Prevalence of and risk factors for active tuberculosis in migrants screened before entry to the UK: a population-based cross-sectional study

Robert W Aldridge, Dominik Zenner, Peter J White, Morris C Muzyamba, Miranda Loutet, Poonam Dhavan, Davide Mosca, Andrew C Hayward, Ibrahim Abubakar**

Summary

Background **An increasing number of countries with low incidence of tuberculosis have pre-entry screening programmes for migrants. We present the first estimates of the prevalence of and risk factors for tuberculosis in migrants from 15 high-incidence countries screened before entry to the UK.**

Methods **We did a population-based cross-sectional study of applicants for long-term visas who were screened for tuberculosis before entry to the UK in a pilot programme between Oct 1, 2005, and Dec 31, 2013. The primary outcome was prevalence of bacteriologically confirmed tuberculosis. We used Poisson regression to estimate crude prevalence and created a multivariable logistic regression model to identify risk factors for the primary outcome.**

Findings **476 455 visa applicants were screened, and the crude prevalence of bacteriologically confirmed tuberculosis was 92 (95% CI 84–101) per 100 000 individuals. After adjustment for age and sex, factors that were strongly associated with an increased risk of bacteriologically confirmed disease at pre-entry screening were self-report of close or household contact with an individual with tuberculosis (odds ratio 11·6, 95% CI 7·0–19·3; p<0·0001) and being an applicant for settlement and dependant visas (1·3, 1·0–1·6; p=0·0203).**

Interpretation **Migrants reporting contact with an individual with tuberculosis had the highest risk of tuberculosis at pre-entry screening. To tackle this disease burden in migrants, a comprehensive and collaborative approach is needed between countries with pre-entry screening programmes, health services in the countries of origin and migration, national tuberculosis control programmes, and international public health bodies.**

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Introduction

Medical screening of migrants for tuberculosis has been implemented for more than a century, but only recently have data been systematically obtained and analysed to understand its effectiveness.[1–3] Screening can occur before entry (ie, pre-entry screening), at entry (sometimes called port-of-entry screening), or after entry. Australia, Austria, Canada, France, Israel, Jordan, New Zealand, the UK, and the USA have pre-entry screening programmes for tuberculosis.[4] In our 2014 systematic review and meta-analysis,[2] we identified substantial variation in protocols and detection rates of active infection, but the detection rates were in migrants from high-incidence countries. No UK data were included in this review.

Historically, the UK screened migrants before, at, and after entry.[5] In May, 2012, the UK Government announced the transition to a fully pre-entry system, expanding the screening programme from 15 pilot locations in operation from 2005, to 101 high-incidence countries (ie, those with a WHO-estimated prevalence of >40 cases per 100 000 population). This transition occurred in four phases and was completed on March 31, 2014 (appendix p 9). To improve international pre-entry screening programmes, we investigated the prevalence of and risk factors for tuberculosis in migrants from high-incidence countries screened before migration, using historical data from the 15 countries in the UK pilot programme.

Methods

Study design

We did a population-based cross-sectional study of migrants applying for visas to stay in the UK for more than 6 months, who were screened for tuberculosis before entry in 15 countries taking part in a pilot programme. We used data collected by the International Organization for Migration (IOM) between Oct 1, 2005, and Dec 31, 2013, on behalf of the UK as part of the screening process and included demographic and clinical data for all individuals screened, including age, sex, self-report of close or household contact with an individual with tuberculosis before screening (defined as anyone in the household who has been diagnosed with tuberculosis in the past 2 years, or history of recent contact with an individual with active pulmonary tuberculosis who shared the same enclosed air space, household, or other enclosed environment for a prolonged period of days or weeks; appendix p 4), visa

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See Online for appendix

Research in context

Evidence before this study

In 2014, we did a systematic review and meta-analysis of pre-entry screening for tuberculosis, which we have updated to identify new articles published until Nov 19, 2015, by searching Medline and Embase with the same search terms, including "migrants", "pre-entry screening", and "tuberculosis". Only studies reporting culture-positive results by country were included in this updated review and meta-analysis. Prevalence ranged from 19·7 (95% CI 10·3–31·5) cases identified per 100 000 individuals screened in countries with a prevalence of 50–149 cases per 100 000, to 335·9 (283·0–393·2) per 100 000 in countries with a prevalence of greater than 350 per 100 000. Substantial variation exists in the screening protocols used by each study.

Added value of this study

Migrants with a history of close or household contact with an individual with tuberculosis were at an increased risk of being detected with bacteriologically confirmed infection at pre-entry screening. We present direct estimates of the yield of tuberculosis in applicants for student visas (85 [95% CI 75–96] cases per 100 000 individuals); although the risk of tuberculosis in students is lower than the overall detection rate, students account for a large number of cases in many low-incidence countries. Our results will enable further examination of the cost-effectiveness of screening of this group, with operational data from a large number of student visa applicants. We updated a meta-analysis of culture-positive cases by country of origin to include data from our study from all countries where more than 1000 migrants had been screened. Compared with the 2014 meta-analysis, the level of heterogeneity increased, and the prevalence of tuberculosis detected no longer increased with WHO prevalence of tuberculosis in the country of origin.

Implications of all the available evidence

Present evidence supports the case for contact tracing and investigation in the country of origin, and improved coordination between pre-entry screening programmes and national tuberculosis programmes in the applicant's country, both of which are an increasing focus of both the UK and the USA. Our study provides additional support for recent changes to pre-entry screening policies in these two countries, since migrants screened at sites with sputum culture testing were more likely to be detected with active pulmonary tuberculosis, after adjustment for age and sex, than those screened at sites without such testing. To tackle the burden of tuberculosis in migrants, a wide-ranging approach that includes screening and treatment for latent tuberculosis infection, in addition to the existing focus on active disease, will be necessary.

category, and whether the individual was screened at a clinic where culture testing was done. Data were obtained, collated, and cleaned by the IOM Health Research and Epidemiology Unit and Public Health England to ensure that records included all laboratory results of individuals screened. Data for WHO prevalence in migrants' country of origin were from 2010.[6]

During the pilot phase of the pre-entry screening programme, culture testing for *Mycobacterium tuberculosis* was not available at all sites. To ensure comparability of estimates across countries and locations, we restricted the primary analysis to data from sites where culture and smear testing was done on all sputum samples. We removed duplicate screens according to rules in appendix p 3.

Ethics approval was received for this analysis from University College London Research Ethics Committee (3294/002). Public Health England has authority under the Health and Social Care Act 2012 to hold and analyse national surveillance data (including tuberculosis pre-entry screening programme data) for public health and research purposes.

Procedure

For the **UK tuberculosis technical instructions** see https://www.gov.uk/government/publications/uk-tuberculosis-technical-instructions

The UK tuberculosis technical instructions set out procedures for screening, with quality assurance provided by Public Health England. Briefly, applicants aged 11 years or above received standard posteroanterior chest radiography, and all individuals with radiological findings consistent with tuberculosis were required to undergo sputum testing (appendix p 1). Applicants who were unwilling or unable to have radiography (eg, pregnant women) were required to provide sputum specimens taken on three separate occasions, not less than 24 h apart and ideally in the early morning. Specimens were tested for *M tuberculosis* in designated laboratories by smear and culture. All specimens were examined under the microscope for acid-fast bacilli by an auramine stain (or, if necessary, by Ziehl-Neelsen stain). Specimens were cultured for a minimum of 6 weeks in liquid media or 8 weeks in solid media, unless a positive result was obtained earlier than these time periods. If no growth was detected after these time periods, specimens were reported as negative.

Applicants were issued with a clearance certificate if their chest radiographs were classified as free of any radiological changes, or had minor findings that were not associated with tuberculosis. Individuals diagnosed with active tuberculosis could restart the screening process after successful completion of a full course of approved treatment, but not within 6 months of the original screening examination.

Outcomes

The primary outcome was the prevalence of bacteriologically confirmed tuberculosis, with cases specified according to a WHO-revised definition of "one from whom a biological specimen is positive by smear microscopy or culture".[7] Secondary outcomes were prevalence of tuberculosis confirmed by culture testing on liquid or solid

media; tuberculosis confirmed by microscopy for acid-fast bacilli; tuberculosis confirmed by culture testing on liquid or solid media and resistant to one or more anti-tuberculosis drugs; and clinically confirmed tuberculosis.

Statistical analysis

We used Poisson regression (suitable for modelling of rare-event data) to estimate crude prevalence of the primary and secondary outcomes, calculated per 100 000 individuals screened. We also calculated estimates of prevalence adjusted by age and sex for the primary and secondary outcomes, and compared adjusted estimates for each country with WHO population prevalence in 2010.[6] To account for duplicate screens of visa applicants, all crude and adjusted estimates accounted for clustering by individual. We estimated the number needed to screen to detect one case as the inverse of screening prevalence, under the assumption of a comparator of no tuberculosis screening. We built a multivariable logistic regression model to identify risk factors for the primary outcome, and present final results of this model as odds ratios (ORs), with 95% CIs and p values. We estimated population attributable fractions (appendix p 8) with multivariable models, and interpreted the results as the proportion of incident tuberculosis attributable to each risk factor, after controlling for each other and for known confounders. We used Stata version 13 for all statistical analyses.

Our main analysis included migrants screened at sites where culture and smear testing was done on all sputum samples. Sensitivity analysis included all migrants screened before entry by the IOM, irrespective of whether culture testing was available at the screening site, to examine the effect of the introduction of sputum testing on the prevalence of bacteriologically confirmed cases of tuberculosis. At the start of the pilot programme, culture testing was not universally available at IOM screening clinics. As a secondary analysis, we used multivariable logistic regression to examine whether the introduction of culture testing was associated with an increased risk of bacteriologically confirmed tuberculosis after controlling for age, sex, WHO prevalence in the country of origin, self-report of close or household contact with a case of tuberculosis before screening, and visa category.

We also updated our previous systematic review and meta-analysis of pre-entry screening for tuberculosis.[2] Additional details on the method used are provided in appendix p 5.

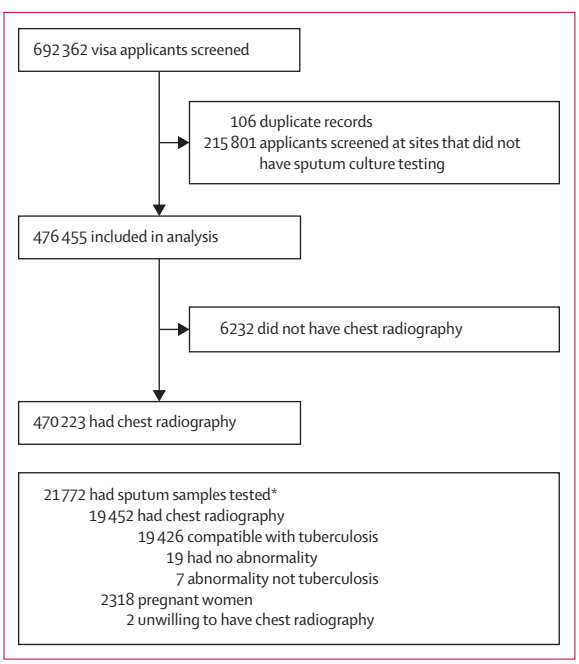

Figure 1: **Results of the screening process between Oct 1, 2005, and Dec 31, 2013, in countries with screening by the International Organization for Migration**

*Sputum testing was not done in 3911 children and <5 pregnant women.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or

	n	Prevalence per 100 000 individuals screened		
		Bacteriologically confirmed cases	Culture-positive cases	Smear-positive cases
All	476 455 (100%)	92 (84–101)	83 (75–92)	55 (49–62)
Age (years)				
0–15	18 729 (3·9%)	37 (18–78)	37 (18–78)	11 (3–43)
16–44	444 579 (93·3%)	92 (83–101)	83 (75–92)	53 (47–60)
45–64	10 413 (2·2%)	134 (80–227)	115 (65–203)	163 (102–262)
≥65	2734 (0·6%)	329 (172–631)	293 (147–584)	256 (122–536)
Sex				
Female	167 393 (35·1%)	116 (101–134)	108 (93–125)	83 (70–98)
Male	309 062 (64·9%)	79 (70–90)	70 (61–80)	40 (33–47)
Close or household contact with an individual with tuberculosis				
No	475 216 (99·7%)	89 (81–98)	80 (72–88)	53 (47–60)
Yes	1239 (0·3%)	1372 (855–2201)	1211 (732–2003)	726 (379–1393)

(Table 1 continues on next page)

	n	Prevalence per 100 000 individuals screened		
		Bacteriologically confirmed cases	Culture-positive cases	Smear-positive cases
(Continued from previous page)				
Visa category				
Student	281 703 (59·1%)	85 (75–96)	76 (66–86)	52 (44–61)
Settlement and dependant	160 436 (33·7%)	108 (93–125)	99 (85–116)	60 (49–73)
Work	14 748 (3·1%)	88 (51–152)	68 (36–126)	102 (61–169)
Working holiday maker	7380 (1·5%)	81 (37–181)	81 (37–181)	14 (2–96)
Family reunion	3389 (0·7%)	59 (15–236)	59 (15–236)	0 (0–0)
Other	8799 (1·8%)	68 (31–152)	57 (24–136)	45 (17–121)
Chest radiography*				
No abnormality†	443 169 (94·2%)	..	..	..
Compatible with tuberculosis	19 654 (4·2%)	2234 (2036–2450)	2010 (1822–2216)	1308 (1158–1476)
Abnormality not tuberculosis	7400 (1·6%)	..	..	..
WHO prevalence (per 100 000) of tuberculosis in country of screening				
40–149	18 910 (4·0%)	32 (14–71)	11 (3–42)	26 (11–64)
150–349	67 574 (14·2%)	225 (192–264)	223 (190–263)	200 (169–236)
≥350	389 971 (81·8%)	72 (64–81)	62 (55–70)	31 (26–37)
Year of examination				
2007	5489 (1·2%)	146 (73–291)	128 (61–267)	109 (49–243)
2008	34 343 (7·2%)	166 (128–215)	154 (118–202)	122 (90–165)
2009	116 899 (24·5%)	87 (72–106)	71 (57–88)	67 (53–83)
2010	109 356 (23·0%)	68 (54–85)	56 (43–72)	47 (35–61)
2011	97 455 (20·5%)	87 (71–108)	82 (66–102)	33 (23–46)
2012	62 338 (13·1%)	106 (83–135)	103 (80–131)	59 (43–82)
2013	50 575 (10·6%)	93 (70–124)	93 (70–124)	32 (19–52)
Country of screening				
Burkina Faso	73 (0·02%)	..	..	..
Bangladesh	143 154 (30·0%)	85 (71–101)	77 (64–93)	39 (30–51)
Cambodia	621 (0·1%)	161 (23–1144)	161 (23–1144)	..
Côte d'Ivoire	1026 (0·2%)	..	..	..
Eritrea	152 (0·03%)	658 (92–4684)	..	658 (92–4684)
Ghana	18 649 (3·9%)	32 (14–72)	11 (3–43)	27 (11–64)
Kenya	12 867 (2·7%)	101 (59–174)	101 (59–174)	39 (16–93)
Laos	193 (0·04%)	..	..	..
Niger	36 (0·01%)	..	..	..
Pakistan	243 243 (51·1%)	63 (54–74)	52 (44–62)	26 (20–33)
Sudan	4025 (0·8%)	25 (4–176)	25 (4–176)	..
Somalia	2760 (0·6%)	181 (76–435)	145 (54–386)	109 (35–337)
Togo	188 (0·04%)	..	..	..
Tanzania	4166 (0·9%)	120 (50–288)	120 (50–288)	24 (3–170)
Thailand	45 302 (9·5%)	291 (245–346)	291 (245–346)	283 (238–336)

Data are n (%) or prevalence (95% CI). *6232 applicants were unable or unwilling to have chest radiography. †No abnormality, or abnormality classified in groups 1, 2, and 3.

Table 1: **Baseline characteristics of applicants screened for tuberculosis and prevalence of primary and secondary outcomes, 2007–13**

writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 1, 2005, and Dec 31, 2013, 692 362 visa applicants were screened for tuberculosis (figure 1). After exclusion of duplicate records and applicants screened at sites that did not have culture testing of sputum, 476 455 screening records were included in the analysis, with 470 223 chest radiographs undertaken and sputum samples collected from 21 772 applicants. Chest radiographs were not done in 3911 children and 2319 pregnant women.

439 cases of bacteriologically confirmed tuberculosis were diagnosed, providing a crude prevalence of 92 (95% CI 84–101) per 100 000 screened (table 1). The

number needed to screen to detect one case in this pilot programme was 1087 (990–1190). The crude prevalence of clinically diagnosed cases, excluding laboratory confirmed cases, was 3 (2–4) per 100 000. The overall prevalence of culture-confirmed samples with resistance to one or more tuberculosis drugs was 3 (2–5) per 100 000 applicants screened or 5 (1·18%) of 422 culture-confirmed samples that underwent drug susceptibility testing.

Crude prevalence of bacteriologically confirmed tuberculosis was highest in migrants from countries with a WHO-estimated prevalence of 150–349 per 100 000 (225 [192–264] per 100 000), and screening of 444 (379–521) applicants was necessary to detect one case. By contrast, crude prevalence of these cases was lower in migrants from countries with WHO-estimated prevalence of more than 350 per 100 000 (72 [64–81] per 100 000).

In Eritrea and Tanzania, age-adjusted and sex-adjusted estimates for prevalence of bacteriologically confirmed tuberculosis in screened visa applicants were consistent with WHO-estimated population prevalence in 2010 (figure 2; see crude rates in appendix p 10). Compared with WHO population prevalence, age-adjusted and sex-adjusted prevalence estimates of such cases were higher in Thailand and lower in all other countries.

Multivariable logistic regression analysis (table 2) showed strong evidence that, after adjustment for age, sex, and clustering by individual, having close or household contact with an individual with tuberculosis was associated with an increased risk of bacteriologically confirmed tuberculosis at pre-entry screening (OR 11·6, 95% CI 7·0–19·3; p<0·0001), with a population attributable fraction of 2·68%. Compared with migrants from countries with a WHO prevalence of 150–349 per 100 000, migrants from countries with a prevalence of 40–149 per 100 000 were at reduced risk of bacteriologically confirmed tuberculosis at pre-entry screening (0·1, 0·1–0·3; p<0·0001), as were those from countries with a prevalence greater than 350 per 100 000 (0·3, 0·3–0·4; p<0·0001), after adjustment for age and sex.

We did a sensitivity analysis to examine the prevalence of the primary and secondary outcomes when including all migrants screened before entry, not only those attending clinics where culture and smear testing was done on all sputum samples. 692 232 migrants were screened under this protocol, and the overall prevalence of bacteriologically confirmed tuberculosis was 75 (69–82) per 100 000 applicants screened (appendix p 6), which was lower than that in our primary analysis, but increased over time.

In multivariable analysis adjusted for age, sex, WHO prevalence in country of origin, self-report of close or household contact with a case of tuberculosis before screening, and visa category, migrants screened at sites where sputum culture testing was done on all samples were associated with increased odds of having bacteriologically confirmed tuberculosis (OR 2·4, 1·9–3·0, p<0·0001; table 3), compared with those being screened at sites where culture testing was not routinely done.

We updated our 2014 meta-analysis[2] to compare our study results with published work. Our updated search identified 257 new studies, but none met the full inclusion criteria. Inclusion of crude estimates from the UK with data from published work[8–13] increased the level of heterogeneity, and the prevalence of culture-positive cases no longer increased with the prevalence of tuberculosis in the country of origin (figure 3). The summary estimates of culture-confirmed cases were

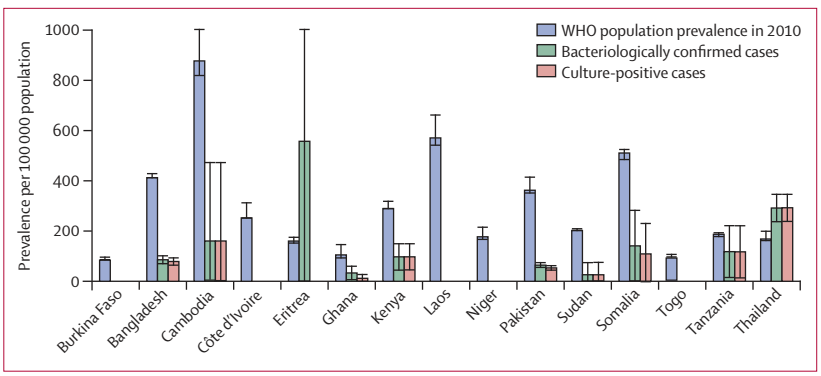

Figure 2: **Age-adjusted and sex-adjusted prevalence of bacteriologically confirmed and culture-positive tuberculosis at pre-entry screening, compared with 2010 WHO population prevalence estimates**
Error bars on WHO prevalence estimates in 2010 represent the highest and lowest estimates for each country between 2007 and 2013. Error bars on bacteriologically confirmed and culture-positive cases represent 95% CIs. CIs are limited to a maximum of 1000 per 100 000 population for convenience of plotting.

	Univariable OR	Multivariable OR	p value
Age (years)			
0–15	0·4 (0·2–0·9)	0·3 (0·2–0·7)	0·0045
16–44	1·0	1·0	..
45–64	1·5 (0·9–2·5)	1·2 (0·7–2·0)	0·56
≥65	3·6 (1·9–6·9)	3·2 (1·6–6·3)	0·0007
Sex			
Female	1·0	1·0	..
Male	0·7 (0·6–0·8)	1·0 (0·8–1·3)	0·73
Close or household contact with an individual with tuberculosis			
No	1·0	1·0	..
Yes	15·7 (9.6–25·5)	11·6 (7.0–19.3)	<0·0001
Visa category			
Student	1·0	1·0	..
Settlement and dependant	1·3 (1·0–1·5)	1·3 (1·0–1·6)	0·0203
Work	1·0 (0·6–1·8)	0·9 (0·5–1·6)	0·73
Working holiday maker	1·0 (0·4–2·2)	1·2 (0·5–2·8)	0·63
Family reunion	0·7 (0·2–2·8)	0·4 (0·1–1·7)	0·21
Other	0·8 (0·4–1·8)	0·9 (0·4–2·1)	0·84
WHO prevalence (per 100 000) of tuberculosis in country of screening			
40–149	0·1 (0·1–0·3)	0·1 (0·1–0·3)	<0·0001
150–349	1·0	1·0	..
≥350	0·3 (0·3–0·4)	0·3 (0·3–0·4)	<0·0001

Data are OR (95% CI), unless otherwise indicated. OR=odds ratio.

Table 2: **Risk factors for bacteriologically confirmed tuberculosis, 2007–13**

	Univariable OR	Multivariable OR	p value
Age (years)			
0–15	0·4 (0·2–0·8)	0·3 (0·1–0·6)	<0·0001
16–44	1·0	1·0	..
45–64	1·4 (0·9–2·3)	1·2 (0·7–1·9)	0·49
≥65	4·0 (2·2–7·3)	3·3 (1·8–6·1)	<0·0001
Sex			
Female	1·0	1·0	..
Male	0·7 (0·6–0·8)	1·0 (0·9–1·3)	0·75
Close or household contact with an individual with tuberculosis			
No	1·0	1·0	..
Yes	16·4 (10·4–26·0)	11·4 (7·0–18·4)	0·0011
Visa category			
Student	1·0	1·0	..
Settlement and dependant	1·2 (1·0–1·5)	1·3 (1·1–1·6)	0·0104
Work	1·1 (0·7–1·7)	1·1 (0·7–1·8)	0·60
Working holiday maker	0·7 (0·4–1·4)	1·5 (0·8–2·8)	0·18
Family reunion	1·8 (0·8–3·8)	1·1 (0·5–2·5)	0·73
Other	0·6 (0·3–1·3)	0·8 (0·3–1·8)	0·54
WHO prevalence (per 100 000) of tuberculosis in country of screening			
40–149	0·1 (0·0–0·2)	0·1 (0·0–0·2)	<0·0001
150–349	1·0	1·0	..
≥350	0·3 (0·3–0·4)	0·3 (0·3–0·4)	<0·0001
Sputum culture testing			
No	1·0	1·0	..
Yes	2·4 (1·9–3·1)	2·4 (1·9–3·0)	<0·0001

Data are OR (95% CI), unless otherwise indicated. OR=odds ratio.

Table 3: **Risk factors for bacteriologically confirmed tuberculosis in all applicants screened, irrespective of whether culture testing of sputum was done, 2005–13**

highest in countries with WHO prevalence of 150–249 per 100 000 (192 [170–216] per 100 000 individuals screened).

Discussion

Nearly 700 000 pre-entry screening episodes for tuberculosis were done, of which almost 500 000 were done at sites where culture testing of sputum samples was a routine practice. After adjustment for age and sex, migrants reporting close or household contact with an individual with tuberculosis, applicants screened in countries with a WHO prevalence of 151–349 per 100 000, and those applying for settlement and dependant visas had an increased risk of being detected with bacteriologically confirmed tuberculosis. Although those reporting contact with a case of tuberculosis had high odds of active-tuberculosis detection, the population attributable fraction was less than 3% in this group. These migrants are likely to benefit from early detection and treatment in their country of origin, and our finding supports the role of contact tracing and investigation in the country of origin, in addition to increased coordination between pre-entry screening programmes and national tuberculosis programmes in the applicant's country.

Our study is the first comprehensive analysis of UK data for pre-entry screening of migrants, and we identified risk factors for tuberculosis in migrants screened before entry in several countries and estimated the number needed to screen to detect one case. The strengths of our study included the large dataset and its representativeness, resulting from a policy that required screening for all migrants applying to stay in the UK for more than 6 months. The UK technical instructions should reduce measurement error and misclassification bias for exposures and outcomes, including in the classification of chest radiographs because of the established system used.

A limitation of this study is that it did not include data for undocumented migrants, refugees, and those with visas for less than 6 months. Undocumented migrants might be at a higher risk of tuberculosis than individuals in this study for complex reasons—eg, malnutrition, history of living in overcrowded situations such as refugee camps, higher rates of HIV, and a disruption in access to health services.[14–16] However, these differences might depend on the protocols determining access to health care for these migrants, as shown by the Israeli experience.[17] Migrants who are planning to stay in the UK for more than 6 months, such as those in this study, are likely to be from higher socioeconomic backgrounds than average in their country of origin.

Close or household contact with an individual with tuberculosis might be under-reported because visa applicants might suspect it would count against their application. If this is true, then we will have underestimated the magnitude of this risk factor. Unmeasured confounding (caused by variables not collected or adjusted for) might explain differences between the prevalence seen in pre-entry screening and WHO population estimates. The availability of confounding variables was scarce, since the data were collected for operational visa processing and not epidemiological analysis. We therefore believe that several factors, including bias and unmeasured confounding, could explain the finding that tuberculosis detection was not the highest in applicants from countries with the highest WHO prevalence, and urge caution in the interpretation of this lack of trend in the UK pilot data and updated meta-analysis.

Our results might differ from published work on pre-entry screening for several other reasons. First, the data presented are for migrants intending to stay for a minimum of 6 months. Second, a large proportion of migrants screened were students or young adults of working age, but no data were available from published studies that would allow adjustment of estimates. Third, not all published studies provide exact details of how culture testing was done, and the investigators of a large study[8] highlighted the fact that the procedure might not have been uniform. In our study, consistent with UK technical instructions, cases could be bacteriologically

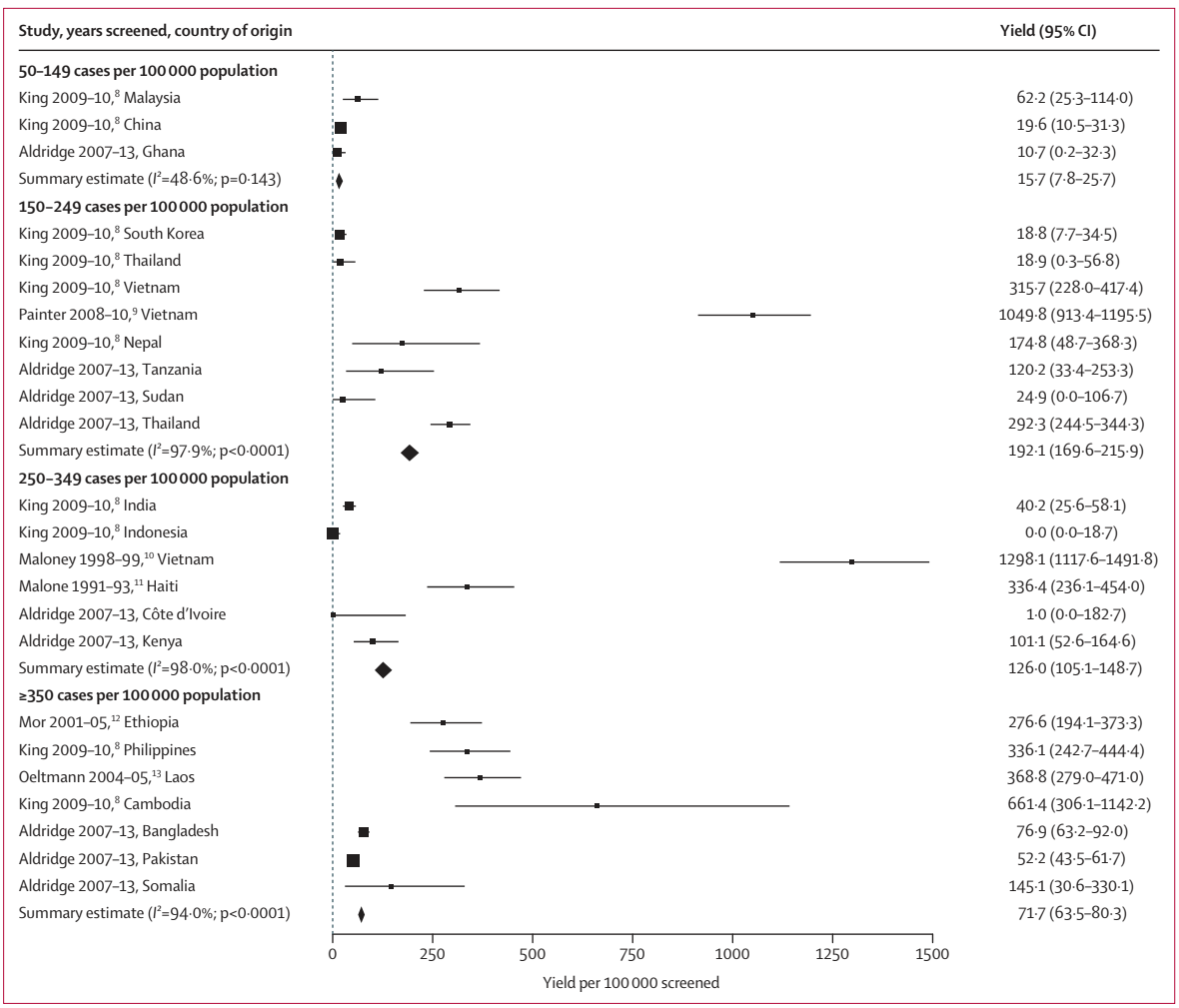

Figure 3: **Forest plot of prevalence of culture-positive cases of tuberculosis at pre-entry screening, stratified and sorted by WHO prevalence of tuberculosis in country of origin[8–13]**

confirmed by smear, culture, or both. Because of the UK technical instructions and quality assurance processes, such variability should not be an issue in our data. Finally, our study excluded duplicate screens in the analysis, which we believe previous studies did not undertake.

Our analysis provides strong support for the previous change to US and UK technical instructions for the inclusion of culture testing in the screening protocol.[13] The groups of migrants identified as being at high risk of active tuberculosis will benefit from improved clinical outcomes and health status as a result of early detection and treatment, and the population will also benefit from reduced onward transmission.[18–20] At present, students are not screened as part of the US pre-entry screening programme. Although their risk of tuberculosis is lower than many other groups, they remain a substantial source of cases, and our findings will enable further analyses, including updated analyses of the cost-effectiveness of screening programmes for students.[21] Delays introduced by the requirement for culture testing of sputum sample, which can take a minimum of 6 weeks in liquid media and 8 weeks in solid media, also pose concern—eg, such delays can result in students missing the beginning of the academic year or skilled migrants being delayed in starting work. New rapid tests with high sensitivity (eg, GeneXpert MTB/RIF system) are available and could potentially reduce these delays, but these tests should be assessed in the operational setting of pre-entry screening and compared with traditional culture methods before being widely rolled out.[22,23]

Migrants from low-prevalence countries were at a reduced risk of active tuberculosis. Countries that have pre-entry screening programmes invest public funds into the quality assurance of such screening, and therefore a threshold above which pre-entry screening is cost-effective should be determined. The number needed to screen to detect one case across all sites in this pilot programme was 1087 and was reduced to 444 when only migrants from countries with prevalence of 150–349 per

100 000 population were screened. Several costs were associated with this pilot screening programme, including initial set-up costs funded by the UK Government (£1·1 million at November, 2010, prices) and the cost to individual applicants, which varied across sites but was around US$50–70 in November, 2011.[24] Therefore, a cost-effective analysis that considers these and other relevant costs is strongly recommended. The analysis should also examine different perspectives, including that of the receiving country, wider society, and an enlightened self-interest approach in which there is investment in tuberculosis control programmes overseas by a receiving country.[25,26]

Risk factors for progression to active tuberculosis need to be identified, and rates of progression in those who tested negative before entry should be estimated. These data would be particularly useful in informing the possible effect of the introduction of pre-entry screening for latent tuberculosis.[27] Unmeasured confounding factors, including socioeconomic and HIV status, could be important, and efforts should be made to obtain relevant data in an appropriately sensitive manner, compliant with information governance and public health legislation.

We identified several groups of migrants at high risk of active tuberculosis at pre-entry screening. To tackle the burden of disease in this population, a wide-ranging approach that includes screening and treatment for latent tuberculosis infection is necessary;[9] however, migrants will remain at higher risk than those born in the UK because of an increased likelihood of exposure to infectious cases in the UK or when travelling back to their country of origin.[28] The inclusion of latent-tuberculosis screening at one point in time would not eliminate this risk, and a more comprehensive approach should therefore be explored. This approach could include improved integration between pre-entry screening and health services after arrival, and appropriate delivery of health care and health improvement programmes, rather than focusing solely on tuberculosis. Such an approach would be welcomed, in view of the documented issues migrants have in accessing health services after arrival in the UK.[29]

Contributors

RWA proposed the initial hypothesis and idea for study. All authors contributed substantially to the conception and design of the study, and acquisition of data. RWA did the analyses and wrote the first draft of the report. All authors interpreted the data and revised the report.

Declaration of interests

DZ is head of the tuberculosis screening unit at Public Health England and has shared responsibilities for quality assurance within the UK pre-entry screening programme. PJW has research funding from Otsuka SA for a retrospective study of multidrug-resistant tuberculosis treatment in several eastern European countries. PD works for the Migration Health Division, International Organization for Migration (IOM), and was Health Research and Epidemiology Coordinator of IOM Manila, the Philippines, during preparation of this work. DM is Director of the Migration Health Division at the IOM. All other authors declare no competing interests.

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