THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Aldridge RW, Zenner D, White PJ, et al. Prevalence of and risk factors for active tuberculosis in migrants screened before entry to the UK: a population-based cross-sectional study. *Lancet Infect Dis* 2016; published online March 21. http://dx.doi.org/10.1016/S1473-3099(16)00072-4.

Supplementary appendix to: Prevalence and risk factors for active tuberculosis in migrants screened pre-entry to the UK: a population-based cross-sectional study. Aldridge et al.

Table 1. Radiographic finding classification system

Minor Findings	
1.1	Single fibrous streak/band/scar
1.2	Bony islets
2.1	Pleural capping with a smooth inferior border (<1cm thick at all points)
2.2	Unilateral or bilateral costophrenic angle blunting (below the horizontal)
2.3	Calcified nodule(s) in the hilum / mediastinum with no pulmonary granulomas
Minor findings occasionally associated with tuberculosis infection	
3.1	Solitary Granuloma (< 1 cm and of any lobe) with an unremarkable hilum
3.2	Solitary Granuloma (< 1 cm and of any lobe) with calcified / enlarged hilar lymph nodes
3.3	Single / Multiple calcified pulmonary nodules / micronodules with distinct borders
3.4	Calcified pleural lesions
3.5	Costophrenic Angle blunting (either side above the horizontal)
Major findings sometimes seen in active tuberculosis (or other conditions)	
4.0	Notable apical pleural capping (rough or ragged inferior border and/or ≥ 1cm thick at any point)
4.1	Apical fibronodular / fibrocalcific lesions or apical microcalcifications
4.2	Multiple / single pulmonary nodules / micronodules (noncalcified or poorly defined) 4.3 Isolated hilar or mediastinal mass/lymphadenopathy (non-calcified)
4.4	Single / multiple pulmonary nodules / masses ≥ 1 cm."
4.5	Non-calcified pleural fibrosis and / or effusion.
4.6	Interstitial fibrosis/ parenchymal lung disease/ acute pulmonary disease
4.7	Any cavitating lesion OR "fluffy" or "Soft" lesions felt likely to represent active TB

It was possible for individuals screened pre-entry to have multiple entries in the IOM database for several reasons, including: 1) clearance certificates are only valid for six months (or three months if migrants reported history of contact with a case of tuberculosis), and if a UK visa application was not processed during this time period then the applicant was required to undergo repeat screening with a duplicate record being created; 2) administrative errors leading to two records being created for one individual during the same screening application; 3) migrants undergoing a clearance screen after an initial positive screen for tuberculosis. The rules used to determine whether more than one entry for an individual was included in this analysis are detailed in supplementary appendix Table S2.

Duplicates were analysed on the basis of whether they occurred less than 12 months apart or not. A period of 12 months was chosen a-priori as this was long enough to capture individuals found to have tuberculosis on their first screen, who were then undergoing repeat screening for visa clearance, but not too long a time period such that tuberculosis exposure and risk factors may have changed significantly for a majority of individuals.

For duplicates occurring less than 12 months apart where the first screen was positive, the second screen has been undertaken for clearance purposes. This second screen is therefore treated as a continuation of the initial screening process taken for the purposes of clearance and was excluded as it is not a newly prevalent case, the primary outcome for this analysis. All duplicates occurring greater than 12 months apart were included as this is sufficient time for the exposure to tuberculosis in an individual to have changed.

Table 2. Rules for dealing with duplicate screens.

		First screen TB result	
		Positive	Negative
Last screen TB result	Positive	*Less than or equal to 12 months apart:* 1st screen - Include 2nd screen - Exclude *Greater than 12 months apart:* Include all duplicates	Include all
	Negative	*Less than or equal to 12 months apart:* 1st screen - Include 2nd screen - Exclude *Greater than 12 months apart:* Include all duplicates	Include all

Table 3. Data sources of variables, methods of assessment, details of subgroups

Variable	Data Source	Methods of assessment	Subgroups chosen for analysis
Age	IOM	From visa application data	0-15; 16-44; 45-64; >65
Sex	IOM	From visa application data	Male; Female
Close or household contact with a case of TB	IOM	Self report to panel physician screening applicant	Yes; No. Where null assumed to be No
Visa Type	IOM	From visa application data	• Student - All students who receive (or do not received) a scholarship; • Settlement and Dependent - Those applicants who are settling permanently in the UK, as well as spouses, partners/civil partners, fiancées, fiancés, proposed partners/civil partners, children, other dependant relatives; • Work - This type of visa is intended for work related visas, including work requiring a permit, and the highly skilled migrant program. This category EXCLUDES the working holiday maker category, which has been assigned a separate category (see below); • Working Holiday Maker - Applicants going to the UK on the working holiday maker program; • Family Reunion - Type of settlement that allows the family members of a recognized refugee to join him/her in the UK; • Other - this category is used when the applicant's visa category is not readily identified.
CXR	IOM	CXR classification chosen by panel physician after double reading by radiologist.	• No abnormality, or abnormality classified in groups 1, 2, and 3 in Table 1. • Compatible with TB – As detailed in Table 1 of appendix - major findings sometimes seen in active tuberculosis (or other conditions); or Minor findings occasionally associated with tuberculosis infection and that panel physician determines on basis of clinical history and examination require sputum sampling to rule out TB disease. • Abnormality not TB – Finding on CXR that is not normal, but does not consistent with TB
Prevalence of TB in country of migration	WHO	WHO modelling data taken from http://www.who.int/tb/publications/global_report/en/	40-149; 150-349; 350+
Year of examination	IOM	Based on IOM data and date of screening recorded by panel physician.	2005 ;2006; 2007; 2008; 2009; 2010; 2011; 2012; 2013
Country of	IOM	From screening	Burkina Faso; Bangladesh; Cambodia; Cote D'Ivoire;

screening		location recorded in IOM dataset	Eritrea; Ghana; Kenya; Laos; Niger; Pakistan; Sudan; Somalia; Togo; Tanzania; Thailand
Sputum culture testing	IOM	From IOM dataset based on dates of the roll out of culture testing according to UK technical instructions.	Yes; No

Updated systematic review and meta-analysis

For this analysis we updated our our previous systematic review and meta-analysis.[1] We identified new articles published since the original review up until 19th November 2015. The updated review used the original search terms, summarised as: the populations of interest (migrants, refugees, asylum seekers, new entrants, undocumented migrants), the intervention (pre-entry screening), and standard terms for tuberculosis. The updated search was conducted in Medline and Embase. Experimental, observational and systematic reviews were included. Only studies reporting culture positive results by country were included in this updated review and meta-analysis.

Fixed effects models with Freeman-Tukey transformation of data were used to estimate the summary prevalence of pre-entry screening across studies and subgroups where appropriate.[2,3] The I-squared transformation was used to describe the proportion of total variation in study estimates that is due to heterogeneity.[4] Where overlapping data on an individual screening programme were identified, the publication with the largest amount of data (by time period or number of individuals screened) was included in this review.

Subgroup analysis was carried out for the primary outcomes to examine the impact of prevalence in the country of origin. Consistent with our previous review, we chose to use the following groups: 20-49; 50–149; 150–249; 250–349, and ≥350/100 000 cases per 100,000 population.

Table 4. Baseline characteristics of all applicants screened (regardless of whether culture testing of sputum was performed) for tuberculosis and prevalence of primary and secondary outcomes (2005-2013).

		Prevalence per 100,000		
	N (%)	Bacteriologically confirmed (95%CIs)	Culture positive (95%CIs)	Smear positive (95%CIs)
All	692232 (100.0%)	75 (69, 82)	58 (52, 63)	52 (47, 58)
Age group				
0-15	25555 (3.7%)	27 (13, 57)	27 (13, 57)	8 (2, 31)
16-44	647178 (93.5%)	75 (69, 82)	57 (52, 64)	50 (45, 56)
45-64	15829 (2.3%)	107 (67, 173)	76 (43, 133)	152 (102, 226)
>65	3670 (0.5%)	300 (166, 540)	218 (109, 435)	245 (128, 471)
Sex				
Female	242592 (35.0%)	94 (83, 108)	75 (64, 86)	73 (63, 85)
Male	449640 (65.0%)	65 (58, 73)	48 (42, 55)	40 (35, 47)
Close or household contact with a case of TB				
No	688296 (99.8%)	73 (67, 80)	56 (50, 62)	50 (45, 56)
Yes	1604 (0.2%)	1185 (757, 1853)	935 (565, 1548)	686 (380, 1236)
Visa Type				
Student	390803 (56.5%)	70 (62, 79)	55 (48, 63)	48 (41, 55)
Settlement and Dependent	233015 (33.7%)	87 (76, 100)	69 (59, 81)	56 (47, 67)
Work	26823 (3.9%)	78 (51, 120)	37 (20, 69)	0 (0, 0)
Working Holiday Maker	21043 (3.0%)	52 (29, 94)	29 (13, 63)	29 (13, 63)
Family Reunion	5639 (0.8%)	124 (59, 260)	35 (9, 142)	0 (0, 0)
Other	14909 (2.2%)	40 (18, 90)	34 (14, 81)	34 (14, 81)
CXR				
No abnormality	652313 (94.2%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
TB suspected	28552 (4.1%)	1821 (1672, 1983)	1394 (1264, 1537)	1229 (1108, 1364)
Abnormality not TB	11367 (1.6%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
WHO prevalence of TB in country of migration				
40-149	39060 (5.6%)	15 (7, 34)	5 (1, 20)	13 (5, 31)
150-349	99114 (14.3%)	181 (156, 209)	153 (131, 180)	168 (145, 196)
350+	554058 (80.0%)	61 (55, 67)	44 (39, 50)	34 (29, 39)
Year of examination				
2005	994 (0.1%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
2006	31266 (4.5%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
2007	97828 (14.1%)	52 (40, 69)	8 (4, 16)	0 (0, 0)
2008	109604 (15.8%)	67 (53, 84)	48 (37, 63)	0 (0, 0)
2009	132816 (19.2%)	83 (69, 100)	64 (52, 79)	63 (51, 78)

2010	109356 (15.8%)	68 (54, 85)	56 (43, 72)	47 (35, 61)
2011	97455 (14.1%)	87 (71, 108)	82 (66, 102)	33 (23, 46)
2012	62338 (9.0%)	106 (83, 135)	103 (80, 131)	59 (43, 82)
2013	50575 (7.3%)	93 (70, 124)	93 (70, 124)	32 (19, 52)
Country of screening				
Burkina Faso	117 (0.0%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Bangladesh	180612 (26.1%)	80 (68, 94)	61 (51, 73)	44 (36, 55)
Cambodia	741 (0.1%)	135 (19, 958)	135 (19, 958)	0 (0, 0)
Cote D'Ivoire	1531 (0.2%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Eritrea	238 (0.0%)	420 (59, 2989)	0 (0, 0)	420 (59, 2989)
Ghana	38644 (5.6%)	16 (7, 35)	5 (1, 21)	13 (5, 31)
Kenya	16868 (2.4%)	119 (77, 184)	77 (45, 133)	77 (45, 133)
Laos	229 (0.0%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Niger	82 (0.0%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Pakistan	369194 (53.3%)	49 (42, 57)	35 (29, 42)	27 (22, 33)
Sudan	7596 (1.1%)	26 (7, 105)	13 (2, 93)	0 (0, 0)
Somalia	3282 (0.5%)	274 (143, 526)	122 (46, 324)	213 (102, 447)
Togo	299 (0.0%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Tanzania	10859 (1.6%)	55 (25, 123)	46 (19, 111)	37 (14, 98)
Thailand	61940 (9.0%)	242 (206, 285)	215 (181, 255)	239 (203, 281)
Sputum culture testing				
Yes	215777 (31.2%)	92 (84, 101)	83 (75, 92)	55 (49, 62)
No	476455 (68.8%)	38 (31, 47)	0 (0, 0)	38 (31, 47)

Equation 1. Formula used for calculation of Population attributable fraction (PAF).[5]

$$\boldsymbol{PAF = \frac{p * (Relative\ risk - 1)}{p * (Relative\ risk - 1) + 1}}$$

p=proportion of the total population exposed to the risk factor.

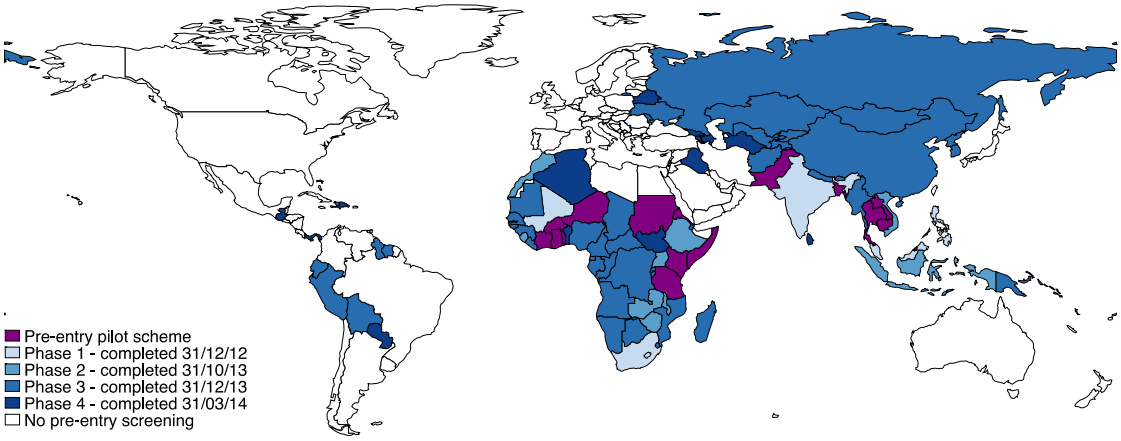


Figure 1. Location of pre-entry screening sites globally (includes IOM and non-IOM sites).

Note: IOM pre-entry pilot scheme countries were Bangladesh, Burkina Faso, Cambodia, Cote D'Ivoire, Eritrea, Ghana, Kenya, Laos, Niger, Pakistan, Somalia, Sudan, Tanzania, Thailand, and Togo. Some additional countries after the pre-entry pilot have been conducted directly with countries and without the involvement of IOM.

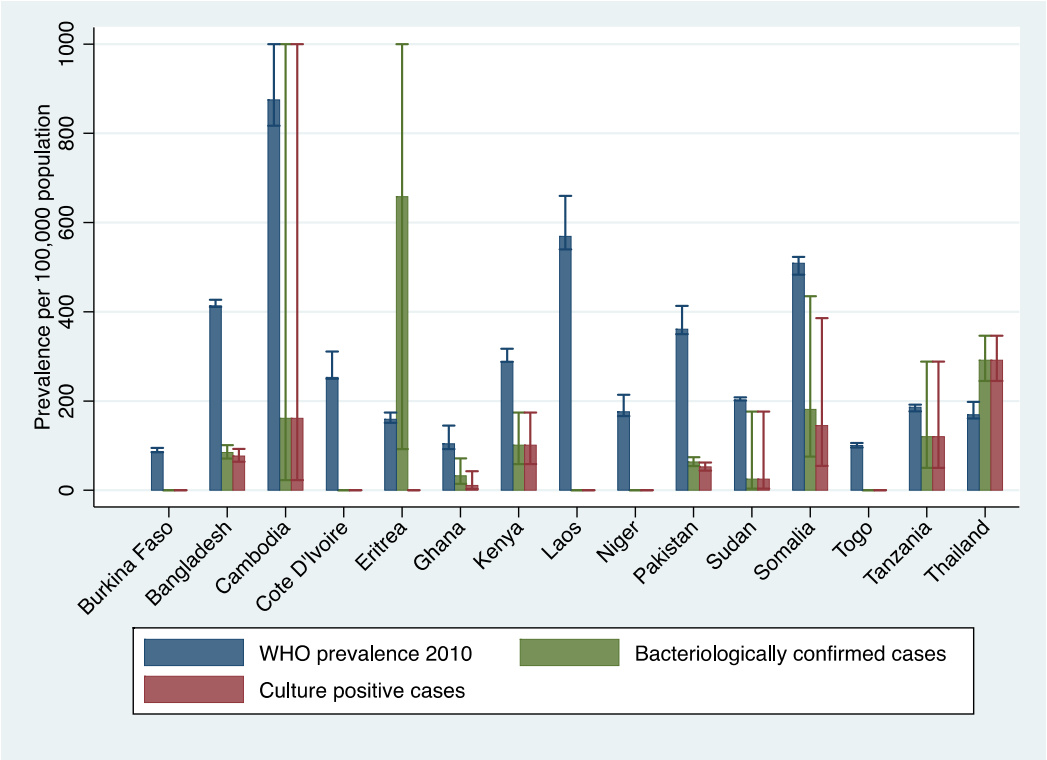


Figure 2. Crude prevalence of bacteriological and culture confirmed TB diagnosed at pre-entry screening compared to 2010 WHO country prevalence estimates (2007-2013).

Note: Error bars on bacteriological and culture confirmed tuberculosis estimates are 95%confidence intervals. Error bars on WHO 2010 prevalence country estimates are highest and lowest prevalence estimate for each country between 2007 and 2013. Confidence intervals limited to a maximum of 1,000 per 100,000 population for convenience of plotting.

References:

1 Aldridge RW, Yates TA, Zenner D, White PJ, Abubakar I, Hayward AC. Pre-entry screening programmes for tuberculosis in migrants to low-incidence countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; **14**: 1240–9.

2 Freeman MF, Tukey JW. Transformations Related to the Angular and the Square Root. *Ann Math Stat* 1950; **21**: 607–11.

3 Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013; : jech – 2013–203104.

4 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–58.

5 Ilona C, Natasha H. Introduction To Epidemiology. McGraw-Hill Education (UK), 2011.