI in comparison with active TB patients (Fig. 3). Additionally, antigens which elicited significantly higher IFNγ in individuals with LTBI compared to active TB patients observed in a single study included Rv2003c, Rv2005c, and Rv2007c, and Rv2034.

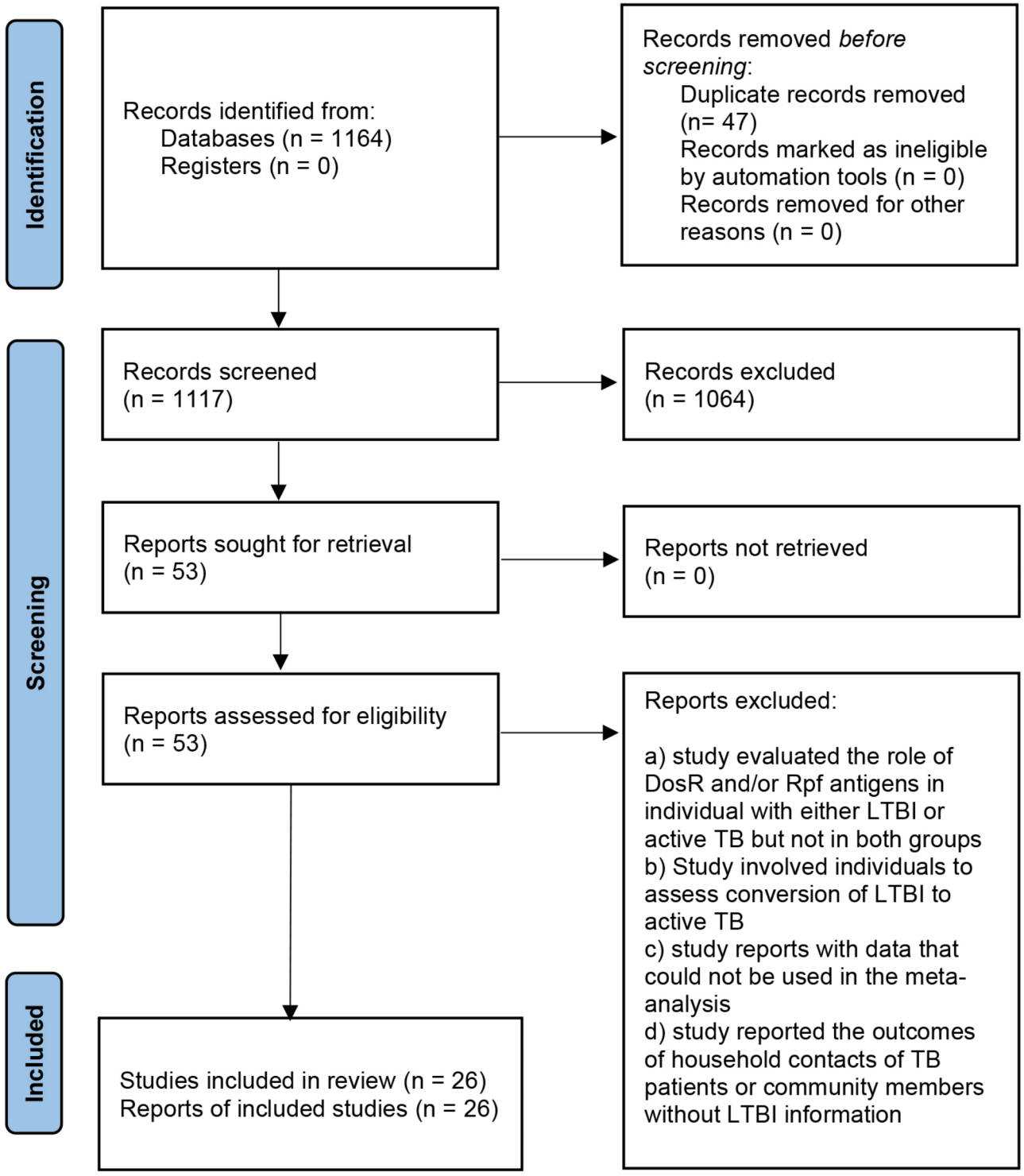

Fig. 1 A flowchart of study screening and selection process

However, some DosR antigens including Rv0081 (SMD 0.285 [95% CI: −1.059, 1.630; p=0.678), Rv2028c (SMD 0.188 [95% CI: −0.917, 1.294]; p=0.738), Rv2031c (SMD 0.311 [95% CI: −0.184, 0.786]; p=0.240), Rv2627c (SMD 0.188 [95% CI: −0.224, 0.600]; p=0.371), Rv2660c (SMD −0.063 [95% CI: −0.660, 0.535]; p=0.838), and Rv3131c (SMD 0.347 [95% CI: −0.302, 0.996]; p=0.294) did not differ significantly in IFNγ production between individuals with LTBI and active TB patients (Figure S1).

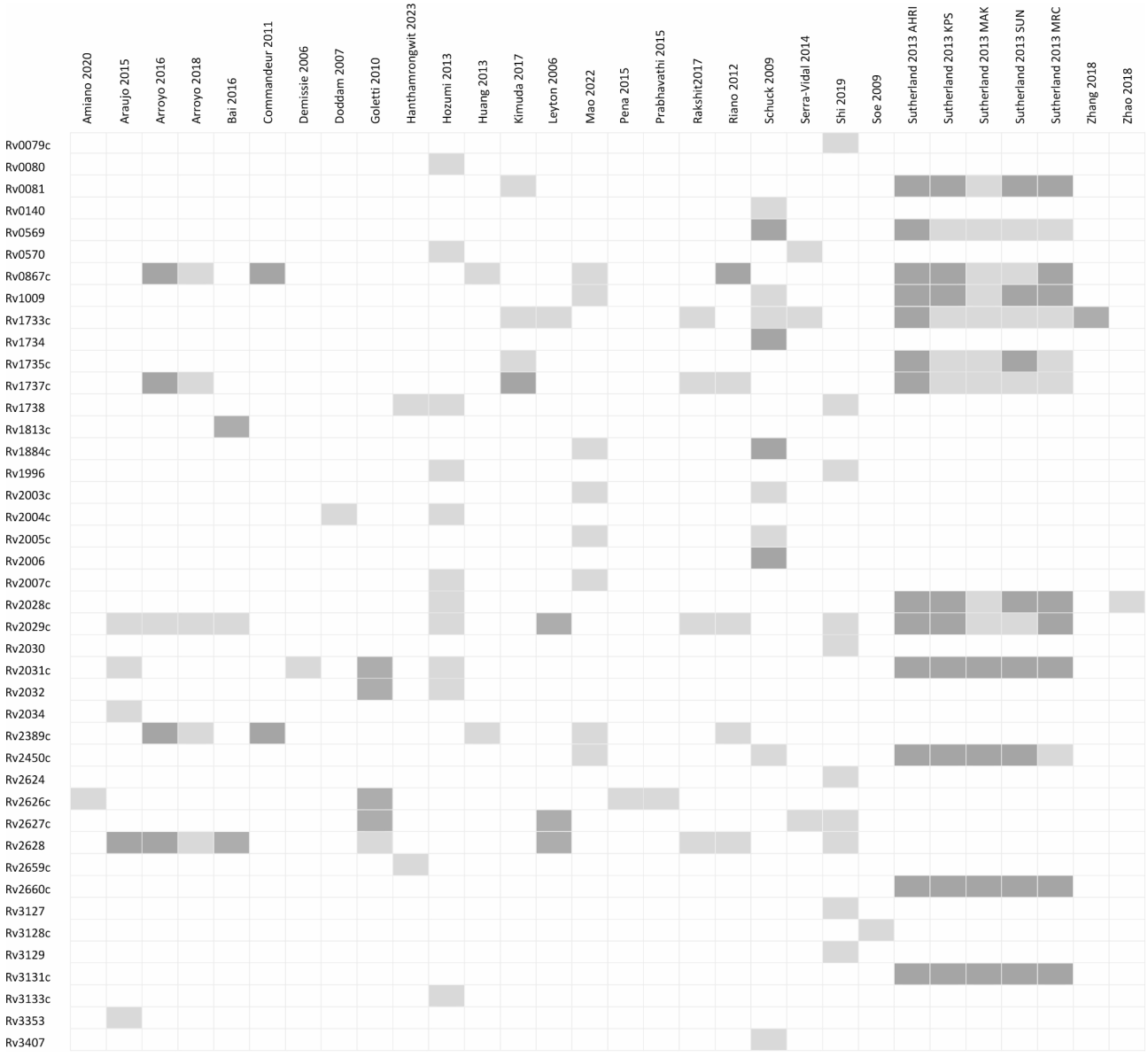

Fig. 2 A visual presentation of antigens used in the included studies and their roles in immunogenicity. Light grey boxes show significantly higher immunogenicity in individuals with LTBI compared to active TB patients (as observed by the individual studies) and dark grey boxes show otherwise

The antigens belonging to Rpf class including Rv0867c (SMD 1.332 [95% CI: 0.481, 2.183]; $p=0.002$), Rv1009 (SMD 0.647 [95% CI: 0.048, 1.246]; $p=0.034$), and Rv2450c (SMD 1.539 [95% CI: 0.917, 2.161]; $p<0.0001$) also elicited higher IFNγ levels in individuals with LTBI in comparison with active TB patients (Fig. 4). However, for Rv2389c the difference was not statistically significant (SMD 0.852 [95% CI: –0.027, 1.730]; $p=0.057$).

The number of IFNγ immunoresponsive cells was significantly higher in individuals with LTBI than in active TB patients for antigens Rv1733c (SMD 1.017 [0.151, 1.883]; $p=0.021$), Rv2029c (SMD 0.568 [95% CI: 0.051, 1.085]; $p=0.031$), and Rv2628 (SMD 0.378 [0.147, 0.610]; $p=0.001$). The number of IFNγ immunoresponsive cells was not significantly different between individuals with LTBI and active TB patients for antigens Rv1737c (SMD 0.543 [95% CI: –0.119, 1.206]; $p=0.108$), Rv0867c (SMD −0.259 [−1.232, 0.713]; $p=0.601$), and Rv2389c (SMD −0.339 [−1.236, 0.558]; $p=0.459$) (Fig. 5). In individual studies, Rv0140, Rv3407, and Rv2031c had significantly higher immunoresponsive cells in individuals with LTBI than in active TB patients.

Five studies reported the AUROC values for differentiating LTBI from active TB. Higher AUROC values were observed for Rv2003c, Rv2005c, Rv2007c, Rv2029c, Rv2028c, and Rv2626c in individual studies (Table 1).

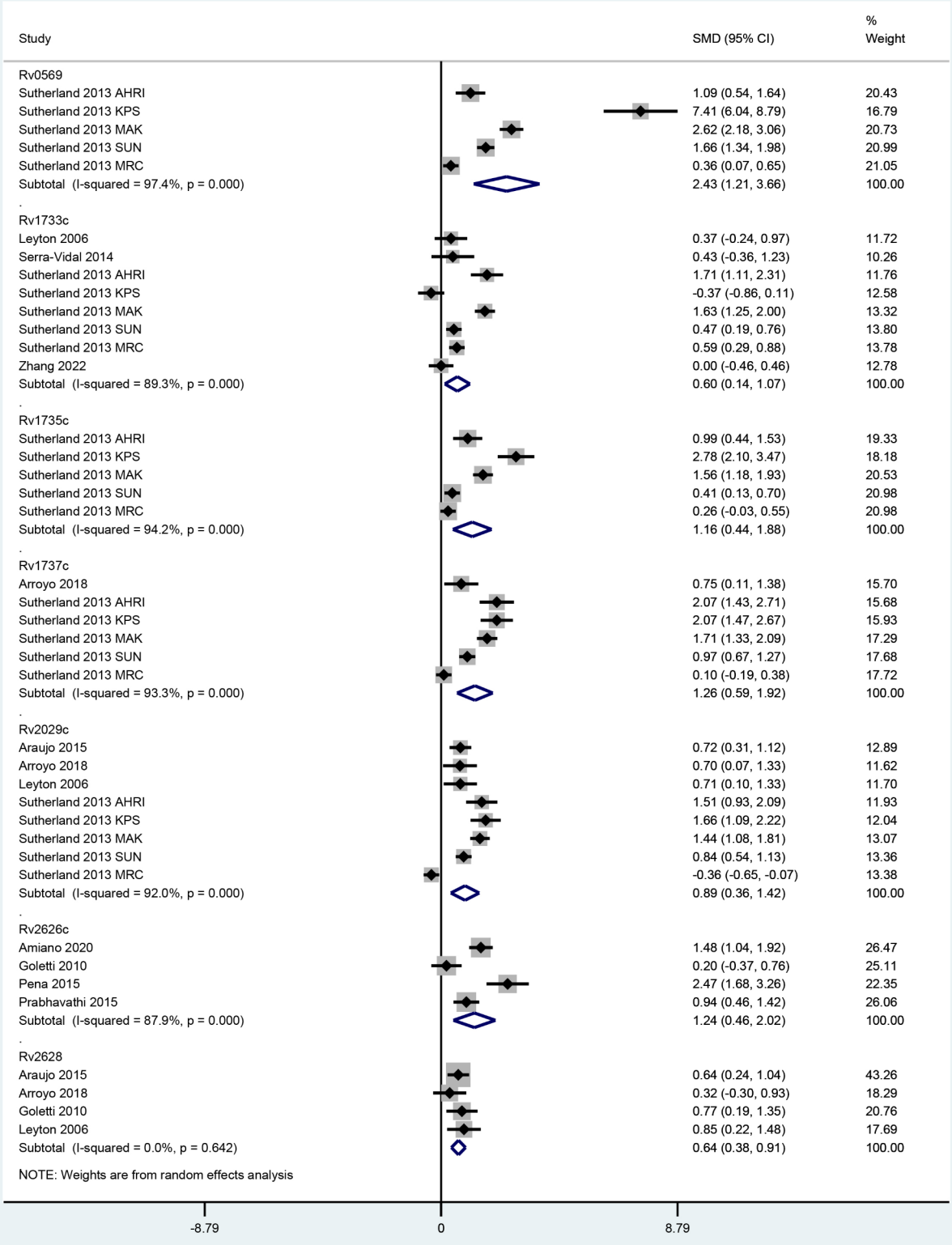

Fig. 3 A forest graph showing DosR antigens which elicited significantly higher IFNγ levels in individuals with LTBI than in active TB patients

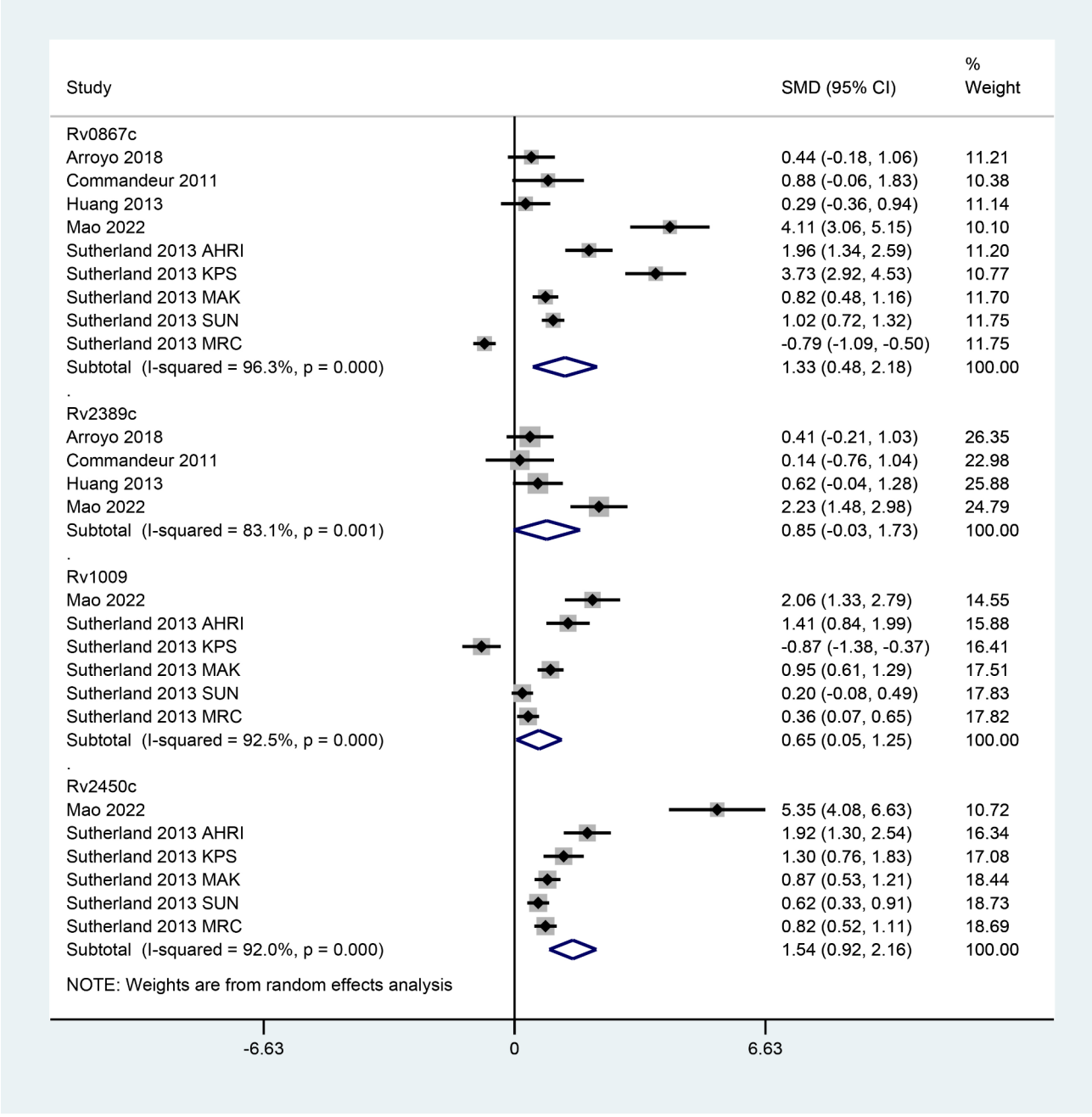

Fig. 4 A forest graph showing Rpf antigens which elicited significantly higher IFNγ levels in individuals with LTBI than in active TB patients

Discussion

In this meta-analysis, we found that several Mtb antigens including Rv0569, Rv1737c, Rv2029c, Rv2628, Rv1733c, Rv1735c, Rv2003c, Rv2005c, Rv2007c, Rv2034, and Rv2626c of DosR regulon and Rv0867c, Rv1009, Rv2450c of Rpf class raised IFNγ levels higher in individuals with LTBI in comparison with active TB patients. Moreover, the number of IFNγ-positive responsive cells was also higher in individuals with LTBI compared to active TB patients for Rv1733c, Rv2029c, and Rv2628 antigens. Only a few studies reported the AUROC values of DosR or Rpf antigens in differentiating LTBI from active TB.

Soon after entering the body, Mtb infects alveolar macrophages where it replicates and secretes proteins which bring macrophages into an activated state and present bacterial proteins to T cells. This follows the secretion of several inflammatory cytokines from immune cells and a cell-mediated inflammatory response to arrest bacterial growth [21, 30, 40]. Mtb antigens belonging to DosR and Rpf classes induce immune responses that maintain

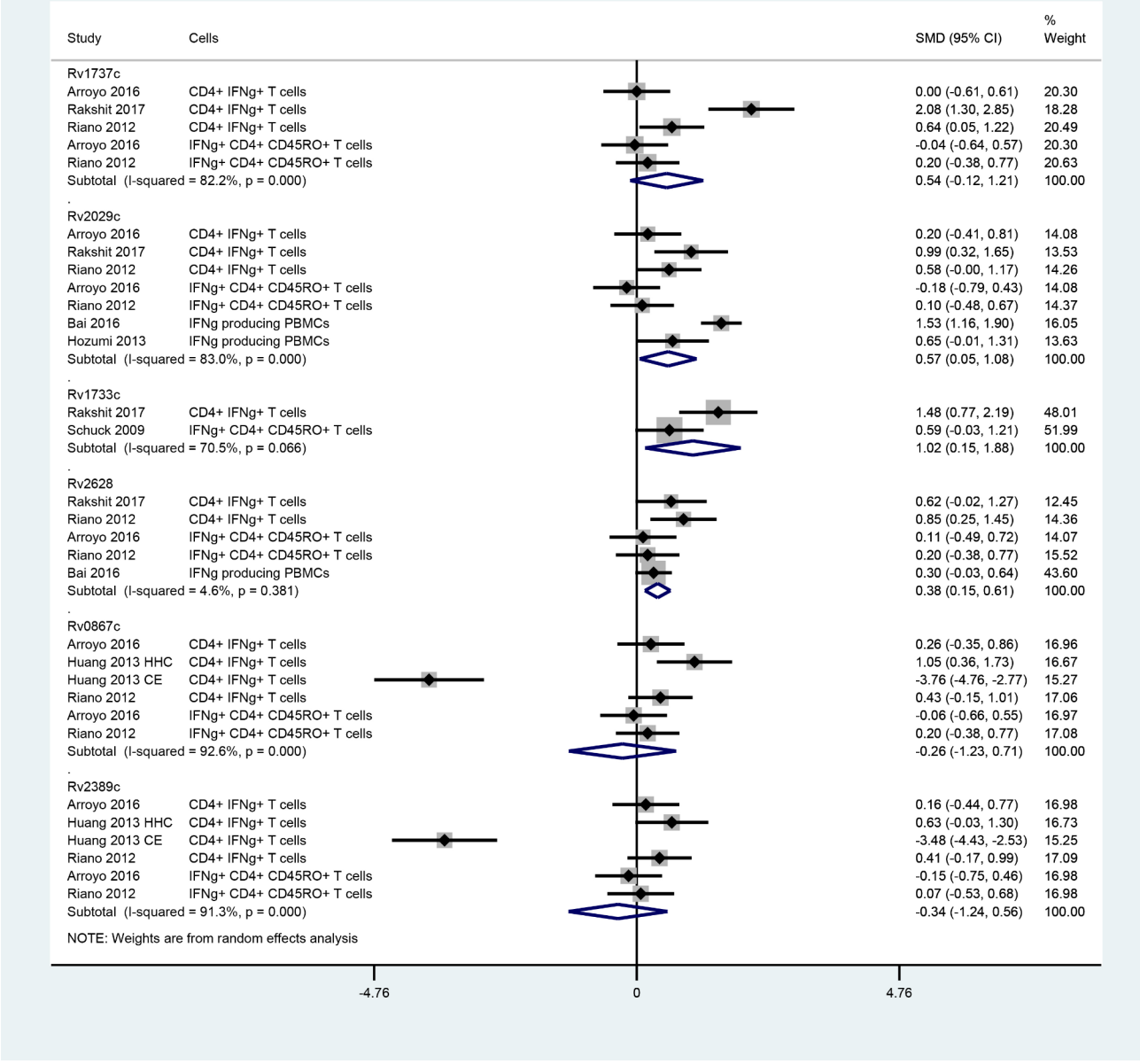

Fig. 5 A forest graph showing the pooled SMDs in IFNγ-positive T cells between individuals with LTBI and active TB patients for DosR and Rpf antigens

LTBI and prevent reactivation of TB [32]. A weakening of immunity through any means such as HIV infection or anti-tumor necrosis factor-alpha inhibition can abolish defense causing reactivation of bacteria to cause disease [21]. This makes it important to study the immune response to bacterial proteins for diagnosis and treatment of latent, transitionary, and pathological states of TB.

Latent infection of Mtb can give rise to active disease at any time. Immunity of the T-cells is necessary in individuals with LTBI for the prevention of resuscitation and reactivation of Mtb [33, 41]. A tug of war between the immune system and the pathogen may continue for months to decades with prospects for the eradication of bacteria as well as active disease. Inadequate control of TB can be attributed to high prevalence of LTBI besides other factors such as drug resistance, and comorbid HIV infection. Thus, one of the main target areas of TB research is to improve diagnosis of LTBI. A strong IFNγ response to DosR antigens protects against TB which may indicate that generating or boosting immune response against latency antigens may reduce reactivation risk [21].

Table 1 AUROC values of Mtb antigens in differentiating between LTBI and active TB observed in included studies

Study	Antigen	Class	Measure	Cutoff	AUROC [95% CI]	Sensitivity	Specificity
Arroyo 2018	Rv2029c	DosR	IFNγ levels	763 pg/ml	0.82 [0.69, 0.96]	90%	76.2%
Bai 2016			SFC number	11 (count)	0.89 [0.82, 0.96]	80.4%	90%
Arroyo 2018	Rv2628	DosR	IFNγ levels	1569 pg/ml	0.72 [0.55, 0.88]	65%	81%
Bai 2016			SFC number	8 *	0.69 [0.57, 0.81]	48.6%	90%
Arroyo 2018	Rv2389c	Rpf	IFNγ levels	28.4 pg/ml	0.73 [0.57, 0.89]	85%	61.9%
Mao 2022			IFNγ levels	> 2644 mg/ml	0.52	100%	46.5%
Arroyo 2018	Rv0867c	Rpf	IFNγ levels	455 pg/ml	0.74 [0.58, 0.89]	65%	81%
Mao 2022			IFNγ levels	> 4331 mg/ml	0.52	100%	46.5%
Arroyo 2018	Rv1737c	DosR	IFNγ levels	1015 pg/ml	0.76 [0.6, 0.92]	65%	90.5%
Bai 2016	Rv1813c	DosR	SFC number		0.39 [0.26, 0.52]		
Mao 2022	Rv2003c	DosR	IFNγ levels	> 41,017 mg/ml	0.92	48%	97.7%
Mao 2022	Rv2005c	DosR	IFNγ levels	> 40,184 mg/ml	0.87	32%	97.7%
Mao 2022	Rv2007c	DosR	IFNγ levels	> 46,728 mg/ml	0.89	36%	97.7%
Zhao2018	Rv2028c	DosR	IFNγ levels		0.94 [0.89, 0.99]		
Mao 2022	Rv1009	Rpf	IFNγ levels	> 2250 mg/ml	0.53	100%	46.5%
Mao 2022	Rv1884c	Rpf	IFNγ levels	> 2925 mg/ml	0.54	100%	46.5%
Mao 2022	Rv2450c	Rpf	IFNγ levels	> 4037 mg/ml	0.53	100%	46.5%
Zhang 2022	Rv1733c SLP	DosR	IL-2 secreting cells	1 (count)	0.77 [0.66–0.97]	73%	74%
Pena 2015	Rv2626c	DosR	IFNγ levels		0.86 [0.78, 0.93]		

Abbreviations: AUROC, area under receiver-operator curve; DosR, dormancy survival regulator; IFNγ, interferon-gamma; LTBI, latent tuberculosis infection; Rpf, Resuscitation promoting factor; SFC, spot forming cell; SLP, synthetic long peptides; TB, tuberculosis

*Optimal cut-off value corresponded to a specificity of 90%

Identification of immunogenic Mtb antigens is essential for the prevention of TB or its reactivation. Based on their findings, Arroyo et al. [18] have suggested that Rv0867c, Rv2029, and Rv2389c can be the favorite diagnostic candidates that may improve the discrimination power of ESAT-6 and CFP-10 for differential diagnosis of LTBI and active TB. It has also been suggested that Rv2628 can be one of the potential candidates for differentiating LTBI from active TB. Other authors have also suggested that Rv2628 can be helpful in differentiating remote LTBI from recent infection [23]. We have found significantly better performance of Rv2628 in a pooled analysis with 0% I^2. Among others, Rv1733c has been found to be one of the most recognized DosR antigen in household contacts of active TB patients in three African countries; Gambia, South Africa, and Uganda [42]. Sutherland et al. who studied five countries (Gambia, Ethiopia, Malawi, South Africa, and Uganda) found that Rv0569, Rv1733c, and Rv1737c elicited higher IFNγ levels in 4 countries and Rv1735c elicited higher IFNγ levels in 3 countries in individuals with LTBI than active TB patients [37]. They found no differences in Ethiopia and much weaker responses in Malawi between LTBI and active TB for all antigens they tested. Country specific differences were much profound in this study. Authors suggested that confounding factors such as ethnicity might have played a role in antigen reactivity. In general, African TB patients have relatively weaker responses to Mtb antigens in comparison with European TB patients [21]. Study of Sutherland et al. indicates that there can be ethnic differences between different regions in Africa in antigen reactivity. Moreover, nutritional status, and microbial environment can also affect antigen reactivity [37].

Antibody response to DosR and Rpf antigens was much variable in studies included in this meta-analysis. Amiano et al.found significantly higher anti-Rv2626c antibody levels in individuals with LTBI compared to active TB patients [15]. Significantly higher antibody intensities against Rv0079, Rv1738, Rv2030, Rv2624, Rv2627, and Rv3129 but significantly lower antibody intensities against Rv2029, Rv2628, and Rv3127 are found in LTBI individuals compared to active TB patients [35]. Moreover, significantly higher anti-Rv1813c antibodies are reported in individuals with LTBI than in active TB patients. A study found significantly lower antibodies against Rv0080, Rv1738, Rv2007c, Rv2031c, and Rv2032 in individuals with LTBI than in active TB patients [25]. No significant differences are found in anti-Rv1738 and anti-Rv3128 antibodies between LTBI individuals and TB patients [24, 36]. Kimuda et al. did not find any significant difference between individuals with LTBI and active TB patients in antibody levels against Rv1733c, Rv0081, Rv1735c, and Rv1737c [27]. Higher levels of antibodies are found against Rv0440, Rv0867c, Rv1737c, Rv2029c, Rv2215, Rv2389c, and Rv3616c in active TB patients compared to healthy individuals [43].

Inconsistencies in the immunoreactivity outcomes of different studies may be due to different host immune responses, use of differing Mtb strains, methodological

variabilities, ethnicity of study population, nutritional conditions, and microbial environments. Moreover, because there is no gold standard for diagnosing LTBI, the selection of individuals from varying pools such as the contact tracing and screening surveys may affect the recruitment. Mtb exposures such as for visitors of high active TB burden country, household contacts, random community members or clinics can also lead to varying results [34]. Moreover, inconsistencies in the results of detecting tests can also affect the outcomes. Of the included studies, Pena et al. have reported 13% discordant results between TST and IGRA tests whereas Amiano et al. have observed a discordant rate of 22% between QuantiFERON and TST [13, 15]. Araujo et al. also reported a low concordance between TST and IGRA-RD1. LTBI is asymptomatic [16]. However, individuals with LTBI should undergo clinical evaluations including sputum smear and culture, chest X-ray/computed tomography for confirmation [44]. Although, genes with DosR operon are highly conserved between Mtb and BCG, BCG vaccination status may not affect results as studies have shown that BCG vaccination do not induce immune responses to DosR antigens [25, 45, 46].

Among the foremost limitations of the present study, the observation of high statistical heterogeneity as indicated by I^2 values is an important consideration. There can be several reasons such as those mentioned in the above paragraph. Because LTBI definition is not yet adequately refined, outcomes may vary across studies and populations. Authors of the included studies have used methods such as the TST, and IGRA for the identification of individuals with LTBI, therefore, inclusion of false-positive cases cannot be fully ruled out. This might have had some impact on the overall outcomes of this meta-analysis. Another important limitation of this review is that only a few studies could be identified that reported the statistical indices of diagnostic accuracy due to which meta-analyses were not possible for individual antigens. Same was true for the immune response in terms of antibody production which was also reported by fewer studies. Use of different cut-off values in included studies also increases the heterogeneity and affects the overall outcomes. Thus, the outcomes achieved herein need validation in future studies.

Conclusions

This meta-analysis has identified several DosR and Rpf antigens capable of exhibiting immunogenicity differently in individuals with LTBI and active TB patients. DosR antigens Rv0569, Rv1737c, Rv2029c, Rv2628, Rv1733c, Rv1735c, Rv2003c, Rv2005c, Rv2007c, Rv2034, and Rv2626c whereas Rpf antigens Rv0867c, Rv1009, and Rv2450c elicited significantly higher IFNy levels in individuals with LTBI than in active TB patients. Differences can also be found in immune cell activation and antibody production. So far, there are less studies to report diagnostic accuracy indices of DosR/Rpf antigens for LTBI diagnosis. However, several constraints including, heterogeneity, inconsistencies in the outcomes of individual studies with respect to some antigens, and less availability of data for some antigens found in current literature necessitates further studies in larger cohorts.

Abbreviations

DosR	Dormancy survival regulator
Rpf	Resuscitation-promoting factor
TB	Tuberculosis
LTBI	Latent tuberculosis infection
SMDs	Standardized mean differences
Mtb	Mycobacterium tuberculosis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03348-4.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Conceptualization: YW and YYX; Data curation: YZ, JJL, JW; Formal Analysis: YZ, JJL, JW; Funding acquisition: YW; Supervision: YW and YYX; Writing – original draft: YW and YYX; Writing – review & editing: all authors.

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Data availability

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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