PUBLICATIONS

Selected T-SPOT.*TB* test publications, by area of interest, up to 31st August 2016.

Category	Description / Key Findings	Publication
Background	A useful primer on the evolution, administration and interpretation of the tuberculin skin test and its limitations.	Huebner RE, et al. The tuberculin skin test. *Clin Infect Dis.* 1993;17(6): 968-975.
	A useful summary describing the evolution, principle and methodology of the T-SPOT.*TB* test and its advantages over the TST.	Lalvani A. Diagnosing tuberculosis infection in the 21st century: new tools to tackle an old enemy. *Chest.* 2007;131(6):1898-1906. doi:10.1378/chest.06-2471.
	A useful primer on the history and current state of tuberculosis as an infectious disease.	Pai M,et al. Tuberculosis. *Nat. Rev. Dis. Primers* 2016;16076(6) doi:10.1038/nrdp.2016.76.
Utility in active disease / sensitivity	T-SPOT.*TB* test sensitivity was 98% (57/58) in subjects with culture confirmed TB.	Janssens JP,et al. Quantitative scoring of an interferon-gamma assay for differentiating active from latent tuberculosis. *Eur Respir J*. 2007;30(4):722-728. doi:10.1183/09031936.00028507..
	T-SPOT.*TB* sensitivity was 91% (30/33) in subjects with active TB.	Dominguez J, et al. Comparison of Two Commercially Available Gamma Interferon Blood Tests for Immunodiagnosis of Tuberculosis. *Clinical and Vaccine Immunology*. 2008;15(1):168-171.
	T-SPOT.*TB* sensitivity was 94.1% (254/270) in subjects with culture confirmed TB.	Chee CB, et al. Comparison of sensitivities of two commercial gamma interferon release assays for pulmonary tuberculosis. *J Clin Microbiol.* 2008;46(6):1935-1940. doi:10.1128/JCM.02403-07.
	T-SPOT.*TB* sensitivity was 94% (33/35) in immunocompetent subjects and 95% (20/21) in immunosuppressed subjects with confirmed extrapulmonary TB. "…the ELISPOT assay is a useful adjunct test for excluding active tuberculosis in patients with suspected extrapulmonary tuberculosis regardless of immunosuppressive condition".	Kim SH, et al. Diagnostic usefulness of a T-cell-based assay for extrapulmonary tuberculosis in immunocompromised patients. *Am J Med*. 2009;122(2):189-195. doi:10.1016/j.amjmed.2008.07.028.
	T-SPOT.*TB* sensitivity was 94.2% (81/86) in subjects with confirmed or probable osteoarticular TB. "…the results of our study suggest that the IGRA assay is a useful adjunctive tool for diagnosing osteoarticular TB".	Jia H, et al. Evaluation of interferon-gamma release assay in the diagnosis of osteoarticular tuberculosis. *Diagn Microbiol Infect Dis*. 2013;76(3):309-313. doi:10.1016/j.diagmicrobio.2013.03.030.
	T-SPOT.*TB* sensitivity was 93% (40/43) in subjects with miliary TB. The T-SPOT.*TB* test "may be a helpful adjunct test for miliary tuberculosis."	Lee Y-M, et al. Diagnostic Usefulness of a T-Cell–Based Assay in Patients With Miliary Tuberculosis Compared With Those With Lymph Node Tuberculosis. *Clin Infect Dis*. 2013;56(2):e26-e29.
	T-SPOT.*TB* sensitivity was 90% (91/101) for patients with disseminated or miliary TB. In a subgroup analysis of the 58 patients in whom both QFT-GIT and the T-SPOT.*TB* results were available, the sensitivity of T-SPOT.*TB* was 95% (55/58) compared to 67% (39/58) for QFT-GIT.	Yu SN, et al. Diagnostic Usefulness of IFN-Gamma Releasing Assays Compared With Conventional Tests in Patients With Disseminated Tuberculosis: *Medicine*. 2015;94(28):e1094. doi:10.1097/MD.0000000000001094.
	Patients confirmed for active TB (culture or a positive TB PCR) were tested by QFT-GIT (192 patients) or T-SPOT.*TB* (212 patients). Considering all age groups, the overall sensitivity was 80.2% (154/192) for QFT-GIT and 91.0% (193/212) for T-SPOT.*TB*. The sensitivities of QFT-GIT and T-SPOT.*TB* according to age group were as follows: <29 years, 93.3% (28/30) and 96.7% (29/30); 30-49 years, 86.5% (45/52) and 94.7% (72/76); 50-69 years, 76.8% (53/69) and 87.5% (56/64); and >70	Bae W, et al. Comparison of the Sensitivity of QuantiFERON-TB Gold In-Tube and T-SPOT.TB According to Patient Age. Shams H, ed. *PLOS ONE*. 2016;11(6):e0156917. doi:10.1371/journal.pone.0156917.

	years, 68.3% (28/41) and 85.7% (36/42), respectively. While the trend of age-related changes in sensitivity was significant for both QFT-GIT and T-SPOT.*TB*, a multivariate analysis indicated that only QFT-GIT was significantly affected by age	
Specificity	The specificity of T-SPOT.*TB* test in 326 Naval recruits in the USA was 98% (275/278).	Bienek DR, Chang CK. Evaluation of an interferon-gamma release assay, T-SPOT.TB, in a population with a low prevalence of tuberculosis. *Int J Tuberc Lung Dis.* 2009;13(11):1416-1421.
	The specificity of T-SPOT.*TB* test in individuals from Ohio State University and the Nationwide Children's Hospital was 99% (107/108)	Wang SH, et al. Evaluation of a modified interferon-gamma release assay for the diagnosis of latent tuberculosis infection in adult and paediatric populations that enables delayed processing. *Scand J Infect Dis*. 2010;42(11-12):845-850. doi:10.3109/00365548.2010.498021.
	The specificity of T-SPOT.*TB* test in low risk military recruits in the USA was 98.7% (1336/1354).	Mancuso JD, et al. Discordance among commercially available diagnostics for latent tuberculosis infection*. Am J Respir Crit Care Med*. 2012;185(4):427-434. doi:10.1164/rccm.201107-1244OC.
	The specificity of T-SPOT.*TB* test in low risk controls in Japan was 99% (110/111).	Higuchi K, et al. Comparison of specificities between two interferon-gamma release assays in Japan*. Int J Tuberc Lung Dis.* 2012;16(9):1190-1192. doi:10.5588/ijtld.11.0829.
	T-SPOT.*TB* observed specificity was at least 98.6% during serial screening programs of healthcare workers in 19 US hospitals. In the largest study of its kind, 42,155 T-SPOT.*TB* test results from healthcare workers were analyzed and the rates of positivity, reversion, and conversion were 2.3%, 0.8% and 17.6% respectively, correlating with known TB risk factors. The findings suggest that the T-SPOT.*TB* test is an accurate and reliable way to screen healthcare workers.	King TC, et al. T-SPOT.TB Interferon-γ Release Assay Performance in Healthcare Worker Screening at Nineteen U.S. Hospitals. *Am J Respir Crit Care Med*. 2015;192(3):367-373. doi:10.1164/rccm.201501-0199OC.
Positive/negative predictive value for development of active TB disease	312 patients awaiting kidney transplant from Seoul were tested with the TST and the T-SPOT.*TB* test. Patients were followed up prospectively for the subsequent development of active TB disease to demonstrate the positive and negative predictive value of the tests. 4/71 (5.6%) patients with positive T-SPOT.*TB* test but negative TST developed active TB after kidney transplant, whereas none of the 231 patients with negative or indeterminate T-SPOT.*TB* test developed TB after kidney transplant.	Kim SH, et al. A prospective longitudinal study evaluating the usefulness of a T-cell-based assay for latent tuberculosis infection in kidney transplant recipients. *Am J Transplant*. 2011;11(9):1927-1935. doi:10.1111/j.1600-6143.2011.03625.x.
	50/520 HIV infected subjects attending an out patients clinic in London were positive by the T-SPOT.*TB* test. Follow-up of these patients identified 3 with subclinical active TB. No patient with a negative | T-SPOT.*TB* test result has developed TB in 3 years of follow-up.	Kall MM, et al. Latent and subclinical tuberculosis in HIV infected patients: a cross-sectional study. *BMC Infect Dis*. 2012;12:107. doi:10.1186/1471-2334-12-107.
	583 household contacts were tested with the T-SPOT.*TB* test and followed-up every 6 months for 3 years. 6.3% (9/144) T-SPOT.*TB* positive contacts who did not receive preventive therapy converted to active disease. None of the 407 household contacts who were T-SPOT.*TB* negative or the 32 who received TB therapy developed active TB.	Wang JY, et al. Interferon-gamma release assay and Rifampicin therapy for household contacts of tuberculosis. *J Infect.* 2012;64(3):291-298. doi:10.1016/j.jinf.2011.11.028.
	1049 asymptomatic household contacts of smear-positive patients were tested with T-SPOT.*TB* test and TST. T-SPOT.*TB* gave a significantly higher positive rate (32.7% vs 22.1%) and better association with exposure time than TST at the 15 mm cut-off. Using a TST cut-off of 15 mm, 56% of future TB cases and 62.5% of bacteriologically confirmed cases were missed. Lowering the TST cut-off to 10 mm or 5 mm could achieve sensitivity comparable with that of T-SPOT.*TB*, but at the expense of lower specificities, with more positive tests (thus requiring treatment) per case of TB predicted. "T-SPOT.*TB* outperformed TST in predicting TB among household contacts in a high-income area with widespread BCG vaccination coverage."	Leung CC, et al. T-Spot.*TB* outperforms tuberculin skin test in predicting development of active tuberculosis among household contacts. *Respirology*. 2015;20(3):496-503. doi:10.1111/resp.12483.
Immuno-suppressed	138 patients with various hematology disorders had been in contact with an infectious TB case. Subjects were split into a cohort with normal WBC count and a cohort with abnormal WBC count. T-SPOT.*TB* positivity was 44.6% and 44.3% respectively. TST's positivity declined from 26% to 15% respectively in the same cohorts	Piana F, et al. Use of a T-cell-based test for detection of tuberculosis infection among immunocompromised patients. Eur Respir J. 2006;28(1):31-34. doi:10.1183/09031936.06.00110205.

	50/201 HIV positive subjects were T-SPOT.*TB* test positive, of which 33 (66%) had a CD4 count < 300 and 9 (18%) had a CD4 count <100. The T-SPOT.*TB* test's responses were shown to be unaffected by CD4 count.	Clark SA, et al. Tuberculosis antigen-specific immune responses can be detected using enzyme-linked immunospot technology in human immunodeficiency virus (HIV)-1 patients with advanced disease. Clin Exp Immunol. 2007;150(2):238-244. doi:10.1111/j.1365-2249.2007.03477.x.
	197 immunosuppressed, hematological patients who were contacts of 2 infectious TB cases were tested with TST and T-SPOT.*TB* test. A control group of 324 community contacts of infectious TB cases was also tested. In the control cohort, TST and T-SPOT.*TB* results were positive in 84.9% (275/324) and 51.5% (167/324) of the contacts respectively. In the immunosuppressed cohort, positivity for TST and T-SPOT.*TB* was 17.3% (34/197) and 35.5% (70/197) respectively. "Our findings highlight that TST is 10-fold more affected immunosuppression than T-SPOT.*TB*, and confirm that T-SPOT.*TB* is a better marker for LTBI."	Piana F,et al. Use of T-SPOT.TB in latent tuberculosis infection diagnosis in general and immunosuppressed populations. *The new microbiologica.* 2007;30(3):286-290.
	In subjects with chronic renal infection undergoing hemodialysis T-SPOT.*TB* positivity was associated with TB risk factors, whereas the TST did not and was shown to only be associated with prior BCG vaccination. "The TST is insensitive in hemodialysis patients and is not recommended to be used in isolation to diagnose latent tuberculosis infection."	Passalent L, et al. Detecting latent tuberculosis infection in hemodialysis patients: a head-to-head comparison of the T-SPOT.*TB* test, tuberculin skin test, and an expert physician panel. *Clin J Am Soc Nephrol*. 2007;2(1):68-73. doi:10.2215/CJN.01280406.
	Rheumatic disease patients were tested with T-SPOT.*TB* assay and TST. A history of BCG was associated with TST positive /T-SPOT.*TB* test negative discordance. Steroid use was associated with TST negative/ T-SPOT.*TB* test positive discordance. "Elispot assay is a useful test for diagnosis of LTBI in rheumatic patients scheduled for anti-TNF therapy and identification of patients with false-positive TST results due to previous BCG vaccination."	Vassilopoulos D, et al. Usefulness of enzyme-linked immunospot assay (Elispot) compared to tuberculin skin testing for latent tuberculosis screening in rheumatic patients scheduled for anti-tumor necrosis factor treatment. *J Rheumatol*. 2008;35(7):1271-1276.
	T-SPOT.*TB* test results were not affected in subjects with silicosis or old age.	Leung CC, et al. Comparison of T-Spot.*TB* and tuberculin skin test among silicotic patients. *Eur Respir J.* 2008;31(2):266-272. doi:10.1183/09031936.00054707.
	Psoriasis patients were tested with the T-SPOT.*TB* test and TST. The T-SPOT.*TB* test was correlated with risk factors for LTBI whereas the TST was not.	Laffitte E, et al. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-gamma release assay vs. tuberculin skin test. *Br J Dermatol*. 2009;161(4):797-800. doi:10.1111/j.1365-2133.2009.09331.x.
	1529 Patients from 62 German rheumatology centres were evaluated for LTBI using the TST, the T-SPOT.*TB* assay and the Cellestis In Tube assay. Only the TST and T-SPOT.*TB* test results significantly correlated to clinical risk factors for TB in the 852 subjects diagnosed with rheumatoid arthritis.	Kleinert S, et al. Screening for latent tuberculosis infection: performance of tuberculin skin test and interferon-gamma release assays under real-life conditions. *Ann Rheum Dis*. 2012;71(11):1791-1795.
Immuno-suppressed (cont.)	1343 children from 6 months to < 15 years of age from high TB/HIV burden setting were evaluated for LTBI using TST and IGRAs; associations with child characteristics were measured. Contact tracing detected TB in 8% of child contacts within 3 months of exposure and IGRAs correlated better with contact than TSTs. QFT® indeterminate rates were more frequent in children infected with HIV (4.7%) while the T-SPOT.*TB* test invalid rates were rare (0.2%) and not affected by HIV status. In children with no documented contact, TST and QFT had greater positivity rates than T-SPOT.*TB* test and would result in treating a higher proportion of children with little to no documented TB exposure.	Mandalakas AM, et al. Optimizing the Detection of Recent Tuberculosis Infection in Children in a High Tuberculosis-HIV Burden Setting. *Am J Respir Crit Care Med*. 2015;191(7):820-830. doi:10.1164/rccm.201406-1165OC.
	108 pediatric patients with rheumatic disease were evaluated for LTBI using T-SPOT.*TB* and QFT. The study identified overall a 9.9% indeterminate rate for QFT while for the T-SPOT.TB assay it was 0%. "The T-SPOT.TB test was suitable for evaluating latent tuberculosis infection even under immunosuppression, when TB tests are generally hard to perform."	Nozawa T, et al. Usefulness of two IFN-γ release assays for patients with rheumatic disease. *Pediatr Int.* December 2015. doi:10.1111/ped.12885.

Cost effectiveness	Results from contact tracing clinic obtained over a one year period were used to determine the most cost-effective TB screening strategy. Costs of a T-SPOT.*TB* test only strategy were much less than a TST only strategy. Costs were lowest in the strategy where TST was used first followed by T-SPOT.*TB* test in those that were +ve, however the study did not take into account false +ve who would be missed by TST.	Wrighton-Smith P, et al. Direct costs of three models for the screening of latent tuberculosis infection. *Eur Respir J*. 2006;28(1):45-50. doi:10.1183/09031936.06.00005906.
	A 2 year screening model directed at screening 1,000 contacts in the UK was used to perform a cost-effectiveness comparison of TST, T-SPOT.*TB* test and QFT In Tube test using either a single (TST or IGRA) or dual (TST followed by IGRA) strategy. The cost per active case of TB prevented was lowest when the T-SPOT.*TB* test was used alone followed by 2 step testing using the TST followed by the T-SPOT.*TB* test.	Pooran A, et al. Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis. *BMC Pulm Med.* 2010;10:7. doi:10.1186/1471-2466-10-7.
	A single-centre, retrospective review and economic evaluation of 125 adult IBD patients (109 of which were BCG vaccinated) tested for LTBI using the T-SPOT.*TB* test. 98% (122/125) of subjects had a negative T-SPOT.*TB* result, 2% (2/125) had a positive result, and 1% (1/125) had an invalid. "A strategy using IGRA to guide TB preventative treatment produced cost savings of £10.79 per person compared to the BTS guidance."	Greveson K, et al. Yield and cost effectiveness of mycobacterial infection detection using a simple IGRA-based protocol in UK subjects with inflammatory bowel disease suitable for anti-TNFalpha therapy. *J Crohns Colitis.* 2013;7(5):412-418. doi:10.1016/j.crohns.2012.08.010.

Abbreviations: TB – tuberculosis
TST – Tuberculin Skin Test
LTBI - Latent Tuberculosis Infection

TB-UK-LP-0025-V1

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