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MAJOR ARTICLE

A Systematic Review on the Safety of *Mycobacterium tuberculosis*–Specific Antigen–Based Skin Tests for Tuberculosis Infection Compared With Tuberculin Skin Tests

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Background. A systematic review showed that the accuracy of *Mycobacterium tuberculosis* antigen–based skin tests (TBSTs) for tuberculosis is similar to that of interferon γ release assay, but the safety of TBSTs has not been systematically reviewed.

Methods. We searched for studies reporting injection site reactions (ISRs) and systemic adverse events associated with TBSTs. We searched Medline, Embase, e-library, the Chinese Biomedical Literature Database, and the China National Knowledge Infrastructure database for studies through 30 July 2021, and the database search was updated until 22 November 2022.

Results. We identified 7 studies for Cy-Tb (Serum Institute of India), 7 (including 2 found through the updated search) for C-TST (Anhui Zhifei Longcom), and 11 for Diaskintest (Generium). The pooled risk of any injection site reactions (ISRs) due to Cy-Tb (n = 2931; 5 studies) did not differ significantly from that for tuberculin skin tests (TSTs; risk ratio, 1.05 [95% confidence interval, .70–1.58]). More than 95% of ISRs were reported as mild or moderate; common ISRs included pain, itching, and rash. In 1 randomized controlled study, 49 of 153 participants (37.6%) given Cy-Tb experience any systemic adverse event (eg, fever and headache), compared with 56 of 149 participants (37.6%) given TST (risk ratio, 0.85 [95% confidence interval, .6–1.2]). In a randomized controlled study in China (n = 14 579), the frequency of systemic adverse events in participants given C-TST was similar to that for TST, and the frequency of ISRs was similar to or lower than that for TST. Reporting of the safety data on Diaskintest was not standardized, precluding meta-analysis.

Conclusion. The safety profile of TBSTs appears similar to that of TSTs and is associated with mostly mild ISRs.

Keywords. LTBI; IGRA; TST; diagnostics classification description; skin tests.

Preventing the development of tuberculosis in people who have *Mycobacterium tuberculosis* infection through tuberculosis-preventive treatment is essential to reduce tuberculosis mortality and morbidity rates, and achieve the goal of the End TB Strategy [1]. Currently, 2 types of tests for tuberculosis infection are available, tuberculin skin test (TST) and interferon γ release assay (IGRA). The TST has poor specificity because of cross-reactivity with BCG vaccination and nontuberculous mycobacteria. Although IGRAs have higher specificity because of the use of *M tuberculosis*–specific antigens, their implementation needs a laboratory set-up and trained laboratory technicians, and the scale-up of IGRAs has thus been a challenge in resource-constrained settings. Furthermore, while formal economic evaluation needs to be considered for selecting tests, TSTs are considered cheaper. Thus, despite their limitations, TSTs have been used most commonly globally.

An *M tuberculosis* antigen–based skin test (TBST) named Diaskintest (Generium) has been available for >10 years,

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though limited geographically to the Russian Federation and its neighboring countries. Other TBSTs have also emerged, including Cy-Tb (formerly known as C-Tb; Serum Institute of India) and C-TST (formerly known as ESAT6-CFP10 test; Anhui Zhifei Longcom). All of these TBSTs contain the recombinant *M tuberculosis*–specific RD1 antigens ESAT-6 and CFP10, as used in IGRAs. In a systematic review by Krutikov et al [2], the diagnostic performance of these tests appeared comparable to that of TST or IGRA. The review identified 6 studies reporting adverse events associated with the Cy-Tb and C-TST. No studies reported serious adverse events, and the frequency of injection site reactions (ISRs), such as pain and itching, was similar to that for TSTs. While these data are reassuring, the evaluation of the safety of TBSTs was not the main scope of the review [2]. Thus, we conducted a systematic review to assess the safety of TBSTs compared with TSTs.

METHODS

The protocol for this review is registered with PROSPERO. (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=274445). The original review, including 29 studies, was performed to inform the development of World Health Organization (WHO) guidelines [3].

Search Strategy

We searched Medline, Embase, the Chinese Biomedical Literature Database, the China National Knowledge Infrastructure database, and e-library (www.e-library.ru) to identify studies from inception until 30 July 2021 with no language restrictions. We contacted the test manufacturers for supplementary studies and abstracts. We also reviewed studies that were identified through a public call for data by WHO (https://www.who.int/news-room/articles-detail/public-call-for-data-on-diagnostic-accuracy-of-newer-skin-based-tests-based-on-specific-m.-tuberculosis-antigens). Studies found through the above processes constituted the original search that informed the WHO guidelines. After the WHO guideline development group meeting, the database search was updated until 22 November 2022. Detailed search strategy and terms are presented in the Supplementary Materials.

Eligibility Criteria

We included longitudinal and case-control studies reporting adverse events of the index tests alone or compared with TSTs, with no language restrictions. We included studies without a comparator test as we anticipated limited availability of studies with a comparator test. The tests of interest were Cy-Tb, Diaskintest, C-TST, and others for tuberculosis infection. The full criteria are presented in the Supplementary Materials.

Screening and Data Extraction

Two investigators screened abstracts identified through the search and then full-text articles of potentially eligible studies. Discrepancies in inclusion/exclusion between the 2 reviewers were resolved by discussion or, if needed, with additional reviewers. Two reviewers independently extracted the following information: study design, country, setting, recruitment period, sample size, age, sex, history of immunosuppression, human immunodeficiency virus (HIV) status, and the type, severity, and seriousness of adverse events. We contacted study authors and manufacturers for additional data. Some early-phase studies tested multiple different amounts of doses of the same antigens. In that case, we extracted safety data pertaining to the dose that was later adopted in the product.

Quality Assessment of Individual Studies and Grading of Evidence

Two independent reviewers assessed the study quality using a tool appropriate to the study design. We used the RoB2 tool for randomized controlled trials (RCTs) [4], the ROBINS-I tool for nonrandomized controlled studies [5], and McMaster tool for safety studies without control groups [6]. One of the domains in ROBINS-I is bias due to confounding, a "pre-intervention prognostic factor that predicts whether an individual receives one or the other intervention of interest," such as the severity of preexisting disease and sociodemographic factors [5]. For studies in which participants received both TBST and TST, we did not rate down for this domain. We used the GRADE framework [7] to systematically assess the quality of evidence regarding the use of TBST.

Statistical Analysis

We estimated the risk ratios (RRs) for adverse events or their frequency in the absence of a control group. We performed random effects meta-analysis using the Mantel-Haenszel method with Paule-Mandel estimator of τ^2 and Hartung-Knapp-Sidik-Jonkman adjustment to calculate RRs. We used a mixed-effects logistic regression model with a maximum-likelihood estimator for τ^2 and Hartung-Knapp adjustment for pooling proportions. We assessed heterogeneity visually using forest plots and characterized it using the I^2 statistic. We also presented data in subgroups of children, people living with HIV, and pregnant women.

Because of the limited number of studies (<10) that could be pooled, we did not test for publication bias. We primarily report the findings from the original search that informed the WHO guidelines. We also report the findings after the updated search.

Patient Consent Statement

This was a systematic review of previously published studies and did not involve any direct patient contact or data collection.

RESULTS

Search Results

We included 26 articles reporting 29 studies in the original review that informed the WHO guidelines (Figure 1). Among those, 7 studies reported on Cy-Tb [8–13], 5 on C-TST [14–16], and 11 on Diaskintest [17–27]. The updated search identified 2 additional C-TST studies [28, 29]. We also found studies of early products that were not translated into the final products (Supplementary Table 1) [30–35].

Characteristics of Individual Studies

Of the 7 studies that evaluated Cy-Tb, 5 reported data on ISRs compared with TSTs (Supplementary Table 2) [8–10, 12, 13]. In the remaining 2 studies, participants received only Cy-Tb. In the 5 comparative studies, Cy-Tb and TST were randomly allocated to the left or right arm for each participant, and the allocation was blinded for both participants and health care workers. In 4 of the 5 studies, participants received both tests. In 1 of the 5 [10], participants were randomly allocated to receive Cy-Tb + TST, Cy-Tb alone, or TST alone, with data provided on ISRs as well as systemic adverse events. Of studies in which participants were given both Cy-Tb and TST, 1 reported that the 2 tests were administered immediately one after the other [9], but the other studies did not report the interval between tests [8, 10, 12, 13].

Three of 7 studies of C-Tb were conducted in South Africa [9, 10, 12], while the rest were in European high-income countries [8, 13]. Five studies included only adults, and 2 included both adults and children (Supplementary Table 2) [9, 13]. Studies in South Africa included 20%–40% of HIV-positive individuals. All of the Cy-Tb studies were conducted as clinical trials and hence included safety events as predefined outcomes. All 5 studies that allowed comparison of the frequency of ISRs between Cy-Tb and TST were considered at low risk of bias (Supplementary Materials).

Of the 5 C-TST studies found through the original search, 3 studies gave both C-TST and TST to participants (Supplementary Table 2) [14, 16]. The updated search found another study giving both C-TST and TST [28]. These 4 studies administered tests to either of the participant's arms; allocation was nonblinded in 3 studies [14, 16], with the choice determined a priori without randomization, and it was blinded in 1 study [28]. In these studies, 2 tests were administered ≥30 minutes apart. The updated search also found a study that randomly administered C-TST in 1 group and TST in the other group while blinding the allocation [29]. Two studies did not compare C-TST and TST. In the first study [15], a subset of the participants received C-TST in one arm and placebo in the other, and in the second [14], participants received only

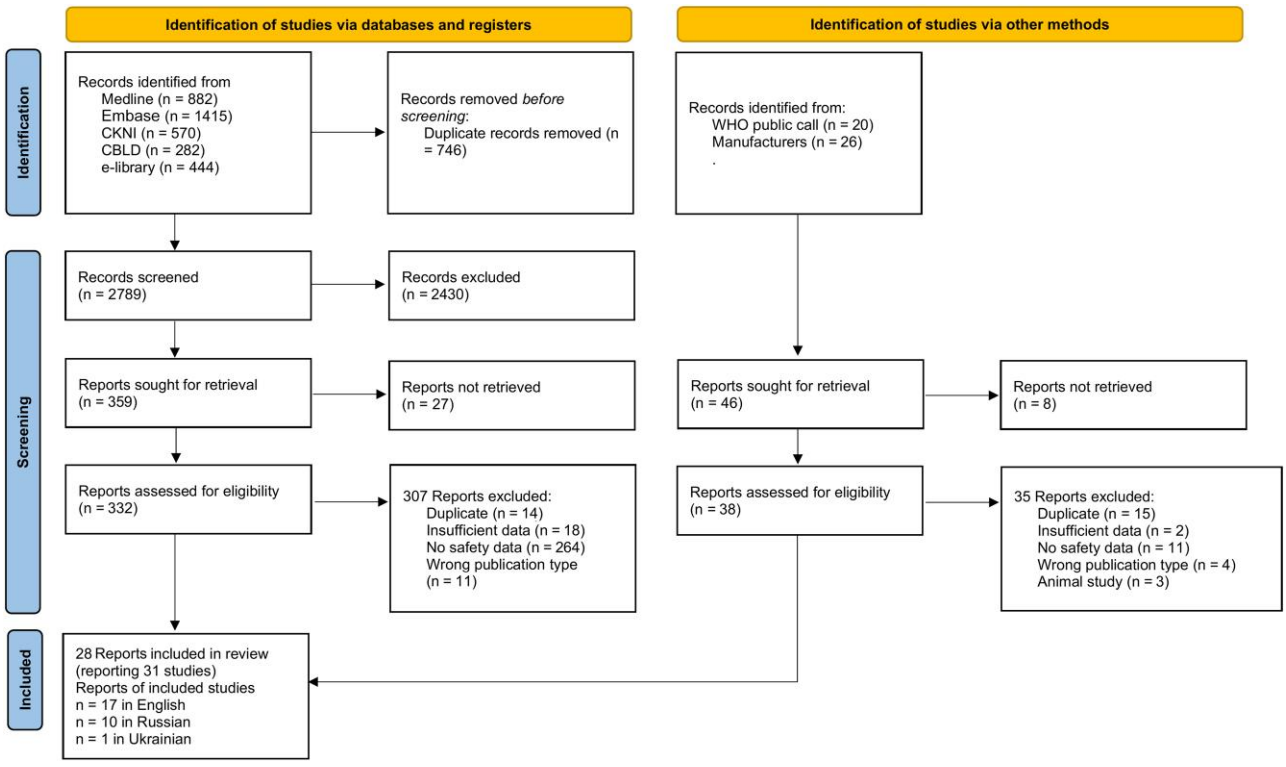

Figure 1. Study selection. The original review that informed the World Health Organization (WHO) guidelines included 26 reports on 29 studies. The updated search found 2 additional English-language reports. Abbreviations: CBLD, Chinese Biomedical Literature Database; CKNI, China National Knowledge Infrastructure database.

C-TST. Only 1 study provided data for the comparison of systemic adverse events [29].

All studies were conducted in China and included only HIV-negative adults or adults with unknown HIV status. Studies of C-TST were conducted as clinical trials and safety events were included as predefined outcomes. In 5 studies that allowed a comparison of C-TST versus TST, 2 were considered at low risk of bias [28, 29] while the rest were considered at serious risk of bias in the measurement of outcomes because of the lack of blinding [15, 16] (Supplementary Materials). While four of the C-TST studies did not randomize allocation of the tests, we did not rate down the risk of bias due to confounding in the ROBINS-I since the same participants received both tests.

Ten studies of Diaskintest were conducted in the Russian Federation, all using data collected through routine patient care programs in Russia (Supplementary Table 3). In addition, 1 study included tuberculosis care workers in Ukraine [27]. Five included children <18 years old, and 6 included individuals with active tuberculosis only. One study included people with both HIV and active tuberculosis [21], and 1 included pregnant women [20]. In 2 studies [23, 27], participants received both Diaskintest and TST without random allocation or blinding, and ISRs were reported for each. They did not specify the interval between the 2 tests. The remaining 8 studies reported ISRs and systemic adverse events only for Diaskintest.

The 2 studies that reported the risk of ISRs from Diaskintest versus TST were considered at serious risk of bias in the measurement of outcomes because of the lack of blinding [23, 27]. In the remaining 9 studies, both injection site and systemic adverse events were poorly defined, and they were collected only passively, using existing data not specifically collected for the studies, and thus were considered at high risk of bias overall.

Injection Site Reactions

For Cy-Tb, the frequency of any ISRs ranged from 23.7% to 53.1% (Table 1). Most ISRs (> 95%) were reported as mild to moderate by the investigators. Common ISRs included itching, pain, and rash. One study reported only mild reactions [8], and in 4 studies, <5% were of severe intensity (ie, sufficient to prevent normal activity) [9, 10, 12, 13]. No study allowed the comparison of ISRs stratified by its severity. The pooled RR did not show evidence of a significant difference in the frequency of any ISR between Cy-Tb and TST (Figure 2 and Supplementary Figure 1). However, there was significant heterogeneity ($I^2 = 92\%$). Two studies conducted in European countries reported a higher frequency of ISRs associated with Cy-Tb (Supplementary Figure 2) [8, 13].

When stratified by types of ISRs (Supplementary Figures 3–9), Cy-Tb was associated with a slightly lower frequency of itching/pruritus than TST (RR, 0.87 [95% confidence interval (CI), .76–.99]) and erythema (0.82 [.67–1.00]) (Supplementary

Table 1. Frequencies of Local Injection Site Reactions in Studies of Cy-Tb

Study	Test	Participants, No.	ISRs, No. (%)									
			Any ISR	Itching	Pain	Rash	Erythema	Swelling	Vesicle	Induration	Ulceration	Discoloration	Severity
Aggerbeck et al [8]	Cy-Tb	26	…	16 (61.5)	6 (23.1)	1 (3.8)	…	1 (3.8)	…	…	…	…	Not reported
	TST	…	…	…	…	…	…	…	…	…	…	…	Not reported
Aggerbeck et al [8]	Cy-Tb	151	48 (31.8)	…	…	…	…	…	…	…	2 (0.7)	1 (0.3)	Mild: 100%
	TST	151	31 (20.5)	…	…	…	…	…	…	…	1 (0.3)	4 (1.3)	Mild: 100%
Aggerbeck et al [9]	Cy-Tb	1188	282 (23.7)	210 (17.7)	90 (7.6)	58 (4.9)	3 (0.3)	5 (0.4)	24 (2)	15 (1.3)	…	…	Mild-moderate: >95%
	TST	1190	290 (24.4)	221 (18.6)	81 (6.8)	63 (5.3)	3 (0.3)	4 (0.3)	24 (2)	8 (0.7)	…	…	Mild-moderate: >95%
Aggerbeck et al [10]	Cy-Tb	307	163 (53.1)	138 (45)	51 (16.6)	50 (16.3)	7 (2.3)	…	17 (5.5)	8 (2.6)	…	…	Mild-moderate: >95%
	TST	303	205 (67.7)	167 (55.1)	52 (17.2)	68 (22.4)	9 (3)	…	36 (11.9)	5 (1.7)	…	…	Mild-moderate: >95%
Bergstedt et al [11]	Cy-Tb	21	…	0 (0)	0 (0)	…	…	…	…	…	…	0 (0)	Not reported
	TST	…	…	…	…	…	…	…	…	…	…	…	Not reported
Hoff et al [12]	Cy-Tb	253	120 (47.4)	88 (34.8)	42 (16.6)	2 (0.8)	43 (17)	38 (15)	11 (4.3)	…	1 (0.4)	…	Mild: 81%; moderate: 15%; severe: 4%
	TST	253	150 (59.3)	109 (43.1)	45 (17.8)	8 (3.2)	52 (20.6)	38 (15)	19 (7.5)	…	1 (0.4)	…	Mild: 83%; moderate: 15%; severe: 3%
Ruhwald et al [13]	Cy-Tb	979	288 (29.4)	126 (12.9)	41 (4.2)	13 (1.3)	0 (0)	1 (0.1)	17 (1.7)	2 (0.2)	0 (0)	1 (0.1)	Mild-moderate: 99%
	TST	929	182 (19.6)	134 (14.4)	32 (3.4)	13 (1.4)	1 (0.1)	0 (0)	13 (1.4)	1 (0.1)	1 (0.1)	1 (0.1)	Mild-moderate: 99%

This paper reported the results of two RCT in a single report.

Abbreviations: ISR, injection site reaction; TST, tuberculin skin test.

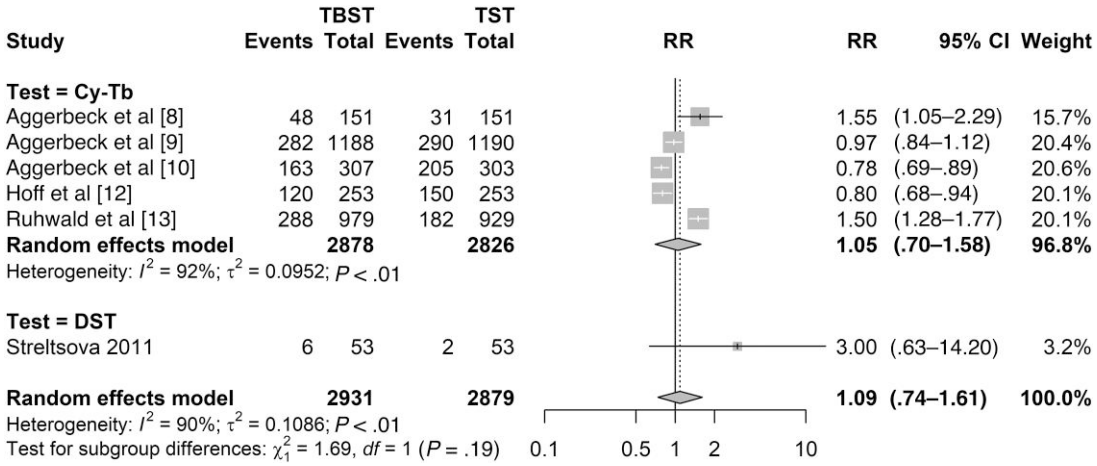

Figure 2. Any injection site reactions based on studies that informed World Health Organization guidelines. The proportions of participants who were human immunodeficiency virus (HIV) positive were 25% for Aggerbeck et al [9], 20% for Aggerbeck et al [10], and 39.5% for Hoff et al [12]. Other studies included only HIV-negative participants. Numbers indicate the numbers of participants who experienced adverse events. Aggerbeck et al [9] included children (20% <5 and 31% 5–17 years old), as did Ruhwald et al [13] (3.5% <5 and 8.8% 5–17 years old); other studies included only adults. Hoff et al [12], Aggerbeck et al [10], and Streltsova et al [23] included only people with tuberculosis. Abbreviations: CI, confidence interval; DST, Diaskintest; RR, risk ratio; TBST, *Mycobacterium tuberculosis* antigen–based skin test; TST, tuberculin skin test.

Table 2. Frequencies of Local Injection Site Reactions in Studies of C-TST Versus Tuberculin Skin Test

			ISRs, No. (%)[b]								
Study	Test[a]	Participants, No.	Pruritus	Pain	Rash	Allergy	Muscle Pain	Bleeding	Discoloration	Induration	Swelling
Li et al [15]	C-TST	28	2 (7.1)	0 (0)	…	…	…	…	…	…	…
	TST	28	2 (7.1)	0 (0)	…	…	…	…	…	…	…
Xu et al [16][c]	C-TST	NA	13.5%	5.3%	0.83%	0.17%	0.83%	…	…	…	…
	TST	NA	10.5%	6.5%	0.70%	0%	0%	…	…	…	…
Xia et al [28][d]	C-TST	1090	106 (9.7)	26 (2.3)	…	…	…	…	…	…	…
	TST	1090	103 (9.5)	15 (1.4)	…	…	…	…	…	…	…
Yang et al [29][d]	C-TST	7351	109 (1.5)	117 (1.6)	9 (0.12)	…	…	414 (5.6)	314 (4.3)	287 (3.9)	183 (2.5)
	TST	7228	112 (1.6)	115 (1.6)	14 (0.19)	…	…	467 (6.5)	440 (6.1)	933 (12.9)	258 (3.6)

Abbreviations: ISRs, injection site reactions; NA, not available; TST, tuberculin skin test.

[a]In all studies but that of Yang et al [29], participants received both tests.

[b]Data represent no. (%) of participants except where only percentages were available.

[c]This article reported 2 controlled trials but only aggregated data were reported. The denominator was unclear, and the authors did not respond to our query.

[d]Not included in the original search that informed World Health Organization guidelines.

Figures 3 and 6). On the other hand, Cy-Tb was associated with an increased risk of indurations ≥50 mm, which was defined as a notable ISRs in these studies (Supplementary Figure 9).

A single article in China reported combined data from 2 phase 2b studies; there were more local reactions from C-TST than for TST (27.8% vs 16.5%; P < .001) [16]. The authors noted that "most adverse reactions were mild and self-limiting." We did not derive RRs with 95% CIs because of the unavailability of raw data, resulting in unclear denominators (Table 2) [14].

The updated search found 2 RCTs [28, 29]. In 1 RCT (n = 14 579), the frequency of pain and itching was similar between C-TST and TST, but bleeding, discoloration, induration (not defined), and swelling were significantly more common for TST [36]. In a split-body RCT (n = 1090) in which participants received both C-TST and TST, the frequencies of itching (9.7% vs 9.5%, respectively; P = .88) and pain (2.3% vs 1.4%, P = .11) were similar [16].

Safety data on the Diaskintest were reported insufficiently, and standardization of types of adverse events and assessment of severity based on a priori criteria were lacking, thus precluding pooling of data (Table 3). Two studies reported the frequency of ISRs in participants given Diaskintest and TST at the same time in different arms; 1 included adults with active tuberculosis (n = 53), and the other, tuberculosis care health workers (n = 25) [23]. In the study in adults with active tuberculosis,

6 developed hyperallergic reactions with vesicles/necrosis and lymphangitis due to Diaskintest, compared with 2 due to TST (RR, 3.0 [95% CI, .6–14.1]). In the study in tuberculosis care workers, 1 of 25 developed hyperallergic reactions with local lymphadenitis, lymphangitis, and pain at the Diaskintest injection site, compared with none at the TST injection site. In the same study, the RR for itching/pruritus at the Diaskintest injection site was 0.43 (95% CI, .12–1.47). Other studies reported hyperallergic reactions and local reactions (Table 3).

Figure 3 summarizes the pooled estimates for each type of ISR based on the original search that informed the WHO guidelines. Supplementary Figure 10 shows the estimates including 2 studies found through the updated search.

Systemic Adverse Events

In 5 studies of Cy-Tb, the frequency of any systemic adverse events reported in individual studies ranged from 28.5% to 53.0% (Supplementary Figure 11) [8–10, 12, 13]. The most commonly reported systemic adverse events included fever, headache, and dizziness (Supplementary Table 4). The pooled proportions of participants who experienced fever and headache were 2.6% (95% CI, 1.2%–5.4%; n = 2478) and 11.3% (7.8%–16.0%; n = 2723), respectively (Supplementary Figures 12 and 13). Severe systemic adverse events (eg, fever and headache) were uncommon (Supplementary Table 4).

In all but 1 study, participants received both Cy-Tb and TST; thus, it was not possible to estimate the RR of systemic reactions compared with TST, nor was it possible to disentangle effects. In 1 study allowing comparison of effects [10], 32.0% of participants (49 of 153) given Cy-Tb developed any systemic adverse events, compared with 37.6% (56 of 149) in those given TST (RR, 0.85 [95% CI, .6–1.2]) [10].

In 3 of the 5 reviewed studies, study investigators assessed the relatedness of adverse events to Cy-Tb. In 1 study, out of 550 systemic adverse events, 31 (6%) were deemed to be certainly or possibly related to the skin tests [13]. The study states that "as systemic adverse events in participants who received both Cy-Tb and the TST could not be related to either agent separately, they were ascribed to Cy-Tb." In 2 studies, the frequencies of systemic adverse events deemed at least possibly related to Cy-Tb among participants were 5% (7 of 151) [8%], and 14% (36 of 253) [12].

Four studies of C-TST found through the original search reported data on systemic adverse events (Supplementary Table 5). In 2 studies, participants received both C-TST and TST [15, 16]. In 1 article reporting 2 phase 2b studies [16], only proportions aggregating data from the 2 could be extracted without raw data. Fever was the most common adverse events (7.1%), and other events were uncommon (<1%). In the phase 2a study (n = 144) [14], 9 systemic adverse events related to the test were reported.

Two RCTs found through the updated search reported similar results [28, 29]. In 1 RCT (n = 14 579), systemic adverse events such as fatigue and headache were uncommon (up to 0.24%), and their frequency was similar between participants given C-TST and those given TST (Supplementary Table 5) [36]. In the phase 3 study (n = 1090) [28], about 1% of participants reported fever, fatigue, and headache, respectively, and all were mild to moderate.

Data for Diaskintest were limited (Table 3). Six studies reported fever, with frequencies ranging from 0% to 7% and a pooled frequency of 2.6% (95% CI 2.7%–1.5%) (Supplementary Figure 12) [17, 18, 22, 23, 25, 26]. In 1 study, there were no adverse events in 385 children and adolescents who received Diaskintest [19].

Serious Adverse Events

In 7 studies of Cy-Tb (n = 2924) [8–13] and 4 studies of C-TST (n = 8491), including 2 found through the updated search) [14, 15, 28, 29], no participants reported serious adverse events related to the test for C-TST or Cy-Tb. None of the Diaskintest studies explicitly mentioned the presence or absence of serious adverse events.

Subgroups

Only 2 studies provide data among people living with HIV; 1 evaluated Cy-Tb and the other the Diaskintest. In the Cy-Tb study by Hoff et al [12], most of the local reactions due to Cy-Tb and TST were reported as mild in intensity in both HIV-negative (>80%) and HIV-positive individuals (>75%). Likewise, most systemic adverse events were considered mild in intensity for both the HIV-negative (85.0%) and the HIV-positive (76.6%) groups. In a study including 88 tuberculosis/HIV-coinfected adults who received Diaskintest, 4 experienced fever, weakness, chills, and headache [21].

Five studies reported adverse events in children who received Diaskintest [17–19, 25, 26]. As mentioned above, adverse events were not systematically ascertained (Table 3). Only 1 study included pregnant women [20]. The study by Borisova and Suleimanova [20] used Diaskintest in 267 pregnant women with tuberculosis. Diaskintest was performed in the first half of pregnancy (but after 12 weeks) in 124 patients (46.4%), and in the second half in the other patients. The study reported that "no embryo toxicity was registered," without further details.

Quality of Evidence

The quality of evidence was considered high for any injection site reactions and moderate for any systemic reactions, owing to the small sample size and a wide CI (Supplementary Table 6).

DISCUSSION

Our review found that ISRs due to TBSTs were similar in frequency to those seen with TSTs, including primarily mild reactions, such as itching and pain. This finding was also replicated

Table 3. Frequencies of Adverse Events in Studies of Diaskintest

Study	Population	DST vs TST	Fever	Other Adverse Events
Aksenova et al [17][a]	Children and adolescents with tuberculosis	No data	2/63 (3.2%)	…
Barmina and Baryshnikova [19][a]	Child and adolescent household contact	No data	No data	Any adverse events: 0/385 (0%)
Belushkov et al [18]	Children suspected of tuberculosis	No data	4/88 (4.5%)	Hyperallergic reaction without details: 3/48 (6.3%)
Borisova and Suleimanova [20]	Pregnant women with tuberculosis	No data	No data	Any adverse events: 0/267 (0%)
Dotsenko [27]	Tuberculosis care workers	Itching: 3/25 (12%) in DST site vs 7/25 (28%) in TST site; hyperallergic reaction with local lymphadenitis, lymphangitis, and pain: 1/25 (4.0%) in DST site vs 0/25 (0%) in TST site		Any systemic reactions: 0/25 (0%)
Patsyuk [24]	Adults	No data	No data	Hyperallergic reaction with local edema, lymphangitis or lymphadenitis, vesiculosis, or a blister with a tight lid: 7/33 (21.2%)
Rutkovsky and Chekalina [25]	Children with tuberculosis, posttuberculosis changes, and tuberculosis infection	No data	14/474 (3%)	Vomiting: 1/474 (0.2%)
Slogotskaya et al [21][a]	Tuberculosis/HIV-coinfected adults	No data	No data	Fever, weakness, chills, and headache: 4/88 (4.5%)
Slogotskaya et al [22][a]	People with tuberculosis, including people living with HIV	No data	5/71 (7.0%)	Local reaction (hyperemia, swelling, edema, pain, local high skin temperature): 2/71 (1.4%)
Streltsova et al [23][a]	Adults with tuberculosis	Hyperallergic reactions with vesicles/necrosis and lymphangitis: 6/53 (11.3%) versus 2/53 (3.8%)	0/53 (0%)	Hyperallergic reaction with vesicles/necrosis and lymphangitis: 6/53 (11.3%); constitutional symptoms: 0/53 (0%)
Yarovaya et al [26][a]	Children (tuberculosis infected, residual tuberculosis changes, or active tuberculosis)	No data	7/452 (1.5%)	Papular rash: 3/452 (0.7%); herpetiform rash: 1/452 (0.2%)

Abbreviations: DST, Diaskintest; HIV, human immunodeficiency virus; TST, tuberculin skin test.

[a]Participants received both tests, but adverse events were not reported separately for each test.

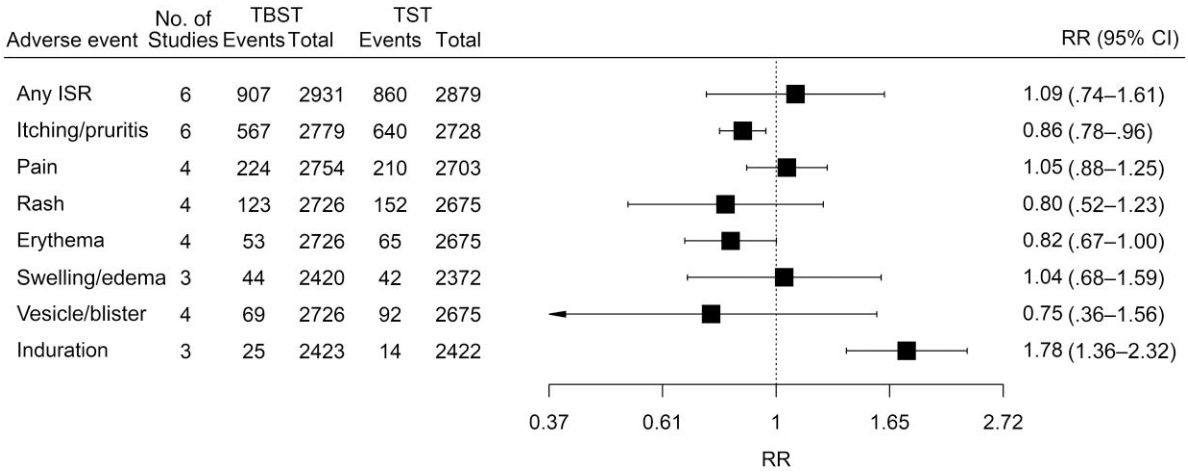

Figure 3. Pooled estimates of the risk for any injection site reaction (ISR) and individual ISRs based on the studies that informed World Health Organization guidelines. Numbers indicate the numbers of participants who experienced adverse events. Abbreviations: CI, confidence interval; RR, risk ratio; TBST, *Mycobacterium tuberculosis* antigen–based skin test; TST, tuberculin skin test.

in 2 RCTs on C-TST found through the updated search. However, available data on Diaskintest were limited or of insufficient quality. Data stratified by subgroups and in pregnant women were limited.

Two studies of Cy-Tb in European countries reported a higher frequency of ISRs associated with Cy-Tb. This appeared to be driven by frequent reporting of hematoma at the Cy-Tb injection site [13]. One of the studies reported a joint analysis of 2957 participants from 7 trials, in which hematoma at the Cy-Tb injection site was seen in 172 participants (6%), compared with 25 of 2826 (1%) at the TST site [13]. Most hematomas (99%) were mild, and 92% were reported in participants with negative test results. The authors therefore, speculated that hematomas were underestimated in participants with indurations. Regardless of the mechanism, given the mildness of hematoma, it is unlikely to affect the choice of the tests.

Data comparing Diaskintest with TST were limited. Few studies provided comparable data on injection site reactions allowing the comparison between Diaskintest and TST. They ascertained adverse events passively using routine data rather than ascertaining them prospectively according to a predefined protocol, which might have underestimated their frequency. In addition, it was unclear how adverse events were monitored. The WHO framework for the evaluation of new tests for tuberculosis infection stresses the need for predefining injection site reactions, given that skin tests are intended to induce reactions. Unless predefined, the frequency of those events cannot be determined accurately. It should be noted that Diaskintest has been widely used in Russia and its neighboring countries since 2008. According to the postmarketing surveillance data shared with WHO, >55.7 million Diaskintest tests were performed between 2019 and 2021, with 27 serious and 30 nonserious adverse effects [3].

We found limited data for the comparison of systemic adverse events between a specific TBST and TST. In most studies, participants received both TBST and TST, and thus it was not possible to ascribe those events to either of the tests. Nonetheless, included studies did not report unexpected severe or serious systemic reactions potentially associated with a specific TBST. Our updated search found 1 large RCT in China that reported a similar frequencies of various systemic reactions, such as fatigue, headache, and nausea, for C-TST and TST [29]. Still, the current sample size limits our ability to understand the frequency of rare adverse events, such as anaphylaxis reactions. Thus, postmarketing surveillance of adverse events is essential.

There are additional limitations in the current body of evidence. First, only 1 study reported the use of TBST in pregnant women. We contacted test manufacturers for clinical as well as preclinical data, but no further data were provided. Second, it should be noted that test manufacturers were involved in most studies of Cy-Tb and C-TST; thus, there has been limited independent evaluation of these tests. The involvement of manufacturers was unclear in studies of Diaskintest.

In conclusion, the present review suggests that the safety profile of TBST appears similar to that of TST, especially with robust data for Cy-Tb and C-TST. Given the accuracy of TBST comparable to IGRA reported in an earlier review, TBST may be used as an alternative to existing tests. Further data are required among pregnant women.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the

posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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