Tables and Figures

Figure 1: PRISMA diagram¹⁷

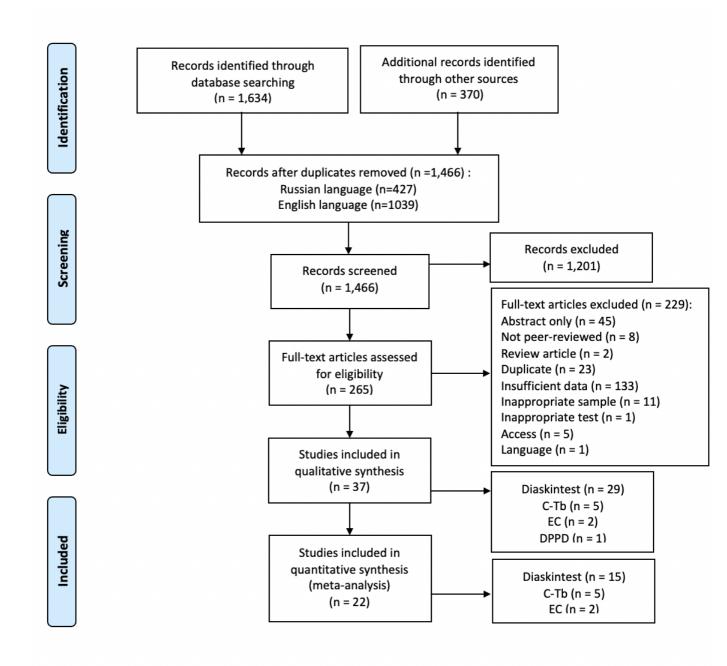


Table 1: Description of Included Studies (Diaskintest, C-Tb, EC and DPPD)

First author and publication year,	Index Test	Comparators	Age, years (a)	Sample size (in review)			Review Objective Addressed			
Country of conduct (Russia for all diaskintest studies)						Test concordance	Sensitivity	Specificity (c)	Dose-response association (d)	
				Diaskintes	st studies (e)					
Aksenova 2011	Diaskintest ^{AI}	TST ^{5mm}	NS	1551(63)	Children; TB Screening	X	X			
Baryshnikova 2017	Diaskintest ^{AI}	TST ^{5mm}	NS	811(163)	Children; active PTB	X				
Borodulina 2012	Diaskintest ^{AI}	TST ^{5mm}	28	274 (100)	HIV- adults, active Tb	X	X			
Borodulina 2014	Diaskintest ^{AI}	None	NS	185 (12)	Children with and without TB		X			
Dovgalyuk 2013	Diaskintest ^{AI}	TST ^{5mm}	4.2	570 (570)	Children; TB Screening	X				
Fedorovykh 2014	Diaskintest ^{5mm}	None	NS	551(83)	Children, household TB contacts				X	
Kabanets 2016	Diaskintest ^{AI}	TST ^{5mm}	NS	1204 (1204)	Children, TB Screening	X				
Kibrik 2015	Diaskintest ^{AI}	None	NS	2373 (1060)	Medical students; TB contacts; active TB; non-TB disease				X	
Koretskaya 2012	Diaskintest ^{5mm}	TST ^{5mm}	23	109 (109)	Medical students	X				
Laushkina 2017	Diaskintest ^{5mm}	None	42.9	70 (20)	Adults; TB investigation		X			
Losovskaya 2014*	Diaskintest ^{AI}	TST ^{5mm} , IGRA (QFT- TB GIT)	0.5-15	50 (46)	Children; TB investigations	X				
Losovskaya 2016*	Diaskintest ^{AI}	TST ^{5mm} , IGRA (QFT- TB GIT)	3-6	63 (63)	Children; TB investigation	X				

Mishin 2016	Diaskintest ^{AI}	None	NS	529 (103)	HIV- Adults; PTB; Healthy control;		X	
Nikitina 2019	Diaskintest ^{AI}	IGRA (QFT- TB GIT)	Adults: 42, 18-84 Children: 10, 3-16	181 (68)	Adults and children; TB investigation		X	
Salina 2011	Diaskintest ^{5mm}	TST ^{5mm}	17-80	142 (33)	Adult; TB investigation	X	X	
Salina 2019	Diaskintest ^{AI}	None	18-68	69 (69)	Active PTB		X	
Samorodov 2019	Diaskintest ^{AI}	None	37.1	336 (336)	Adults; respiratory illness (undetermined)		X	
Senin 2016	Diaskintest ^{5mm}	None	30-39	207 (124)	HIV+ adults (CD4 < 200 cells/mm³ in 45%); active TB		X	
Shovkun 2014	Diaskintest ^{AI}	TST ^{5mm}	NS	220 (220)	Children; TB investigation	X		
Slogotskaya 2011 (a)	Diaskintest ^{AI}	None	31.5	88 (88)	HIV+ adults (CD4 < 200 cells/mm³ in 46.6%); active TB	X	X	
Slogotskaya 2011 (b)	Diaskintest ^{AI}	TST ^{5mm}	NS	1677 (23)	Children and adults; TB investigation	X		
Slogotskaya 2012	Diaskintest ^{AI}	IGRA (QFT- TB GIT)	12	122 (122)	Children, active PTB; Children, PPD- TST+/Diaskintest+	X		
Slogotskaya 2013	Diaskintest ^{AI}	TST ^{5mm}	7-14	521 (511)	Children, active TB	X		
Slogotskaya 2018	Diaskintest ^{5mm}	TST ^{5mm}	8.8	441(408)	Children; active TB		X	
Starshinova 2018*	Diaskintest ^{5mm}	TST ^{5mm} , IGRA (T.SPOT-TB,	Children 8.1, Adults: 37	860 (860)	HIV-; BCG-vaccinated; TB Screening; Children; Adults		X	

		QFT-TB							
		GIT)							
Starshinova 2019 (a)*	Diaskintest ^{5mm}	TST ^{5mm} , IGRA (QFT- TB GIT, T- SPOT.TB)	18-65	187 (135)	Adults, Culture+ TB; TB unexposed; IGRA+/Diaskintest+		X		
Starshinova 2019 (b)	Diaskintest ^{AI}	None	TB hospital: 42 (0.23), General hospital: 43 (0.27)	154 (154)	Healthcare professionals in TB hospitals and general hospitals				X
Vaganova 2015	Diaskintest ^{AI}	None	NS	321 (321)	Medical doctors and nurses working in TB dispensaries				X
Yablonskiy 2013	Diaskintest ^{5mm}	TST ^{5mm}	Age 3-6: 4.5, Age 7- 14: 12.3	120 (43)	Children; TB investigation	X			
				C-Tb st	udies (f)				
Aggerbeck 2013, United Kingdom*	C-Tb	TST (multiple thresholds) (g), QFT	Cases: 33, 18-60, Controls:34, 18-65	189 (189)	Active Tb (3 participants selected on basis of positive IGRA); TB unexposed adults	X		X	
Aggerbeck 2018, South Africa*	С-Ть	TST ^{5mm/15mm} , QFT	17, 0-65	1190 (1190)	Child case-contacts under 5 years and healthy controls; HIV+ (median CD4+ 314 cells/microlitre (IQR 164-502) and HIV- adults suspected of TB; Active TB	X			

Aggerbeck 2019, South Africa*	C-Tb	TST ^{5mm/15mm} , QFT	35; 18-64	456 (154)	Adults, active TB	X	X				
Hoff 2016, South Africa*	C-Tb	TST (multiple thresholds), QFT	34; 18-64	253 (241)	HIV+ and HIV- adults with active TB	X	X				
Ruhwald 2017, Spain*	C-Tb	TST ^{5mm/15mm} , QFT	Controls: 24.1, Cases: 37.3, Close contacts: 32.9, Occasional: 31.5	979 (970)	Close TB contacts; occasional TB contacts; Active TB; TB- unexposed	X	X	X	X		
				EC stu	dies (h)						
Li 2016, China	EC-skintest	TST ^{5mm} , T- SPOT.TB	Controls: 45, Cases: 41.3	144 (144)	TB unexposed; Active TB		X				
Zhang 2020, China	EC-skintest	None	18.77 (13.11); 18- 65	2257 (743)	Active TB		X				
DPPD study											
Badaro 2020, Brazil	DPPD ^{5mm/10mm}	TST ^{5mm/10mm}	HIV+: 31.2; 18-54, HIV- : 39.9; 19- 64 Healthy: 29.8; 18-47	173 (173)	Active TB; HIV+ adults (6/38 (15.8%) had CD4 < 200 cells/mm³); HIV – adults; healthy volunteers	X	X				

- (a) Age: Average, either mean age (standard deviation) or median and/or range;
- (b) Study population: Where HIV status not indicated=not specifified/unknown (explored in sensitivity analysis).
- (c) Specificity could not be estimated in diaskintest studies (TB not ruled out; studies conducted in a high-burden country).
- (d) Dose-response association: Studies evaluating index test performance amongst TB contacts of varying degrees of exposure.
- (e) All studies were conducted in Russia; All prospectively conducted cross-sectional studies (except, Kabanets, 2016 and Salina, 2019);

^{*} Studies included in three-way head-to-head analysis (index test compared with both IGRA and TST)

- (f) All were prospectively conducted cross-sectional studies; Phase 2 (Aggerbeck 2013) Phase 3 (Aggerbeck, 2018; Ruhwald, 2017); 5mm threshold for C-Tb positivity used in all studies. C-Tb and TST were allocated to either forearm double blinded (All 5 C-Tb studies) None of the studies randomly assigned C-Tb vs comparator. TST5mm (HIV+), TST10 or 15mm (HIV-), TST5mm/15mm (aggregated/combined cohort)
- (g) TST was performed prior to the present trial in 18 of the tuberculosis patients.
- (h) All were prospectively conducted cross-sectional studies; Phase 2a (Li, 2016) Phase 3 (Zhang 2020). 5mm threshold for EC positivity in all studies. Superscript indicates test cutoff

AI (any skin induration); TST: Tuberculin skin test; IGRA: Interferon gamma release assay; QFT-TB GIT: QuantiFERON TB Gold In-Tube. PTB: pulmonary TB; TB Screening: Individuals undergoing routine TB screening; TB Investigation: Individuals with suspected TB undergoing investigation.

NS: not specified

Figure 2 Test agreement in head-to-head studies comparing all three tests

Figure 2a. Diaskintest, IGRA and TST agreement

Study	Conc	N		Agreement (%)	95%CI
Diaskintest AI vs. IGR/ Losovskaya 2014 Losovskaya 2016 Random effects model Heterogeneity: I ² = 0%, p	40 55	46 63 109	—————————————————————————————————————	87.30	[73.74; 95.06] [76.50; 94.35] [79.47 ; 92.24]
Diaskintest AI vs. TST Losovskaya 2014 Losovskaya 2016 Random effects model Heterogeneity: $I^2 = 0\%$, p	25 36	47 63 110		57.14	[38.08; 67.89] [44.05; 69.54] [46.08; 64.45]
IGRA vs. TST 5mm Losovskaya 2014 Losovskaya 2016 Random effects model Heterogeneity: $I^2 = 0\%$, p		46 -63 109	40 50 60 70 80 90 10	53.97	[32.89; 63.05] [40.94; 66.61] [42.05; 60.60]

Includes HIV-uninfected children under investigation for TB and those with active TB (clinical and confirmed). AI = Any induration; Conc = Concordant; N = Total, concordant + discordant; % Agreement: represents agreement with IGRA as the comparator

Figure 2b. C-Tb, IGRA and TST agreement

Study	Conc	N		Agreement (%) 95%CI
CTb vs. IGRA				
Aggerbeck 2018	46	56		82.14 [69.60; 91.09]
Aggerbeck 2019	187	232	-	80.60 [74.92; 85.49]
Hoff 2016	174	222		78.38 [72.38; 83.61]
Random effects mode	I	510	⇔	79.80 [76.10; 83.07]
Heterogeneity: $I^2 = 0\%$, p	= 0.76			• , •
CTb vs. TST 5mm HIV-	+, 15mm	HIV-		
Aggerbeck 2018	59	75	-	78.67 [67.68; 87.29]
Aggerbeck 2019	112	150	-	74.67 [66.93; 81.41]
Hoff 2016	197	241	-	81.74 [76.28; 86.41]
Random effects mode	I	466	\Leftrightarrow	78.92 [74.65; 82.63]
Heterogeneity: $I^2 = 8\%$, p	= 0.25			- , -
CTb vs. TST 5mm (HIV	/ +)			
Aggerbeck 2018	29	34		85.29 [68.94; 95.05]
Aggerbeck 2019	26	32	-	81.25 [63.56; 92.79]
Hoff 2016	80	95		84.21 [75.30; 90.88]
Random effects mode	I	161		83.85 [77.34; 88.76]
Heterogeneity: $I^2 = 0\%$, p	= 0.90			• , •
CTb vs. TST 15mm (Hi	IV–)			
Aggerbeck 2018	30	41	-	73.17 [57.06; 85.78]
Aggerbeck 2019	86	118	-	72.88 [63.92; 80.65]
Hoff 2016	117	146	-	80.14 [72.74; 86.28]
Random effects mode Heterogeneity: $I^2 = 0\%$, p		305		76.39 [71.30; 80.82]
IGRA vs. TST 5mm HIV	V+. 15m	m HIV-		
Aggerbeck 2018	33	56	_	58.93 [44.98; 71.90]
Aggerbeck 2019	188	231		81.39 [75.76; 86.19]
Hoff 2016	172	222		77.48 [71.41; 82.80]
Random effects mode	I	509		74.67 [64.01; 83.01]
Heterogeneity: $I^2 = 80\%$,	p < 0.01			• , •
IGRA vs. TST5mm (HI	V+)			
Aggerbeck 2018	14	23 -		60.87 [38.54; 80.29]
Aggerbeck 2019	41	45		91.11 [78.78; 97.52]
Hoff 2016	70	89		78.65 [68.69; 86.63]
Random effects mode		157		79.54 [63.97; 89.48]
Heterogeneity: $I^2 = 68\%$,	p = 0.02			
IGRA vs. TST15mm (H	IIV–)			
Aggerbeck 2018	19	33 -		57.58 [39.22; 74.52]
Aggerbeck 2019	147	186		79.03 [72.47; 84.64]
Hoff 2016	102	133		76.69 [68.58; 83.58]
Random effects mode		352		74.74 [64.99; 82.50]
Heterogeneity: $I^2 = 49\%$,	p = 0.03	_		
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		40) 50 60 70 80 90 10	00

Includes individuals with bacteriologically-confirmed active TB. Ruhwald 2017 and Aggerbeck 2013, although did three- test comparisons, did not report data suitable for estimation of %TST-IGRA agreement. Conc = Concordant; N = Total, concordant + discordant; % Agreement: represents agreement with IGRA as the comparator

Figure 3. Test sensitivity in three-way head-to-head studies comparing Diaskintest, IGRA and TST

Study TP	TP+FN		Sensitivi	ty (%) 95%CI
TST 5mm Starshinova 2019 (a) 45 Starshinova 2018 15 Random effects model Heterogeneity: $I^2 = 0\%$, $p = 1.0$	15 68			84.91 [72.41; 93.25] 100.00 [78.20; 100.00] 88.24 [78.20; 94.01]
IGRA (QFT) Starshinova 2019 (a) 40 Starshinova 2018 12 Random effects model Heterogeneity: $I^2 = 0\%$, $p = 1.0$	12 58		<u>-⊪</u>	86.96 [73.74; 95.06] 100.00 [73.54; 100.00] 89.66 [78.83; 95.28]
IGRA (T-SPOT.TB) Starshinova 2019 (a) 48 Starshinova 2018 2 Random effects model Heterogeneity: $I^2 = 0\%$, $p = 1.6$	2 — 55		<u>-</u> #-	90.57 [79.34; 96.87] 100.00 [15.81; 100.00] 90.91 [79.95; 96.16]
Diaskintest 5mm Starshinova 2019 (a) 47 Starshinova 2018 15 Random effects model Heterogeneity: $I^2 = 0\%$, $p = 1.0$	15 68	0 40 60	80 100	88.68 [76.97; 95.73] 100.00 [78.20; 100.00] 91.18 [81.72; 95.98]
	TP = Tru	ie positive	FN = False negation	ve

Includes HIV-uninfected adults with microbiologically-confirmed active TB.

Figure 4. Test sensitivity in head-to-head studies comparing C-Tb, IGRA and TST

Study	TP T	P+FN		Sensitivity (%)	95%CI
TST 15mm					
Ruhwald 2017	61	100			[50.73; 70.60]
Aggerbeck 2018	30	41	-	73.17	[57.06; 85.78]
Aggerbeck 2019	98	118		83.05	[75.04; 89.33]
Hoff 2016	205	241		85.06	[79.92; 89.31]
Random effects mode		500		77.18	[66.44; 85.25]
Heterogeneity: $I^2 = 81\%$,	p < 0.01				
TST 5mm					
Aggerbeck 2019	23	32	-	71.88	[53.25; 86.25]
Aggerbeck 2018	26	34			[58.83; 89.25]
Hoff 2016	79	95	-		[74.10; 90.06]
Ruhwald 2017	90	100	-		[82.38; 95.10]
Random effects mode	el	261			[74.91; 88.42]
Heterogeneity: $I^2 = 45\%$,	p = 0.07				
TST 5mm HIV+, 15mm	n HIV-				
Ruhwald 2017	63	100	-	63.00	[52.76; 72.44]
Aggerbeck 2018	56	75		74.67	[63.30; 84.01]
Aggerbeck 2019	121	150	-	80.67	[73.43; 86.65]
Hoff 2016	212	241		87.97	[83.18; 91.79]
Random effects mode		566		78.18	[67.75; 85.94]
Heterogeneity: $I^2 = 84\%$,	p < 0.01				
IGRA					
Aggerbeck 2018	41	70		58.57	[46.17; 70.23]
Aggerbeck 2019	196	289	-		[62.10; 73.17]
Hoff 2016	181	241			[69.15; 80.43]
Ruhwald 2017	82	100	-		[73.05; 88.97]
Random effects mode		700		71.67	[63.44; 78.68]
Heterogeneity: $I^2 = 78\%$,	p < 0.01				
CTb					
Ruhwald 2017	68	100	-		[57.92; 76.98]
Aggerbeck 2018	54	75			[60.44; 81.76]
Hoff 2016	112	146	-		[69.01; 83.30]
Aggerbeck 2019	117	150			[70.51; 84.35]
Random effects mode		471	\Leftrightarrow	74.52	[70.39; 78.25]
Heterogeneity: $I^2 = 0\%$, μ	0 = 0.29			,	
			1 1 1 1	I	

 $TP = True \ positive; \ FN = False \ negative.$ Results include individuals with microbiologically-confirmed active TB.

Figure 5. Test specificity in head-to-head studies comparing C-Tb, IGRA and TST

Study	TN TI	N+FP				Spe	ecificity (%)	95%CI
TST 15mm Aggerbeck 2013 Ruhwald 2017 Random effects model Heterogeneity: $I^2 = 0\%$, p		147 212 359	_	-	-		91.84 94.34 93.31	[
IGRA Ruhwald 2017 Aggerbeck 2013 Random effects model Heterogeneity: I ² = 72%, p		263 147 410 —			-	_ 	100.00	[93.12; 98.16] [97.52; 100.00] [79.66 ; 99.97]
Ruhwald 2017 Aggerbeck 2013 Random effects model Heterogeneity: $I^2 = 21\%$, p		262 147 409	85	90	95	100		[93.58; 98.42] [96.27; 99.98] [93.96; 99.25]

Individuals without active TB in studies conducted in TB low-incidence settings. TN = True negative FP = False positive