

Recombinant Tuberculosis Allergen (Diaskintest®) in Tuberculosis Diagnostic in Russia (Meta-Analysis)

Anna Starshinova¹, Irina Dovgalyk¹, Anna Malkova², Yulia Zinchenko¹, Maria Pavlova¹, Ekaterina Belyaeva^{1,3}, Natalia Basantsova^{1,2}, Michail Nazarenko^{1,4}, Dmitry Kudlay⁵, Piotr Yablonskiy^{1,2}

¹Department of Phthiopulmonology, St. Petersburg Research Institute of Phthiopulmonology, ²Department of Medical, St. Petersburg State University, ³Department for Treatment Patients With MDR and XDR Tuberculosis, St. Petersburg City Tuberculosis Hospital №2, Saint-Petersburg, ⁵Department of Immunology, Institute of Immunology, FMBA of Russia, Moscow, Russia, ⁴Department of Phthiopulmonology, St. Petersburg Pushkin Tuberculosis Health Care

Abstract

Immunological testing for tuberculosis has been one of the most rapidly developing areas in the last decade. A new-generation immunological skin test, Diaskintest (DST), has been developed in the Russian Federation and successfully implemented into clinical practice since 2009. This article presents the results of a meta-analysis of publications reporting data on the use of the recombinant tuberculosis allergen DST ($n = 121$) from 2009 to 2019 included in Russian and international databases. The analysis included a total of 61 papers consistent with the study design, which cumulatively presented the results of 3,777,083 patients tested with DST (83.0%). The obtained data showed that the overall diagnostic sensitivity of the test in this population, regardless of age, was 86.0%, with 98.0% negative results. It was found that the intensity of the immune response of tuberculosis patients to specific ESAT-6 and CFP-10 antigens of DST may depend on the biological properties of the pathogen characteristic to various *Mycobacterium tuberculosis* genotypes, tuberculosis severity, and the presence of concomitant diseases. These factors are more prevalent in the adult population. In children, however, the test sensitivity reaches 100%. The proportion of positive DST results in HIV-positive patients tested for tuberculosis was 60.0%. The analysis showed that the accuracy (overall validity) of DST was 95.1% in the total studied population (95% confidence interval [CI]: 95.06–95.1) and 92.4% in HIV-positive patients (95% CI: 91.9–92.7).

Keywords: Diagnostics, Diaskintest, IGRA tests, immunodiagnostics, recombinant tuberculosis allergen, tuberculosis

Submitted: 28-Jul-2020

Revised: 04-Aug-2020

Accepted: 06-Aug-2020

Published: 15-Dec-2020

INTRODUCTION

Despite the numerous years of studying, tuberculosis still remains a complicated medical issue and serves as a marker of the social and economic well-being of a society.^[1-3] In 2014, a global WHO project was launched, and in 2017, the Moscow Declaration was introduced, both highlighting that the development of methods for the early diagnosis of tuberculosis is of utmost importance.^[4-6] Immunological testing, which has been applied since R. Koch described tuberculin, is still one of the most rapidly advancing and highly demanded fields.^[7]

The need for vaccine prevention of tuberculosis in countries with a high burden of disease averts the use of the 2 TU Mantoux test, despite its simplicity, low cost, and high sensitivity, as it reacts similarly to both postvaccination and infection-related sensitization.^[8-10]

Genetic testing of *Mycobacterium tuberculosis* (MTB) genome with the identification of ESAT-6 and CFP-10 proteins, which are highly specific for this microorganism, has become a new milestone in the immunodiagnostics of tuberculosis.^[11,12] In combination with current laboratory

Address for correspondence: Prof. Starshinova Anna, Research Institute of Phthiopulmonology, Ligovskii Prospect, 2-4, St. Petersburg, 191036, Russia. E-mail: starshinova_777@mail.ru

ORCID:

<http://orcid.org/0000-0002-9023-6986>
<http://orcid.org/0000-0001-8383-8519>
<https://orcid.org/0000-0002-3880-1781>
<https://orcid.org/0000-0002-6273-4304>
<https://orcid.org/0000-0002-2957-410X>
ID 0000-0002-3653-5918
<http://orcid.org/0000-0003-4385-9643>

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Starshinova A, Dovgalyk I, Malkova A, Zinchenko Y, Pavlova M, Belyaeva E, *et al.* Recombinant tuberculosis allergen (Diaskintest®) in tuberculosis diagnostic in Russia (Meta-Analysis). *Int J Mycobacteriol* 2020;9:335-46.

Access this article online

Quick Response Code:



Website:
www.ijmyco.org

DOI:
10.4103/ijmy.ijmy_131_20

testing methods, this discovery opened the way for the development of a new generation of immunological tests.^[13,14] Nowadays, both *in vitro* and *in vivo* technologies are applied. Available *in vitro* tests implemented into practice (T-SPOT.TB and QuantiFERON-TB) showed high sensitivity and specificity (90%–98%).^[15] However, at this moment, they are expensive and must be performed by highly qualified laboratory personnel, which make them difficult to use as screening tests.

Under the leadership of the academician of the Russian Academy of Medical Sciences and the Russian Academy of Sciences M. A. Paltsev and the corresponding member of the Russian Academy of Sciences V. I. Kiselev, scientists were tackling to create a highly effective and easy-to-use skin test for the diagnosis of tuberculosis in the population with mass bacillus Calmette–Guérin (BCG) vaccination. For this purpose, recombinant strains producing MTB ESAT-6 (early secreted antigenic target) and CFP-10 (culture filtrate protein) were created.^[16,17]

In 2008, a fundamentally new skin test named Diaskintest (DST) was developed and approved.^[9,16] After the required testing was completed, this diagnostic test was introduced into clinical practice. To date, a decade of experience has been accumulated for the use of this test in the diagnosis of tuberculosis, which was described in multiple publications. The analysis of data gained in the last 10 years will provide a true representation of the test’s informative value in the diagnosis of tuberculosis in the Russian Federation.

The aim of the study

The aim of this study was to evaluate the diagnostic value of a skin test containing a recombinant tuberculosis allergen (DST®)

in the diagnosis of acute and latent tuberculosis infection based on the meta-analysis results.

MATERIALS

The analysis included the results of studies published from 2008 to 2019 in Russian and international databases (PubMed, Web of Science, SCOPUS, Elsevier, ScienceDirect, and eLibrary) searched using the following keywords: Diaskintest®, recombinant tuberculosis allergen testing, immunological tests, tuberculosis, tuberculosis diagnostics, and immunodiagnosics.

The following inclusion criteria were applied: publications which included the description of the study design and presented DST results in patients of various ages, HIV-negative individuals, HIV-positive patients, patients with pulmonary and extrapulmonary tuberculosis, HIV-positive patients with pulmonary and extrapulmonary tuberculosis, and tuberculosis

Table 1: General characteristics of the tested individuals

Characteristics (n=4,192,351)	Number of patients, n (%)
Adults aged under 18 years and older	34,811 (0.9)
Children from 1 to 18 years	4,157,540 (99.1)
Healthy persons	4,136,534 (98.7)
HIV-positive persons	22,727 (0.54)
Close contact persons	21,186 (0.51)
TB patients (TB)	11,538 (0.25)
HIV-positive patients with tuberculosis	366 (0.01)
Number of evaluated Diaskintest results	3,769,988 (89.9)
Number of evaluated 2 TU Mantoux test	1,800,987 (42.9)
Number of evaluated T-SPOT.TB	912 (0.02)
Number of evaluated QFT	2119 (0.05)

TB: Tuberculosis, QFT: QuantiFERON-TB Gold

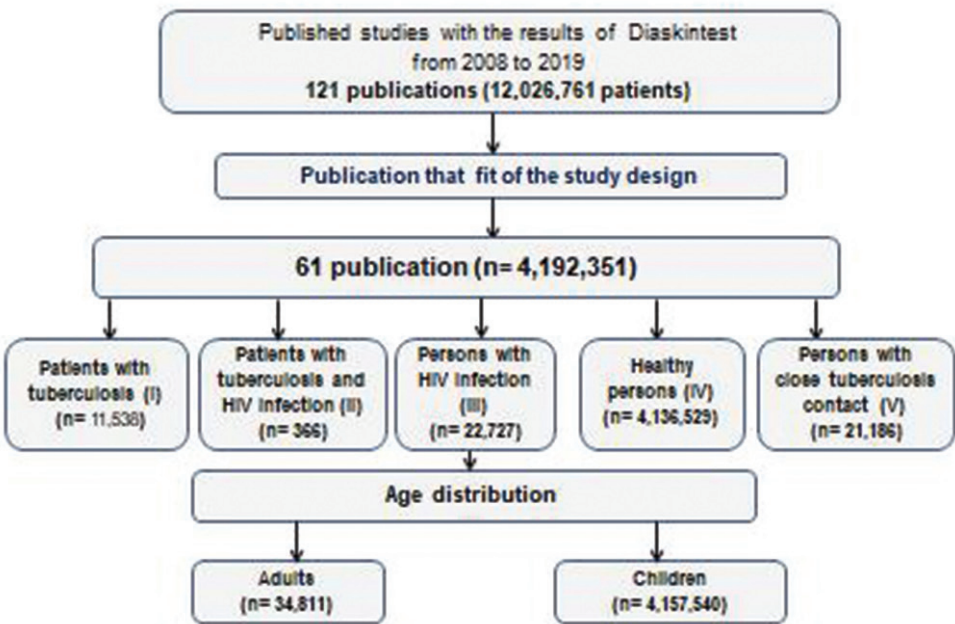


Figure 1: Study design

contacts. The applied exclusion criteria: publications with analytical data, without results of DST were test included in diagnostic complex in the Russian population, patients with nontuberculosis, concomitant diseases (activation of chronic diseases, oncology diseases, autoimmune diseases, hepatitis and other).

Publications presenting reviews and those that did not provide reliable data were excluded from the analysis. A total of 121 publications were found, of which 34 were cohort studies, 53 were prospective studies, 5 were retrospective studies, 8 were control-group studies and publications reviewing results of DST in 12,026,761 patients. Sixty-one articles, which matched the criteria of inclusion and exclusion with the description of DST results, were selected. Subsequent analysis included 61 publications complying with the eligibility criteria [Figure 1].

Overall, the studies presented test results for 4,192,351 individuals (34,811 adults aged under 18 years or older and 4,157,540 children aged 0–18 years).

Table 1 shows the basic characteristics of the tested participants. Overall, 98.7% of the tested participants were healthy, 0.54% were HIV-positive, 0.25% patients had tuberculosis, 0.01% were HIV-positive patients with tuberculosis, and 0.51% were individuals who were in contact with tuberculosis infection.

The data provided in the selected publications were grouped for analysis as follows: Group I included patients with tuberculosis ($n = 11,538$), who were divided into patients with positive sputum smears ($n = 150$) and patients with negative sputum smears ($n = 11,388$); Group II included HIV-positive tuberculosis patients ($n = 366$); Group III included HIV-positive cases ($n = 22,727$); Group IV included healthy persons, who did not have active tuberculosis, contact with TB patients, HIV infections, and other concomitant diseases ($n = 4,136,534$); and Group V included patients who had a contact with TB ($n = 21,186$) [Figure 1].

Considering the high incidence rate of tuberculosis in Russia and the rate of latent tuberculosis in risk groups, the healthy persons' category includes all patients without active tuberculosis and the presence of individuals with latent tuberculosis in this category cannot be excluded.

Table 2 presents the publications complying with the established study design and the number of included cases by group and DST results.

Overall, the studies provided the results of 3,769,988 tests conducted using DST, of which 197,220 (5.2%) were positive, 7484 (0.2%) were doubtful, and 3,565,283 (94.6%) were negative.

The study demonstrates the 2 TU Mantoux test data in 1,800,987 patients, where the positive results were in 83.3% of cases (1,499,753), doubtful in 8.3% (150,015), and negative in 8.4% (151,203). According to T-SPOT.TB (T-SPOT), the positive results were in 35.2% (321), doubtful in 1.5% (4), and negative in 63.3% (577). In the results of QuantiFERON-TB

Gold (QFT), there were positive in 53.6% (1135), doubtful in 0.47% (10), and negative in 45.9% (974).

METHODS

Patients with nontuberculous mycobacterial infections, granulomatous pulmonary disease of nontuberculous origin, patients with various comorbidities, and tuberculosis patients receiving treatment were excluded from the analysis. In all the studies, patients underwent a set of investigations recommended in the local guidelines. The set of diagnostic tests for tuberculosis included the assessment of clinical manifestations of the disease, radiographic changes on the chest X-ray examination, and in some publications, multislice computed tomography and laboratory analyses of respiratory tract samples (sputum) for MTB.

Patients were tested using a recombinant tuberculosis allergen (DST) (registration number LSP – 006435/08 of August 11, 2008). DST is a recombinant ESAT-6/CFP-10 protein produced by *Escherichia coli* DLT 1270 (derivative of DH10B strain containing the *lacI* gene in its chromosome). CFP-10 and ESAT-6 genes were amplified on MTB H37Rv DNA using the following primers: CFP-F – gc gga tcc gat gac gat gac aaa gca gag atg aag acc gat gc and CFP-R – tca ggt acc gaa gcc cat ttg cga gga ca; ESAT-F – gg ggt acc gat gac gat gac aaa aca gag cag cag tgg aat ttc and ESAT-R – ccc aag ctt cta tgc gaa cat ccc agt ga. The obtained fragments were cloned on plasmid pQE30 (Qiagen), which allows protein expression with the addition of 6 histidine bases on the N-terminal. The recombinants were selected using a restriction analysis. The selected clone pQE30 – *esat* – *cfp* ensured the synthesis of a hybrid protein of expected size. Due to the ESAT-6 and CFP-10 proteins, which are specific for tuberculosis mycobacteria and are absent in other mycobacteria, including those used for BCG vaccination, this test may be used for the differential diagnosis of allergic reactions.^[17,78] The product dose is 0.2 µg in 0.1 mL. According to the developers, the specificity of this test is 90%–100%, making it one of the most informative and reliable of the available tests for the diagnosis of tuberculosis.^[18]

Application of the DST was similar to the tuberculin skin test. The injections were performed intradermally, and the results were recorded after 72 h by measuring the papule diameter at the injection site. According to the guidelines, in the presence of a papule of any size, the DST was considered positive. The presence of hyperemia in the absence of a papule was considered as an inconclusive test. A cutoff of ≥5 mm was established in this study for an objective assessment of the presence of a papule.

Stata14 (Corp LLC, US) was used for the statistical analysis of the obtained data. Results were presented using descriptive statistics based on the analysis of absolute and relative values. Diagnostic value was determined as a ratio between the diagnostic sensitivity, i.e., the proportion of patients with positive test results among patients with tuberculosis, and

Table 2: Results of Diaskintest in studies

Author and year of publication	Number of individuals with Diaskintest	Diaskintest results, <i>n</i> (%) (95%CI)			Individuals (aged 1-18 years or adults over 18 years)	Study groups
		Negative	Doubtful	Positive		
Kiselev <i>et al.</i> (2009) ^[18]	49	47 (95.9) 86.0-99.5	2 (4.1) 0.5-14.0	0	Aged 1-18 years	Healthy persons
Kiselev <i>et al.</i> (2009) ^[18]	41	0	0	41 (100) 91.4-100	Aged 1-18 years	TB patients, MBT (-)
Kiselev <i>et al.</i> (2009) ^[18]	18	0	0	18 (100) 81.5-100	Adults over 18 years	TB patients, MBT (-)
Litvinov <i>et al.</i> (2009) ^[18]	26	26 (100) 86.8-100	0	0	Aged 1-18 years	Healthy persons
Litvinov <i>et al.</i> (2009) ^[19]	12	12 (100) 73.5-100	0	0	Adults over 18 years	Healthy persons
Aksenova <i>et al.</i> (2009) ^[20]	63	10 (15.9) 7.9-27.3	6 (9.5) 3.6-19.6	47 (74.6) 62.1-84.7	Aged 1-18 years	TB patients, MBT (-)
Ovsyankina <i>et al.</i> (2010) ^[21]	50	1 (2.0) 0.1-10.6	0	49 (98.0) 89.4-99.9	Aged 1-18 years	TB patients, MBT (-)
Slogotskaya <i>et al.</i> (2010) ^[22]	60	11 (18.3) 9.5-30.4	0	49 (81.7) 69.9-90.5	Aged 1-18 years	TB patients, MBT (-)
Slogotskaya <i>et al.</i> (2010) ^[22]	155	109 (70.3) 62.5-77.4	0	46 (29.7) 22.6-37.5	Aged 1-18 years	Healthy persons
Slogotskaya <i>et al.</i> (2011) ^[23]	114	19 (16.7) 10.3-24.8	0	95 (83.3) 75.2-89.7	Aged 1-18 years	TB patients, MBT (-)
Slogotskaya <i>et al.</i> (2011) ^[23]	60	44 (73.3) 60.3-83.9	0	16 (26.7) 16.1-39.7	Aged 1-18 years	Close contact
Slogotskaya <i>et al.</i> (2011) ^[23]	589	438 (74.4) 70.6-77.8	0 0	151 (25.6) 22.2-29.4	Aged 1-18 years	Healthy persons
Aksenova <i>et al.</i> (2011) ^[24]	2068	1575 (76.2) 74.3-78.0	254 (12.3) 10.9-13.8	239 (11.5) 10.2-13.0	Aged 1-18 years	Healthy persons
Slogotskaya <i>et al.</i> (2011) ^[25]	87	52 (59.7) 48.7-70.1	0	35 (40.3) 29.9-51.3	Adults over 18 years	TB patients with HIV infection
Aksenova (2011) ^[26]	63	4 (6.3) 1.8-15.5	0	59 (93.7) 84.5-98.2	Aged 1-18 years	TB patients, MBT (-)
Aksenova (2011) ^[26]	1797	1434 (79.8) 77.9-81.6	234 (13.1) 11.5-14.7	129 (7.1) 6.0-8.5	Aged 1-18 years	Healthy persons
Litvinov and Slogotskaya (2011) ^[27]	425	92 (21.6) 17.8-25.9	0	333 (78.4) 74.2-82.2	Adults over 18 years	TB patients, MBT (-)
Litvinov and Slogotskaya (2011) ^[27]	182	182 (100) 98.0-100	0	0	Aged 1-18 years	Healthy persons
Slogotskaya <i>et al.</i> (2011) ^[28]	5	0	0	5 (100) 47.8-100	Aged 1-18 years	TB patients, MBT (-)
Slogotskaya <i>et al.</i> (2011) ^[28]	143	135 (94.4) 89.3-97.6	0	8 (5.6) 2.4-10.7	Aged 1-18 years	Close contact
Aksenova <i>et al.</i> (2011) ^[29]	345	149 (43.2) 37.9-48.6	146 (42.3) 37.0-47.7	50 (14.5) 11.0-18.7	Aged 1-18 years	Healthy persons
Baryshnikova <i>et al.</i> (2012) ^[30]	1377	1274 (92.5) 91.0-93.9	69 (5.1) 3.9-6.3	34 (2.4) 1.7-3.4	Aged 1-18 years	Healthy persons
Starshinova <i>et al.</i> (2012) ^[31]	67	15 (22.4) 13.1-34.2	2 (3.0) 0.4-10.4	50 (74.6) 62.5-84.5	Aged 1-18 years	TB patients, MBT (-)
Starshinova <i>et al.</i> (2012) ^[32]	47	38 (80.9) 66.7-90.9	3 (6.3) 1.3-17.5	6 (12.8) 4.8-25.7	Aged 1-18 years	Healthy persons
Starshinova <i>et al.</i> (2012) ^[32]	104	20 (19.3) 12.2-28.1	5 (4.8) 1.6-10.9	79 (75.9) 66.6-83.8	Aged 1-18 years	TB patients, MBT (-)
Starshinova <i>et al.</i> (2012) ^[32]	76	57 (75.0) 63.7-84.2	8 (10.5) 4.7-19.7	11 (14.5) 7.5-24.4	Aged 1-18 years	Healthy persons
Dolzhenko (2012) ^[33]	8600	8010 (93.1) 92.6-93.7	119 (1.4) 1.1-1.7	471 (5.5) 5.0-6.0	Aged 1-18 years	Healthy persons

Contd...

Table 2: Contd...

Author and year of publication	Number of individuals with Diaskintest	Diaskintest results, <i>n</i> (%) (95%CI)			Individuals (aged 1-18 years or adults over 18 years)	Study groups
		Negative	Doubtful	Positive		
Dolzhenko (2012) ^[33]	686	497 (72.4) 68.9-75.5	22 (3.2) 2.0-4.8	167 (24.4) 21.2-27.7	Aged 1-18 years	Close contact
Dolzhenko (2012) ^[33]	63	4 (6.3) 1.8-15.5	0	59 (93.7) 84.5-98.2	Aged 1-18 years	TB patients, MBT (-)
Baryshnikova <i>et al.</i> (2012) ^[34]	1377	1274 (92.5) 91.0-93.9	69 (5.1) 3.9-6.3	34 (2.4) 1.7-3.4	Aged 1-18 years	Healthy persons
Yablonsky <i>et al.</i> (2012) ^[35]	120	58 (48.3) 39.1-57.6	6 (5.0) 1.9-10.6	56 (46.7) 37.5-56.0	Aged 1-18 years	TB patients, MBT (-)
Aksenova <i>et al.</i> (2012) ^[36]	2222	2146 (96.6) 95.7-97.3	49 (2.2) 1.6-2.9	27 (1.2) 0.8-1.8	Aged 1-18 years	Healthy persons
Dovgalyuk <i>et al.</i> (2013) ^[37]	570	495 (86.8) 83.8-89.5	61 (10.7) 8.3-13.5	14 (2.5) 1.3-4.1	Aged 1-18 years	Healthy persons
Slogotskaya <i>et al.</i> (2013) ^[38]	210	38 (18.1) 13.1-24.0	0	172 (81.9) 76.0-86.9	Aged 1-18 years	TB patients, MBT (-)
Yablonskiy <i>et al.</i> (2013) ^[39]	120	58 (48.3) 39.1-57.6	6 (5.0) 1.9-10.6	56 (46.7) 37.5-56.0	Aged 1-18 years	TB patients, MBT (-)
Motanova <i>et al.</i> (2013) ^[40]	142	90 (63.4) 54.9-71.3	36 (25.4) 18.4-33.3	16 (11.2) 6.6-17.7	Aged 1-18 years	Healthy persons
Dovgalyuk <i>et al.</i> (2013) ^[41]	104	20 (19.2) 12.2-28.1	5 (4.8) 1.6-10.9	79 (76.0) 66.6-83.8	Aged 1-18 years	TB patients, MBT (-)
Dovgalyuk <i>et al.</i> (2013) ^[41]	76	57 (75.0) 63.7-84.2	8 (10.5) 4.7-19.7	11 (14.5) 7.5-24.4	Aged 1-18 years	Healthy persons
Ikonina <i>et al.</i> (2014) ^[42]	56	4 (7.1) 2.0-17.3	3 (5.3) 1.1-14.9	49 (87.6) 75.9-94.8	Aged 1-18 years	TB patients, MBT (-)
Starshinova <i>et al.</i> (2014) ^[43]	70	36 (51.4) 39.2-63.6	5 (7.1) 2.4-15.6	29 (41.6) 29.8-53.8	Aged 1-18 years	Healthy persons
Starshinova <i>et al.</i> (2014) ^[43]	143	18 (12.5) 7.6-19.2	4 (2.8) 0.8-7.0	121 (84.7) 77.6-90.1	Aged 1-18 years	TB patients, MBT (-)
Vaganova and Russkikh (2015) ^[44]	116	58 (50.0) 40.6-59.4	0	58 (50.0) 40.6-59.4	Adults over 18 years	Close contact
Aksenova and Baryshnikova (2015) ^[45]	810,943	793122 (97.89) 97.8-97.8	68 (0.001) 0-0	17753 (2.1) 2.2-2.2	Aged 1-18 years	Healthy persons
Krat <i>et al.</i> (2015) ^[46]	326	227 (69.6) 64.3-74.6	34 (10.4) 7.3-14.3	65 (19.9) 15.7-24.7	Adults over 18 years	Close contact
Slogotskaya <i>et al.</i> (2015) ^[47]	1,419,768	1416796 (97.9) 99.8-99.8	0	2972 (2.1) 0.2-0.2	Aged 1-18 years	Healthy persons
Pavlova <i>et al.</i> (2015) ^[48]	64	2 (3.1) 0.4-10.8	0	62 (96.9) 89.2-99.6	Aged 1-18 years	TB patients, MBT (-)
Pavlova <i>et al.</i> (2015) ^[48]	48	34 (70.8) 55.9-83.0	0	14 (29.2) 17.0-44.1	Aged 1-18 years	Healthy persons
Shilova <i>et al.</i> (2015) ^[49]	202	99 (49.1) 41.9-56.1	14 (6.8) 3.8-11.4	89 (44.1) 37.1-51.2	Aged 1-18 years	Close contact
Shilova <i>et al.</i> (2015) ^[49]	231	138 (59.7) 53.1-66.1	35 (15.2) 10.8-20.4	58 (25.1) 19.7-31.2	Aged 1-18 years	Healthy persons
Eysmont (2015) ^[50]	2324	1810 (77.9) 76.1-79.6	0	514 (22.1) 20.4-23.9	Adults over 18 years	HIV-infected patients
Poddubnaya <i>et al.</i> (2015) ^[51]	36	9 (25.0) 12.1-42.2	4 (11.1) 3.1-26.1	23 (63.9) 46.2-79.2	Adults over 18 years	TB patients with HIV infection
Poddubnaya <i>et al.</i> (2015) ^[51]	54	35 (64.8) 50.6-77.3	4 (7.4) 2.1-17.9	15 (27.8) 16.5-41.6	Adults over 18 years	HIV-infected pensions
Belokurov <i>et al.</i> (2015) ^[52]	32	6 (18.8) 7.2-36.4	0	26 (81.2) 63.6-92.8	Adults over 18 years	TB patients, MBT (-)
Starshinova <i>et al.</i> (2014) ^[53]	56	46 (82.1) 69.6-91.1	0	10 (17.9) 8.9-30.4	Adults over 18 years	TB patients with HIV infection

Contd...

Table 2: Contd...

Author and year of publication	Number of individuals with Diaskintest	Diaskintest results, <i>n</i> (%) (95%CI)			Individuals (aged 1-18 years or adults over 18 years)	Study groups
		Negative	Doubtful	Positive		
Starshinova <i>et al.</i> (2015) ^[53]	41	9 (21.9) 10.6-37.6	0	32 (78.10) 62.4-89.4	Adults over 18 years	TB patients, MBT (+)
Starshinova <i>et al.</i> (2015) ^[53]	58	51 (87.9) 76.7-95.0	0	7 (12.1) 5.0-23.3	Adults over 18 years	Healthy persons
Starshinova <i>et al.</i> (2016) ^[54]	46	40 (86.9) 73.7-95.1	0	6 (13.1) 4.9-26.3	Adults over 18 years	HIV-infected persons
Starshinova <i>et al.</i> (2016) ^[54]	63	7 (11.1) 4.6-21.6	4 (6.3) 1.8-15.5	52 (82.6) 70.9-90.9	Adults over 18 years	TB patients with HIV infection
Starshinova <i>et al.</i> (2016) ^[54]	37	8 (2.7) 9.8-38.2	2 (5.7) 0.7-18.2	27 (91.6) 55.9-86.2	Adults over 18 years	TB patients, MBT (+)
Yu and Khasanshin (2016) ^[55]	108,729	10,751 (98.9) 98.8-98.9	168 (0.001) 0.1-0.2	1044 (0.97) 0.9-1.0	Aged 1-18 years	Healthy persons
Barmina <i>et al.</i> (2016) ^[56]	22,018	21,365 (97.03) 96.8-97.3	177 (0.8) 0.7-0.9	476 (2.1) 2.0-2.4	Aged 1-18 years	Healthy persons
Senin <i>et al.</i> (2016) ^[57]	124	27 (21.8) 14.9-30.1	0	97 (78.2) 69.9-85.1	Adults over 18 years	TB patients with HIV infection
Baronova <i>et al.</i> (2016) ^[58]	106,091	104736 (98.7) 98.7-98.8	212 (0.2) 0.2-0.2	1143 (1.1) 1.0-1.1	Aged 1-18 years	Healthy persons
Parfenova (2016) ^[59]	549	20 (3.6) 2.2-5.6	58 (10.6) 8.1-13.4	471 (85.8) 82.6-88.6	Aged 1-18 years	TB patients, MBT (-)
Parfenova (2016) ^[59]	18,963	14,811 (78.1) 77.5-78.7	923 (4.8) 4.6-5.2	3229 (17.1) 16.5-17.6	Aged 1-18 years	Close contact
Parfenova (2016) ^[59]	59,954	53,966 (90.1) 89.8-90.3	1978 (3.3) 3.2-3.4	4010 (6.6) 6.5-6.9	Aged 1-18 years	Healthy persons
Starshinova <i>et al.</i> (2017) ^[60]	258	0	44 (17.1) 12.7-22.2	214 (82.9) 77.8-87.3	Aged 1-18 years	TB patients, MBT (-)
Starshinova <i>et al.</i> (2017) ^[60]	396	269 (67.9) 63.1-72.5	52 (13.1) 10.0-16.9	75 (19.0) 15.2-23.2	Aged 1-18 years	Healthy persons
Laushkina <i>et al.</i> (2017) ^[61]	19	3 (15.8) 3.4-39.4	1 (5.3) 0.1-26.0	15 (78.9) 54.4-93.9	Adults over 18 years	TB patients, MBT (-)
Barmina <i>et al.</i> (2017) ^[62]	99	1 (1.1) 0.0-5.5	1 (1.1) 0.0-5.5	97 (97.8) 92.9-99.8	Aged 1-18 years	TB patients, MBT (-)
Sotneva (2017) ^[63]	407,712	403,069 (98.8) 98.8-98.9	470 (0.18) 0.1-0.1	4173 (1.02) 1.0-1.1	Aged 1-18 years	Healthy persons
Zubareva and Turkin (2017) ^[64]	24,473	7466 (30.5) 27.5-32.4	382 (1.6) 1.4-1.7	16,625 (67.9) 66.7-67.9	Aged 1-18 years	Healthy persons
Zubareva and Turkin (2017) ^[64]	7368	7088 (96.2) 95.7-96.6	126 (1.7) 1.4-2.0	154 (2.1) 1.8-2.4	Adults over 18 years	Healthy individuals with HIV infection
Ilchenko and Bogorodskaya (2017) ^[65]	87	5 (5.7) 1.9-12.9	0	82 (94.3) 87.1-98.1	Adults over 18 years	TB patients, MBT (-)
Ilchenko and Bogorodskaya (2017) ^[65]	10,068	9274 (92.2) 91.6-92.6	0	794 (7.8) 7.4-8.4	Adults over 18 years	Healthy persons
Sinitsyn <i>et al.</i> (2017) ^[66]	5260	4928 (93.7) 93.0-94.3	47 (0.9) 0.7-1.2	285 (5.4) 4.8-6.1	Adults over 18 years	Healthy individuals with HIV infection

Contd...

Table 2: Contd...

Author and year of publication	Number of individuals with Diaskintest	Diaskintest results, <i>n</i> (%) (95%CI)			Individuals (aged 1-18 years or adults over 18 years)	Study groups
		Negative	Doubtful	Positive		
Biron <i>et al.</i> (2017) ^[67]	27	9 (33.3) 16.5-54.0	0	18 (66.7) 46.0-83.5	Adults	TB patients, MBT(–)
Frolova and Myakisheva (2017) ^[68]	47,142	45,620 (96.8) 96.6-96.9	407 (0.9) 0.8-1.0	1115 (2.3) 2.2-2.5	Aged 1-18 years	Healthy persons
Frolova and Myakisheva (2017) ^[68]	31	3 (9.7) 2.0-25.8	0	28 (90.3) 74.2-98.0	Aged 1-18 years	TB patients, (MBT–)
Frolova and Myakisheva (2017) ^[68]	30	19 (63.3) 43.9-80.1	0	11 (36.7) 19.9-56.1	Aged 1-18 years	Close contact
Vozyakova <i>et al.</i> (2017) ^[69]	14,363	11,465 (78.3) 79.2-80.5	732 (5.0) 4.7-5.5	2439 (16.7) 16.4-17.6	Aged 1-18 years	Healthy persons
Aksyonova <i>et al.</i> (2017) ^[70]	7631	1531 (20.1) 19.2-21.0	0	6100 (79.9) 79.0-80.0	1-18 years	TB patients, MBT (–)
Aksyonova <i>et al.</i> (2017) ^[70]	595,129	46,7852 (78.6) 78.5-78.7	0	127,277 (21.4) 21.3-21.5	Aged aged 1-18 years	Healthy persons
Barmina and Baryshnikova (2018) ^[71]	42	0	2 (4.7) 0.6-16.2	40 (95.3) 83.8-99.4	Aged 1-18 years	TB patients, MBT (–)
Barmina and Baryshnikova (2018) ^[71]	385	274 (71.2) 66.4-75.6	17 (4.4) 2.6-7.0	94 (24.4) 20.2-29.0	Aged 1-18 years	Close contact
Bogorodskaya <i>et al.</i> (2018) ^[72]	9783	9246 (94.5) 94.0-95.0	100 (1.02) 0.8-1.2	437 (4.5) 4.1-4.9	Adults over 18 years	Healthy individuals with HIV infection
Starshinova <i>et al.</i> (2018) ^[73]	116	89 (76.7) 68.0-84.1	0	27 (23.3) 15.9-32.0	Adults over 18 years	Close contact
Starshinova <i>et al.</i> (2018) ^[73]	27	25 (92.6) 75.7-99.1	0	2 (7.4) 0.9-24.3	Adults over 18 years	Healthy persons
Slogotskaya <i>et al.</i> (2018) ^[74]	408	6 (1.5) 0.5-3.2	0	402 (98.5) 96.8-99.5	Aged 1-18 years	TB patients, MBT (–)
Shurygin <i>et al.</i> (2018) ^[75]	12	1 (8.3) 0.2-38.5	2 (16.7) 2.1-48.4	9 (75.0) 42.8-94.5	Aged 1-18 years	TB patients, MBT (–)
Shurygin <i>et al.</i> (2018) ^[75]	4	0	0	4 (100) 39.8-100	Aged 1-18 years	TB patients, MBT (+)
Shurygin <i>et al.</i> (2018) ^[75]	66,527	65,226 (98.1) 97.9-98.1	378 (0.5) 0.5-0.6	923 (1.4) 1.3-1.5	Aged 1-18 years	Healthy persons
Starshinova <i>et al.</i> (2018) ^[76]	434	307 (70.7) 66.2-75.0	0	127 (29.3) 25.0-33.8	Aged 1-18 years	Healthy persons
Starshinova <i>et al.</i> (2018) ^[76]	15	0	0	15 (100) 78.2-100	Aged 1-18 years	TB patients, MBT (+)
Starshinova <i>et al.</i> (2018) ^[76]	245	0	0	245 (100) 98.5-100.0	Aged 1-18 years	TB patients (MBT–)
Starshinova <i>et al.</i> (2018) ^[76]	111	98 (88.3) 80.8-93.6	0	13 (11.7) 6.4-19.2	Adults over 18 years	Close contact
Starshinova <i>et al.</i> (2018) ^[76]	53	6 (11.3) 4.3-23.0	0	47 (88.7) 77.0-95.7	Adults over 18 years	TB patients, MBT (+)
Lozovskaya <i>et al.</i> (2018) ^[77]	26	5 (19.2) 6.6-39.4	0	21 (80.8) 60.6-93.4	Aged 1-18 years	TB patients
Lozovskaya <i>et al.</i> (2018) ^[77]	29	19 (65.5) 45.7-82.1	0	10 (34.5) 17.9-54.3	Aged 1-18 years	Healthy persons

TB: Tuberculosis

diagnostic specificity, i.e., the proportion of participants with negative test results among healthy persons without active tuberculosis. The Stata 14 metaprop module was used to present graphically the meta-analysis results of these values. Data heterogeneity was assessed using I^2 values. An $I^2 = 0.0\%$ was obtained for all subgroups, suggesting a high level of agreement between the results of different studies and the fact that the differences are likely arbitrary. The following was evaluated for the quantitative parameters: arithmetic mean (mean), standard deviation, and 95% confidence interval (CI) for the mean.

RESULTS

The analysis of 30 studies presenting DST results in tuberculosis patients ($n = 11,506$) showed that the test was positive in 80.5%, doubtful in 1.3% of cases, and negative in 17.4% [Table 3].

The whole positive results of QFT and T-SPOT varied from 67.0% and 72.2% accordingly were the results of the 2 TU Mantoux test and DST were comparable (91.2% and 80.5%). The negative results may be explained by the difficulty in diagnostic active tuberculosis and immune deficiency.

The higher diagnostic sensitivity and specificity of TSPOT.TB (90% - 98%) according to the international data [15] indicates insufficient implementation of this method in

Russian clinical practice, despite its inclusion in current clinical recommendations, which requires further analysis after widespread use.

The analysis of DST results in tuberculosis patients with positive sputum smears [Figure 2] showed the positive results in 86.0% (95% CI: 0.8–0.92). In children, all the results were 100% positive.

An analysis of DST results in the diagnosis of tuberculosis in HIV-positive patients could be conducted based on data from 5 publications reporting test findings of 366 patients. DST results were positive in 60% of cases [Figure 3].

According to the presented data, DST was positive in 59.3% of cases that in 1.4 times lower than in the tuberculosis diagnostic in HIV patients (81.5%) [Table 4].

However, the DST results were comparable with T-SPOT (67.2%) and QFT (61.3%). 2 TU Mantoux test was positive significantly less frequently than the DST (59.3% vs. 15.1, $\chi^2 = 70.12$, $P < 0.001$).

DST results in healthy persons were reported in 40 studies [Figure 4]. In the presented papers, the data for 3,714,251 persons, 10,223 (0.27%) of which were adults over 18 years and 3,704,028 (99.73%) were children aged 1–18

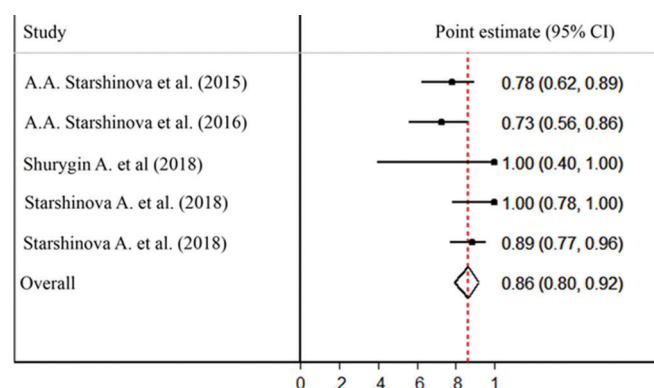


Figure 2: Diagnostic sensitivity of Diaskintest in the diagnosis of tuberculosis

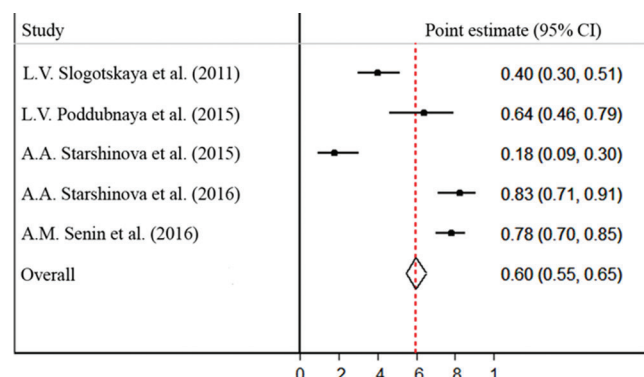


Figure 3: The proportion of positive Diaskintest results in HIV-positive patients with tuberculosis (with positive or negative sputum smears)

Table 3: Immunologic test results in the tuberculosis patients

Results	DST ($n=11,506$), n (%)	2 TU Mantoux test ($n=2058$), n (%)	T-SPOT.TB ($n=181$), n (%)	QFT ($n=1141$), n (%)
Negative	2089 (18.2)	152 (7.3)	50 (27.6)	373 (32.7)
Doubtful	147 (1.3)	11 (1.5)	4 (2.2)	4 (0.3)
Positive	9270 (80.5)	1895 (91.2)	127 (72.2)	764 (67.0)

DST: Diaskintest, QFT: QuantiFERON-TB Gold, TB: Tuberculosis

Table 4: The result of tuberculosis patients with HIV infection

Results	DST ($n=366$), n (%)	2 TU Mantoux test ($n=119$), n (%)	T-SPOT.TB ($n=119$), n (%)	QFT ($n=119$), n (%)
Negative	141 (38.5)	97 (81.5)	36 (30.3)	41 (34.5)
Doubtful	8 (2.2)	4 (3.4)	3 (2.4)	1 (4.2)
Positive	217 (59.3)	18 (15.1)	80 (67.2)	73 (61.3)

DST: Diaskintest, QFT: QuantiFERON-TB Gold, TB: Tuberculosis

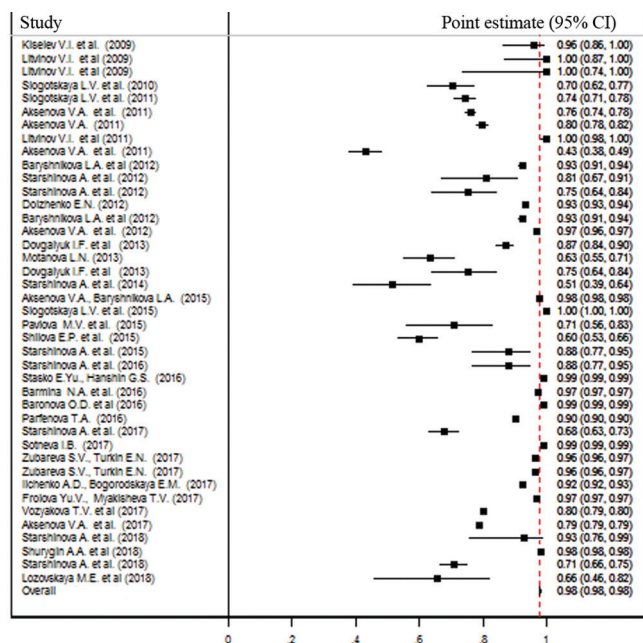


Figure 4: The proportion of negative Diaskintest results in healthy subjects

years. In 94.9% (95% CI: 0.92–0.98) of cases, the results were negative.

A total of 5 studies in which 17,467 adults were tested provided the results of DST testing in HIV-positive patients. The DST was positive in 6.7% (1542) of cases, negative in 92.4% (20,987), and doubtful in 0.95 (198). There were no data about contact with patients with tuberculosis in HIV-positive patients, however, positive results of DST in these participants evidenced for the presence of latent tuberculosis infection.

The accuracy (overall validity) of DST was 95.1% in the total studied population (95% CI: 95.06–95.1) and 92.4% in HIV-positive patients (95% CI: 91.9–92.7).

DISCUSSION

Based on the results of clinical and multiple research studies, DST started being applied in Russian Federation in 2014.^[79] The need for the implementation of this test arises from the fact that children are vaccinated against tuberculosis in their 1st day of life, which precludes the possibility of assessing the activity of tuberculosis using a 2 TU Mantoux test, since it gives positive results following vaccination.

The results of multiple studies mostly performed in the pediatric population showed a rate of tuberculosis detection using DST of 9.52 per 1000 children, whereas the same rate using the 2 TU Mantoux test was 0.16, suggesting a high efficacy of this method in cases when a significantly lower number of participants are tested as part of mass screening.^[42]

In the study conducted by Salina *et al.* (2019), it was found that the intensity of the immune response in tuberculosis

patients to specific ESAT-6 and CFP 10 antigens included in DST may depend on the biological properties of the pathogen, specifically various MTB genotypes.^[80] Moreover, some publications suggest that DST results may be negative in patients with severe tuberculosis and patients with somatic comorbidities, which is more prevalent in the adult population. This is consistent with the results observed in our study. In children, however, the test sensitivity attains 100%.

DST is more effective in detecting tuberculosis in risk groups.^[81,82] In the general population, 2 TU Mantoux test results were positive in about 76%–80% of cases, whereas a positive DST result was reported in up to 8%–10% of cases, including migrants.^[44,65,83–85] On the other hand, in risk groups, for example, HIV-positive patients, DST helped to detect tuberculosis in 4.8 times more cases than 2 TU Mantoux test.^[50,57] However, it should be noted that according to data obtained in domestic and foreign studies, the results of immunological tests in HIV-positive patients depend on the level of immune suppression.^[51,53,54,67] The most recent meta-analysis showed that T-SPOT.TB is the test of choice in patients with immune suppression over 2 TU Mantoux test and QuantiFERON-TB.^[86] Our analysis showed that from the perspective of diagnostic criteria in the diagnosis of TB in HIV-positive individuals, DST is different to IGRA tests.^[54,72] The analysis of DST results obtained from areas of tuberculosis outbreak showed that test results were positive in 95.2% and inconclusive in 4.8% of affected children, with a mean papule size of 14.98 ± 3.00 mm.^[71] Some studies demonstrated a direct correlation between the incidence of latent infection detected with DST results and an unfavorable epidemic situation in that region.^[84] In children and adolescents from areas of tuberculosis outbreak with positive sputum smears and multidrug-resistant MTB (MDR MBT [+]), DST results were positive 2.6 times more frequently than in the pediatric population from MBT (–) areas and 2.1 times more frequently than in MBT (+) areas without MDR ($P < 0.05$). In children from areas of tuberculosis outbreak, the frequency of positive reactions to DST was significantly higher than the 2 TU Mantoux test ($P < 0.05$).^[71]

According to data from various studies, test results were positive in 46%–50% of health-care professionals who contacted with tuberculosis patients.^[44,73] This method enables the identification of the group of high risk for this disease and reduces the exposure to radiation associated with X-ray examinations performed twice a year.

The analyzed studies showed that DST was also used for the differential diagnosis between pulmonary tuberculosis and other lung diseases. In patients with various nontuberculosis pulmonary disorders, DST results were negative in 88.7% of cases.^[61,83,87]

CONCLUSION

The results of the studies presented here showed that the immunological skin test using a recombinant tuberculosis

allergen (DST) developed by Russian scientists has a high informative value in the diagnosis of tuberculosis in countries with a high burden of this disease, where vaccination against tuberculosis is implemented. Multiple studies showed an overall diagnostic sensitivity of the test of 86.0% (95% CI: 0.8–0.92) with 98.0% negative results (95% CI: 0.98–0.98).

“It should be noted, that this study has certain limitations on the IGRA-tests results. The small number of Russian publications with the results of IGRA tests in comparison with skin tests does not allow to reliably reflect the effectiveness of these laboratory tests in the practice. Further study is required to assess the results of the IGRA tests in the Russian population”.

The introduction of DST in clinical practice helped to overcome the challenges of differential diagnostics between postvaccination and infection-related sensitization, changed the previously existing perceptions regarding the diagnosis and incidence of latent tuberculosis, increased the efficacy of tuberculosis diagnostic tests in children, and helped to define the tuberculosis risk groups among HIV-positive individuals. Indeed, the development and implementation of DST into clinical practice represents an important step in the progress of immunodiagnostic procedures for tuberculosis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Zellweger JP. Current options for the management of multidrug-resistant tuberculosis (review). *Med Alliance* 2017;1:22-8.
- World Health Organization. Global Tuberculosis Report 2016 (End TB Strategy). Geneva, Switzerland: World Health Organization; 2016. p. 18.
- World Health Organization. Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care. Geneva, Switzerland: WHO; 2017. p. 80.
- World Health Organization. Global Tuberculosis Report 2017. Geneva: WHO; 2017. p. 250.
- World Health Organization. Global Tuberculosis Report 2018. Geneva: WHO; 2018. p. 270.
- WHO Guidelines on Tuberculosis Infection Prevention and Control. Geneva: WHO; 2019. p. 265.
- Khan K. The global threat of infections and Robert Koch, founder of medical microbiology and world-renowned scientist. *Med Alliance* 2016;3:6-18.
- Guidelines on the Management of Latent Tuberculosis Infection. WHO; 2015. p. 38. Available from: <http://apps.who.int/medicinedocs/documents/s21682ru/s21682ru.pdf>. ISBN: 978 92 4 154890 8. <https://www.who.int/tb/publications/latent-tuberculosis-infection/en/>. [Last accessed on 2020 Aug 29].
- Slogotskaya LV. Skin immunological tests for tuberculosis—history and modern times. *Tuberculosis Lung Dis* 2013;5:39-46.
- Bamford AR, Crook AM, Clark JE, Zohreh N, Dixon G, Paton JY, *et al.* Comparison of interferon- γ release assays and tuberculin skin test in predicting active tuberculosis (TB) in children in the UK: A paediatric TB network study. *Arch Dis Childhood* 2010;95:180-6.
- Kobashi Y, Mouri K, Miyashita N, Okimoto N, Matsushima T, Kageoka T, *et al.* QuantiFERON TB-2G test for patients with active tuberculosis stratified by age groups. *Scand J Infect Dis* 2009;41:841-6.
- Kampmann B, Whittaker E, Williams A, Walters S, Gordon A, Martinez-Alier N, *et al.* Interferon- γ release assays do not identify more children with active tuberculosis than the tuberculin skin test. *Eur Respir J* 2009;33:1374-82.
- Bruzzese E, Bocchino M, Assante LR, Alessio M, Bellofiore B, Bruzzese D, *et al.* Gamma interferon release assays for diagnosis of tuberculosis infection in immune-compromised children in a country in which the prevalence of tuberculosis is low. *J Clin Microbiol* 2009;47:2355-7.
- Seyhan EC, Sökücü S, Altın S, Günlüoğlu G, Trablus S, Yılmaz D, *et al.* Comparison of the QuantiFERON-TB Gold In-Tube test with the tuberculin skin test for detecting latent tuberculosis infection in hemodialysis patients. *Transpl Infect Dis* 2010;12:98-105.
- World Health Organization. Latent Tuberculosis Infection Updated and Consolidated Guidelines for Programmatic Management. World Health Organization; 2018. p. 78.
- Litvinov VI. New skin test for the diagnosis of tuberculosis infection. *Russian Med J* 2009;1:1-4.
- Kiselev VI, Severin ES, Perelman MI, Paltsev MA. New biotechnological solutions in the diagnosis and prevention of tuberculosis infection. *Bull Res Instit Molec Med* 2009;5:37-45.
- Kiselev VI, Baranovsky PM, Rudykh IV, Schuster AM, Martyanov VA, Medniko BL, *et al.* Clinical trials of the new skin test Diaskintest® for the diagnosis of tuberculosis. *Tuberc Lung Dis* 2009;86:11-6.
- Litvinov VI, Slogotskaya LV, Seltsovsky PP, Shuster AM, Martyanov VA, Demin AV, *et al.* New skin test for the diagnosis of tuberculosis infection. *Russ Med J* 2009;1:1-4.
- Aksyonova VA, Klevno NI, Baryshnikova LA, Dolzhenko EN, Ilyasova EV, Medvedev SY, *et al.* Diaskintest® in assessing tuberculosis activity in children and adolescents. *Tuberc Lung Dis* 2009;86:13-6.
- Ovsyankina ES, Gubkina MF, Ershova NG, Kobulashvili MG. The experience of using a new skin test (Diaskintest®) for the diagnosis of respiratory tuberculosis in children and adolescents in the TB department. *Tuberc Lung Dis* 2010;87:16-9.
- Slogotskaya LV, Litvinov VI, Filippov AV, Kochetkov YA, Seltsovsky PP, Stakheeva LB, *et al.* The sensitivity of a new skin test (Diaskintest®) for tuberculosis infection in children and adolescents. *Tuberc Lung Dis* 2010;87:10-5.
- Slogotskaya LV, Litvinov VI, Kochetkov YA, Sinchikhina OY. Possibilities of a new skin test “Diaskintest” in the diagnosis of tuberculosis infection in children. *Diagn Issues Pediatr* 2011;3:20-5.
- Aksenova VA, Sevostyanova TA, Klevno NI, Lapshina VN. Tuberculosis in children and adolescents in Russia (problems and solutions in the 21st century). *Issues Modern Pediatr* 2011;10:7-11.
- Slogotskaya LV, Filippov AV, Kochetkov YA, Seltsovsky PP, Litvinov VI. The sensitivity and specificity of Diaskintest for extrapulmonary localization of tuberculosis in patients with and without HIV infection. *Immunology* 2011;32:116-9.
- Aksenova VA. The new skin test Diaskintest as a screening method for the detection of tuberculosis. *Doktor Ru* 2011;6:35-9.
- Litvinov VI, Slogotskaya LV. Diaskintest is a new immunological tool for the diagnosis of tuberculosis. *Physiology and Pathology of the Immune System. Immunopharmacogenomics* 2011;15:11-21.
- Slogotskaya LV, Kochetkov YA, Senchikhina OY. The effectiveness of a new skin test (Diaskintest) in identifying infected and diseased adolescents among subjects contacting TB patients. *Issues Modern Pediatr* 2011;10:70-5.
- Aksenova VA, Baryshnikova LA, Sokolskaya EA. New diagnostic possibilities for tuberculosis infection in children and adolescents. *Russ Bull Perinatol Pediatr* 2011;56:90-6.
- Baryshnikova LA, Lebedeva NO, Katkova LI, Vdovenko SA, Ilyasova EV, Kryukova AM, *et al.* The effectiveness of a new product for the diagnosis of tuberculosis in children and adolescents. *Issues Modern Pediatr* 2012;11:104-8.
- Starshinova AA, Dovgalyuk IF, Gavrilov PV, Yakunova OA. A new approach in the diagnosis of tuberculosis of the intrathoracic lymph nodes in children using immunological and radiation methods. *Pract Med* 2012;6:32-6.
- Starshinova AA, Pavlova MV, Dovgalyuk IF, Yakunova OA. Diagnostic capabilities of modern immunological tests in determining the activity

- of tuberculosis infection in children. *Tuberc Lung Dis* 2012;89:40-3.
33. Dolzhenko EN, The importance of the recombinant tuberculosis allergen (Diaskintest) in the detection of active tuberculosis in children. *Tuberc Lung Dis* 2012;9:31-5.
34. Baryshnikova LA, Lebedeva NO, Katkova LI, Vdovenko SA, Ilyasova EV, Kryukova AM. Experience with a new technology for screening children and adolescents for tuberculosis infection in the Samara region. *Tuberc Lung Dis* 2012;89:27-31.
35. Yablonsky PK, Dovgalyuk IF, Starshinova AA, Gavrilov PV, Yakunova OA. Application of modern immunological tests and x-ray methods in the diagnosis of the intrathoracic lymph nodes in children. *Int J Biomed* 2012;2:204-10.
36. Aksyonova VA, Baryshnikova LA, Dolzhenko EN, Kudlay DA. Current issues of mass screening of the child population for tuberculosis in modern conditions. *Doctor Ru* 2012;8:27-9.
37. Dovgalyuk IF, Starshinova AA, Zubareva SV. Possibilities of using Diaskintest in the practice of a pediatrician. *Pediatr G N Speransky J* 2013;92:65-8.
38. Slogotskaya LV, Ivanova DA, Senchikhina OY, Makarova MV, Aleschenkova OI, Kulikovskaya NV, *et al.* A comparative study of the results of a skin test with a recombinant tuberculosis allergen and a Quantiferon-QT laboratory test in children and adolescents with tuberculosis infection. *Tuberc Soc Significant Dis* 2013;2:45-51.
39. Yablonsky PK, Dovgalyuk IF, Starshinova AA, Yakunova OA. The importance of modern immunological tests in the diagnosis of tuberculosis in children. *Med Immunol* 2013;15:37-44.
40. Motanova LN, Kovalenko GE, Popova YV. Experience with the use of Diaskintest in areas with an unfavorable epidemic situation. *Tuberc Lung Dis* 2013;9:37-42.
41. Dovgalyuk IF, Starshinova AA, Ovchinnikova YE, Korneva NV, Yakunova OA. A new approach to the diagnosis of respiratory tuberculosis in children. *Med Alliance* 2013;2:43.
42. Ikonina IV, Kornienko SV, Kondrasheva LV, Odnolko OV, Skovzgid IN. The experience of using a skin test with a recombinant tuberculosis allergen in children of the Voronezh region. *Tuberc Lung Dis* 2014;7:1-6.
43. Starshinova A, Dovgaliuk I, Korneva N, Ovchinnikova U, Yakunova O, Potapenco E, *et al.* Efficiency of immunological methods in the diagnosis of active tuberculosis in children. *J US China Med Sci* 2014;11:61-7.
44. Vaganova US, Russkikh OE. Ways to increase the detection of tuberculosis among healthcare professionals. *Pharmacol Clin Pharmacol* 2015;2:61-7.
45. Aksyonova VA, Baryshnikova LA. The effectiveness of the recombinant tuberculosis allergen in the early detection of tuberculosis infection in children and adolescents in a general treatment network. *Issues Modern Pediatr* 2015;14:358-62.
46. Krat A, Ryzhkov SI, Lagunova OS, Shkrabak TN, Sagakyants OG, Zhmaylova EE. Experience with the use of the recombinant tuberculosis allergen (Diaskintest) during mass screening for tuberculosis. *Head Phys* 2015;2:2-4.
47. Slogotskaya LV, Senchikhina OY, Nikitina GV, Bogorodskaya EM. The effectiveness of a skin test with a recombinant tuberculosis allergen in the detection of tuberculosis in children and adolescents in Moscow in 2013. *Pediatr Pharmacol* 2015;12:99-103.
48. Pavlova MV, Starshinova AA, Sapozhnikova NV, Chernokhaeva IV, Zhuravlev VY. Diagnosis and clinical and radiological characteristics of respiratory tuberculosis in adolescents. *Tuberc Lung Dis* 2015;1:3-7.
49. Shilova EP, Poddubnaya LV, Stepchenko IM, Kononenko VG. The dynamics of sensitivity to a skin test with a recombinant tuberculosis allergen in children with latent tuberculosis infection. *Tuberc Lung Dis* 2015;9:19-23.
50. Eysmont NV. Experience with the use of a recombinant tuberculosis allergen for the diagnosis of tuberculosis in patients with HIV infection. *Tuberc Lung Dis* 2015;10:54-7.
51. Poddubnaya LV, Chikurova TN, Fedorova MV, Igonina OV, Dorgan VA, Zyryanova TV. Sensitivity of a skin test with a tuberculosis allergen in patients with tuberculosis and HIV infection. *Tuberc Lung Dis* 2015;11:16-21.
52. Belokurov MA, Starshinova AA, Zhuravlev VY, Koryukhina LD, Pavlova MV, Chernokhaeva IV, *et al.* Possibilities of immunological methods in the differential diagnosis of sarcoidosis and respiratory tuberculosis. *J Infectol* 2015;7:98-104.
53. Starshinova AA, Panteleev AM, Vasilyeva EV, Manina VV, Pavlova MV, Sapozhnikova NV. The use of modern immunological methods in the diagnosis of tuberculosis in patients with HIV infection. *J Infectol* 2015;7:126-31.
54. Starshinova AA, Panteleev AM, Manina VV, Istomina EV, Afonin DN, Zhuravlev VY. Possibilities of various immunological tests in the diagnosis of tuberculosis in patients with HIV infection. *Tuberc Lung Dis* 2016;94:14-22.
55. Stasko EYu, Khasanshin GS. An analysis of the use of a skin test with a recombinant tuberculosis allergen product as a screening method for tuberculosis in children over 7 years old in the Penza region in 2015. *Tuberculosis and Lung Diseases* 2016;94:52-6.
56. Barmina NA, Baryshnikova LA, Shurygin AA, Reikhard VV. Screening for latent tuberculosis infection using a recombinant tuberculosis allergen. *Tuberc Lung Dis* 2016;94:56-60.
57. Senin AM, Eysmont NV, Golubev DN. The use of Diaskintest to assess the tuberculosis activity in the TB service HIV-infected patients. *Bull Modern Clin Med* 2016;9:101-7.
58. Baronova OD, Odinets VS, Moiseeva NN, Terekhina TV. The effectiveness of the recombinant tuberculosis allergen in the screening diagnosis of tuberculosis infection in children and adolescents in the Stavropol Territory. *Tuberc Lung Dis* 2016;94:30-4.
59. Parfenova TA. The experience of using a recombinant tuberculosis allergen in anti-TB facilities for the diagnosis of tuberculosis infection. *Tuberc Lung Dis* 2016;94:49-52.
60. Starshinova AA, Ananyev SM, Ovchinnikova YE, Korneva NV, Dovgalyuk IF. The results of the use of new generation immunological tests in children under conditions of mass vaccination against tuberculosis. *Tuberc Lung Dis* 2017;95:46-52.
61. Laushkina ZA, Krasnov VA, Petrenko TI. Possibilities of immunological methods in the differential diagnosis of pulmonary tuberculosis. *Tuberc Lung Dis* 2017;95:26-30.
62. Barmina NA, Baryshnikova LA, Reichardt VV, Zhdakaev MS, Kudlay DA. Efficacy criteria for the treatment of tuberculosis in children in modern conditions. *Tuberc Lung Dis* 2017;95:69-74.
63. Sotneva IB. Experience with the use of recombinant tuberculosis allergen for mass screening for tuberculosis in children and adolescents in the Nizhny Novgorod region. *Issues Pract Pediatr* 2017;12:43-8.
64. Zubareva SV, Turkin EN. Experience with the use of recombinant tuberculosis allergen for tuberculosis screening in children and adolescents in the Kaliningrad region. *Tuberc Lung Dis* 2017;95:20-3.
65. Ilchenko AD, Bogorodskaya EM. The prevalence of latent tuberculosis among foreign citizens and stateless persons in the city of Moscow. *Tuberc Soc Significant Dis* 2017;2:30-4.
66. Sinitsyn MV, Ayusheeva LB, Kolpakova LV. Detection of latent tuberculosis infection in patients with HIV infection. *Diary Kazan Med Sch* 2017;2:86-90.
67. Biron EV, Pozdnyakova EI, Semenova OV. The possibility of using a recombinant tuberculosis allergen in the differential diagnosis of respiratory tuberculosis in adults. *Tuberculosis and Socially Significant Diseases* 2017;2:35-41.
68. Frolova YV, Myakisheva TV. Screening of the pediatric population for tuberculosis infection and their effectiveness. *Bull Smolensk State Med Acad* 2017;16:148-52.
69. Vozyakova TR, Masterova AV, Elenkina ZV, Kudlay DA. Comprehensive assessment of diagnostic methods for detecting tuberculosis infection in children and adolescents in the Chuvash Republic. *Russ Bull Perinatol Pediatr* 2017;62:105-12.
70. Aksyonova VA, Levi DT, Alexandrova NV, Kudlay DA, Baryshnikova LA, Klevno NI. Tuberculosis in children: modern methods of prevention and early diagnosis. *Doktor Ru* 2017;15:9-15.
71. Barmina NA, Baryshnikova LA. Possibilities for increasing the effectiveness of disease prevention in children in foci of tuberculosis infection using the example of Perm Territory. *Tuberc Lung Dis* 2018;96:50-6.
72. Bogorodskaya EM, Mazus AI, Sinitsyn MV, Krasnova SV, Golokhvastova EL, Belilovsky EM, *et al.* Epidemiological effectiveness of the organization of prevention and early detection of tuberculosis among patients with HIV infection. *Tuberc Soc Significant Dis* 2018;2:4-15.

73. Starshinova AA, Istomina EV, Belyaeva EN, Yablonsky PK. Detection of latent tuberculosis infection in various units of an anti-TB facility. *Med Alliance* 2018;4:11-8.
74. Slogotskaya L, Bogorodskaya E, Ivanova D, Sevostyanova T. Comparative sensitivity of the test with tuberculosis recombinant allergen, containing ESAT6-CFP10 protein, and Mantoux test with 2 TU PPD-L in newly diagnosed tuberculosis children and adolescents in Moscow. *PLoS One* 2018;13:e0208705.
75. Shurygin AA, Furina EV, Nemytykh SM, Druzhinina EA. Methods for the detection of tuberculosis in adolescents. *Tuberc Lung Dis* 2018;96:68-9.
76. Starshinova A, Zhuravlev V, Dovgaluk I, Panteleev A, Manina V, Zinchenko U, *et al.* A comparison of intradermal test with recombinant tuberculosis allergen (diaskintest) with other immunologic tests in the diagnosis of tuberculosis infection. *Int J Mycobacteriol* 2018;7:32-9.
77. Lozovskaya ME, Gurina OP, Dementieva EA, Vasilieva EB, Klochkova LV, Shibakova ND, *et al.* Features of the response of *in vitro* tests and skin tests with tuberculosis allergens, depending on the variant of tuberculosis infection in children. *Med Theory Pract* 2018;3:13-8.
78. Litvinov VI, Schuster AM, Slogotskaya LV, Seltsovsky PP, Ovsyankina ES, Ayu M, *et al.* The effectiveness of the use of the new diagnostic product DIASKINTEST® in children for the detection and diagnosis of tuberculosis. *Tuberc Lung Dis* 2009;86:19-22.
79. Order No. 951 On Approval of Guidelines for Improving the Diagnosis and Treatment of Respiratory Tuberculosis of the Ministry of Health of the Russian Federation of December 29, 2014. Ministry of Health of the Russian Federation. Moscow; 2014. Available from: <https://www.garant.ru/products/ipo/prime/doc/70749840/> (Russ). [Last accessed on 2020 Aug 20].
80. Salina TY, Morozova TI, Kudlay DA. Results of the skin test of diaskintest in pulmonary tuberculosis patients caused by different genotypes of *M. tuberculosis*. *Tuberculosis and Lung Diseases* 2019;97:66-7. (In Russ.) <https://doi.org/10.21292/2075-1230-2019-97-12-66-67>.
81. Shovkun L, Aksenova V, Kudlay D, Sarychev A. The role of immunological tests in the diagnosis of tuberculosis infection in children with juvenile idiopathic arthritis (JIA). *Eur Respir J* 2018;52:2733.
82. Slogotskaya LV, Litvinov V, Kudlay DA, Ovsyankina E, Seltsovsky P, Ivanova D, *et al.* New skin test with recombinant protein CFP10-ESAT6 in patients (children and adults) with tuberculosis, non-tuberculosis disease and latent TB infection. *Eur Respir J* 2012;40:416.
83. Slogotskaya LV, Bogorodskaya E, Sentchichina O, Ivanova D, Nikitina G, Litvinov V, *et al.* Effectiveness of tuberculosis detection using a skin test with allergen recombinant (CFP-10-ESAT-6) in children. *Eur Respir J* 2015;46:PA4524.
84. Starshinova AA, Kudlay DA, Dovgalyuk IF, Basantsova NY, Zinchenko YS, Yablonsky PK. The effectiveness of new methods of immunodiagnosis of tuberculosis infection in the Russian Federation. *Pediatrics* 2019;98:229-35.
85. Slogotskaya LV, Sinitsyn MV, Kudlay DA. Possibilities of immunological tests in the diagnosis of latent tuberculosis infection and tuberculosis. *Tuberc Lung Dis* 2019;97:46-59.
86. Meier NR, Ritz N, Heininger U, Volken T, Geiger M, Tebruegge M. Risk factors for indeterminate interferon-gamma release assay for the diagnosis of tuberculosis in children – A systematic review and meta-analysis. *Front Pediatr* 2019;7:1-21.
87. Biron EV, Pozdnyakova EI, Semenova OV. The possibility of using a recombinant tuberculosis allergen in the differential diagnosis of respiratory tuberculosis in adults. *Tuberc Soc Significant Dis* 2017;2:35-41.