Tables and Figures

Figure 1: PRISMA diagram[17]

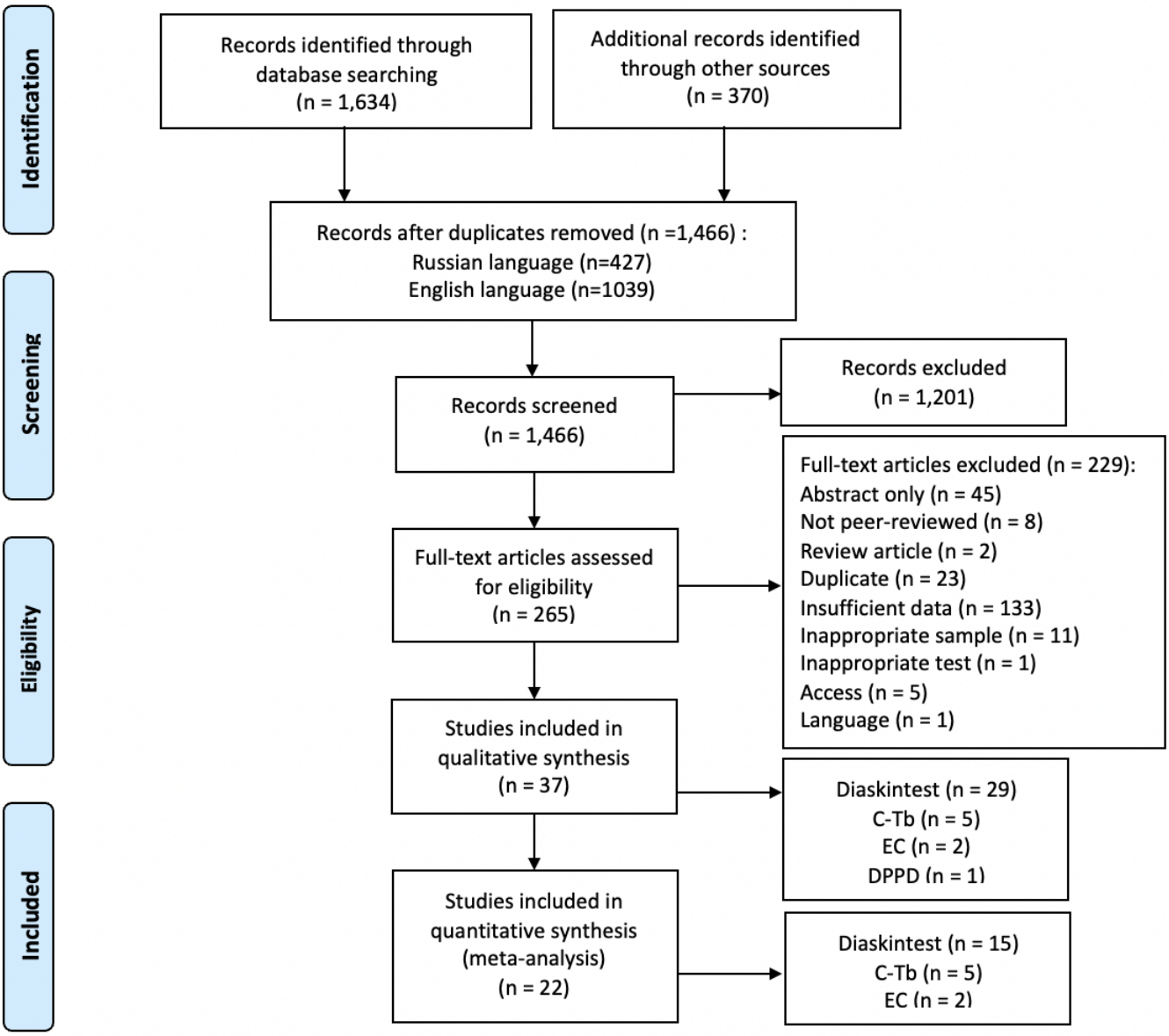


Table 1: Description of Included Studies (Diaskintest, C-Tb, EC and DPPD)

First author and publication year, Country of conduct (Russia for all diaskintest studies)	Index Test	Comparators	Age, years (a)	Sample size (in review)	Study population (b)	Review Objective Addressed			
						Test concordance	Sensitivity	Specificity (c)	Dose-response association (d)
Diaskintest 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/mm^3 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/mm^3 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 studies (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*	C-Tb	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 studies (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/mm^3); HIV – adults; healthy volunteers	X	X		

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

(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);

(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.

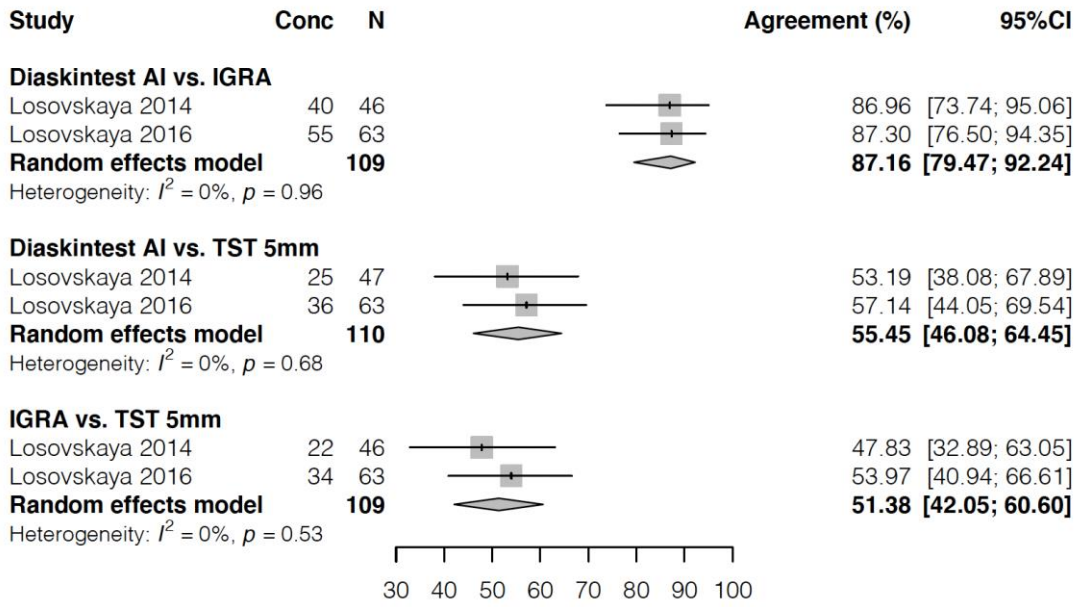
Superscript indicates test cutoff

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

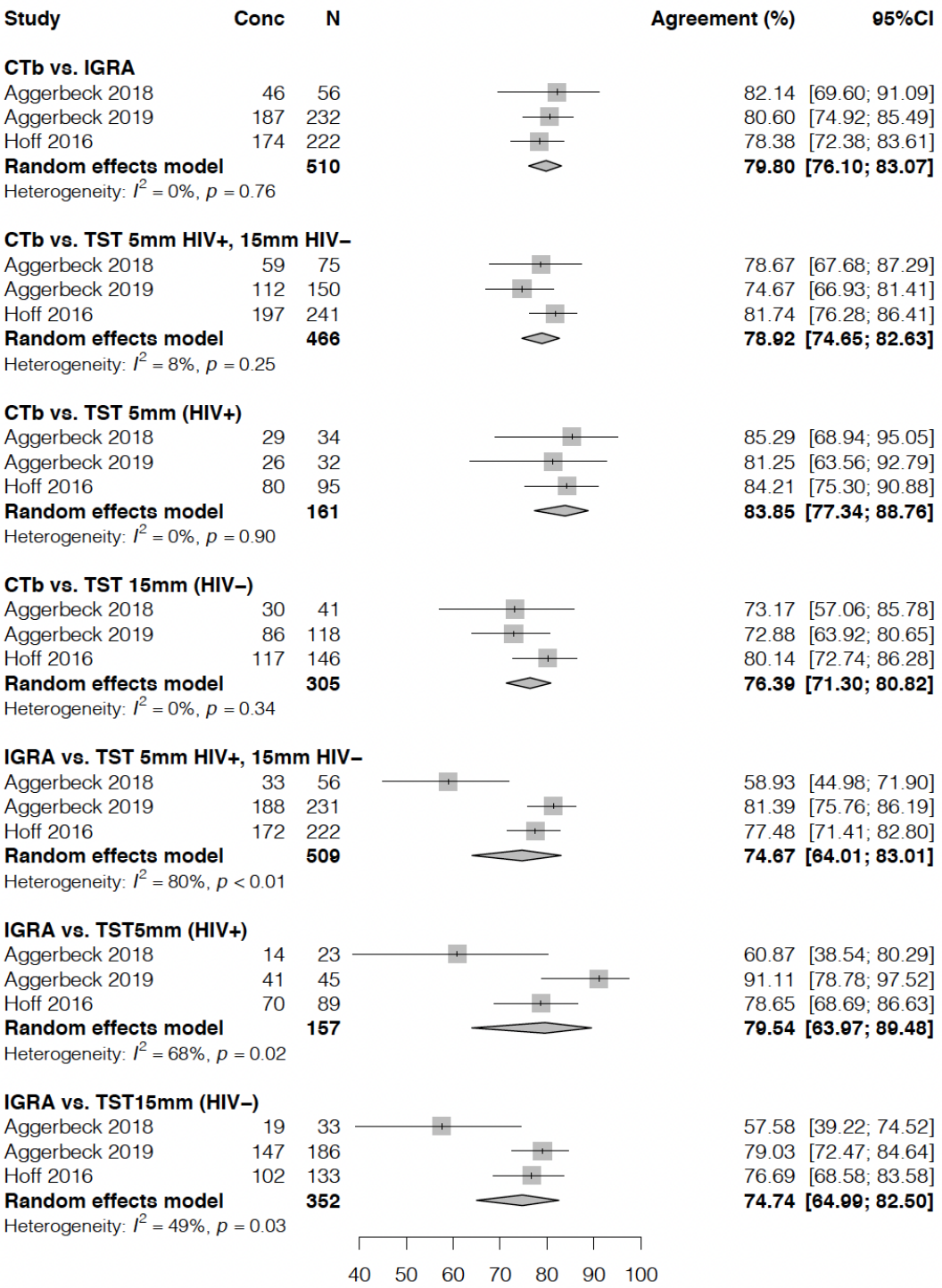
Figure 2 Test agreement in head-to-head studies comparing all three tests

Figure 2a. Diaskintest, IGRA and TST agreement



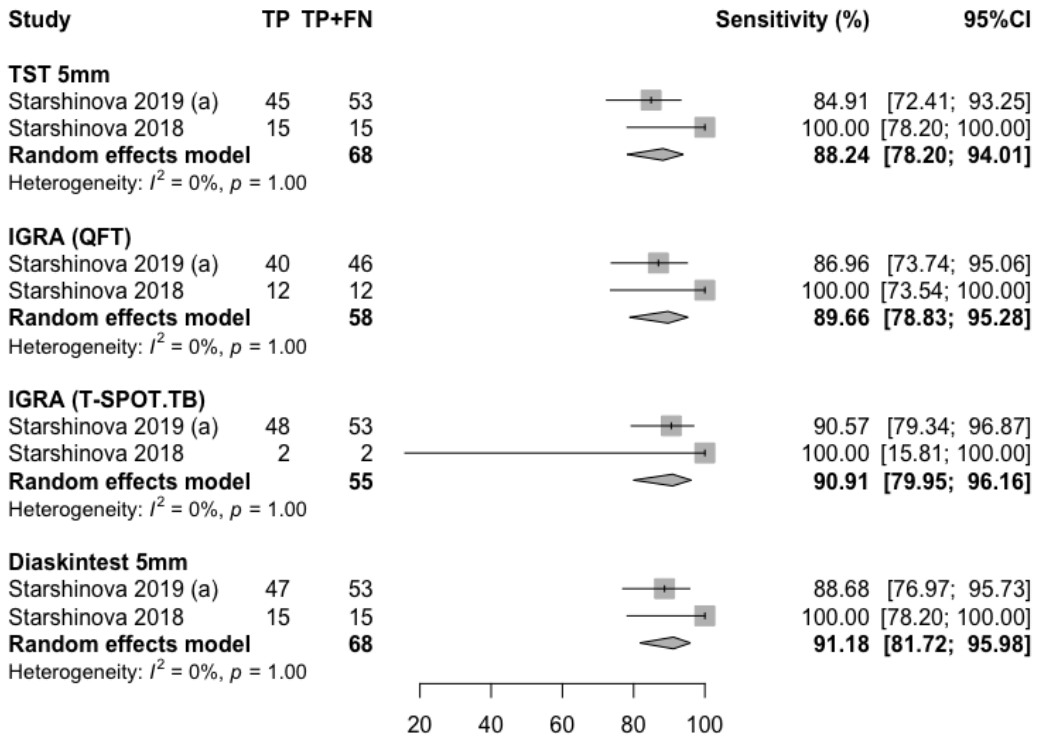
Includes HIV-uninfected children under investigation for TB and those with active TB (clinical and confirmed). AI = Any induration ; Conc = Concordant; N = Total, concordant + discordant; % Agreement: represents agreement with IGRA as the comparator

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



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

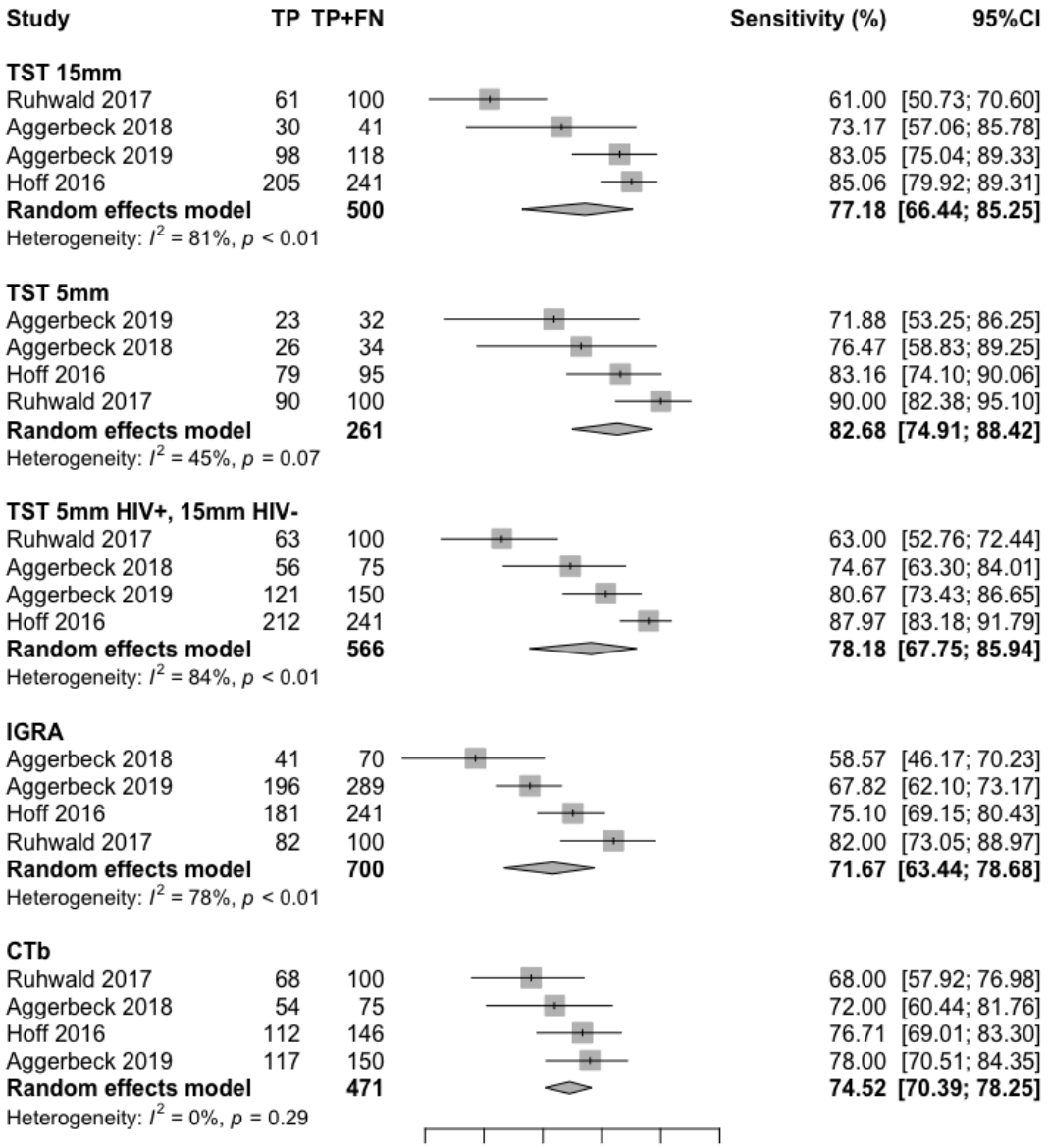
Figure 3. Test sensitivity in three-way head-to-head studies comparing Diaskintest, IGRA and TST



TP = True positive FN = False negative

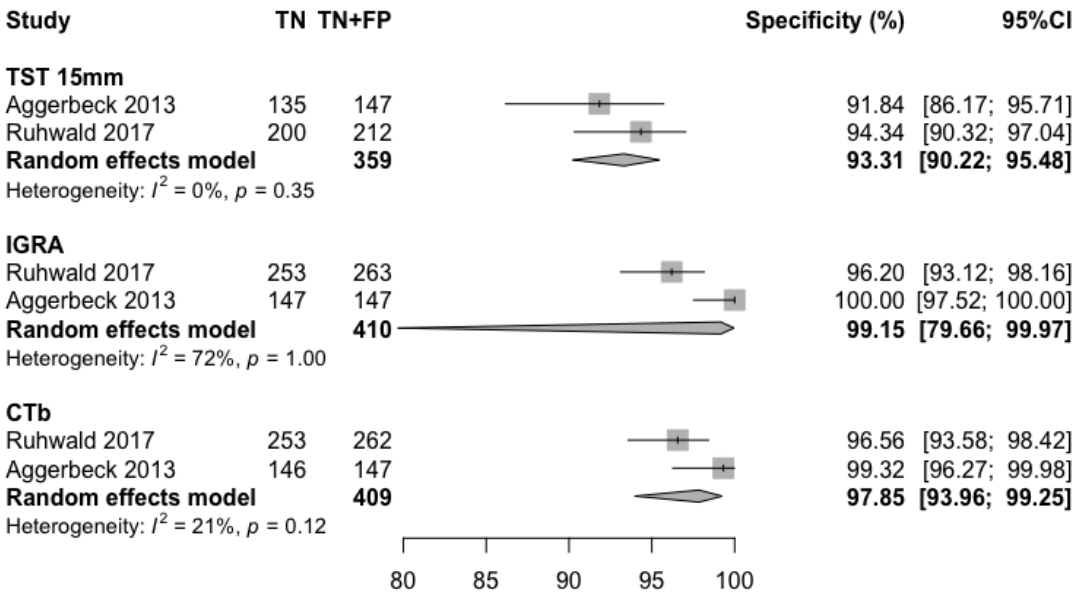
Includes HIV-uninfected adults with microbiologically-confirmed active TB.

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



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



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