Prevalence of subclinical pulmonary tuberculosis in adults in community settings: an individual participant data meta-analysis

Logan Stuck, Eveline Klinkenberg, Nahid Abdelgadir Ali, Egbal Ahmed Basheir Abukaraig, Yaw Adusi-Poku, Zeleke Alebachew Wagaw, Razia Fatima, Nathan Kapata, Pascalina Kapata-Chanda, Bruce Kirenga, Llang B Maama-Maime, Sayoki G Mfinanga, Sizulu Moyo, Lindiwe Mvusi, Ndahafa Nandjebo, Hai Viet Nguyen, Hoa Binh Nguyen, Joshua Obasanya, Bashorun Adedapo Olufemi, Philip Patrobas Dashi, Thato J Raleting Letsie, Nunurai Ruswa, Elizeus Rutebemberwa, Mbazi Senkoro, Tieng Sivanna, Huot Chan Yuda, Irwin Law, Ikushi Onozaki, Edine Tiemersma, Frank Cobelens, on behalf of the scTB Meta Investigator Group

Summary

Background Subclinical pulmonary tuberculosis, which presents without recognisable symptoms, is frequently detected in community screening. However, the disease category is poorly clinically defined. We explored the prevalence of subclinical pulmonary tuberculosis according to different case definitions.

Methods We did a one-stage individual participant data meta-analysis of nationally representative surveys that were conducted in countries with high incidence of tuberculosis between 2007 and 2020, that reported the prevalence of pulmonary tuberculosis based on chest x-ray and symptom screening in participants aged 15 years and older. Screening and diagnostic criteria were standardised across the surveys, and tuberculosis was defined by positive *Mycobacterium tuberculosis* sputum culture. We estimated proportions of subclinical tuberculosis for three case definitions: no persistent cough (ie, duration ≥2 weeks), no cough at all, and no symptoms (ie, absence of cough, fever, chest pain, night sweats, and weight loss), both unadjusted and adjusted for false-negative chest x-rays and uninterpretable culture results.

Findings We identified 34 surveys, of which 31 were eligible. Individual participant data were obtained and included for 12 surveys (620 682 participants) across eight countries in Africa and four in Asia. Data on 602 863 participants were analysed, of whom 1944 had tuberculosis. The unadjusted proportion of subclinical tuberculosis was 59·1% (n=1149/1944; 95% CI 55·8–62·3) for no persistent cough and 39·8% (773/1944; 36·6–43·0) for no cough of any duration. The adjusted proportions were 82·8% (95% CI 78·6–86·6) for no persistent cough and 62·5% (56·6–68·7) for no cough at all. In a subset of four surveys, the proportion of participants with tuberculosis but without any symptoms was 20·3% (n=111/547; 95% CI 15·5–25·1) before adjustment and 27·7% (95% CI 21·0–36·4) after adjustment. Tuberculosis without cough, irrespective of its duration, was more frequent among women (no persistent cough: adjusted odds ratio 0·79, 95% CI 0·63–0·97; no cough: adjusted odds ratio 0·76, 95% CI 0·62–0·93). Among participants with tuberculosis, 29·1% (95% CI 25·2–33·3) of those without persistent cough and 23·1% (18·8–27·4) of those without any cough had positive smear examinations.

Interpretation The majority of people in the community who have pulmonary tuberculosis do not report cough, a quarter report no tuberculosis-suggestive symptoms at all, and a quarter of those not reporting any cough have positive sputum smears, suggesting infectiousness. In high-incidence settings, subclinical tuberculosis could contribute considerably to the tuberculosis burden and to *Mycobacterium tuberculosis* transmission.

Funding Mr Willem Bakhuys Roozeboom Foundation.

Introduction

In the past couple of decades great progress has been made in diagnosing and treating tuberculosis.[1] Yet, of the estimated 10·6 million people getting ill with tuberculosis globally in 2022, only 7·5 million were notified.[2] The 3·1 million difference largely reflects patients who were not diagnosed. Part of this diagnostic gap might be missed diagnoses in people with tuberculosis pathology who do not report clinically recognisable symptoms (tuberculosis-suggestive symptoms). For this state, the term subclinical tuberculosis disease has been introduced, as opposed to clinical tuberculosis in which tuberculosis-suggestive symptoms are present.[3,4]

In a systematic review of 28 tuberculosis prevalence surveys conducted in high-incidence countries since 1990 until August, 2019, a median of 50·4% (range 36·1–79·7%) of detected bacteriologically confirmed tuberculosis was subclinical, defined as the absence of the survey-specified screening symptoms.[5] This proportion showed no correlation with the tuberculosis

Lancet Infect Dis 2024

Published **Online** March 12, 2024 https://doi.org/10.1016/S1473-3099(24)00011-2

See **Online/Comment** https://doi.org/10.1016/S1473-3099(24)00069-0

Department of Global Health, Amsterdam University Medical Centers, Amsterdam, Netherlands (L Stuck PhD, E Klinkenberg PhD, Prof F Cobelens PhD); **Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands** (L Stuck, Prof F Cobelens); **Global Fund Project Management Unit, International Health, Federal Ministry of Health, Khartoum, Sudan** (N Abdelgadir Ali MD); **Research and Development Centre, Alfjr College for Science and Technology, Khartoum, Sudan** (E A Basheir Abukaraig MD); **National Tuberculosis Control Programme, Ghana Health Service, Accra, Ghana** (Y Adusi-Poku MD); **Sustaining Technical and Analytical Resources, Accra, Ghana** (Z Alebachew Wagaw MD); **Research Unit, Common Management Unit [TB, HIV/AIDS & Malaria], Islamabad, Pakistan** (R Fatima MD); **Ministry of Health, Lusaka, Zambia** (N Kapata PhD, P Kapata-Chanda PhD); **Zambia National Public Health Institute, Lusaka, Zambia** (N Kapata); **Makerere University Lung Institute & Division of Pulmonary Medicine, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda** (B Kirenga PhD); **Ministry of Health National TB and Leprosy Programme, Maseru, Lesotho** (L B Maama-Maime MD,

T J Raleting Letsie MD); **National Institute for Medical Research, Muhimbili Research Centre, Dar es Salaam, Tanzania** (Prof S G Mfinanga PhD, M Senkoro PhD); **University College London, London, UK** (Prof S G Mfinanga); **Alliance for Africa Health and Research (A4A), Dar es Salaam, Tanzania** (Prof S G Mfinanga); **Human Sciences Research Council, Cape Town, South Africa** (S Moyo PhD); **Tuberculosis Programme, National Department of Health, Pretoria, South Africa** (L Mvusi MD); **National Tuberculosis and Leprosy Programme, Windhoek, Namibia** (N Nandjebo RN); **Ministry of Health, Ha Noi, Viet Nam** (H V Nguyen PhD); **National Lung Hospital, National Tuberculosis Control Programme, Ha Noi, Viet Nam** (H B Nguyen PhD); **Nigeria Centre for Disease Control, Abuja, Nigeria** (J Obasanya MD); **Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, Banjul, The Gambia** (B Adedapo Olufemi PhD); **WHO, Abuja, Nigeria** (P Patrobas Dashi MD*); **Ministry of Health and Social Services, Windhoek, Namibia** (N Ruswa MD); **Makerere University School of Public Health, Kampala, Uganda** (E Rutebemberwa PhD); **National Center for TB and Leprosy Control, Phnom Penh, Cambodia** (T Sivanna MD, H C Yuda MD); **Global Tuberculosis Programme, WHO, Geneva, Switzerland** (I Law MBBS); **Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, Japan** (I Onozaki MD); **KNCV Tuberculosis Foundation, The Hague, Netherlands** (E Tiemersma PhD)

*Dr Patrobas Dashi retired in November, 2022

Correspondence to: Prof Frank Cobelens, Amsterdam Institute for Global Health and Development, 1105 BP Amsterdam, Netherlands. **f.cobelens@aighd.org**

Research in context

Evidence before this study

Subclinical tuberculosis has gained attention as a form of tuberculosis disease that could contribute considerably to the burden of pulmonary tuberculosis among adults in high-incidence settings. Estimating the proportion of prevalent tuberculosis in the general population that is subclinical requires data from community prevalence surveys in which bacteriological sputum examination was done on all participants or (as is most common) on participants who had tuberculosis-suggestive abnormalities on chest x-ray or tuberculosis-suggestive symptoms upon screening.

We searched MEDLINE and Embase for original full-length articles, published between Jan 1, 1990, and July 1, 2021, of community prevalence surveys with combinations of the search terms "tuberculosis", "prevalence", "community", "survey", "screening", "subclinical", and "asymptomatic". In addition, we searched a database of reports of national tuberculosis prevalence surveys done with WHO. We excluded studies that primarily included children, pregnant people, people living with HIV, incarcerated people, migrants, and household contacts of tuberculosis patients. We found articles and reports for 48 single surveys, of which 24 were national surveys and 24 were surveys done in subnational populations. All these surveys detected subclinical alongside clinical tuberculosis, but with varying prevalence and proportions, with diverse definitions for tuberculosis and in particular for subclinical tuberculosis, including absence of persistent cough, absence of cough of any duration, or absence of cough or additional symptoms (eg, fever and weight loss). A systematic review that included 28 of these surveys concluded that a median of half of the survey participants with bacteriologically confirmed tuberculosis had not reported the screening symptoms, acknowledging that these symptoms were different for different surveys. An in-depth analysis of data from a national prevalence survey in Zambia showed that 40% of participants detected with bacteriologically confirmed tuberculosis did not report cough persisting for 2 or more weeks but that, of these, 78% had at least one other tuberculosis-suggestive symptom. This finding suggests that the burden of subclinical tuberculosis strongly depends on the definition used. An individual participant meta-analysis of 26 national and subnational surveys published in 2023 investigated the association between subclinical versus clinical tuberculosis prevalence and prevalence of non-communicable diseases and related risk factors. That study found that a median of 38% of tuberculosis was subclinical, defined as absence of any of four tuberculosis-suggestive symptoms, but with different definitions of tuberculosis across the included surveys. These differences in definitions hamper comparisons between populations and between subgroups across populations that are necessary to address major evidence gaps, such as how much the burden of subclinical tuberculosis is determined by its clinical definition, how it varies demographically (by gender, age, and geography), and to what extent it represents a burden of infectiousness.

Added value of this study

Our study quantified, across countries in Africa and Asia, the prevalence of subclinical tuberculosis according to different case definitions of this condition. We used data from 602 863 adults in 12 national tuberculosis prevalence surveys conducted with a similar protocol and we applied standardised definitions across the individual survey datasets. Our study provides robust estimates for the proportion of prevalent tuberculosis that is subclinical across surveys and countries, both unadjusted and adjusted for incomplete sensitivity of chest x-ray and missing or contaminated culture results. This approach takes the underestimation of subclinical tuberculosis prevalence into account, which is inherent to surveys in which not all participants have bacteriological sputum examination. We estimated that, overall, up to 83% of adults in the community with culture-confirmed tuberculosis report no cough persisting for 2 or more weeks, up to 63% report no cough of any duration, and (based on a subset of surveys) up to 28% report no tuberculosis-suggestive symptoms (ie, cough, fever, chest pain, night sweats, or weight loss) at all. Tuberculosis without persistent cough or any cough was significantly more frequent among women than among men. Our study also provides an estimate of the proportion of subclinical tuberculosis that is infectious based on microscopic sputum smear examination; this is 29% among people without persistent cough and 23% among people without any cough.

Implications of all the available evidence

Our study shows that the burden of subclinical pulmonary tuberculosis strongly depends on how the term subclinical is defined, and that earlier estimates of burden that do not distinguish between different definitions will be biased. These previous estimates should also not be interpreted as reflecting asymptomatic tuberculosis, because only a subset of subclinical tuberculosis is entirely without tuberculosis-suggestive symptoms. In high-incidence communities, most people with pulmonary tuberculosis do not report persistent cough. Since, in routine health care, persistent cough is often the entry symptom for the tuberculosis diagnostic pathway, these people will face long diagnostic delays or might not be diagnosed at all. This could be an even bigger problem for women, who (in our data) had tuberculosis without any cough more often than men. The considerable percentage of people with tuberculosis who do not cough but do have a positive sputum smear, which is known to be associated with infectiousness, adds to recent epidemiological observations and modelling studies that suggest that tuberculosis without persistent cough still contributes to transmission. The large burden of untreated subclinical tuberculosis could be an important contributor to the shortfall in decline in the global tuberculosis incidence despite intensive programmatic efforts. Ending the global tuberculosis epidemic in accordance with the Sustainable Development Goals requires urgent scale up in community case finding approaches that are independent of cough for high-incidence settings, such as mass chest x-ray screening.

prevalence measured in the survey, suggesting that many patients with tuberculosis could go unnoticed by diagnostic services.[4,6]

Despite growing attention to subclinical tuberculosis, the clinical phenotype remains poorly defined. Most surveys in the review used persistent cough of 2 weeks or more as the only screening symptom, whereas several others included other tuberculosis-suggestive symptoms, such as cough of any duration, fever, night sweats, and weight loss.[5] In a prevalence survey from Zambia, 60% of detected patients with tuberculosis did not report persistent cough; however, a third of these patients had other tuberculosis-suggestive symptoms for at least 4 weeks and only 9% reported no symptoms at all.[7] This finding suggests that the prevalence of subclinical tuberculosis strongly depends on its definition. Such reports also show the need for epidemiological data from various parts of the world, based on well defined clinical case definitions, to understand the importance of subclinical disease for health care, its contribution to the global tuberculosis burden and, potentially, to *Mycobacterium tuberculosis* transmission.

We aimed to investigate the prevalence of subclinical pulmonary tuberculosis according to different case definitions and explore its association with demographic characteristics, sputum bacterial load, and selected tuberculosis risk factors.

***Panel:* Different definitions for subclinical tuberculosis used in this study**

Definition 1: no persistent cough
Tuberculosis that has a positive sputum culture but not accompanied by self-reported cough persisting for 2 weeks or more before the date of screening, irrespective of other symptoms

Definition 2: no cough
Tuberculosis that has a positive sputum culture but not accompanied by self-reported cough (regardless of its duration), irrespective of other symptoms

Definition 3: no symptoms
Tuberculosis that has a positive sputum culture but not accompanied by any of cough, fever, night sweats, weight loss, or chest pain, regardless of reported symptom duration

Methods

Study selection, design, and population

For this systematic review and individual participant data meta-analysis, we used national tuberculosis prevalence surveys done from 2007 up to and including 2019 with WHO, which followed largely similar protocols and applied standardised methods for data collection.[8,9] We selected these surveys based on a WHO publication[9] that listed all national tuberculosis prevalence surveys done between 2007 and 2016. For the surveys done since 2016, WHO provided the details. LS and FC contacted the investigators for each survey to request the survey dataset and additional information. The datasets obtained were harmonised and assembled into a single aggregated dataset by LS. For all surveys there had been external quality assurance of data collection and data management (appendix pp 3–4); therefore we did not perform quality appraisal of the obtained datasets.

Each survey included stratified multistage cluster selection, an enumeration census, tuberculosis screening for those aged 15 years or older in the enumerated household by chest x-ray and symptoms reporting with standard staff-administered questionnaires, and diagnostic testing for those who screened positive.[8] In some surveys, data were collected on smoking status and educational attainment, or HIV testing was offered. Individuals with abnormalities on chest x-ray or reporting screening symptoms (or both) that were suggestive of tuberculosis provided sputum samples for diagnostic tests, including culture, and were interviewed about their clinical history. Culture methods were standardised across the included surveys as part of the survey design (appendix pp 3–4).

Data preparation and standardisation

Included in the individual participant data meta-analysis were all survey participants aged 15 years or older with non-missing data from the symptom screening, non-missing data from the chest x-ray screening, and no self-reported previous history of tuberculosis. A standardised meta-analytical screening rule was applied across surveys, ignoring the original survey-specific screening rules. In this screening rule, a positive screen resulted from either the presence of cough for 2 weeks or more or an abnormality suggestive of tuberculosis detected on field-read chest x-ray, which were the only two screening metrics reliably collected across all surveys. Similarly ignoring survey-specific case definitions, we standardised the definition for tuberculosis disease across all surveys as a positive *M tuberculosis* sputum culture (the only tuberculosis diagnostic test systematically done across all surveys), regardless of other examination results. If participants were eligible for sputum testing based on survey-specific criteria but not on the standardised meta-analytical screening criteria, their culture results were discarded. This data extraction resulted in a single standardised multicountry survey dataset.

See Online for appendix

Case definitions of subclinical tuberculosis

Our analyses considered three case definitions for subclinical tuberculosis used in other studies (panel).[10–12] First, no persistent cough: sputum-culture-positive tuberculosis not accompanied by self-reported cough persisting for 2 weeks or more before the date of screening, irrespective of other symptoms. Second, no cough: sputum-culture-positive tuberculosis not accompanied by self-reported cough regardless of its duration, irrespective

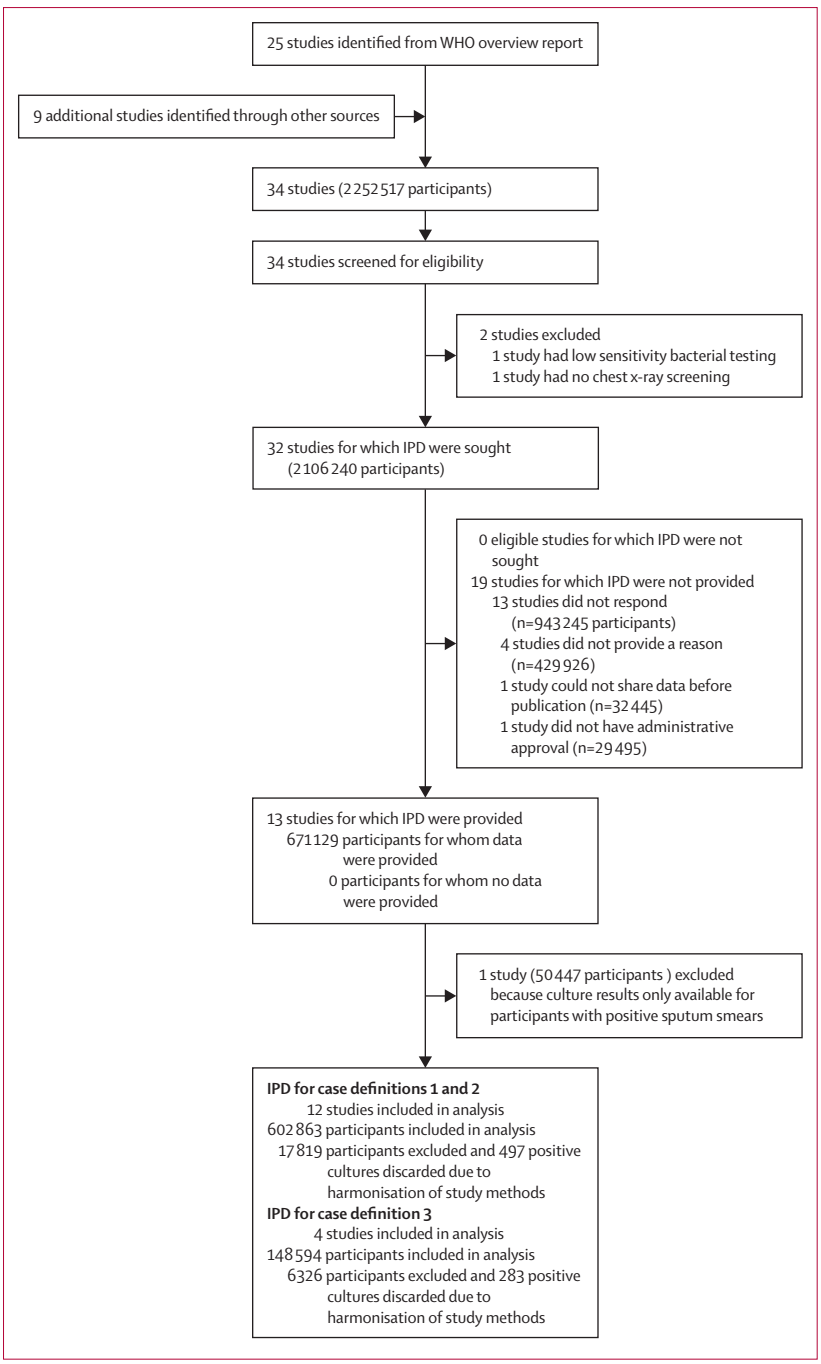

Figure 1: **Study selection, including numbers of participants**
PRISMA flow chart adapted for IPD meta-analyses. Case definitions are in the panel. IPD=individual participant data.

of other symptoms. Third, no symptoms: sputum-culture-positive tuberculosis not accompanied by any of cough, fever, night sweats, weight loss, or chest pain, regardless of reported symptom duration. For each case definition for subclinical tuberculosis, clinical tuberculosis was defined as sputum-culture-positive tuberculosis not meeting that case definition.

Data analysis

Analyses were done in R (version 4.2.2),[13–15] with a one-stage individual participant meta-analysis approach in which individual participant data were assembled in a single dataset and analyses done on the pooled data.[16] We estimated both unadjusted and adjusted proportions of subclinical tuberculosis, as follows.

Six screening groups were definable across all datasets based on combinations of chest x-ray results (positive or negative) and duration of cough reported during screening. Group A had no cough and a negative chest x-ray, group B had cough for less than 2 weeks and a negative chest x-ray, group C had cough for at least 2 weeks and a negative chest x-ray, group D had no cough and a positive chest x-ray, group E had cough for less than 2 weeks and a positive chest x-ray, and group F had cough for at least 2 weeks and a positive chest x-ray. Participants in groups C and F met our standardised definition for screen-positive, whereas participants in groups A, B, D, and E did not. In all source datasets, participants in screening groups D, E, C, and F were eligible for sputum culture; tuberculosis disease status for the participants in screening groups A and B was considered unknown, regardless of any testing data available from the source.

We calculated the proportion of subclinical tuberculosis defined as no persistent cough (definition 1) as the observed or estimated number of participants with tuberculosis in screening groups A, B, D, and E divided by the observed or estimated total number of participants with tuberculosis across all screening groups. The proportion of subclinical tuberculosis when defined as no cough (definition 2) was calculated similarly but replacing the numerator with the number of participants with tuberculosis disease in screening groups A and D. Assessment of the proportion of subclinical tuberculosis by definition 3 (no symptoms) was restricted to participants in Cambodia, The Gambia, Ghana, and Lao People's Democratic Republic (referred to as Laos hereafter), as the symptoms fever, night sweats, weight loss, and chest pain were measured at screening in only these surveys. This proportion was calculated as the estimated number of instances of tuberculosis that reported no symptoms divided by the estimated total number of participants with tuberculosis across all screening groups (appendix pp 4, 9). These analyses were repeated within strata defined by country, geography (ie, urban or rural), age, and gender. Gender in these surveys was self-reported.

We based the unadjusted analyses on the number of participants with subclinical tuberculosis according to the three case definitions as observed in the individual participant data meta-analysis dataset. In the adjusted analyses we imputed uninterpretable culture results (ie, missing or contaminated cultures among the ordered tests) and missed positive cultures among participants who were not eligible for sputum testing because of

	Case definition 1: no persistent cough		Case definition 2: no cough		Overall (n=602 863)
	No cough or cough for <2 weeks (n=574 029)	Cough for ≥2 weeks (n=28 834)	No cough (n=495 634)	Cough (n=107 229)	
Region					
Africa	343 854 (59·9%)	14 116 (49·0%)	315 876 (63·7%)	42 094 (39·3%)	357 970 (59·4%)
Asia	230 175 (40·1%)	14 718 (51·0%)	179 758 (36·3%)	65 135 (60·7%)	244 893 (40·6%)
Country					
Cambodia	34 364 (6·0%)	1307 (4·5%)	15 398 (3·1%)	20 273 (18·9%)	35 671 (5·9%)
Ghana	57 581 (10·0%)	1787 (6·2%)	53 997 (10·9%)	5371 (5·0%)	59 368 (9·8%)
Laos	35 623 (6·2%)	3042 (10·6%)	33 649 (6·8%)	5016 (4·7%)	38 665 (6·4%)
Lesotho	18 213 (3·2%)	975 (3·4%)	16 939 (3·4%)	2249 (2·1%)	19 188 (3·2%)
Nigeria	41 349 (7·2%)	2235 (7·8%)	38 710 (7·8%)	4874 (4·5%)	43 584 (7·2%)
Pakistan	96 297 (16·8%)	7051 (24·5%)	76 941 (15·5%)	26 407 (24·6%)	103 348 (17·1%)
South Africa	30 569 (5·3%)	1236 (4·3%)	29 343 (5·9%)	2462 (2·3%)	31 805 (5·3%)
Sudan	74 282 (12·9%)	2316 (8·0%)	73 568 (14·8%)	3030 (2·8%)	76 598 (12·7%)
The Gambia	41 583 (7·2%)	870 (3·0%)	37 841 (7·6%)	4612 (4·3%)	42 453 (7·0%)
Uganda	37 644 (6·6%)	2495 (8·7%)	31 616 (6·4%)	8523 (7·9%)	40 139 (6·7%)
Viet Nam	63 891 (11·1%)	3318 (11·5%)	53 770 (10·8%)	13 439 (12·5%)	67 209 (11·1%)
Zambia	42 633 (7·4%)	2202 (7·6%)	33 862 (6·8%)	10 973 (10·2%)	44 835 (7·4%)
Geography					
Rural	340 537 (59·3%)	18 589 (64·5%)	289 582 (58·4%)	69 544 (64·9%)	359 126 (59·6%)
Urban	233 492 (40·7%)	10 245 (35·5%)	206 052 (41·6%)	37 685 (35·1%)	243 737 (40·4%)
Age group (years)					
15–24	168 818 (29·4%)	4432 (15·4%)	147 592 (29·8%)	25 658 (23·9%)	173 250 (28·7%)
25–34	127 863 (22·3%)	4339 (15·0%)	110 815 (22·4%)	21 387 (19·9%)	132 202 (21·9%)
35–44	100 084 (17·4%)	4780 (16·6%)	86 861 (17·5%)	18 003 (16·8%)	104 864 (17·4%)
45–54	77 545 (13·5%)	4924 (17·1%)	66 509 (13·4%)	15 960 (14·9%)	82 469 (13·7%)
55–64	51 845 (9·0%)	4444 (15·4%)	43 747 (8·8%)	12 542 (11·7%)	56 289 (9·3%)
≥65	47 874 (8·3%)	5915 (20·5%)	40 110 (8·1%)	13 679 (12·8%)	53 789 (8·9%)
Gender					
Women	332 299 (57·9%)	14 735 (51·1%)	288 410 (58·2%)	58 624 (54·7%)	347 034 (57·6%)
Men	241 730 (42·1%)	14 099 (48·9%)	207 224 (41·8%)	48 605 (45·3%)	255 829 (42·4%)
Cough status					
No cough	495 634 (86·3%)	0	495 634 (100%)	0	495 634 (82·2%)
Cough for <2 weeks	78 395 (13·7%)	0	0	78 395 (73·1%)	78 395 (13·0%)
Cough for ≥2 weeks	0	28 834 (100%)	0	28 834 (26·9%)	28 834 (4·8%)
Chest x-ray screen result					
Positive	42 466 (7·4%)	10 938 (37·9%)	35 241 (7·1%)	18 163 (16·9%)	53 404 (8·9%)
Negative	531 563 (92·6%)	17 896 (62·1%)	460 393 (92·9%)	89 066 (83·1%)	549 459 (91·1%)
Culture result					
Positive	1148 (0·2%)	796 (2·8%)	773 (0·2%)	1171 (1·1%)	1944 (0·3%)
Negative	32 918 (5·7%)	20 224 (70·1%)	27 126 (5·5%)	26 016 (24·3%)	53 142 (8·8%)
Contaminated, not done when ordered, or not ordered	539 963 (94·1%)	7814 (27·1%)	467 735 (94·4%)	80 042 (74·6%)	547 378 (90·8%)

Table 1: **Sample descriptions, disaggregated by screening group**

false-negative chest x-ray screen (ie, abnormalities missed by the reader or a normal image despite a positive culture). Missed positive cultures among those ordered were assumed to be missing at random. To estimate the tuberculosis prevalence among individuals with a screen-negative chest x-ray, we did single imputation with survey-stratified logistic regressions, producing participant-level probabilities of having culture-positive tuberculosis across the entire sample, summed within screening groups to estimate total screening group-level

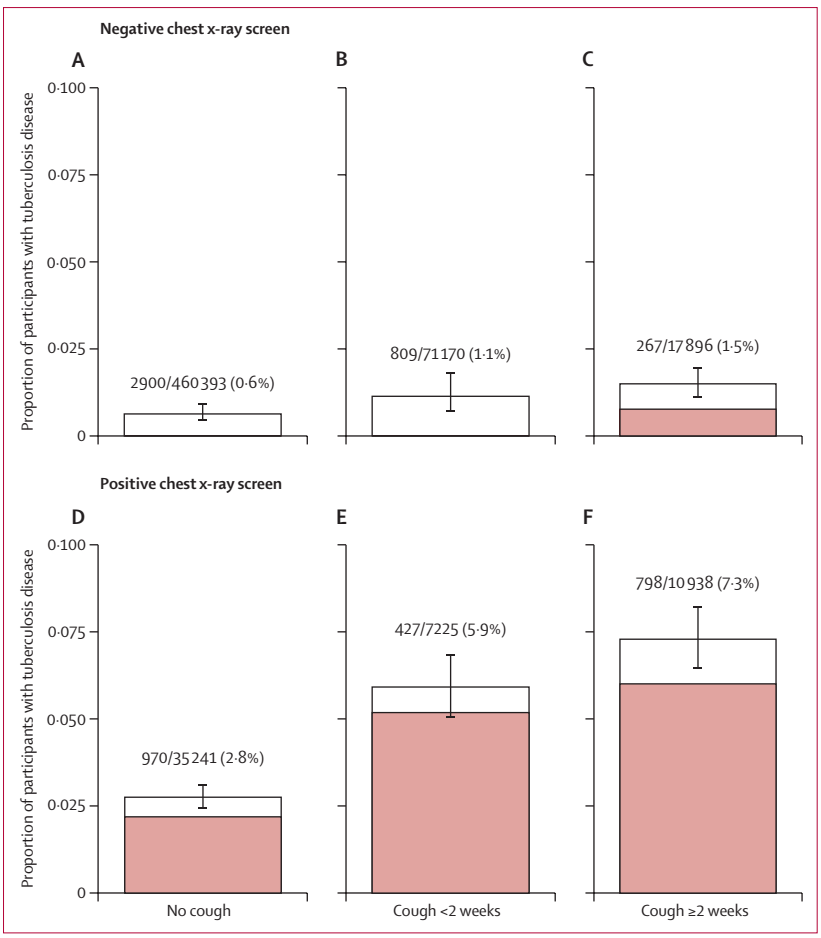

Figure 2: **Estimated counts and proportions of tuberculosis disease from bootstrapped median models with 95% CIs**

The full sample was split into six screening groups defined by cough presence and duration and chest x-ray screening result. Darker bars represent positive cultures observed in the surveys: group A=0, group B=0, group C=158, group D=773, group E=375, group F=658.

prevalence (appendix p 4). In sensitivity analyses, we varied the additional number of positive cultures estimated to have occurred among participants with screen-negative chest x-ray to examine its effect on the proportion of tuberculosis disease that was subclinical by each case definition.

Next, subgroup analyses investigated the effect modification of HIV status, smoking, and educational attainment on the proportion of subclinical tuberculosis on three separate subsets of surveys for which the individual's status for the effect modifier in question was known. These subgroup analyses were based on the adjusted estimates; therefore, we did not assess statistical significance.

All these estimations and analyses, including each single imputation, were repeated 10 000 times in a hierarchical bootstrap to provide confidence limits for the reported numbers (appendix p 4). Results are reported as medians of the bootstrap distributions, with 95% CIs defined at the 0·025 and 0·975 quantiles.

We then summarised within each screen-positive screening group the bacillary load for participants with confirmed tuberculosis disease, measured by sputum smear microscopy in a subset of surveys.

Finally, we assessed risk factors for subclinical tuberculosis, relative to clinical tuberculosis. As this could be done only for participants with tuberculosis disease who had an abnormality on chest x-ray, this analysis was restricted to screening groups D, E, and F. We analysed associations between putative risk factors and the odds of subclinical tuberculosis by each of the three case definitions in hierarchical logistical regression models that included a random intercept for source dataset and fixed effects for gender, age group, geography (urban or rural), and region (Asia or Africa).

Role of the funding source

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

Results

We identified 34 nationally representative tuberculosis prevalence surveys, 18 from Asia and 16 from Africa (figure 1; appendix p 6). Two surveys were excluded because no chest x-ray screening had been done or because the culture method was considered low sensitivity. We sought individual participant data for the remaining 32 surveys and obtained full datasets for 13, of which one was excluded because culture results were available only for participants with sputum smear-positive results. Datasets were assembled from the remaining 12 nationally representative surveys conducted between 2010 and 2019 in The Gambia, Ghana, Lesotho, Nigeria, South Africa, Sudan, Uganda, and Zambia (Africa); and Cambodia, Laos, Pakistan, and Viet Nam (Asia; appendix pp 7–8).[9,17–19] The combined dataset contained records for 602 863 participants (table 1; appendix pp 7–9). Of these, 357 970 (59·4%) were from Africa, 244 893 (40·6%) were from Asia, 347 034 (57·6%) were women, 305 452 (50·7%) were younger than 35 years, and 359 126 (59·6%) lived in areas designated as rural. Cough for 2 weeks or more was reported by 28 834 (4·8%) participants, cough for less than 2 weeks by 78 395 (13·0%), and 495 634 (82·2%) did not report any cough. All chest x-rays were human read, and tuberculosis-suggestive abnormalities were detected for 53 404 (8·9%). On the basis of the meta-analysis criteria, 71 300 (11·8%) participants were screen-positive eligible for culture testing, of whom 55 485 (77·8%) had an interpretable culture result. 1944 (0·3%) cultures of the 602 863 participants were positive for *M tuberculosis*.

The median proportion of participants with tuberculosis that did not report the screening symptom in the original surveys was 50·4% (range 36·1–70·4%, IQR 42·0–59·1%) in the 12 included surveys and 55·7% (range 30·3–86·0%, IQR 50·5–68·1%) in 18 of the

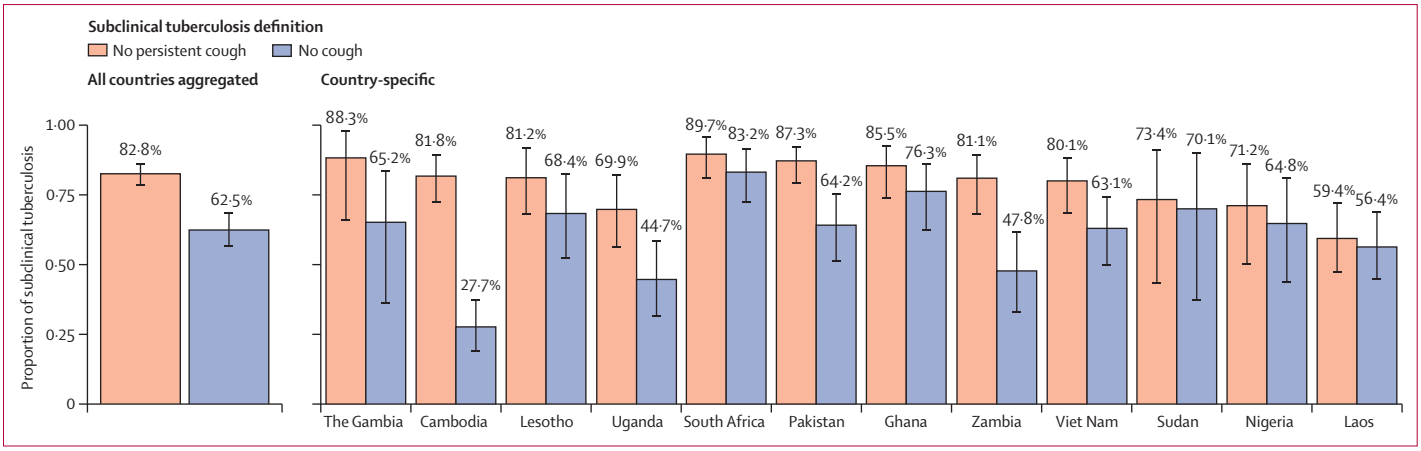

Figure 3: **Proportion of tuberculosis disease that is subclinical by two definitions, and by country**
The left panel is aggregated over the full 12-country dataset. The right panel is disaggregated by country.

19 surveys for which individual participant data were not obtained (data unavailable for one).

Of all 1944 participants with tuberculosis, 796 (40·9%) reported cough for 2 weeks or more, 375 (19·3%) reported cough for less than 2 weeks, and 773 (39·8%) reported no cough, resulting in unadjusted proportions of subclinical tuberculosis of 59·1% (95% CI 55·8–62·3) for no persistent cough and 39·8% (36·6–43·0) for no cough (figure 2; appendix pp 9–10). The adjusted number of tuberculosis cases was 1065 (896–1257) among participants reporting cough for 2 weeks or more, 1237 (854–1804) among participants reporting cough for less than 2 weeks, and 3870 (2808–5419) among those not reporting any cough (figure 2). This resulted in adjusted proportions of subclinical tuberculosis of 82·8% (78·6–86·6) for no persistent cough and 62·5% (56·6–68·7) for no cough. The adjusted country-specific proportion without persistent cough ranged from 59·4% in Laos to 89·7% in The Gambia; the adjusted proportion without any cough ranged from 27·7% in Cambodia to 83·2% in South Africa (figure 3). Halving the estimated number of additional tuberculosis cases reduced the pooled proportions to 77·1% for no persistent cough and 57·2% for no cough (appendix pp 11–12).

In the restricted dataset from four countries for which information about symptoms other than cough was available (appendix pp 13–14), the unadjusted proportion of subclinical tuberculosis was 69·7% (95% CI 63·8–75·4) when defined as no persistent cough and 33·9% (28·4–39·7) when defined as no cough at all. The adjusted proportions were 85·2% (80·7–89·4) for no persistent cough and 45·4% (36·1–57·0) for no cough (appendix p 15). Of the 547 participants with tuberculosis in this restricted dataset, 436 (79·7%) reported at least one other symptom and 111 (20·3%) reported none of these symptoms, resulting in an unadjusted proportion of tuberculosis without symptoms of 20·3% (95% CI 15·5–25·1; appendix pp 10, 16). The adjusted number of tuberculosis cases was 774 (530–1111) among participants who did report other symptoms and 292 (165–538) among participants who did not report any other symptom. These adjusted numbers resulted in an adjusted proportion of tuberculosis without symptoms of 27·7% (21·0–36·4), ranging from 13·7% in Cambodia to 53·7% in Lesotho (appendix p 15). Halving the estimated number of additional tuberculosis cases reduced the pooled proportion to 25·0% (appendix pp 11–12).

Younger age groups, women, and urban residents tended to have higher average proportions of subclinical tuberculosis disease, regardless of the case definition (appendix pp 17–18).

Hierarchical regressions included 1813 observations for subclinical tuberculosis definitions 1 and 2 and 555 observations for definition 3 from participants with positive cultures and chest x-ray results and non-missing gender, age, geography, and region data (table 2). Subclinical tuberculosis made up 63·7% of the subset for definition 1 of subclinical tuberculosis. Tuberculosis in men was significantly less likely to be subclinical by definitions 1 and 2 than tuberculosis in women (table 2). Otherwise, no associations were found, although statistical significance was almost reached for an increased probability in urban compared with rural areas of subclinical tuberculosis by any definition (table 2).

Sputum smear grading was associated with both chest x-ray screen positivity and cough duration. Subclinical tuberculosis was less likely to be smear positive, but nonetheless presented with 29·1% (95% CI 25·2–33·0) positive (grades 1+ to 3+) or scanty smear results for definition 1, and 23·1% (18·8–27·4) for definition 2 (figure 4; appendix p 19). Of 796 participants with culture-positive tuberculosis and persistent cough, 262 (32·9%) had a positive or scanty smear result despite a chest x-ray reported as normal.

Subgroup analyses included data from three surveys for HIV, from seven surveys for smoking history, and

	Case definition 1: no persistent cough (n=1813)		Case definition 2: no cough (n=1813)		Case definition 3: no symptoms (n=555)	
	OR (Wald's 95% CI)	p value	OR (Wald's 95% CI)	p value	OR (Wald's 95% CI)	p value
Intercept	2·78 (1·57–4·91)	<0·001	0·93 (0·53–1·63)	0·80	0·27 (0·07–0·99)	0·049
Gender						
Male	0·79 (0·63–0·97)	0·021	0·76 (0·62–0·93)	0·006	0·82 (0·51–1·33)	0·429
Age group (years)						
25–34	0·83 (0·54–1·29)	0·385	1·38 (0·90–2·11)	0·151	1·57 (0·63–3·87)	0·331
35–44	0·65 (0·43–1·00)	0·056	1·05 (0·69–1·59)	0·70	1·06 (0·43–2·62)	0·91
45–54	0·87 (0·57–1·34)	0·55	1·07 (0·7–1·63)	0·72	0·92 (0·34–2·47)	0·87
55–64	0·68 (0·43–1·05)	0·092	1·1 (0·71–1·69)	0·62	1·17 (0.44–3.10)	0·749
≥65	0·79 (0·52–1·20)	0·29	1·23 (0·82–1·85)	0·29	0·84 (0·33–2·16)	0·72
Geography						
Urban	1·23 (0·99–1·54)	0·062	1·18 (0·95–1·46)	0·12	1·64 (1·00–2·68)	0·051
Region						
Asia	0·78 (0·38–1·60)	0·50	0·61 (0·3–1·24)	0·17	0·47 (0·06–3·44)	0·45

The dataset for case definition 3 was restricted to the surveys from Cambodia, The Gambia, Lesotho, and Uganda. The reference group for age was 15–24 years. OR=odds ratio.

Table 2: **Hierarchical regression results for three case definitions for subclinical tuberculosis**

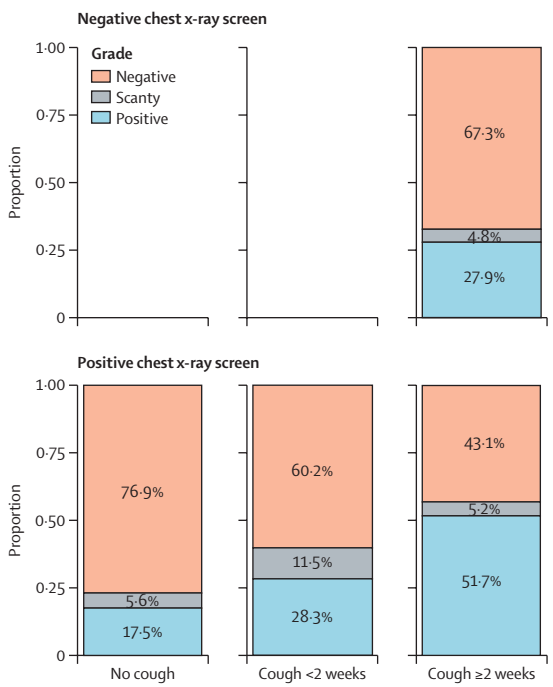

Figure 4: **Distribution of sputum smear examination grade in people with positive *Mycobacterium tuberculosis* culture, disaggregated by chest x-ray screen result and self-reported duration of cough**

from eight surveys for educational attainment. Little difference, if any, was seen between people with and without HIV (appendix p 20). Tuberculosis disease among both people with high educational attainment and those with a smoking history was somewhat less likely to be subclinical, although all confidence intervals were overlapping.

Discussion

Across 12 nationally representative surveys from Africa and Asia, to which we applied standardised screening and diagnostic criteria, up to 83% of prevalent pulmonary tuberculosis was without persistent cough for 2 weeks or more and up to 63% was without any cough; across a subset, up to 28% was without any typical tuberculosis symptom. Tuberculosis without persistent or any cough was more frequent in women. Subclinical tuberculosis, regardless of definition, showed no apparent association with age, HIV status, smoking, or educational attainment. Although sputum bacterial load increased with duration of cough, 23% of people with tuberculosis without any cough had positive or scanty sputum smears.

Subclinical tuberculosis appears not to be a distinct state of disease. Rather, it defines the situation in which an individual with bacteriologically confirmed tuberculosis does not report the screening symptom. For example, although one survey classified tuberculosis with fever, weight loss, and cough for no more than 1 week as subclinical, another classified this as clinical. The prevalence of subclinical tuberculosis thereby strongly depends on the case definition. Clearly, tuberculosis without any tuberculosis-suggestive symptom was much less common than tuberculosis without persistent cough or any cough.

For this analysis we selected three case definitions used in previous studies. Although each of these could be proposed as a case definition for subclinical tuberculosis, they probably have different relevance for diagnostic practice and perceived association with *M tuberculosis* transmission.

In many tuberculosis control programmes, persistent cough is the primary symptom that sets off the

diagnostic process for HIV-negative patients presenting at health facilities. Since persistent cough is highly prevalent in any population (ranging from 3% to 25% across the 12 surveys in our analysis), clinicians generally take the presence of other symptoms into account when ordering tuberculosis diagnostic tests.[20] Although few qualitative data exist on these diagnostic considerations, tuberculosis patients not reporting persistent cough will probably face diagnostic delays. Cough has for long been perceived as the primary mechanism by which *M tuberculosis* is transmitted,[21] although recent bioaerosol studies suggest that cough is not needed for expelling bacilli.[22–24] In resource-constrained settings, diagnosing and treating patients with tuberculosis who do not cough might therefore not be seen as a public health priority. Fever, weight loss, night sweats, and chest pain are commonly considered additional tuberculosis-suggestive symptoms.[20] On the basis of an individual participant meta-analysis of cross-sectional studies,[25] WHO recommends people living with HIV be tested for tuberculosis if they have any of cough, fever, weight loss, or night sweats, irrespective of duration (WHO four-symptom screen).[26] For any patient presenting at a health facility, particularly those not in HIV care, not reporting any tuberculosis-suggestive symptom will probably not trigger the tuberculosis diagnostic process. For those meeting our no symptoms definition, the tuberculosis diagnosis will therefore almost certainly be missed, except in active case finding based on radiological screening.

Our unadjusted estimates of the subclinical tuberculosis burden (59% for definition 1, 40% for definition 2, and 20% for definition 3) provide nuance to the 50% reported in a systematic review that included all but two surveys included in our analysis and defined subclinical tuberculosis as absence of the survey-defined screening symptoms.[5] We consider these unadjusted estimates conservative, because they disregard uninterpretable culture results and false-negative chest x-ray readings that clearly occurred (tuberculosis cases in group C [people with cough for at least 2 weeks but a negative chest x-ray]; figure 2). The chest x-ray misclassification in particular will bias the proportion of subclinical tuberculosis, since it primarily missed tuberculosis diagnoses among survey participants who did not report the screening symptom of persistent cough that we applied consistently in our meta-analysis. Our adjusted estimates, which included missed subclinical tuberculosis diagnoses due to false-negative chest x-ray screening or uninterpretable culture results (83% for definition 1, 63% for definition 2, and 28% for definition 3), are therefore closer to reality. The regression models underlying the imputation for missed diagnoses due to false-negative chest x-ray also considered potential differences in chest x-ray detection between tuberculosis patients with subclinical versus clinical presentation. The main limitation of these results is that these regression models included age, gender, and urban versus rural designation but not HIV status, smoking, or indicators of socioeconomic status, because these data were not available for all surveys. We could thereby have overestimated or underestimated the number of missed diagnoses. However, our sensitivity analyses show that, across a plausible range of deviations, the effect on the estimated proportion of subclinical tuberculosis was small.

This high prevalence of subclinical tuberculosis poses major problems for tuberculosis control because modelling of data from the prechemotherapy era suggests that subclinical tuberculosis often leads to clinical tuberculosis or death,[27,28] and a study from Viet Nam suggested that subclinical smear-positive tuberculosis contributes to transmission of *M tuberculosis*, regardless of the case definition used.[10] In our study, 21% of detected tuberculosis patients without persistent cough and 18% of patients without any cough had a positive sputum smear. Smear-positive tuberculosis is 4–5 times more infectious than smear-negative tuberculosis.[29,30] Subclinical tuberculosis could therefore be a major source of transmission globally, and delayed or missed diagnoses associated with it could have contributed to the less than anticipated effect of tuberculosis control efforts on global tuberculosis incidence over the past decades.[31,32]

Our estimates are based on tuberculosis detected in community surveys. Compared with patients presenting with tuberculosis disease at health care facilities, those detected in community surveys are more likely to have been missed when they sought health care earlier,[33] or not to have symptoms that prompted them to seek care.[5] Therefore, prevalence surveys tend to overestimate the subclinical proportion that can be expected in clinical settings. Nonetheless, current diagnostic practice in most resource-poor settings will miss large numbers of patients with tuberculosis, and enhanced case finding approaches, both in clinical settings and in the community, need to be scaled up urgently.

Although universal sputum testing might be indicated for selected groups at high risk, the approach currently most feasible is chest x-ray screening.[34] Reduced costs for digital x-ray equipment and availability of computer-aided detection software make chest x-ray screening a potentially cost-effective option in high-incidence settings.[35] Development of alternative inexpensive, sputum-free tests that indicate whether an individual has a high probability of tuberculosis should be prioritised.[36]

Our study shows that most subclinical tuberculosis is not asymptomatic. Therefore, another approach might be an adapted version of the WHO four-symptom screen for routine use that has sufficient positive predictive value in HIV-negative patients to warrant tuberculosis diagnostic testing. Since self-reported cough and its duration can be unreliable,[37] novel ways of detecting cough could be explored.[38]

Our data suggest that women with tuberculosis report cough less often than men, although it is possible that men with subclinical tuberculosis participated less often in the surveys (eg, by being away for work). We did not identify other potential target groups for prioritising enhanced case finding, but were limited by the availability of data across the surveys. Future community case finding studies should collect more detailed and standardised data on potential determinants of subclinical tuberculosis, including sociodemographic, clinical, microbiological, and environmental information.

Our study had limitations. We could include only 12 of 31 eligible surveys. Although in the original survey reports the median proportion of tuberculosis patients without the screening symptom was lower for the included than for the excluded studies, selection bias could have occurred. Despite the survey population samples being representative of the countries' populations, low participation rates for some subgroups (eg, young men) could have resulted in underestimation or overestimation of the proportion of subclinical tuberculosis. We considered including sampling weights for each individual survey, but the data required for this were incomplete and different surveys had applied weighting at different levels. HIV status of survey participants was not consistently ascertained. Even though we did not observe a clear difference in proportions of subclinical tuberculosis between people with culture-positive tuberculosis who are HIV positive and HIV negative, this limitation could have biased our adjusted estimates of subclinical tuberculosis prevalence, both for people living with HIV and overall. Neither did we have details on socioeconomic status. Although some surveys included socioeconomic status based on household asset scores, these are relative rather than absolute measures of wealth, precluding their use across countries.[39] Different culture methods, different numbers of sputum specimens inoculated, and potential differences in quality of sputum specimens could have resulted in between-survey variation in false-negative cultures. Similarly, differences in the way that participants were asked about specific symptoms could have led to between-survey variation in sensitivity and specificity of symptom screens. Finally, participants who do not cough can have difficulty producing sputum, which could have biased our results towards underestimating the proportion of tuberculosis disease without cough.

In conclusion, in countries with a high burden of tuberculosis in Asia and Africa, the majority of people with yet undiagnosed pulmonary tuberculosis do not report cough, irrespective of its duration. Diagnostic pathways only based on cough as the initiating symptom will delay diagnosis and treatment, potentially resulting in avoidable morbidity, mortality, and *M tuberculosis* transmission. Alternative case finding approaches should be expanded urgently.

Contributors
LS and FC conceptualised the study, with methodological input by EK, IL, IO, and ET, who also assisted in contacting the investigators of the included surveys and the data curation. LS performed the formal analyses, visualised the data, and wrote the original draft of the manuscript. NAA, EABA, YA-P, ZAW, RF, NK, PK-C, BK, LBM-M, SGM, SM, LM, NN, HVN, HBN, JO, BAO, PPD, TJRL, NR, ER, MS, TS, and HCY were investigators for the surveys for which individual-participant data were obtained and provided details on the data, their interpretation, and the appropriate standardisation of screening and diagnostic data. All authors provided comments on one or more draft versions and approved the final manuscript. LS and FC had access to all the data and FC had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
The study did not produce original data. De-identified individual participant data and a corresponding data dictionary defining each field in the set will be made available to others, conditional on approval by the providers of the respective original data. Additional related documents for the original datasets (eg, study protocol, statistical analysis plan, and informed consent form) can be made available upon request by the providers of the respective original data. Criteria for sharing depend on the data providers' institutional and national regulations. The corresponding author can be contacted to help to initiate these processes.

Acknowledgments
The study was supported by a grant to LS by the Mr Willem Bakhuys Roozeboom Foundation, Amsterdam, Netherlands (grant number 2022–8). We acknowledge the work of all who contributed to the design, field work, laboratory investigations, data management, and data analyses of the tuberculosis prevalence surveys that contributed to the individual-participant meta-analysis dataset.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in institutional affiliations and country names.

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