WHO consolidated guidelines on tuberculosis

Module 3: diagnosis. Tests for TB infection

Web Annex B

Safety of *Mycobacterium tuberculosis* antigen-based skin tests: a systematic review and meta-analysis

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Contents

Abbreviations

AE	adverse events
BCG	bacille Calmette-Guérin
CI	confidence interval
CI	confidence interval
DAIDS	division of AIDS
DST	diaskintest
GDG	guideline development group
IGRA	interferon gamma release assay
ISR	injection site reaction
MTB	mycobacterium tuberculosis
PICO	population, intervention, comparison, outcome
PPD	purified protein derivative
QFT	quantiferon
RR	risk ratio
TB	tuberculosis
TBST	novel skin-based tests for TB infection using TB specific antigens (TBST)
TST	tuberculin skin test
WHO	World Health Organization

Executive summary

Background

The diagnostic tests in current use for identification of TB infection are the tuberculin skin test (TST) and interferon-gamma release assay (IGRA). The safety of TST, an in-vivo test, is well established and associated with only uncommon adverse reactions. Over the last decade, novel skin-based tests for TB infection using TB specific antigens (TBST) have been developed. Evidence on the safety of these tests has not been systematically reviewed.

Method

We systematically searched for studies reporting the outcomes of our interest: local reactions (i.e. injection site reactions) and systemic adverse events from TBST. We searched Medline, Embase, e-library, the Chinese Biomedical Literature Database, and the China National Knowledge Infrastructure database for studies from inception until 30 July 2021. We also contacted the test manufacturers and reviewed studies that were identified through a public call for data by WHO. We included longitudinal and case-control studies reporting adverse events of the index tests alone or compared with recognised comparator tests (QFT, T-SPOT, TST) in humans with no language restrictions. Screening of titles and abstracts as well as full text articles and the assessment of quality was performed by two investigators in duplicate. We conducted a meta-analysis using a random-effects model and pooled studies that were considered to be clinically homogenous.

Results

We identified seven studies for C-Tb (Serum Institute of India, India), five for C-TST (formerly known as EC-test, Anhui Zhifei Longcom, China), and 11 for Diaskintest (Generium, Russia).

In five out of the seven studies on C-Tb, participants received both C-Tb and TST and there were data on injection site reactions (ISR) compared to TST. In the five studies, C-Tb and TST were randomly allocated to either of the arms in each participant and the allocation was blinded; the risk of bias was considered low. One of the five studies included additional two groups, one of which received C-Tb alone and the other TST, allowing the comparison of the frequency of systemic adverse events. Of the five studies, three were conducted in South Africa and two in Spain and UK, respectively.

Out of the five studies that tested C-TST in China, participants received both C-TST and TST in three studies. Tests were administered to either of the arms; allocation was non-blinded and the choice was determined a priori without randomization. The risk of bias was considered high in the measurement of outcomes due to a lack of blinding.

Ten studies on Diaskintest were conducted in Russian, all using data collected through the routine patient care programmes in Russia and one in TB care workers in Ukraine. Only two

studies provided comparable data on injection site reactions allowing the comparison between Diaskintest and TST. All studies were considered at high risk of bias. The above two studies with comparable data were considered at high risk of bias due to lack of blinding and the other studies without a control group had passive ascertainment of adverse events, a lack of systematic data collection, and a lack of the information about what adverse events were assessed.

The pooled risk of any injection site reaction (ISR) due to C-Tb (N= 2931, 5 studies) was not significantly different from TST (RR 1.05; 95%CI 0.70-1.58). Over 95% of ISR were reported as mild or moderate; common ISR included pain, itching and rash. In one study that allowed, 49/153 (37.6%) of participants given C-Tb developed any systemic adverse events (e.g. fever and headache) in comparison with 37.6% (56/149) in those given TST (RR 0.85 95%CI 0.6-1.2). The remaining studies did not allow the comparison of systemic adverse events.

In a single paper in China reporting combined data from two Phase 2b studies among participants that received both C-TST and TST, there were more ISR from C-TST than for TST (27.8% vs 16.5%, p<0.001). The authors noted that “most adverse reactions were mild and self-limiting”. In one study (n=144), 9 (6.3%) participants developed systemic adverse events such as increased blood pressure and vasculitis.

Reporting of the safety data on Diaskintest was not standardized precluding pooling of data. Two studies reported the frequency of ISR in participants given Diaskintest and TST at the same time in different arms. In one study in adults with active TB (n=53), six developed hyperallergic reactions with vesicles/necrosis and lymphangitis due to Diaskintest compared to two due to TST (RR 3.0; 95%CI 0.6-14.1). In the other study among TB care workers (n=25), an individual developed hyperallergic reaction with local lymphadenitis, lymphangitis and pain at the Diaskintest injection site compared to none at the TST injection site. Six studies reported fever whose frequency ranged from 0% to 7%. Other reported events included vomiting (1/474, 0.2% in one study) and “constitutional symptoms” (0/53, 0% in one study).

We did not find studies that reported safety data on DPPD.

We assessed the quality of evidence on the safety of TBST overall. The quality of evidence was considered high for any injection site reactions. The quality of evidence for any systemic reactions was considered moderate due to the small sample size and a wide confidence interval.

Interpretation

The safety profile of novel TBST appear similar to TST and is associated with mostly mild injection site reactions such as itching and pain. However, data comparing Diaskintest to TST

are limited. From the reviewed studies, there appears to be no safety signal that might affect the choice between specific TBST vs TST.

Background

Approximately 25-27% of the world's population is estimated to have TB infection[1] [2] with a lifetime risk of progression to active infection of 5-10%[3]. Individuals with risk for progression to active TB such as people living with HIV and those who are known to be recently infected (i.e. household contacts of people with TB) are important targets for treatment of TB infection, also known as TB preventive treatment.[4] Currently, available tests for LTBI are imperfect, as they cannot accurately distinguish between active TB disease and TB infection, nor are they useful predictors of progression to active disease.[5] More accurate diagnostic tests are critical to the achievement of the targets of End TB Strategy.[6]

The diagnostic tests in current use are the tuberculin skin test (TST) and interferon-gamma release assay (IGRA). The safety of TST is well established associated with only rare adverse reactions (e.g. hypersensitivity reactions)[7] while IGRA is an *in-vitro* test. However, TST has relatively low specificity (false positives in those with previous recent BCG vaccination), lacks sensitivity in immunosuppressed individuals (e.g. HIV infected), requires two clinic visits (one to administer the test and one to read the result), and failure to attend the clinic for evaluation of reaction within 48-72 hours renders the results invalid. Despite its limitations, due to its low cost and wide availability, it remains the most commonly used test for TBI globally, however current shortages of PPD threaten its continued use.

Examples of new class TB Ag-based skin tests are the C-Tb (Serum Institute of India), Diaskintest (Generium) and C-TST (formerly known as ESAT6-CFP10 test [Anhui Zhifei Longcom]), all of which contain recombinant ESAT-6 (dimer) and CFP10 (monomer) antigens derived from MTB that may provide diagnostic performance improvements over the standard TST (particularly in respect to specificity). Another new test is DPPD skin test which contains a recombinant protein rv0061, named DPPD. The gene coding DPPD is present only in the MTB complex (including mycobacterium bovis-BCG) and is absent in NTMs.[8] Our recent systematic review by Krutikov et al suggested the diagnostic performance of these tests appeared comparable to TST or IGRA.[9]

In that review, Krutikov et al identified six studies reporting adverse events associated with the C-Tb and C-TST. No studies reported serious adverse events. Mild systemic reactions such as fever and headache were observed.[10] Injection site reactions such as itching and pain for C-Tb were common (30.86%) but was similar to TST (827/2819, 29.34%). While these data are reassuring, evaluation of the safety of TBST was not the main scope of the review.[9] Thus safety of novel TBST has not hitherto been systematically reviewed.

The objective of this current systematic review was to assess the safety of TBST compared to that of currently available *in vitro* IGRA tests and TST to inform the development of WHO guidelines.

Aims and Objectives

Aim

To evaluate the safety of novel TBST for detection of TB infection compared to currently available *in vitro* IGRA tests or TST.

PICO

Do TBST cause more adverse reactions compared to TST or IGRA?

Outcomes:

- Relative risks of both local and systemic reactions adverse reactions, where possible, graded by type, severity and seriousness and stratified by sub-group;
- Frequency (%) of adverse events (if a control group receiving a comparator test is unavailable).

METHODS

Inclusion criteria

Longitudinal (prospective or retrospective) and case-control studies reporting adverse events of the index tests alone or compared with recognised comparator tests (QFT, T-SPOT, TST) in humans were reviewed, with no language restrictions.

Index tests:

- C-Tb (Serum Institute of India)
- Diaskintestest (Generium)
- C-TST (Anhui Zhifei Longcom)
- DPPD
- Others

Comparator tests:

- QFT-gold or plus (Qiagen)
- T-SPOT TB test (Oxford Immunotec)
- TST

Based on published literature, we expected the most frequent adverse reactions to be injection site reactions, although systemic reactions like headache, fever and even lymphadenitis have also been reported.[11 12] Induration/swelling/inflammation are the intent of the skin tests and may not necessarily be "adverse" reactions in all instances, however some clinical trials consider these as adverse reactions if exuberant (e.g. induration size ≥ 50mm and erythema ≥ 80mm)[12]. We report them as defined by the authors.[12]

Data on the severity of adverse reactions were collected according to the following widely-accepted DAIDS (The Division of AIDS) classification[13] or, if unavailable, as defined by the study authors. Unless defined by the study authors, we followed the standard definition of serious adverse events: an adverse reaction that results in death, is life-threatening,

requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect).[14]

Exclusions:

1) Letters without original data; 2) case reports and case series reporting participants who developed adverse events without the denominator (i.e. number tested); 3) reviews; 4) mathematical modelling or case-based studies; 5) animal studies.

Search strategy:

The systematic review protocol and search strategy were registered on PROSPERO (CRD42021274445), and we followed PRISMA guidelines. We conducted the search in Medline and Embase including studies from inception until 30 July 2021 with no language restrictions. We looked for additional Chinese language studies on skin tests manufactured by Chinese manufacturers such as C-TST in the Chinese Biomedical Literature Database and the China National Knowledge Infrastructure database. As Generium is a Russian company and most studies evaluating Diaskintest have been carried out in the ex-Soviet bloc, we searched e-library (www.e-library.ru) to look for additional Russian language studies. In order to include as many studies as possible, 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). The detailed search strategy and search terms are provided in Appendix 1.

Study Screening and Data Collection Process:

In support of data synthesis for the GDG, we developed a broad search strategy for English papers to allow title and abstract screening informing multiple systematic reviews addressing other objectives. The initial list of English titles and abstracts were reviewed by two independent reviewers (YH and LEZ) to identify studies reporting any new skin tests regardless of the outcomes of interest. This was followed by screening of titles and abstracts by two independent reviewers (YH and IK) and screening of full-text articles. Two Russian

speakers (ES and IK) independently screened titles and abstracts identified from the e-library and followed by reviewing full-text articles as well as papers identified through the public call. Chinese abstracts and titles were screened by two reviewers independently, relying on web-based Google translation to identify relevant studies. Full-text articles were independently reviewed by two Chinese speaking individuals.

Discrepancies in inclusion/exclusion between the 2 reviewers were resolved by discussion between the 2 reviewers or if needed with additional reviewers. Bibliographies of studies included in the review were hand-searched for additional relevant studies. We used the systematic review management platform Rayyan[15] for study screening and tracking of exclusion reasons. Data extraction was carried out using specific data extraction sheet in Microsoft Excel.

Data variables:

Table 1 details the principal variables of interest. Although not all studies included all of these data, the minimum data for inclusion are stated in the inclusion criteria. Data extraction was done by two reviewers independently. We contacted study authors and manufacturers for additional data. For early phase clinical studies that tested multiple doses of antigens, we extracted data pertaining to the dose that was later adopted in the product. If data on a specific dose was not extractable, we extracted data combining all doses and reported it as such.

Quality assessment (risk of bias) and grading of evidence:

The quality of each included study was formally evaluated by two independent reviewers using a quality assessment tool appropriate to the study design. We used RoB2 for randomized controlled trials,[16] ROBINS-I for non-randomized controlled studies,[17] and McMaster tool for safety studies without control groups.[18] When assessing studies in which participants received both a new skin test and TST, bias due to confounding was considered irrelevant.

For the purpose of the review, studies that randomized TBST and a comparator test to different arms or different groups of participants were considered randomized trials. While

some studies randomized participants into different doses of TBST, this was not considered randomized studies.

We used the GRADE framework[19] to systematically assess the quality of evidence regarding the use of novel skin tests.

Data Analysis:

The summary measures for dichotomous outcomes were relative risks for dichotomous data or proportions in the absence of a control group, with 95% confidence intervals. We conducted a meta-analysis using a random-effects model if included studies were considered to be clinically homogenous (ie ignoring statistical heterogeneity in places). We used the Mantel-Haenszel method with Paule-Mandel estimator of tau-squared and Hartung-Knapp-Sidik-Jonkman adjustment to calculate risk ratios. We used a mixed-effects logistic regression model with Maximum-likelihood estimator for tau-squared and Hartung-Knapp adjustment for pooling proportions. Data derived from randomized trials were pooled together with data from observational studies if they are considered otherwise clinically homogenous, as recommended for systematic reviews of adverse events.[20]

Heterogeneity was visually assessed using forest plots and heterogeneity characterised using the I-squared statistic and statistically tested using the chi-squared test. We also intended to present data in subgroups of children, people living with HIV, and pregnant women.

Because of the limited number of studies (< 10), we did not test for publication bias.

RESULTS

Search results

Figure 1 illustrates the systematic review process. A total of 2676 records were screened after the removal of duplicates. They included 1424 English, 847 Chinese, and 405 Russian language records. After screening of full-text articles, 26 papers reporting 29 studies were included in the review. Among those, seven studies reported on C-Tb (Serum Institute of India),[10 12 21-24] five on C-TST (Anhui Zhifei Longcom),[25-27] and eleven on Diaskintest.[28-38] One

study reported a skin test using a recombinant fusion protein of ESAT6 and CFP10 named RP22.[39] Two studies reported on ESAT-6 recombinant protein provided by Beijing Xiangrui Biological Products Co., Ltd.[40 41] Two studies reported on rdESAT-6, which was later adopted in C-Tb.[42 43] One study reported on ESAT-6 developed in-house.[44] These studies are summarized in Tables 2 and 3. We did not find studies that reported safety data on DPPD. Hereafter, this report focuses on C-Tb, C-TST, and Diaskintest since the other tests or antigens are different from those translated into the final products or have not reached the late stage of the product development.

Characteristics of individual studies

C-Tb

Out of the seven studies that evaluated C-Tb, five reported data on injection site reactions (ISR) compared to TST (Table 2) [10 12 21 22 24] and in the remaining two studies, participants received only C-Tb and no comparable data on ISR was available.[21 23] In the five studies, C-Tb and TST were randomly allocated to either of the arms in each participant and the allocation was blinded to both participants and health care workers (i.e. double-blind). In four studies, participants received both tests and thus systemic effects could not be attributed to either test; thus we could not use data to compare the frequency of systemic adverse events between C-Tb and TST. In one of the five studies,[22] participants were randomly allocated into C-Tb+TST, C-Tb alone, and TST alone, providing data on ISR as well as data on systemic adverse events comparing C-Tb and TST.

Three studies were conducted in South Africa[12 22 24] while the rest were in European high-income countries.[10 21] Five studies included only adults and two studies included both adults and children (Table 2).[10 12] Studies in South Africa included 20-40% of HIV-positive individuals. Three included only active TB patients,[21 22 24] while two included healthy adults,[21 23] and two included mixed groups including contacts and people with TB and healthy individuals.[10 12]

All of the five studies that allowed comparison of the frequency of ISR between C-TB and TST were considered at low risk of bias (Supplementary-risk of bias assessment).

C-TST

Out of the five studies that evaluated C-TST, participants received both C-TST and TST in three studies (Table 2).[25 27] Tests were administered to either of the arms; allocation was non-blinded and the choice was determined *a priori* without randomization. In one of the remaining two studies, a sub-set of the participants received C-TST in one arm and placebo in the other arm[26] and, in the other study,[25] participants received only C-TST; thus, these studies did not provide safety data for the comparison of ISR between the two tests. None of the studies provided data for the comparison of systemic adverse events. All studies were conducted in China and included only HIV-negative adults. One study included only people with TB,[25] one included a mix of people with TB and people with other pulmonary disease[27] and three studies included healthy adults.[25-27]

In three studies that allowed a comparison of C-TST vs TST, all of them were considered at serious risk of bias in the measurement of outcomes because of the lack of blinding.[26 27] They were considered at low risk of bias in the other domains (Supplementary-risk of bias assessment).

Diaskintest

Ten studies on Diaskintest were published in Russian, all using data collected through the routine patient care programmes in Russia (Table 3). In addition, one study included TB care workers in Ukraine.[38] Five of them included children < 18 years old, and six included individuals with active TB only. One study included people with both HIV and active TB[32] and one included pregnant women.[31] In two studies,[34 38] participants received both Diaskintest and TST without random allocation or blinding and ISR was reported for each. The remaining eight studies reported data on ISR and systemic adverse events only for Diaskintest.

The two studies that reported the risk of ISR from Diaskintest vs TST were considered at serious risk of bias in the measurement of outcomes because of the lack of blinding.[34 38] In

the remaining nine studies, both injection site and systemic adverse events were poorly defined and they were collected only passively and thus were considered at high risk of bias overall.

Injection site reactions

For C-Tb, the frequency of any ISR reactions ranged from 23.7% to 53.1% (Table 4). Most (>95%) ISR were reported as mild to moderate by the investigators (mild: easily tolerated; moderate: sufficient to interfere with daily activities; severe: sufficient to prevent normal activity). Common ISR included itching, pain, and rash. One study reported only mild reactions and in four studies, <5% were of severe intensity. The pooled RR did not show evidence of a significant difference in the frequency of any ISR between C-Tb and TST (Figure 2, Figure A1). However, there was significant heterogeneity (I-squared = 92%). Two studies conducted in European countries reported a higher frequency of ISR associated with C-Tb.[10 21] This appeared to be driven by frequent reporting of hematoma at the C-Tb injection site.[10] According to a joint analysis of 2957 participants from seven trials reported in one of the studies,[10] haematoma at the C-Tb injection site was seen in 172 (6%), compared with 25 (1%) of 2826 at the TST site. Most haematomas (99%) were mild and 92% were reported in participants with negative test results. The authors, therefore, speculated that haematomas were underestimated in participants with indurations.

When stratified by types of local reactions, C-Tb was associated with a slightly lower frequency of itching/pruritus (RR 0.87, 95%CI 0.76-0.99) and erythema (0.82 95%CI; 0.67-1.00) than TST (Figure 3 and 6). On the other hand, C-Tb was associated with an increased risk of induration size ≥ 50mm, which was defined as a notable ISR in these studies (Figure 9).

In a single paper in China reporting combined data from two Phase 2b studies, there were more local reactions from C-TST than for TST (27.8% vs 16.5%, p<0.001).[27] The authors noted that “most adverse reactions were mild and self-limiting”. We did not derive RR with 95% CI because of the unavailability of raw data resulting in unclear denominators; the study authors did not respond to our repeated requests for data. In another study (n=28), the frequency of pruritus and pain was the same between C-TST and TST.[25]

Safety data on the Diaskintest were poorly reported lacking standardization of types of adverse events and assessment of severity based on *a priori* criteria thus precluding pooling of data (Table 6). Two studies reported the frequency of ISR in participants given Diaskintest and TST at the same time in different arms; one included adults with active TB (n=53) and the other TB care health workers (n=25).[34] In the former study in adults with active TB, six developed hyperallergic reactions with vesicles/necrosis and lymphangitis due to Diaskintest compared to two due to TST (RR, 3.0; 95%CI 0.6-14.1). In the latter study among TB care workers, 1/25 developed hyperallergic reaction with local lymphadenitis, lymphangitis and pain at the Diaskintest injection site compared to none at the TST injection site. In the same study, the risk of itching/pruritus at the Diaskintest injection site was RR of 0.43 (95%CI 0.12-1.47). Other studies reported hyperallergic reactions and local reactions (Table 6).

Systemic adverse events

In five studies on C-Tb, the frequency of any systemic adverse events reported in individual studies ranged from 28.5% to 53.0% (Figure 11).[10 12 21 22 24] The most commonly reported systemic adverse events included fever, headache, and dizziness (Table 7). The pooled proportions of participants who experienced fever and headache were 2.6% (95%CI 1.2%-5.4%, N=2478) and 11.3% (95%CI 7.8%-16.0%, N=2723), respectively. (Figure 12 and 13). Severe systemic adverse events (e.g. fever and headache) were uncommon (Table 7).

In all but one study, participants received both C-Tb and TST thus it was not possible to estimate RR of systemic reactions compared to TST nor was it possible to disentangle effects. In one study allowing comparison of effects,[22] 32.0% (49/153) of participants given C-Tb developed any systemic adverse events in comparison with 37.6% (56/149) in those given TST (RR 0.85; 95%CI 0.6-1.2).[22]

In three of the 5 reviewed studies, study investigators assessed the relatedness of adverse events to C-Tb although causal assessment would have been difficult due to the lack of a control group given TST alone. In one study, out of 550 systemic adverse events, 31 (6%) were deemed to be certainly or possibly related to the skin tests.[10] The study states that "as systemic adverse events in participants who received both C-Tb and the TST could not be

related to either agent separately, they were ascribed to C-Tb." In two studies, the frequency of systemic adverse events deemed at least possibly related to C-Tb among participants were 5% (7/151)[21] and 14% (36/253).[24]

Four studies on C-TST reported data on systemic adverse events (Table 8). In two studies, participants received both C-TST and TST.[26 27] In the phase 2a study (n=144),[25] nine systemic adverse events related to the test were reported. For the phase 2b study,[27] only proportions could be extracted without raw data. The authors did not respond to requests for data.

Data for Diaskintest were limited (Table 6). Six studies reported fever, whose frequency ranged from 0% to 7%, with a pooled frequency of 2.6% (95%CI 2.7-1.5%) (Figure 12).[28 29 33 34 36 37] In one study, there were no adverse events in 385 children and adolescents who received Diaskintest.[30]

Serious adverse events

In seven studies on C-Tb comprising 2924 individuals, there was no serious adverse event related to the test such as deaths, life-threatening events, events requiring hospitalization, or persistent morbidity. Similarly, for C-TST, there was no serious adverse event related to the test in four studies. None of the studies on Diaskintest explicitly mentioned the presence or absence of serious adverse events.

Subgroups

People living with HIV

Only two studies provide data among people living with HIV, one evaluated C-Tb and the other the Diaskintest. In the C-Tb study by Hoff et al,[24] most of the local reactions due to C-Tb and TST were reported as mild in intensity in both the HIV-negative (>80%) and the HIV-positive individuals (>75%). Likewise, most of the systemic adverse events were considered mild in intensity for both the HIV- group (85.0%) and the HIV+ group (76.6%). The fraction of HIV+ participants with at least one systemic adverse event was lower than for HIV- participants. In a study including 88 TB/HIV co-infected adults who received Diaskintest, four experienced fever, weakness, chills, and headache.[32]

Children

Five studies reported adverse events in children who received Diaskintest.[28-30 36 37] As mentioned above, adverse events were not systematically ascertained (Table 6).

Pregnant women

Only one study included pregnant women.[31] The study by Borisova et al used Diaskintest in 267 pregnant women with TB.[31] In 124 patients (46.4%) Diaskintest was performed in the first half of pregnancy (but after 12 weeks), the rest in the second half. The study reported that 'no embryo toxicity was registered' without further details. Since the study included pregnant women with signs and symptoms of TB, with regards to systemic adverse events, the paper reported that there were 'no changes in either TB symptoms or blood and urine tests of the pregnant women'. There was no mention of ISR. None of the other test manufacturers provided data on the safety of the tests in pregnant women.

Quality of evidence

We assessed the quality of evidence on the safety of TBST overall (Table 9). The quality of evidence was considered high for any injection site reactions. We did not downgrade inconsistency since sub-group analysis by region could explain the heterogeneity. Furthermore, although the confidence interval of the overall pooled estimate was large, it was due to the heterogeneity and the CI was considered narrow enough in the sub-group analysis (Figure A1). The quality of evidence for any systemic reactions was considered moderate due to the small sample size and a wide CI.

Interpretation

The safety profile of novel TBST appear similar to TST and is associated with mostly mild injection site reactions such as itching and pain. However, data comparing Diaskintest to TST are limited. Data on safety of tests in pregnant women is equally limited. Data was also limited for the comparison of systemic adverse events between specific TBST vs TST. Nonetheless, reviewed studies did not report unexpected severe or serious systemic reactions potentially associated with specific TBST. However, the current sample size (i.e. the total number of participants) limits our ability to understand the frequency of rare

adverse events (e.g. anaphylaxis reaction). It should be noted that test manufactures were involved in most studies on C-Tb and C-TST; thus, there has been limited independent evaluation of these tests. The involvement of manufacturers was unclear in studies on Diaskintest. Nevertheless, based on the currently available evidence from these limited studies, there appears to be no safety signal that might affect the choice between specific TBST *vs* TST.

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Table 1: Variables of interest

Category	Variables
Study design	Study design, country, setting, period of recruitment, sample size
Population summary measures	Age, gender, history of immunosuppression, HIV status, pregnancy and lactating status, co-morbidities
Index test	Recombinant antigen skin test used
Comparator	Types of tests used
Outcome	Type, severity, and seriousness of adverse events.

Table 2. Summary of C-Tb, C-TST, and other studies.

	Test	Study design	Control	Country	Study population	Age	%Female	%HIV
Aggerbeck, 2013a	C-Tb	Dose-finding trial	No control	UK	Adults with TB	Mean: 33	n/d	0
Aggerbeck, 2013b	C-Tb	Double-blind split body RCT	TST	UK	BCG vaccinated healthy adults	Mean: 34	60.9 %	0
Aggerbeck, 2018	C-Tb	Double-blind split body RCT	TST	South Africa	Individuals suspected of TB, active TB, contact and children. Children < 5rs (20%) Children 5-17 yrs (31%)	Median: 17	51%	25%
Aggerbeck, 2019	C-Tb	Double-blind split body RCT	TST	South Africa	Adults with TB	mean: 36	36%	20%
Arend, 2008	rdESAT-6	Double-blind split body RCT	TST	Denmark	Healthy adults and treated TB patients	Mean: Healthy adults: 27.7; people with TB: 46.2	n/d	0
Bergstedt, 2010	C-Tb	Phase 1 non-randomized clinical trial	No control	Denmark	Healthy adults	Mean: 36	n/d	0
Du, 2013	ESAT-6	Phase 1 clinical trial	No control	China	Healthy adults	Range: 19-65	n/d	0
Hoff, 2016	C-Tb	Double-blind split body RCT	TST	South Africa	People with TB	Median: 34	41.9 %	39.50%
Li, 2016a	C-TST	Phase 1 clinical trial	No control	China	Healthy adults	Mean: 30	50%	0
Li 2016b	C-TST	Phase 2a Open-label split body trial (non-RCT)	TST	China	Healthy adults	Mean: 45	82.10 %	0
Li 2016c	C-TST	Phase 2a Placebo-controlled Split body trial (non-RCT)	Placebo	China	People with TB	Mean: 41	30.70 %	0
Lillebaek, 2009	ESAT-6	Phase 1 non-randomized clinical trial	No control	Denmark	Healthy adults	>= 18	n/d	0
Ruhwald, 2017	C-Tb	Double-blind split body RCT	TST	Spain	People with TB, TB contacts, and healthy volunteers Children <5yrs (3.5%) Children 5-17 yrs (8.8%)	Mean: healthy volunteers: 24; Occational contacts: 32; Close contacts: 33; People with TB: 37	53.5 %	0.70 %

	Test	Study design	Control	Country	Study population	Age	%Female	%HIV
Sun, 2013	ESAT-6	Open-label split body trial (non-RCT)	TST	China	People with TB and TB+ and healty adulds	Range: 18-65	35.7 %	0
Wu, 2008	ESAT-6	Phase 1 clinical trial	TST	China	Healthy adults	Median: 34	80%	n/d
Xia, 2021	Rp22	Phase 1 clinical trial	Placebo	China	Healthy adults	Range: 18-45	49.3 %	0
Xu, 2021a	C-TST	Open-label split body trial (non-RCT)	TST	China	Healthy adults	Mean: 46	51.80 %	0
Xu, 2021b	C-TST	Open-label split body trial (non-RCT)	TST	China	Individuals with symptoms of pulmonary disease and people with active TB	Mean: 45	26.3 %	n/d

RCT: randomized controlled trial; TST: tuberculin skin test; BCG: Bacillus Calmette–Guérin; n/d; no data

Table 3. Summary of Diaskintest studies

	Study design	Control	Country	Study population	Age	%Female	%HIV
Aksenova, 2009	Cross-sectional	n/d**	Russia	Children and adolescents with TB	2-17	44.4%	n/d
Slogotskaya, 2011a	Cross-sectional	n/d**	Russia	TB/HIV coinfected adults	mean: 32	31.8%	100.0%
Slogotskaya 2011b	Cross-sectional	n/d**	Russia	People with TB including people living with HIV	n/d	n/d	32.4%
Streltsova, 2011	Cross-sectional	TST	Russia	Adults with TB	mean: 26	58.0%	n/d
Belushkov, 2012	Cross-sectional	n/d	Russia	Children suspected of TB	mean: 7.1	n/d	1.4%
Patsyuk, 2017	Cross-sectional	n/d	Russia	People with TB	mean: 39 in DST- group, 35 in DST+ group	n/d	0.0%
Barmina, 2018	Cross-sectional	n/d**	Russia	Child and adolescent household contact	Range: 0-17	n/d	n/d
Yarovaya, 2019	Case series*	n/d**	Russia	Children with AEs to DST (TB infected; residual TB changes; active TB)	n/d	n/d	n/d
Rutkovsky, 2020	Case series*	n/d	Russia	Children with TB, post-TB changes and TB infection	Range: 8-16	n/d	n/d
Borisova, 2017	Cross-sectional	n/d	Russia	Pregnant women with TB	Range: 23-40	100.0%	7.1%
Dotsenko, 2015	Cross-sectional	TST	Ukraine	TB care workers	n/d	84.0%	n/d

RCT: randomized controlled trial; TST: tuberculin skin test; AE: adverse events; DST: Diaskintest; n/d; no data

*Data on the number of individuals given tests were provided by the study authors.

** Participants received both tests but adverse events were not reported separately for each test.

Table 4. The frequencies of local injection site reactions in studies on C-Tb

Study	Test	N	Any ISR	Itching	Pain	Rash	Erythema	Swelling	Vesicle	induration	Ulceration	Discolouration	Severity
Aggerbeck, 2013a	C-Tb	26	-	16 (61.5%)	6 (23.1%)	1 (3.8%)	-	1 (3.8%)	-	-	-	-	Not reported
	TST	-	-	-	-	-	-	-	-	-	-	-	Not reported
Aggerbeck, 2013b	C-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, 2018	C-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, 2019	C-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, 2010	C-Tb	21	-	0 (0%)	0 (0%)	-	-	-	-	-	-	0 (0%)	Not reporetd
	TST	-	-	-	-	-	-	-	-	-	-	-	Not reported
Hoff, 2016	C-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, 2017	C-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%

ISR: Injection site reaction

Table 5. The frequencies of local injection site reactions in studies on C-TST vs TST

		N	Pruritus	Pain	Rash	Allergy	Muscle pain
Li 2016b	C-TST	28	2 (7.1%)	0 (0%)	-	-	-
	TST	28	2 (7.1%)	0 (0%)	-	-	-
Xu 2021*	C-TST	NA	13.53%	5.28%	0.83%	0.17%	0.83%
	TST	NA	10.54%	6.50%	0.7%	0%	0%

This paper reported two control trials but only aggregated data were reported. The denominator was unclear and the authors did not responded our query.

Table 6. Frequencies of adverse events in studies on Diaskintest

Study	Population	Diaskintest vs TST	Fever	Others
Aksenova, 2009[#]	Children and adolescents with TB	NA	2/63 (3.2%)	
Barmina, 2018[#]	Child and adolescent household contact	NA	NA	Any adverse events: 0/385 (0%)
Belushkov, 2012	Children suspected of TB	NA	4/88 (4.5%)	Hyper allergic reaction without details 3/48 (6.3%)
Borisova, 2017	Pregnant women with TB	NA	NA	Any adverse events: 0/267 (0%)
Dotsenko 2015	TB 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, 2017	Adults	NA	NA	Hyper allergic reaction with local oedema, lymphangitis or l vesiculosis or a blister with a tight lid; 7/33 (21.2%)
Rutkovsky, 2020	Children with TB, post-TB changes and TB infection	NA	14/474 (3%)	Vomiting: 1/474 (0.2%)
Slogotskaya, 2011a[#]	TB/HIV coinfected adults	NA	NA	Fever, weakness, chills, and headache: 4/88 (4.5%)
Slogotskaya, 2011b[#]	People with TB including people living with HIV	NA	5/71 (7.0%)	Local reaction (hyperaemia, swelling, oedema, pain, local hig temperature): 2/71 (1.4%)
Streltsova, 2011[#]	Adults with TB	hyperallergic reactions with vesicles/necrosis and lymphangitis: 6/53 (11.3%) vs 2/53 (3.8%)	0/53 (0%)	Hyperallergic reaction with vesicles/necrosis and lymphangi constitutional symptoms: 0/53 (0%)
Yarovaya, 2019[#]	Children (TB infected; residual TB changes; active TB)	NA	7/452 (1.5%)	Papular rash: 3/452 (0.7%); herpetiform rash 1/452 (0.2%)

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

Table 7 Common systemic adverse events in participants given C-Tb and TST

	Fever	Headache	Dizziness	Severity
Aggerbeck, 2013	2/26 (7.7%)	1/26 (3.8%)	NA	Mild-moderate: 100%
Aggerbeck, 2018	29/1188 (2.4%)	107/1188 (9%)	NA	Mild-moderate: >95%
Aggerbeck, 2019	-	44/256 (17.2%)	15/256 (5.9%)	Mild-moderate: >95%
Bergstedt, 2010	1/21 (4.8%)	2/21 (9.5%)	NA	Mild:100%
Hoff, 2016	NA	22/253 (8.7%)	NA	Mild: 85.0% in HIV- and 76.6% in HIV+ group
Ruhwald, 2017	NA	137/979 (14%)	NA	Mild-moderate: 100%

Table 8. Systemic adverse events in studies on C-TST

Study	Systemic reactions
Li 2016a	No systemic reactions in 6 participants
Li 2016b	9 adverse events in 144 patients. Abnormal percentage of eosinophil (n=1); Increased blood pressure (n=2); fever (n=1); phlebitis (n=2); vasculitis (n=3)
Xu 2021*	Fever (7.1%); nausea (0.3%); headache (0.7%); allergy (0.2%); muscle pain (0.8%)

*This paper reported two control trials but only aggregated data were reported.

Table 9

Question: Do TBST cause more adverse reactions compared to tuberculin skin tests?

Setting: Global

Bibliography: Aggerbeck 2013; Aggerbeck 2018; Aggerbeck 2019; Hoff 2016, Ruhwald 2017; Streltsova 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TBST	tuberculin skin tests	Relative (95% CI)	Absolute (95% CI)		
Any injection site reactions												
6	5 randomised trials and 1 NRS	not serious	not serious[a]	not serious	not serious[b]	none	907/2931 (30.9%)	860/2879 (29.9%)	**RR 1.05** (0.70 to 1.58)	**15 more per 1,000** (from 90 fewer to 173 more)	⊕⊕⊕⊕ High	
Any systemic reactions												
1	randomised trials	not serious	not serious	not serious	serious[c]	none	49/153 (32.0%)	56/149 (37.6%)	**RR 0.84** (0.60 to 1.10)	**60 fewer per 1,000** (from 150 fewer to 38 more)	⊕⊕⊕◯ Moderate	

CI: confidence interval; **RR:** risk ratio; **NRS**: non-randomized study

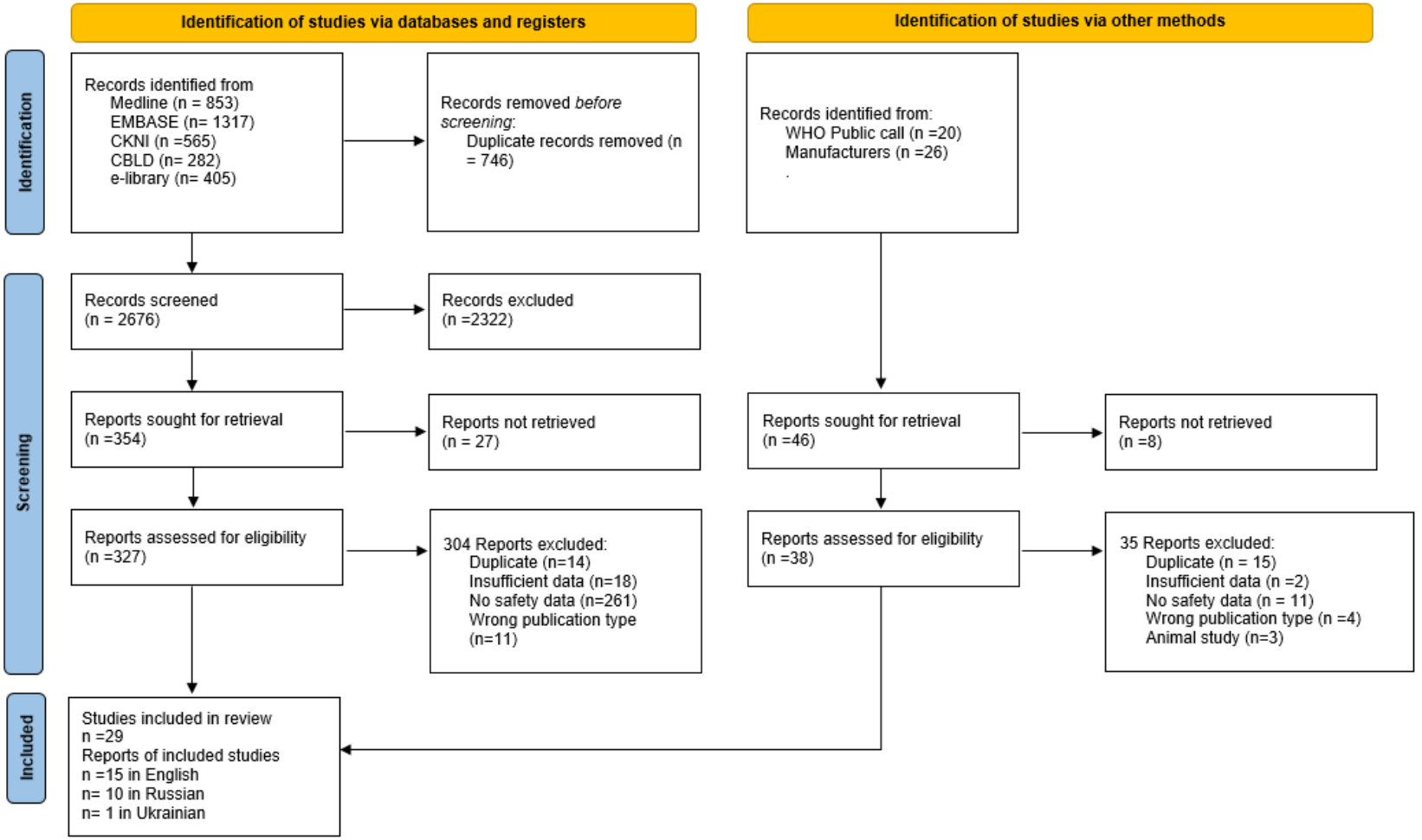
Explanations

a. Heterogeneity could be explained by country. Not downgraded.

b. Wide CI due to heterogeneity and CIs were considered narrow enough in the sub-group analysis by country. Not downgraded.

c. Small sample size and a wide CI crossing appreciable benefits and harms.

Figures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Manufacturers (n =26)
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Records excluded
(n =2322)
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Reports not retrieved
(n = 27)
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(n =46)
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(n =8)
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Figure 1. Study selection

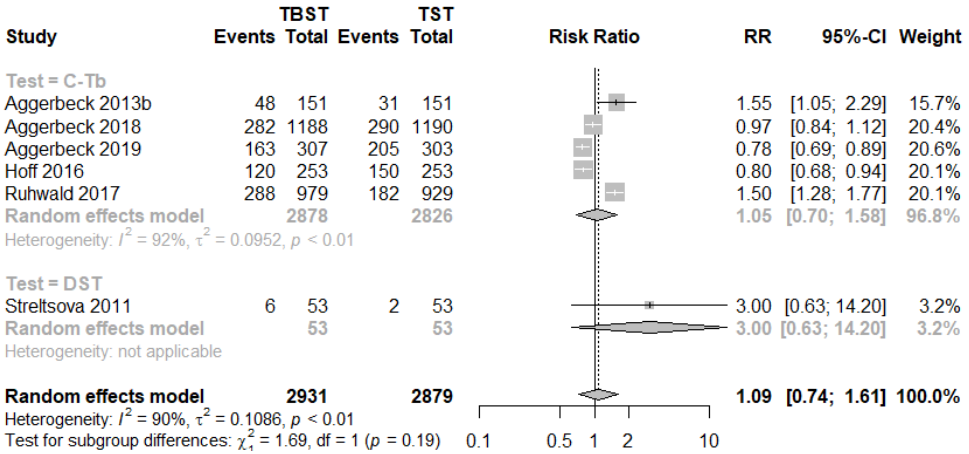


Figure 2. Any injection site reactions

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Hoff 2016, Aggerbeck 2019, and Streltsova, 2011 included people with TB only.

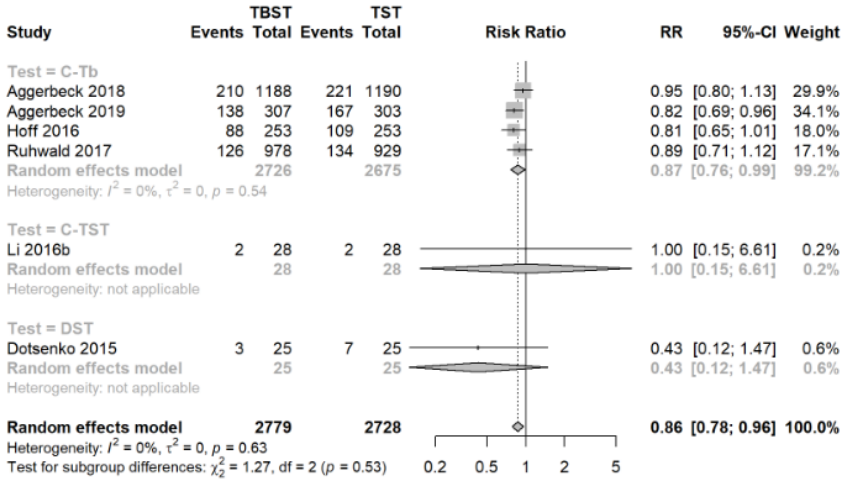


Figure 3. Itching/ Pruritus

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Hoff 2016 and Aggerbeck 2019 included people with TB only.

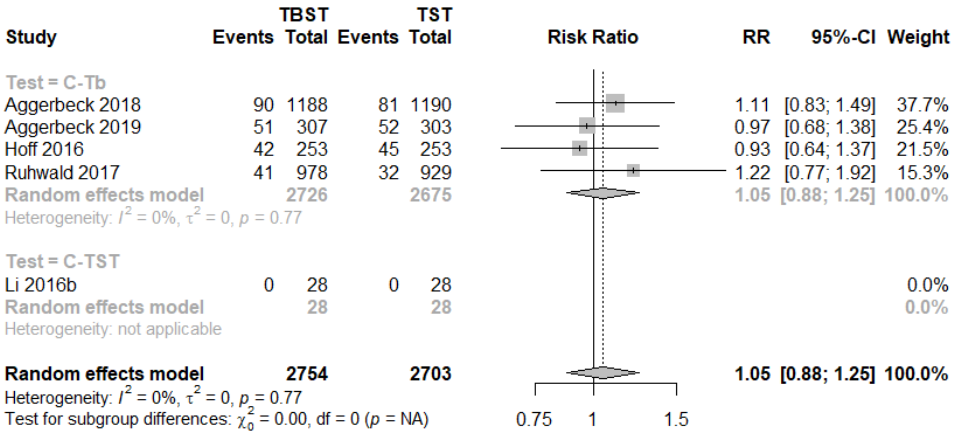


Figure 4. Pain

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Hoff 2016, Aggerbeck 2019, and Streltsova, 2011 included people with TB only.

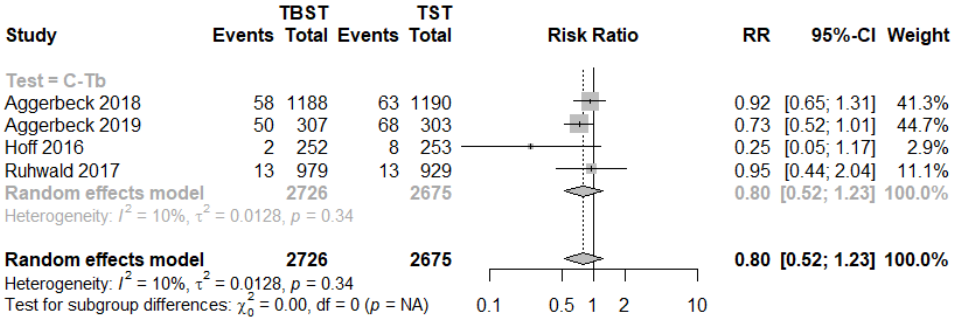


Figure 5. Rash

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Hoff 2016, Aggerbeck 2019, and Streltsova, 2011 included people with TB only.

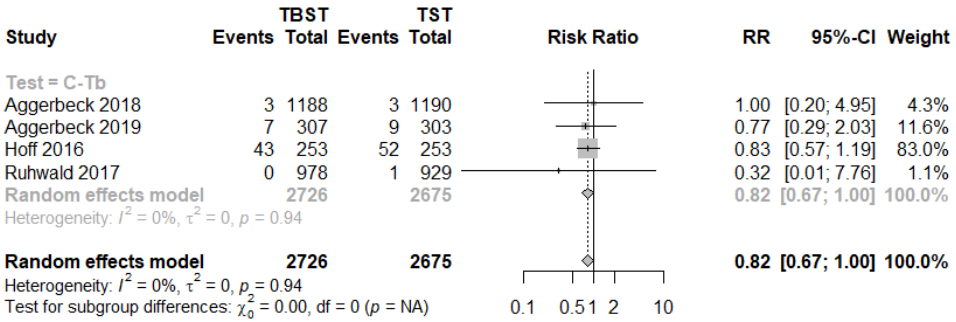


Figure 6. Erythema

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Hoff 2016, Aggerbeck 2019, and Streltsova, 2011 included people with TB only.

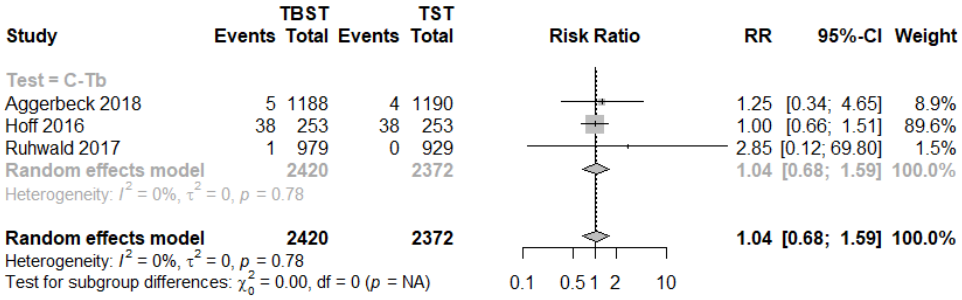
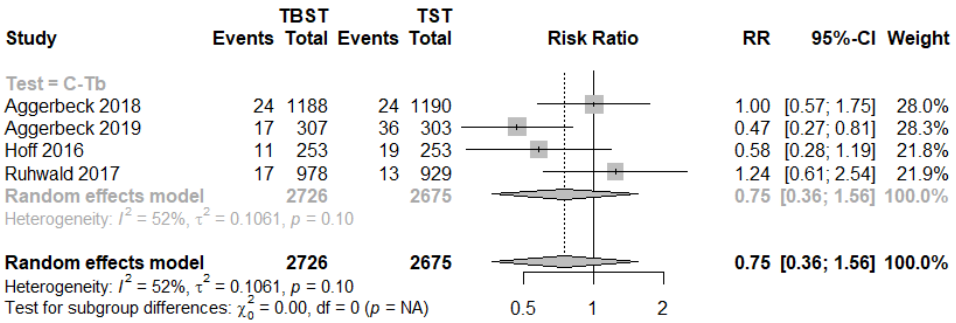


Figure 7. Swelling/Oedema

Proportion of HIV+: Aggerbeck 2018 (25%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Hoff 2016 included people with TB only.



Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Aggerbeck 2019 and Hoff 2016 included people with TB only.

Figure 8. Vesicle

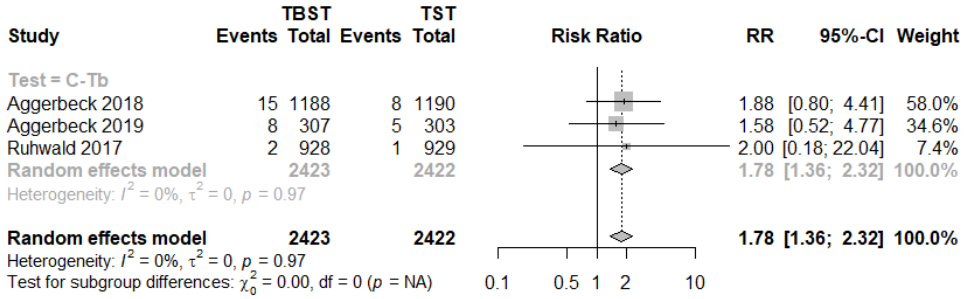


Figure 9. Induration

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Aggerbeck 2019 included people with TB only.

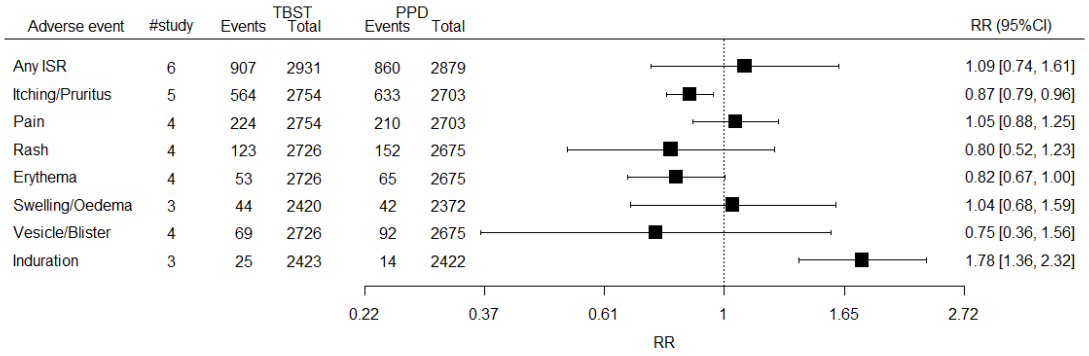


Figure 10. Pooled estimates of the risk for any ISR and individual ISR.

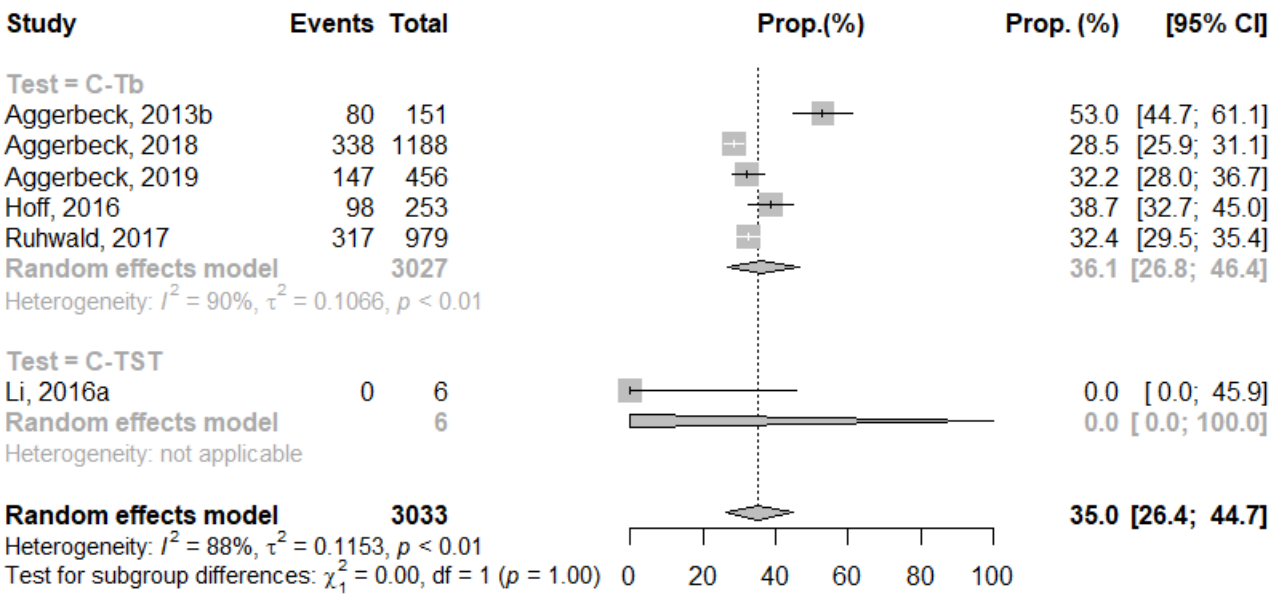


Figure 11. Frequencies of any systemic adverse events

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%); Other studies included adults. Aggerbeck 2019 and Hoff 2016 included people with TB only.

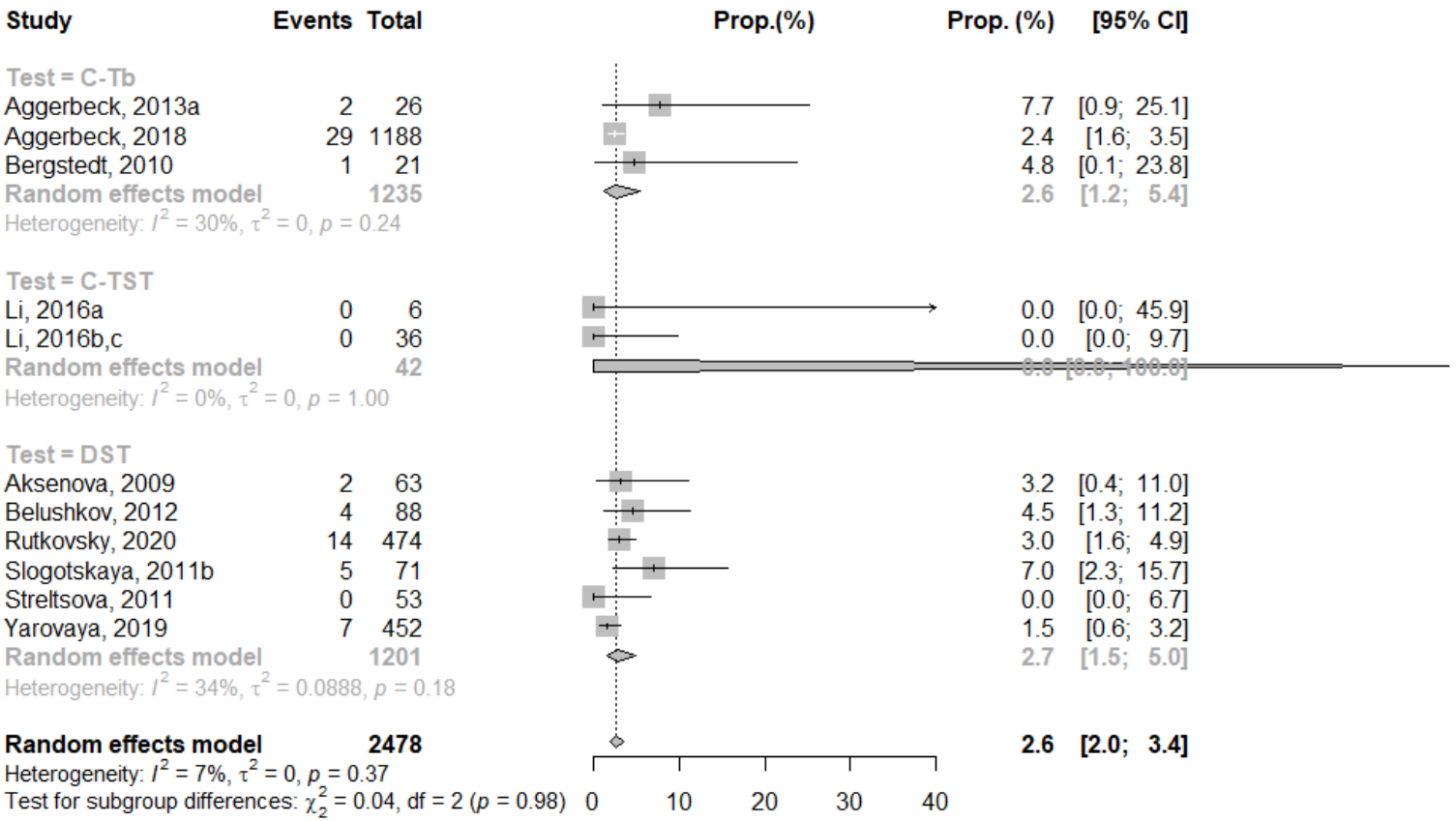


Figure 12. Frequencies of fever

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%).

Aksenova 2009, Belushkov 2018, Rutkovsky 2020, and Yarovaya, 2019 included only children and adolescents <18 years old. Aksenova 2009, Slogotskaya, and Streltsova included people with active TB only.

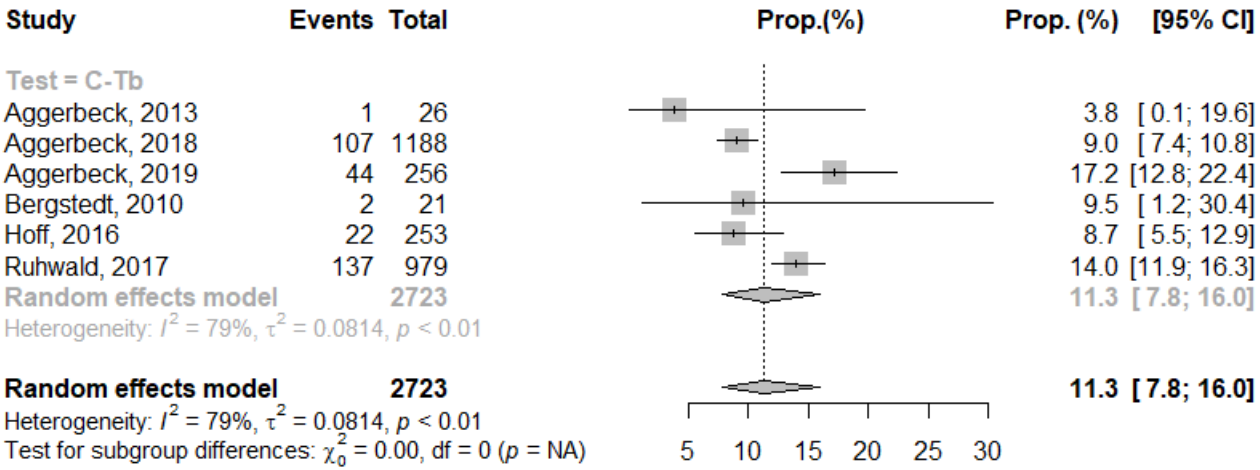


Figure 13. Frequencies of headache

Proportion of HIV+: Aggerbeck 2018 (25%), Aggerbeck 2019 (20%); Hoff 2016 (39.5%). Other studies included HIV-negative individuals.

Aggerbeck 2018 included children < 5 years old (20%) and 5-17 years old (31%); Ruhwald included children < 5 years old (3.5%) and 5-17 years old (8.8%). Aggerbeck 2019 and Hoff 2016 included people with active TB only.

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