Active case-finding of tuberculosis in general populations and at-risk groups: a systematic review and meta-analysis

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Active case-finding of tuberculosis can produce substantial yields in general populations and at-risk groups and may outperform current case-finding practices. This provides evidence for extending active case-finding beyond current WHO recommendations. http://bit.ly/3lOHVER

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Abstract

Background The World Health Organization (WHO) recommends active case-finding (ACF) of tuberculosis (TB) in certain high-risk groups; however, more evidence is needed to elucidate the scope of ACF beyond the current recommendations. In this study we aimed to systematically review yields (the prevalence of active TB) of studies on ACF in general populations and at-risk groups.

Methods A literature search in PubMed, Embase and the Cochrane Central Library (CENTRAL) was performed for studies concluded after 31 December 1999 and published before 1 September 2020. Screening yields were estimated and yield/prevalence ratios (ratio between yield of study and WHO estimated prevalence of TB) were calculated to assess which groups might especially benefit from ACF. Finally, risk of bias was assessed and heterogeneity was investigated using meta-regression and sensitivity analyses.

Results We included 197 studies, with a total of 12 372 530 screened and 53 158 cases found. Yields were high among drug users, close contacts, the poor and marginalised, people living with HIV, and prison inmates across incidence strata, and estimated yield/prevalence ratios in screenings of general populations tended to be >1 with an overall ratio of 1.4 and ranging between 1.0 and 1.5. Sensitivity analyses suggested that inclusion of studies at high risk of bias contributed to underestimation of yields.

Conclusion Despite many studies using insensitive screening methods, these results suggest that more at-risk groups should be considered for inclusion in future screening recommendations and that screening of general populations may outperform current case-finding practices, providing evidence for extending ACF beyond the current recommendations.

Introduction

Tuberculosis (TB) is a major contributor to the global disease burden with an estimated 10 million cases annually and 1.5 million deaths, making it the leading cause of death from a single infectious agent [1]. At the same time, TB burden follows a socioeconomic gradient between and within countries, with some population groups at higher risk of contracting, developing and dying from active TB disease [2].

The World Health Organization (WHO) aims at a 95% reduction in TB deaths by 2035 compared with 2015, while the United Nations Sustainable Development Goals aim to end the TB epidemic by 2030 [3, 4]. Meanwhile, the global case detection rate of active TB is 70% and global TB incidence is declining only slowly [5, 6]. Thus, current case-finding practices appear insufficient in halting the TB epidemic [6]. Consequently, if these aims are to be realised, effective strategies for TB detection need to be developed and implemented.

Active case-finding (ACF) is defined as a systematic identification of people with TB in a pre-determined target group and may supplement the more commonly employed strategy of passive case-finding (PCF) [7].

A 2013 review by the WHO indicated that ACF may be warranted in settings of high baseline TB risk and a recent Cochrane review concluded that ACF may increase TB detection when applied in moderate-to-high TB prevalence settings [7, 8]. Currently, the WHO recommends screening of certain high-risk groups; however, more evidence is needed to elucidate the scope of ACF beyond these recommendations [7, 9].

In this systematic review and meta-analysis, we sought to shed light on the yields that ACF produces in general populations and at-risk groups. We further aimed to discern trends in yields by region, and TB burden and incidence in the country of screening, and how screening yields compare with existing prevalence estimates by the WHO.

Methods and study selection

Search strategy and study selection

The study protocol was registered with PROSPERO with identifier number CRD42020206856 in August 2020 in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) statement and the review was conducted in accordance with PRISMA guidelines [10, 11].

A systematic literature search was carried out independently by two reviewers (A.S.B. and V.S.H.) in September 2020. The literature search was performed in PubMed, Embase and the Cochrane Central Library (CENTRAL) using the following search words: "tuberculosis screening and diagnostic yield", "tuberculosis case-finding effectiveness" and "tuberculosis active case-finding" (with and without hyphen). The complete search history is included in annex A of the supplementary material. All published English language studies on ACF of TB in either general populations or at-risk groups were screened for eligibility. We excluded: 1) qualitative studies, 2) studies on patients with presumed TB, 3) studies including only children/adolescents <15 years of age, 4) studies focusing on patients with multidrug-resistant and/or extensively drug-resistant TB, 5) studies on screenings concluded prior to 1 January 2000 or published after 31 August 2020, 6) studies on PCF or enhanced case-finding and 7) duplicates. Randomised controlled clinical trials were included in the review; however, only results from the intervention arm were used in the analysis.

Both reviewers independently assessed all titles and abstracts for inclusion. Finally, a full-text analysis was carried out on each remaining study to evaluate eligibility for analysis and reference lists were examined to identify further eligible studies. In cases of any discrepancy between reviewers, disagreement was resolved by consensus.

Data extraction and definitions

Data extraction was performed by two reviewers (A.S.B. and V.S.H.). Data extracted included population screened, cases found, country of screening, type of population screened, screening method, year of screening, TB burden, and estimated incidence and prevalence rates of TB in the country of screening.

Classification by region was based on WHO regions modified to reflect greater intra-regional homogeneity [12]. The Region of the Americas was split in two: the USA and Canada constituting "North America", and the remaining countries of the region constituting "South and Central America". "North America" was subsequently combined with the Region of Europe to form "North America and Europe". The Region of the Eastern Mediterranean was termed "Middle East", and the Regions of South-East Asia and the Western Pacific were combined to form "Asia", for a total of five regions.

Classification by high-burden country (HBC) *versus* non-HBC as well as TB/HIV HBC *versus* non-TB/HIV HBC was based on WHO designations, which defined HBCs as the 20 countries with the highest numbers of incident TB cases, plus the top 10 countries with the highest TB incidence rate, while TB/HIV HBCs were similarly defined for cases among people living with HIV (PLHIV) [1]. These definitions rely partly on absolute numbers of incident cases, giving disproportionate weight to more populous countries [13]. Therefore, we additionally stratified studies according to incidence of TB in the country of screening. For this, incidence rates were extracted in February 2021 from WHO databases, except for Taiwan, for which the incidence rate was obtained from the Taiwan Centers for Disease Control [14, 15]. For the stratification we used four incidence classes previously defined by the WHO [7]: low incidence (incidence rate <30/100 000 per year), moderate incidence (incidence rate 30–<100/100 000 per year), medium incidence (incidence rate 100–<300/100 000 per year) and high incidence (incidence rate ⩾300/100 000 per year).

Classification of at-risk groups was based on accepted definitions, and included PLHIV, close contacts of active TB cases, people with TB as an occupational hazard, prison inmates, diabetic individuals, pregnant

women, marginalised groups, people living in extreme poverty, residents of poor urban areas, and refugees and immigrants from countries with high endemic rates of TB [6, 7].

The prevalence of active TB in each study, hereafter referred to as the yield, was taken to be the total number of TB cases found per 100 000 screened. Population screened was defined as the number of people who were eligible for and participated in the screening. Cases were defined as the total number of TB cases found in the screened population excluding latent TB infections. Number needed to screen (NNS) was defined as the inverse of the yield.

When possible, the yields of included studies were compared with WHO prevalence estimates for the country of screening [16]. For this we constructed a ratio, which we termed the yield/prevalence ratio. Summary estimates of the yield/prevalence ratio were produced for different strata to assess expected yields of carrying out ACF in the strata compared with each country's baseline prevalence of TB as estimated by the WHO. A factor >1 indicated a higher yield of screening than would be expected if sensitivity of screening was 100% and prevalence in the screened population was equal to the WHO estimated prevalence in the country.

Risk of bias assessment

We assessed risk of bias for each study using the protocol developed by Hoy *et al*. [17]. In accordance with the protocol, each study was assessed using 10 questions, four of which evaluated the external validity of the study and six of which evaluated the internal validity of the study. For each question the study was judged to be either at a high or a low risk of introducing bias. If insufficient information was provided to assess the question, risk was assumed to be high. A summary item described the overall risk of bias as either low, intermediate or high.

Statistical analyses

Statistical analyses were performed in Stata version 16 (StataCorp, College Station, TX, USA). We created a random effects meta-analysis model for generation of yield and yield/prevalence ratio estimates to account for differences in sampling as well as differences in study methods and underlying prevalence [18–20]. The analysis was stratified by population type, type of at-risk group, geographical region, TB burden, TB/HIV burden and TB incidence. Heterogeneity (I^2) was estimated using the meta-analysis model and further assessed by visual inspection of the forest plots and confidence intervals. To investigate sources of heterogeneity further, we performed multivariable random effects meta-regression for both yields and yield/prevalence ratios using risk of bias, initial screening method, confirmatory test, population group, size of population screened, year of study, TB incidence and HIV prevalence. For this, HIV prevalence was extracted from WHO databases in February 2021 [21]. Finally, we performed sensitivity analyses for the effect of excluding outlying studies (identified by visual inspection of the forest plots of different strata) as well as by level of overall risk of bias.

Results

The literature search yielded a total of 5522 articles, of which 112 were included in this review (figure 1). An additional 64 articles were identified through reference lists. The full list of articles is included in the references list in the supplementary material. 14 articles (annex B of the supplementary material) were subsequently split into multiple entries according to groups within the articles, yielding a total of 197 data points, hereafter referred to as studies.

Characteristics of included studies are summarised in table 1 and annex B of the supplementary material. A larger proportion of studies on general populations than at-risk groups were in HBCs and higher incidence countries, screened for cough, and used sputum smear and culture for confirmation.

Studies conducted on general populations comprised 7 593 569 screened and 22 848 cases found, while studies on at-risk groups comprised 4 778 961 screened and 30 310 cases found, for a combined total of 12 372 530 screened and 53 158 cases found. The overall mean±SD population screened per study was 62 805±231 339, with a mean±SD population screened of 143 275±406 543 for general populations and 33 187±99 843 for at-risk groups.

A summary of the risk of bias assessment is presented in table 1 and annex C of the supplementary material. Overall, external validity contributed more to risk of bias, reflecting mainly selection bias. There was no difference in distribution of risk of bias between at-risk populations and general populations.

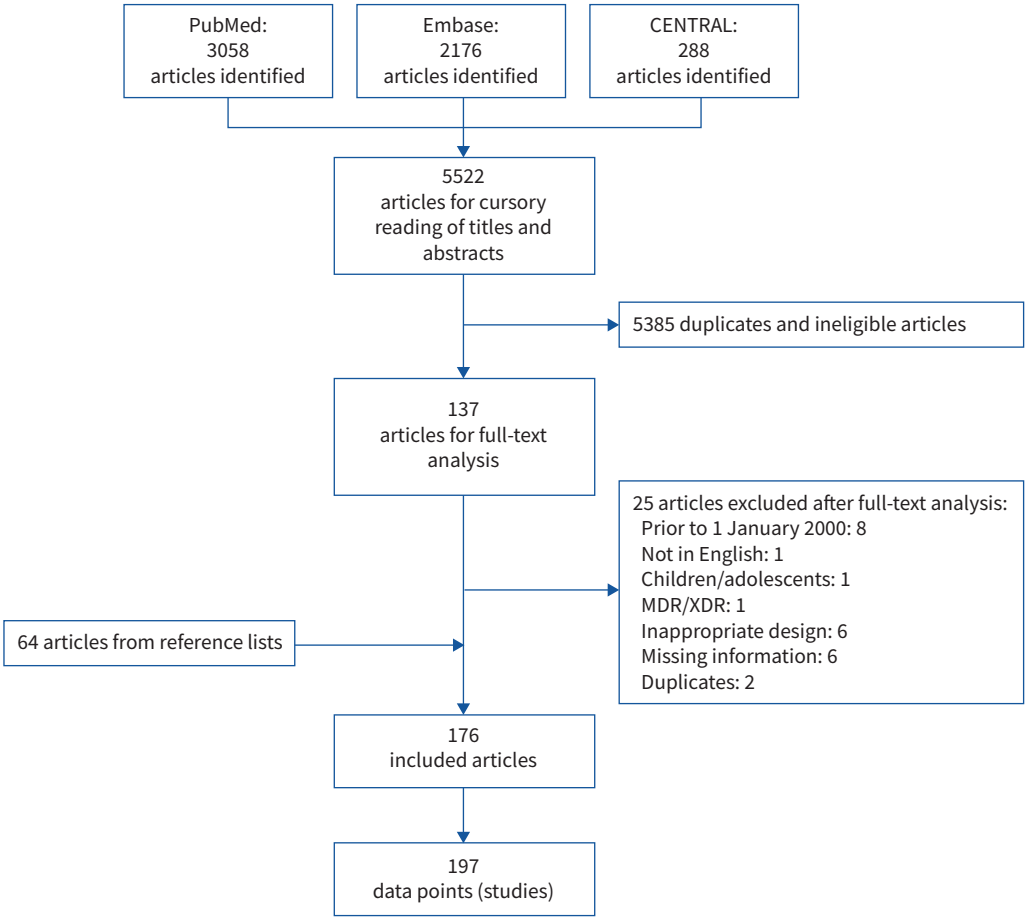

FIGURE 1 Study selection. CENTRAL: Cochrane Central Library; MDR: multidrug resistant; XDR: extensively drug resistant.

Results of the meta-analysis are summarised in table 2 and figure 2. Tables and forest plots of the meta-analysis by burden, incidence and region are presented in annexes D and E of the supplementary material. WHO prevalence estimates were obtained for 22 countries covering 146 (74%) of the studies included in this review.

Considerable yields were found overall in both general populations and at-risk groups, with particularly high yields in TB and TB/HIV HBCs, medium- to high-incidence countries, Africa, South and Central America, and among PLHIV, prison inmates and contacts of TB patients. High yield/prevalence ratios were similarly associated with these groups and regions as well as with health workers and drug users.

Meta-regression models are presented in annex F of the supplementary material. For the yield meta-regression, the included covariates were able to account for 24.5% of the observed variance; however, only the category of population groups displayed significance at $p<0.05$ as predictors of prevalence. For yield/prevalence ratios, the included covariates were able to account for 42.4% of the observed variance, and risk of bias, initial screening methods, population groups and TB incidence all displayed significance at $p<0.05$ as predictors of yield/prevalence ratio.

The sensitivity analysis is summarised in figure 2 and annex G of the supplementary material. Removing outliers from general population studies caused decreases in yield estimates for HBCs, TB/HIV HBCs, medium- and high-incidence countries, and Africa, while for at-risk groups it decreased estimates for HBCs, TB/HIV HBCs, high-incidence countries, the Middle East, Africa, health workers, PLHIV, prison inmates and mixed groups. It was difficult to discern clear trends in yields by risk of bias. Removing outliers from general population studies caused decreases in yield/prevalence ratios for HBCs, TB/HIV HBCs, medium-incidence countries and Africa, while for at-risk groups it decreased estimates for HBCs,

TABLE 1 Summary of characteristics of included studies[#]

	General populations	At-risk groups
Overall	53 (26.8)	144 (73.1)
Burden		
Non-HBCs	9 (17.0)	53 (36.8)
HBCs	44 (83.0)	91 (63.2)
Non-TB/HIV HBCs	17 (32.1)	61 (42.4)
TB/HIV HBCs	36 (67.9)	83 (57.6)
Incidence		
Low	2 (3.8)	20 (13.9)
Moderate	6 (11.3)	24 (16.7)
Medium	32 (60.4)	73 (50.7)
High	13 (24.5)	27 (18.8)
Region		
North America and Europe	2 (3.8)	22 (15.3)
Asia	20 (37.7)	39 (27.1)
Africa	26 (49.1)	56 (38.9)
Middle East	4 (7.6)	11 (7.6)
South and Central America	1 (1.9)	16 (11.1)
Group		
Refugees and immigrants		14 (9.7)
Poor and marginalised		27 (18.8)
Contacts/HHCs		40 (27.8)
Mixed groups		11 (7.6)
Drug users		2 (1.4)
Health workers		6 (4.2)
PLHIV		22 (15.3)
Prison inmates		22 (15.3)
Risk of bias		
High	17 (32.1)	40 (27.8)
Medium	18 (34.0)	48 (33.3)
Low	19 (34.0)	56 (38.9)
Initial screening method		
Any cough	4 (7.6)	6 (4.2)
Prolonged cough	14 (26.4)	17 (11.8)
Any TB symptom	22 (41.5)	71 (49.3)
Xpert	1 (1.9)	5 (3.5)
TST	0 (0.0)	6 (4.2)
Culture	1 (1.9)	13 (9.0)
Chest radiography	11 (20.8)	24 (16.7)
Confirmatory test		
Clinical examination	2 (3.8)	10 (6.9)
Xpert	4 (7.6)	23 (16.0)
Sputum smear	24 (45.3)	51 (35.4)
Culture	22 (41.5)	50 (34.7)
Chest radiography	1 (1.9)	10 (6.9)

Data are presented as n (%). HBC: high-burden country; TB: tuberculosis; HHC: household contact; PLHIV: people living with HIV; TST: tuberculin skin test. [#]: 197 data points. The full list of articles included in the review is provided in the references list in the supplementary material. A more detailed description of the studies is provided in annex B of the supplementary material.

TB/HIV HBCs, medium-incidence countries, the Middle East, Africa, health workers, contacts and mixed groups. Yield/prevalence ratio tended to increase with decreasing risk of bias. This effect was particularly clear in at-risk groups across burden, incidence and group strata.

Discussion

In this review we have provided data on yields of screening for TB to aid decision making when designing future screening programmes.

We found high to extremely high yields and high yield/prevalence ratios across incidence and burden levels in screenings of drug users (yield 1157/100 000; ratio 11.9), close contacts (yield 1690/100 000;

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TABLE 2 Summary of meta-analysis in different strata

	General populations			At-risk groups		
	Yield (95% CI)	NNS (95% CI)	Yield/prevalence ratio (95% CI)	Yield (95% CI)	NNS (95% CI)	Yield/prevalence ratio (95% CI)
Overall	432 (382–482)	231 (207–262)	1.4 (0.8–1.9)	1401 (1328–1475)	71 (68–75)	12.5 (9.1–15.8)
Burden						
Non-HBCs	248 (60–436)	403 (229–1667)	1.3 (0.2–2.5)	987 (891–1082)	101 (92–112)	9.2 (3.0–15.4)
HBCs	504 (438–571)	198 (175–228)	1.4 (0.8–2.0)	1734 (1625–1843)	58 (54–62)	12.9 (9.2–16.6)
Non-TB/HIV HBCs	246 (178–315)	407 (317–562)	0.9 (0.6–1.3)	1043 (955–1130)	96 (88–105)	7.9 (3.8–12.0)
TB/HIV HBCs	604 (514–695)	166 (144–195)	1.6 (0.8–2.3)	2202 (2041–2363)	45 (42–49)	13.9 (9.7–18.1)
Incidence						
Low	4 (0–8)	25 000 (12 500–)[#]		572 (446–698)	175 (143–224)	
Moderate	158 (44–272)	633 (368–2273)	1.0 (0.2–1.8)	1194 (1035–1353)	84 (74–97)	35.1 (19.3–50.9)
Medium	500 (421–579)	200 (173–238)	1.4 (0.6–2.2)	1563 (1453–1672)	64 (60–69)	9.1 (6.5–11.7)
High	603 (457–749)	166 (134–219)	1.5 (0.7–2.3)	4159 (3525–4794)	24 (21–28)	8.0 (3.6–12.5)
Region						
North America and Europe	29 (26–31)	3448 (3226–3846)	0.2 (0.2–0.3)	481 (386–576)	208 (174–259)	6.5 (6.3–6.8)
Middle East	249 (0–508)	402 (197–)[#]	1.4 (0.8–2.1)	1718 (1456–1979)	58 (51–69)	9.8 (0–19.7)
Asia	358 (276–439)	279 (228–362)	1.3 (0.9–1.7)	995 (885–1106)	101 (90–113)	8.0 (4.6–11.5)
South and Central America	394 (356–436)	254 (229–281)		3098 (2599–3597)	32 (28–38)	45.6 (27.5–63.7)
Africa	690 (567–812)	145 (123–176)	1.5 (0.5–2.6)	3062 (2785–3339)	33 (30–36)	9.2 (6.2–12.2)
Group						
Refugees and immigrants				257 (186–328)	389 (305–538)	1.1 (0.9–1.3)
Poor and marginalised				1330 (1165–1495)	75 (67–86)	3.0 (2.0–3.9)
Contacts/HHCs				1690 (1511–1869)	59 (54–66)	8.0 (5.4–10.6)
Mixed groups				658 (511–804)	152 (124–196)	8.8 (0–20.6)
Drug users				1157 (809–1505)	86 (66–124)	11.9 (11.1–12.7)
Health workers				1201 (279–2122)	83 (47–358)	19.4 (0–47.3)
PLHIV				9092 (7229–10 955)	11 (9–14)	19.7 (13.7–25.7)
Prison inmates				2371 (1983–2759)	42 (36–50)	25.2 (11.6–38.8)
Risk of bias						
High	351 (223–480)	285 (208–448)	1.1 (0.5–1.7)	1540 (1342–1738)	65 (58–75)	6.2 (3.7–8.7)
Medium	342 (237–446)	292 (224–422)	1.0 (0.7–1.4)	1035 (927–1143)	97 (87–108)	8.7 (5.1–12.2)
Low	725 (610–839)	138 (119–164)	2.1 (0.5–3.7)	1836 (1703–1969)	54 (51–59)	21.2 (13.4–29.0)
Initial screening method						
Any cough	370 (119–622)	270 (161–840)	1.4 (0.6–2.1)	984 (517–1451)	102 (69–193)	5.2 (0–10.8)
Prolonged cough	381 (277–486)	262 (206–361)	1.2 (0.4–2.0)	1500 (1088–1912)	67 (52–92)	5.4 (0.8–9.9)
Any TB symptom	622 (503–740)	161 (135–199)	1.6 (0.4–2.8)	1259 (1163–1356)	79 (74–86)	9.6 (6.0–13.1)
Xpert	280 (77–1016)	357 (98–1299)	0.4 (0–1.8)	5234 (3077–7391)	19 (14–32)	9.6 (0–23.5)
TST				660 (191–1129)	152 (89–524)	12.7 (0–26.1)
Culture	982 (789–1222)	102 (82–127)		7904 (6317–9491)	13 (11–16)	17.4 (7.9–26.9)
Chest radiography	290 (168–412)	345 (243–595)	1.4 (0.7–2.1)	1461 (1274–1647)	68 (61–78)	35.0 (17.9–52.2)
Confirmatory test						
Clinical examination	231 (157–304)	433 (329–637)		827 (519–1134)	121 (88–193)	6.0 (0–13.9)
Xpert	503 (392–613)	199 (163–255)	1.4 (0–3.0)	1323 (1162–1484)	76 (67–86)	8.2 (2.6–13.7)
Sputum smear	515 (442–588)	194 (170–226)	1.6 (0.5–2.8)	1659 (1518–1800)	60 (56–66)	8.7 (6.0–11.3)
Culture	363 (299–426)	275 (235–334)	1.2 (0.9–1.4)	1877 (1708–2047)	53 (49–59)	19.6 (11.5–27.8)
Chest radiography	68 (53–86)	1471 (1163–1887)	0.3 (0.1–0.6)	778 (412–1145)	129 (87–243)	31.1 (30.5–31.6)

Yields are presented as per 100 000 population. NNS: number needed to screen; TB: tuberculosis; HBC: high-burden country; HHC: household contact; PLHIV: people living with HIV; TST: tuberculin skin test. [#]: upper 95% CI undefined (NNS=1/0).

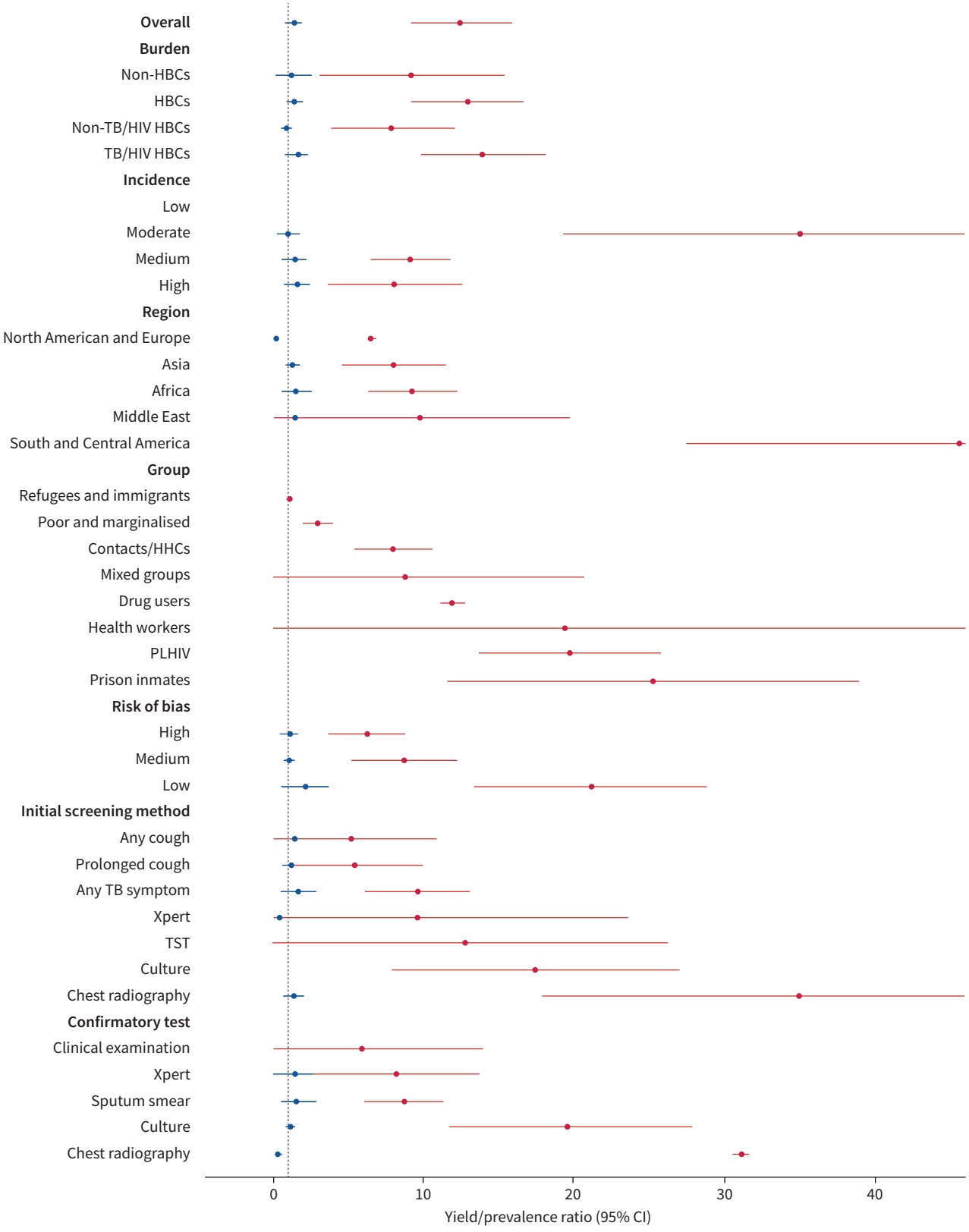

FIGURE 2 Summary of yield/prevalence ratios for different strata, risk of bias levels and screening methods. Blue symbols indicate general populations, red symbols indicate at-risk groups and the dotted line indicates ratio=1. HBC: high-burden country; TB: tuberculosis; HHC: household contact; PLHIV: people living with HIV; TST: tuberculin skin test.

ratio 8.0), the poor and marginalised (yield 1330/100 000; ratio 3.0), PLHIV (yield 9092/100 000; ratio 19.7), and prison inmates (yield 2371/100 000; ratio 25.2). Furthermore, we found that yield/prevalence ratios in screenings of general populations tended to be >1 with an overall ratio of 1.4 and ranging between 1.0 and 1.5 across incidence strata, meaning that higher prevalence was found by ACF than was estimated by the WHO, suggesting that ACF may outperform current case-finding practices. Currently, the WHO strongly recommends screening for TB only among close contacts of patients with TB, PLHIV and workers with silica exposure, while a conditional recommendation of screening is given for prison inmates, people with untreated fibrotic chest radiography lesions, people clinically at risk attending health facilities in higher TB prevalence settings, people with poor access to healthcare and geographically defined subpopulations with extremely high levels of undetected TB (at least 1% prevalence) [7]. Screening of general populations is not recommended. Our results suggest that a strong recommendation ought to be additionally considered for the poor and marginalised, prison inmates, and drug users in future screening guidelines, and that screening of general populations might be considered under certain conditions.

We may consider at what prevalence level screening should be recommended, and whether this is different for general populations and at-risk groups. For instance, it is conceivable that an ACF strategy targeted at a small population group acting as a reservoir of TB may inhibit a wider epidemic and thus represent an effective strategy with limited resource investment in a society of low baseline TB prevalence, while general population screening may be warranted in societies of higher baseline prevalence [22]. A more in-depth examination of this was, however, considered outside the scope of this study. It has also been reported that ACF reduces delay in diagnosis and that screening may reach underserved groups by reducing barriers associated with PCF, thus possibly reducing the time that patients are infectious in their communities and improving outcome of treatment, although the current evidence for this is unclear [7, 9, 23–25]. However, the societal effects of ACF are beyond the scope of this review, nor does it include a comparison between ACF and PCF. Future research should focus on the effect of ACF on TB transmission and burden in a society, *e.g.* as in Marks *et al.* [26].

Our review has limitations. First, all prevalence estimates were extracted from a 2009 WHO report [16], and are therefore matched only by country and not by year of screening. More importantly, significant variability was observed, particularly in studies on at-risk groups. We have attempted to account for this through subgroup analysis, but societies differ greatly in TB risk even within the strata defined for this analysis. Furthermore, studies were performed for different reasons and employed different designs, methods and definitions, and sensitivity analysis suggested that yields may vary substantially with screening method, with yield/prevalence ratios ranging from 5.2 (any cough) to 35.0 (chest radiography) in at-risk groups. Ideally, when comparing yields between studies, these would have been obtained in identical ways. However, such a requirement would have limited the literature search excessively. We used a random effects model to account partly for such inter-study differences. We also performed multivariate meta-regression to determine the predictive power of certain covariates. These models showed that risk of bias, initial screening method, population and TB incidence had predictive power for yield/prevalence ratios, while for yields only population groups did. Moreover, we systematically assessed the risk of bias presented by the methodology employed in each of the included studies and whether this influenced our results, and performed a sensitivity analysis for risk of bias. These analyses showed that studies at high risk of bias tended towards lower yield/prevalence ratios (overall yield/prevalence ratio of 6.2 in high-risk studies of at-risk groups *versus* 21.2 in low-risk studies), indicating that the inclusion of higher risk studies likely contributed to underestimation of the true prevalence. Thus, our review may underestimate the yields that could be expected of a diligently designed screening programme.

Most studies employed a symptom-based initial screening, confirming with sputum smear microscopy or culture. This poses several risks of bias. A symptom-based approach may have relatively low sensitivity and systematically underdiagnose certain patient groups such as PLHIV, as HIV co-infection increases the risk of subclinical manifestation and atypical symptoms [7, 27–30]. Furthermore, many studies based the symptom screening on cough, which exhibits lower sensitivity than screening for any TB symptom [7]. Indeed, in our analysis at-risk groups had higher yield/prevalence ratios in studies using any TB symptom (9.6) compared with prolonged cough (5.4) or any cough (5.2), while chest radiography outperformed both (35.0). Sputum smear microscopy displays higher sensitivity in people with severe disease, leading to underdiagnosis of mild cases, and is less sensitive when performed on women and PLHIV, leading to underdiagnosis in these groups [7, 31, 32]. Overall, an algorithm relying on detecting any TB symptom and confirming by sputum smear microscopy would expectedly detect 47% of cases, while one relying on chest radiography for any TB-compatible abnormality followed by sputum smear microscopy would detect 60% of cases [7]. Moreover, all these methods have limited applicability in diagnosing extrapulmonary TB, again leading to underdiagnosis of TB [31]. This may, however, be acceptable when screening is

designed to break chains of TB transmission, as pulmonary TB is considered the main source of contagion. Future research should be directed at determining the best and most cost-effective screening methods. For instance, given the performance of chest radiography in our analysis, we would welcome studies evaluating newer radiographic technologies such as the CAD4TB software platform [33]. Similarly, future reviews could focus solely on studies using sufficiently sensitive screening methods.

In the present review we identified relatively few studies on ACF in general populations, leading to at times small strata. This may reflect research and public health priorities, particularly as the WHO has discouraged mass screening since 1974 [34]. We may also consider whether the search strategy was successful in identifying all relevant studies, including selection bias as we considered only English language literature for inclusion. Furthermore, potential publication bias cannot be excluded, as it is unknown how many screenings are performed but never published as research results.

Here we have shown that ACF can yield substantial numbers of active TB in drug users, close contacts, the poor and marginalised, PLHIV, and prison inmates, and may outperform current case-finding practices in general populations despite including studies which likely contributed to an underestimation of screening yields. This provides evidence for extending well-designed ACF beyond the current recommendations and should be considered when designing future public health measures against TB.

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