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REVIEW ARTICLE

Subclinical Tuberculosis Disease—A Review and Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology

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While it is known that a substantial proportion of individuals with tuberculosis disease (TB) present subclinically, usually defined as bacteriologically-confirmed but negative on symptom screening, considerable knowledge gaps remain. Our aim was to review data from TB prevalence population surveys and generate a consistent definition and framework for subclinical TB, enabling us to estimate the proportion of TB that is subclinical, explore associations with overall burden and program indicators, and evaluate the performance of screening strategies. We extracted data from all publicly available prevalence surveys conducted since 1990. Between 36.1% and 79.7% (median, 50.4%) of prevalent bacteriologically confirmed TB was subclinical. No association was found between prevalence of subclinical and all bacteriologically confirmed TB, patient diagnostic rate, or country-level HIV prevalence (*P* values, .32, .4, and .34, respectively). Chest Xray detected 89% (range, 73%–98%) of bacteriologically confirmed TB, highlighting the potential of optimizing current TB case-finding policies.

Keywords. subclinical TB; TB screening; TB prevalence surveys; symptom screening; chest X-ray screening.

Tuberculosis disease (TB) remains the leading cause of death from an infectious disease in the world [1]. Not all individuals with bacteriologically confirmed TB will present with or be aware of (clinical) symptoms [2]. When presenting to TB services, this asymptomatic yet infectious group is usually missed, as access to care mostly relies on positive symptom screening to start the TB diagnostic pathway [3]. Individuals with so-called subclinical TB could therefore continue to contribute to transmission [4], hindering global TB care and prevention efforts [1].

While the importance of the subclinical TB subpopulation is recognized, a clear definition has not been agreed upon. Both "asymptomatic" and "bacteriologically confirmed" are inherently ambiguous. The extent and duration of symptoms used for screening will change the proportion of cases that have a positive symptom screening [5]. Similarly, the extent of bacteriological examination, for example, the number of samples or the technique that is used, will change the proportion that will be bacteriologically confirmed [6, 7].

To enable progress, we propose to define asymptomatic and bacteriologically confirmed TB as defined by TB prevalence surveys, which are population-based surveys that investigate representative samples of the population to estimate the national prevalence of bacteriologically confirmed adult pulmonary TB. Through X ray and symptom screening, individuals become eligible for sputum investigation with Xpert and/or culture (Table 1) [8]. While some variation remains, prevalence surveys can provide comparable measurements for the majority of high-burden countries [9], both between and within countries over time for the proportion of TB that is subclinical, that is, asymptomatic (usually defined as negative on screening for cough of a certain duration) and bacteriologically confirmed (usually defined as positive on at least 1 culture or polymerase chain reaction [PCR]–based test). Through this definition, subclinical TB can be placed in a comprehensive framework that reflects the relevant stages and flows in the spectrum of TB infection and disease.

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Table 1. Prevalence of Tuberculosis and Characteristics of Screening

Survey	Crude Prevalence of TB (95% CI), n/100 000 Population	Estimated Incidence (95% CI), n/100 000 Population	Symptom Screening Criteria	X-ray Screening Device	X-ray Screening Criteria	Bacteriological Confirmation Test	Criteria for Eligibility for Bacteriological Examination	Total Number of Individuals Screened	Proportion of Individuals Screened That Is S–X– (%)	Proportion of Individuals Screened That Is S+X– (%)	Proportion of Individuals Screened That Is S+X+ (%)	Proportion of Individuals Screened That Is S–X+ (%)	Other (%)
Bangladesh 2015	287 (244–330)	221 (160–290)	Symptom screening score ≥3	Digital mobile X ray	Any lung abnormality consistent with TB	Culture-positive and/or Xpert-positive	S+ and/or X+ or XNA and symptom score ≥1	98 710	79.4	4.2	3.1	13.8	S+XNA 0.04
Cambodia 2002	1208 (992–1463)	600	Cough ≥3 weeks and/ or hemoptysis in the previous month	Portable X-ray machine	TB-related shadows (active, suspected, and healed TB) or other lung disease, except for those with a single calcification nodule only or a minor pleural adhesion at the costophrenic angle	Smear-positive and/or culture-positive	S+ and/or X+ or XNA	22 160	Not reported	4.6	2.6	8.2	Include XNA
Cambodia 2011	831 (707–977)	Not reported	Cough ≥2 weeks and/or hemoptysis	Portable X-ray machine	Any abnormal shadow in the lung field or mediastinum other than a single small calcification nodule with a size <10 mm or pleural adhesion at the costophrenic angle(s)	Smear-positive and/or culture-positive	S+ and/or X+ or XNA	37 417	87.22	3.1	1.9	7.2	S–XNA 0.4 S+XNA 0.1 "Other" 0.02
China 2000[a]	466	Not reported	Cough ≥3 weeks and/ or hemoptysis ≥3 weeks	Chest fluoroscopy of all patients, then X ray if they showed abnormal results	Abnormal findings except hilar calcification, a few fibrotic indurated lesions, small area of pleural thickening	Smear positive and/or culture positive	S+ and/or X+ and all known TB cases	365 097	Not reported	Not reported	Not reported	Not reported	Not applicable
China 2010[a]	459	Not reported	Not reported	Not reported	Not reported	Smear microscopy and culture	S+ and/or X+ and all known TB cases	25 2940	Not reported	Not reported	Not reported	Not reported	Not applicable
Democratic People's Republic of Korea 2016	567 (510–631)	Not reported	Cough ≥2 weeks and/ or hemoptysis	Portable X-ray machine	Abnormal chest radiograph in the lung field or mediastinum other than a single small calcification nodule with a size <10 mm or pleural adhesion at costphrenic angle(s)	Culture-positive	S+ and/or X+	60 683	Not reported	Not reported	1.7	3.1	S–X– or S–XNA 92 S+X– or S+XNA 3.2
Indonesia 2014	759 (589–961)	Not reported	Cough ≥2 weeks and/ or hemoptysis	Digital mobile X ray	Any lung or pleura abnormality	Smear-positive and/or culture-positive and/or Xpert-positive	S+ and/or X+ or XNA	67 944	77.3	5.7	6.6	9.9	S+XNA 0.37 S–XNA with any symptom of TB 0.2
Lao People's Democratic Republic 2011	595 (457–733)	Not reported	Cough ≥2 weeks and/ or hemoptysis in the previous month	Full-size conventional CXR	Any abnormal lung field shadow	Culture-positive	S+ and/or X+	39 212	83.8	Not reported	3.3	7.9	S+X– or S+XNA 4.9
Mongolia 2015	559.6 (454.5–664.7)	428 (220–703)	Cough ≥2 weeks	Digital mobile X ray	Any abnormal shadow in lung field and mediastinum or pleural effusion	Smear-positive and/or culture-positive	S+ and/or X+ or XNA	50 309	79.3	3.4	1.6	14	S+XNA 0.08 SNA X+ 0.06 SNA XNA 1.5
Myanmar 2009	612.8 (502.2–747.6)	526 (307–802)	Any symptom	Portable X-ray machine	Any abnormality in the lung field or mediastinum greater than a single small calcification nodule or pleural adhesion at the costophrenic angle	Smear-positive and/or culture-positive	S+ and/or X+ or XNA	51 367	76.2	0.8	2.5	18.3	S–XNA 2.1 S+XNA 0.1 Suspected false-negative CXR 0.1

Table 1. Continued

Survey	Crude Prevalence of TB (95% CI), n/100 000 Population	Estimated Incidence (95% CI), n/100 000 Population	Symptom Screening Criteria	X-ray Screening Device	X-ray Screening Criteria	Bacteriological Confirmation Test	Criteria for Eligibility for Bacteriological Examination	Total Number of Individuals Screened	Proportion of Individuals Screened That Is S–X– (%)	Proportion of Individuals Screened That Is S+X– (%)	Proportion of Individuals Screened That Is S+X+ (%)	Proportion of Individuals Screened That Is S–X+ (%)	Other (%)
Philippines 2016	1159 (1016–1301)	554 (311–866)	Cough ≥2 weeks and/ or hemoptysis in the previous month	Mass miniature radiography	Any abnormality suggestive of TB	Culture-positive and/or Xpert-positive	S+ and/or X+ or XNA	46 689	60.2	2.8	2.9	22.9	S+XNA 0.3 S–XNA 10.9
Thailand 2012[b]	142 (166.3–287.8)	Not obtainable	Cough ≥2 weeks	Not obtainable	Not obtainable	Smear-positive and/or culture-positive	Not obtainable	62 536	90.3	2.8	0.8	6	Includes XNA
Vietnam 2007	286	171	Cough ≥2 weeks	Either mass miniature radiography or digital mobile X ray	Any abnormality suggestive of TB	Smear-positive and/or culture-positive	S+ and/or X+ or TB current treatment or history of treatment within 2 years	94 179	92.2	0.01	0.6	Not reported	SNA and XNA 0.4 S+XNA 3.7 SNA X+ 2.9
Ethiopia 2011	277 (208–347)	258(191–335)	Cough ≥2 weeks	Portable X-ray machine	Any abnormality in lung field or mediastinum, including cavities, infiltrates, pleural effusion, hilar or mediastinal lymphadenopathy, pulmonary nodules, interstitial abnormalities suggestive or TB or healed TB	Culture-positive	S+ and/or X+	46 697	Not reported	Not reported	1.7	6.4	S–X– or S–XNA 87.1 S+X– or S+XNA 4.7
Gambia 2012	179 (149–231)	175 (132–215)	Cough ≥2 weeks, or cough ≤2 weeks plus ≥2 symptoms suggestive of TB, or no cough but ≥3 symptoms suggestive of TB	Digital mobile X ray	Any abnormality in lung field or mediastinum, including cavities, infiltrates, pleural effusion, hilar or mediastinal lymphadenopathy, pulmonary nodules, interstitial abnormalities suggestive or TB or healed TB	Culture-positive	S+ and/or X+	43 100	Not reported	5.5	2.4	5.5	S+XNA 0.13 S–XNA or S–X– 86.2
Ghana 2013	327 (282–347)	Not reported	Cough ≥2 weeks	Digital mobile X ray	Any abnormalities in lung, pleura, mediastinum	Culture-positive and/or Xpert-positive with X+	S+ and/or X+ or XNA	61 726	86.6	1.8	1.2	7.1	S+XNA 0.1 S–XNA 3.1
Kenya 2015	558 (455–662)	Not reported	Cough ≥2 weeks	Digital mobile X ray	Any finding suggestive of TB	Culture-positive and/or Xpert-positive	S+ and/or X+ or XNA	63 050	84.6	4.5	2	8.2	S–XNA 0.6 S+XNA 0.5
Malawi 2013[c]	452 (312–593)	Not reported	≥1 week of cough or sputum or blood in sputum or chest pain or weight loss or night sweats or fatigue or fever or shortness of breath	Conventional radiography (film system), portable X-ray generator	Any lung abnormality (opacities, cavitation, fibrosis, calcification)	Culture-positive and/or Xpert-positive	S+ and/or X+ or XNA	31 579	88.8	7.4	1.2	2.3	S+XNA 0.2 S–XNA 0.03 missed 0.2
Namibia 2017	431 (361.4–514.3)	Not reported	Cough or weight loss or fever or night sweats	Portable X-ray machine	Any abnormality suggestive of TB, read by automatic software and radiologist	Culture-positive and/or Xpert-positive	S+ and/or X+ or XNA	29 495	63.2	14	5.8	11.3	S+XNA 1.5 S–XNA 4.3

Table 1. Continued

Survey	Crude Prevalence of TB (95%CI), n/100 000 Population	Estimated Incidence (95% CI), n/100 000 Population	Symptom Screening Criteria	X-ray Screening Device	X-ray Screening Criteria	Bacteriological Confirmation Test	Criteria for Eligibility for Bacteriological Examination	Total Number of Individuals Screened	Proportion of Individuals Screened That Is S–X– (%)	Proportion of Individuals Screened That Is S+X– (%)	Proportion of Individuals Screened That Is S+X+ (%)	Proportion of Individuals Screened That Is S–X+ (%)	Other (%)
Nigeria 2012	524 (378–670)	108 (50–186)	Cough ≥2 weeks	Mass miniature radiography	Any abnormality suggestive of TB	Smear-positive and/or culture-positive	S+ and/or X+ or XNA	44 186	Not reported	Not reported	1.7	5	S–X– or S–XNA 89.4 S+X– or S+XNA 3.9
Rwanda 2012	119.3 (78.8–159.9)	Not reported	Cough any duration	Not reported	Any abnormality suggestive of TB	Culture-positive	S+ and/or X+ or XNA	43 128	88.8	4.8	1.3	4.9	S+ XNA 0.02 S– XNA 0.1 SNA X– 0.02
Sudan 2014	183.4 (129.6–237.2)	Not reported	Cough ≥2 weeks	Digital mobile X ray	Any lung abnormality, including pleura	Culture-positive and/or NAAT-positive	S+ and/or X+ or XNA or TB current treatment	83 202	78.2	Not reported	2.2	Not reported	S–X– or SNA XNA 0.7 SNA XNA 0.13 S+XNA or S+X– 0.8 S–X+ or SNA X+ 11.6 S–XNA 6.3
Tanzania 2012	307 (261–360)	Not reported	Cough ≥2 weeks or hemoptysis or fever ≥2 weeks or weight loss or excessive sweating	Digital mobile X ray	Any abnormalities in the lung field or mediastinum	Culture-positive	S+ and/or X+ or XNA	50 447	87.5	6.4	1.7	3.7	S+XNA 0.6 SNAX+ 0.08
Uganda 2014	401 (292–509)	Not reported	Cough ≥2 weeks	Digital mobile X ray	Any abnormalities in lung	Culture-positive and/or Xpert-positive	S+ and/or X+ or XNA	41 154	87.5	5.2	1.3	5.6	XNA 0.4
Zambia 2014	638 (505–774)	Not reported	Cough ≥2 weeks or fever ≥2 weeks or chest pain ≥2 weeks	Digital mobile X ray	Any lung abnormality excluding heart and bone abnormality	Culture-positive and/or Xpert-positive	S+ and/or X+ or XNA	46 099	84.2	6.3	3.6	4.9	S+XNA 0.09 S–XNA 1.2
Zimbabwe 2014	317.1 (250.5–383.8)	Not reported	Any symptom	Digital mobile X ray	Any abnormalities in lung	Culture-positive and/or Xpert-positive	S+ and/or X+ or XNA	33 736	82.7	3.4	1.9	8.3	S–XNA 3.5 S+XNA 0.1 "other" 0.03

A list of references for included prevalence surveys is available in Supplementary Materials Appendix 1.

Abbreviations: CI, confidence interval; CXR, chest X ray; NA, not applicable, NAAT, nucleic acid amplification tests; used when results for symptom (SNA) or X-ray screening (XNA) were not available; S, symptoms; TB, tuberculosis; X, X ray.

[a]Surveys from China were excluded from the analysis because results active pulmonary cases, of which the proportion of bacteriologically negative clinically diagnosed cases is unknown.

[b] Some data were not obtainable from Thailand in 2012 because the only version of the survey report was in Thai.

[c]Malawi 2013: results were excluded from the analysis because the quality of images observed in some clusters was substandard and could not be compared with results from other countries [10].

Our aim was to review data from TB prevalence population surveys and generate a consistent definition and framework for subclinical TB, thereby enabling us to estimate the proportion of TB that is subclinical, as well as explore associations with overall burden and program indicators. Finally, we considered the potential performance of chest X ray–based screening strategies to replace the current symptom-focused TB care and prevention policies.

METHODS

We considered for inclusion population-based TB prevalence surveys completed since 1990, with reports or articles publicly available through August 2019. A literature search for the period from January 1990 to August 2019, restricted to the English language, was conducted by one author (I. L.) in PubMed (August 2019) using the following search terms: "tuberculosis" and "prevalence" in the title and "survey" as text words. Reference lists of identified studies were also examined. Studies that were about a subset of TB cases (eg, drug-resistant TB, women only, healthcare workers), TB infection rather than TB and risk factors for TB (eg, diabetes), and review articles were excluded. Gray literature, such as unpublished survey reports produced by national TB programs, abstracts, and presentations from international meetings and routine progress updates collated by the World Health Organization Global Task Force on TB Impact Measurement on the status of surveys since 2008, was also systematically reviewed.

Subnational TB prevalence surveys were included from the review by Horton et al [11]. Surveys were included if both symptom screening interview and X ray were performed on all eligible participants and if surveys reported the proportion of bacteriologically confirmed cases by screening modality as well as the proportion of bacteriologically confirmed cases that were negative on symptom screening.

We extracted data on the burden of TB (prevalence of bacteriologically confirmed TB), screening and bacteriological confirmation methods, outcomes of screening of the study population, and outcomes of screening of bacteriologically confirmed cases. To explore the impact of program performance, we generated the patient diagnostic rate (PDR) as the case notification rate (number of individuals diagnosed with TB and reported to the National TB Programme per 100 000 population) divided by the prevalence of bacteriologically confirmed TB [11] (inverse of the prevalence to notification ratio).

We defined subclinical TB cases as all participants who were negative on symptom screening, following the criteria established in each survey but confirmed on bacteriological testing. A framework for the natural history of TB was then developed to place subclinical disease in the spectrum of *Mycobacterium tuberculosis* infection and TB. Bacteriological confirmation generally included at least 1 positive culture or PCR-based test [8]. Participants not eligible for X-ray screening (eg, because of pregnancy) were considered negative at X-ray screening. In settings where TB prevalence surveys were repeated in the same geographical area using similar methodology, we examined longitudinal trends in subclinical TB.

We performed a meta-regression (*metareg* in STATA v15) analysis for the effect of covariates on the proportion of subclinical TB. To avoid interdependency, 1 survey per country or area was included. We explored the association with TB prevalence in the country, continent, country-level HIV prevalence; definition of symptom screen; the PDR as a metric of program performance; and proportion of cases that was male. We also performed a random-effects meta-analysis using the *metaprop* command in STATA v15 [12] to quantify between study heterogeneity.

To examine the relative contribution of symptoms compared to X ray as a screening tool, we analyzed the proportion of bacteriologically confirmed cases identified through each method. We also analyzed the proportion of participants who screened positive via symptoms interview, on X ray, or on both methods and were considered eligible for bacteriological examination.

Table 2. Subnational Surveys in India

Survey	Prevalence of TB (95% Confidence Interval)/100 000 Population	Bacteriological Confirmation Test	Criteria for Eligibility for Bacteriological Examination	S–X+ Cases (%)	S– Cases (%)
Tamil Nadu (India) 1999	605	One culture-positive sample	S+ and/or X+	46.3	46.3
Tamil Nadu (India) 2001	454	Culture-positive	S+ and/or X+ and all known TB cases	33.7	36
Tamil Nadu (India) 2004	309	Culture-positive	S+ and/or X+ and all known TB cases	36.4	39.1
Tamil Nadu (India) 2006	388	Culture-positive	S+ and/or X+ and all known TB cases	34.9	39.2
Tamil Nadu (India) 2010	259	Culture-positive	S+ and/or X+ and all known TB cases	32.9	55

A list of references for included prevalence surveys is available in Supplementary Materials Appendix 1.

Abbreviations: S, symptoms; TB, tuberculosis; X, X ray.

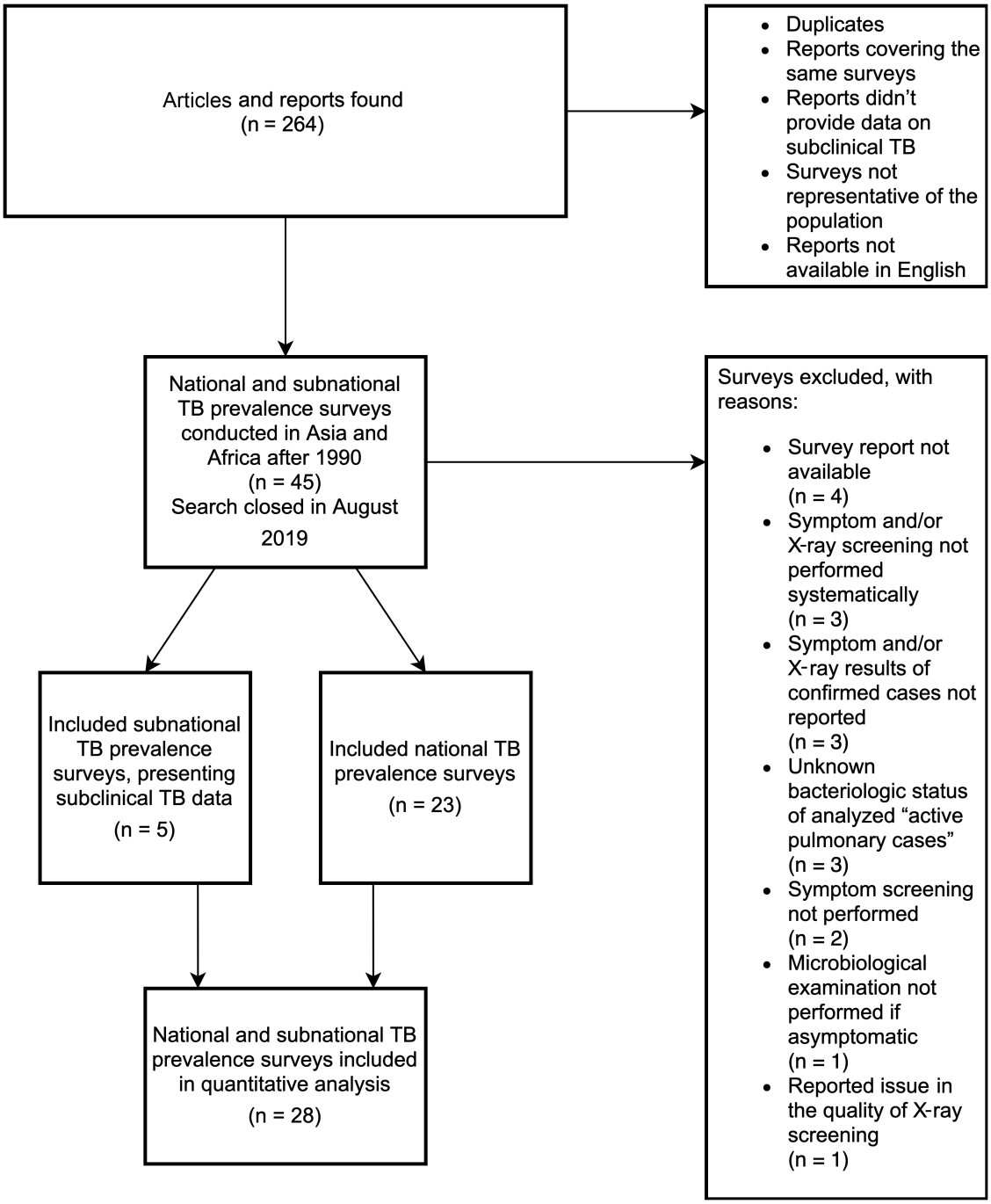

Figure 1. Selection flow chart for tuberculosis prevalence surveys.

RESULTS

We included 23 national surveys and 5 subnational surveys conducted in 23 countries across Africa and Asia, representing 36% of the global TB burden in 2018 [1] and 57.5% (23/40) of all national-level surveys completed since 1990. (Data available in Tables 1–3, list of references for included surveys available in Supplementary Materials Appendix 1.) The reasons for exclusion of the remaining prevalence surveys are shown in Figure 1.

The 2013 Malawi survey was excluded because of reported issues in the quality of X ray in many clusters [10]. Surveys from China were excluded because results were only reported for smear-positive or "active pulmonary cases," the latter including an unknown proportion of bacteriologically negative, clinically diagnosed cases, which did not match our criteria [13]. Data from these surveys are included in Tables 1–3.

Across included surveys, the median percentage of subclinical TB cases was 50.4% (interquartile range [IQR], 39.8%–62.3%;

Table 3. Characteristics of Bacteriologically Confirmed Cases

Survey	S–X+ Cases (%)	S– Cases (%)	S+ Cases (%)	X+ Cases (%)	S+X– Cases (%)	S+X+ Cases (%)	Proportion Negative on any Symptom Among Cases (%)	Proportion of Males Among All Bacteriologically Confirmed Cases (%)	HIV Prevalence Among All Bacteriologically Confirmed Cases (%)	Percentage of Cases Found Already in TB Care (%)	Bacteriologically Confirmed Notification Rate (n/100 000)	Prevalence to Notification Ratio
Bangladesh 2015	61.9	61.9	38.1	90.3	9.7	36	Not reported	72.3	Not measured	1.8	101.7	2.8
Cambodia 2002	60.9	60.9	39.1	95.6	4.4	34.7	15.9	60	Not measured	4.2	222.9	2.0
Cambodia 2011	69.4	70.4	29.1	95.6	3.5	25.6	10.2	59.9	Not measured	2	161.4	1.7
China 2000[a]	Not reported	12.1	87.9	49.5	Not reported	Not reported	Not reported	70.4	Not reported	Not reported	Not reported	Not available
China 2010[a]	Not reported	43.1	56.9	Not reported	Not reported	Not reported	Not reported	69.9	Not reported	Not reported	38.7	1.7
Democratic People's Republic of Korea 2016	42.9	42.9	57	97.9	0.7	55	Not reported	69.7	Not measured	31.2	482.1	1.2
Indonesia 2014	42.5	42.5	57.5	94.1	4.9	51.6	Not reported	65.5	Not measured	4.5	113.3	2.3
Lao People's Democratic Republic 2011	50.2	50.2	49.8	97	2.9	46.8	Not reported	66.2	Not measured	2.5	80.4	3.5
Mongolia 2015	77.8	79.4	20.6	96	2.5	18.1	42.7	64.5	Not measured	4.4	83.2	2.5
Myanmar 2009	Not reported	78.8	19.7	95.2	Not reported	Not reported	38.2	66.2	Not measured	3.5	114.4	2.1
Philippines 2016	63.9	67.8	32.2	92.2	1.7	28.3	26	69	Not measured	6.4	142.2	3.1
Thailand 2012[b]	66.2	66.2	33.8	95.8	4.2	29.6	Not obtainable	Not obtainable	Not obtainable	Not obtainable	56.4	1.8
Vietnam 2007	67.3	73.6	26.4	85.1	8.5	17.8	Not reported	78.8	Not measured	0.07	85.2	2.3
Ethiopia 2011	48.2	48.2	51.8	89	10.9	40.9	Not reported	55.3	8.00	2.7	91.0	1.2
Gambia 2012	36.6	38.	62	81.7	15.5	45	Not reported	62	Not measured	5	145.3	0.6
Ghana 2013	Not reported	59	41	75.2	not reported	not reported	Not reported	50	Not reported	5	45.2	2.5
Kenya 2015	50.5	51.8	40.2	88.2	10.5	38	Not reported	62	13.4	4.9	158.2	3.5
Malawi 2013[c]	30.3	30.3	69.7	49.2	50.76	18.9	Not reported	47.7	16.7	4.5	86.8	2.5
Namibia 2017	Not reported	51.3	48.7	95	not reported	not reported	Not reported	60	15.1	4.2	551.9	0.8
Nigeria 2012	Not reported	36.1	63.9	89	not reported	not reported	22.9	67.7	Not measured	0.2	55	5.8
Rwanda 2012	50	50	50	79.6	20.4	27.8	Not reported	73.7	3.7	5.3	56.1	1.3
Sudan 2014	40	40	45.1	78	7.1	38	Not reported	Not reported	Not measured	7.1	25	3.5
Tanzania 2012	not reported	36.7	63.2	73.5	not reported	not reported	Not reported	60	5.9	Not reported	92.8	3
Uganda 2014	50.6	50.6	49.4	88.7	10	38.1	Not reported	75	26.9	10	141.8	2.8
Zambia 2014	39	39	61	83	17	44	Not reported	66.7	13.2	2.6	159.2	2.0
Zimbabwe 2014	Not reported	63.55	36	86	not reported	not reported	Not reported	54.2	Not reported	Not reported	137.9	2.5

A list of references for included prevalence surveys is available in Supplementary Materials Appendix 1.

Abbreviations: S, symptoms; X, X ray.

[a]Surveys from China were excluded from the analysis because results include active pulmonary cases, of which the proportion of bacteriologically negative clinically diagnosed cases is unknown.

[b]Some data were not obtainable from Thailand in 2012 because the only version of the survey report was in Thai.

[c]Malawi 2013: results were excluded from the analysis because the quality of images observed in some clusters was substandard and could not be compared with results from other countries [10].

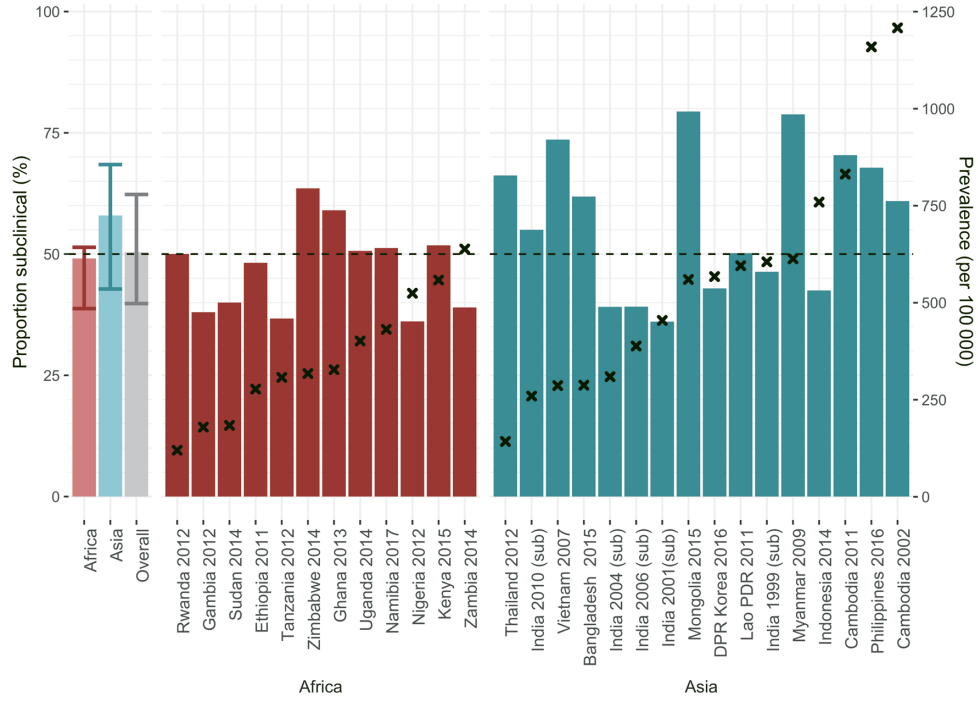

Figure 2. Proportion of subclinical tuberculosis disease (TB) in prevalence surveys. The proportion of all prevalent TB cases that were subclinical (bars: left side *y*-axis) by the adult crude prevalence of bacteriologically confirmed TB found in that survey (crosses: right side *y*-axis). The first 3 bars show the median (bar) and interquartile range (error bars) for values found in surveys in Africa, Asia, and overall. Abbreviations: DPR, Democratic People's Republic; PDR, People's Democratic Republic; sub, subnational surveys.

range, 36.1%–79.7%), which was 49.4% (IQR, 38.8%–52.4%) in African countries. In the Asian countries, the median was 56.4% (IQR, 42.8%–68.5%), with no discernable trend by TB prevalence (Figure 2) in either continent.

Data on repeated surveys were available from Cambodia and Tamil Nadu state in India. Although no clear trend is present, they seemed to suggest that the proportion of subclinical TB increased as TB prevalence declined (Tables 2–3). An indication for this trend was also seen among smear-positive TB in surveys repeated in China from 2000 and 2010 (Table 3).

As Figure 3 shows, X-ray screening identified the vast majority of bacteriologically confirmed cases in all countries (median, 89%; range, 73%–98%). In contrast, the percentage of bacteriologically confirmed TB cases that were negative on X ray but positive on symptom was below 25% (median, 7%; range, 0.7%– 22%) in all surveys, with between 0.01% and 15% of bacteriologically confirmed cases diagnosed through direct bacteriological examination (see Figure 3 and Table 1). In the sampled population, surveys found that 8.8% of individuals screened positive on X ray (range, 4.8%–26%), whereas 6.3% (range, 3%–21%) were positive on symptoms (Figure 4).

We frame subclinical pulmonary TB in the wider context of TB natural history in Figure 5. Here, subclinical TB is a distinct intermediary disease state, which follows after a minimal disease state with initial pathological changes (eg, visible on imaging) but not bacteriologically confirmed (at least within the limits of sampling undertaken) and unlikely to be contributing to transmission. Crucially, individuals can progress and regress from each stage, although how fast or how frequently individuals move between stages will vary widely [14, 15].

Table 4 shows the results from the meta-regression, which provided evidence that in our sample the proportion of subclinical TB cases was higher in surveys from Asia compared with those from Africa (15.2%; 95% confidence interval, 5.6–24.8). There was no evidence for an association with any of the other variables, including country-level TB or HIV prevalence, symptom-screen algorithm, or PDR. Results from the meta-analysis showed very high heterogeneity ($I^2 = 96\%$; $P < .001$). The forest plot is shown in Supplementary Materials Appendix 2.

DISCUSSION

Where measured, around half of the prevalent infectious TB burden is subclinical, making it likely that ignoring this burden will diminish the impact of TB care and prevention efforts.

Our results show that cough, the cornerstone of symptom-based screening policies, was only self-reported by around half of bacteriologically confirmed cases in populations across Asia and Africa. Expecting extensive population-level impact on transmission from such policies seems misplaced. Similar to historical observations that a large bacillary load is not required for transmission [16, 17], cough is unlikely to be required for transmission [18].

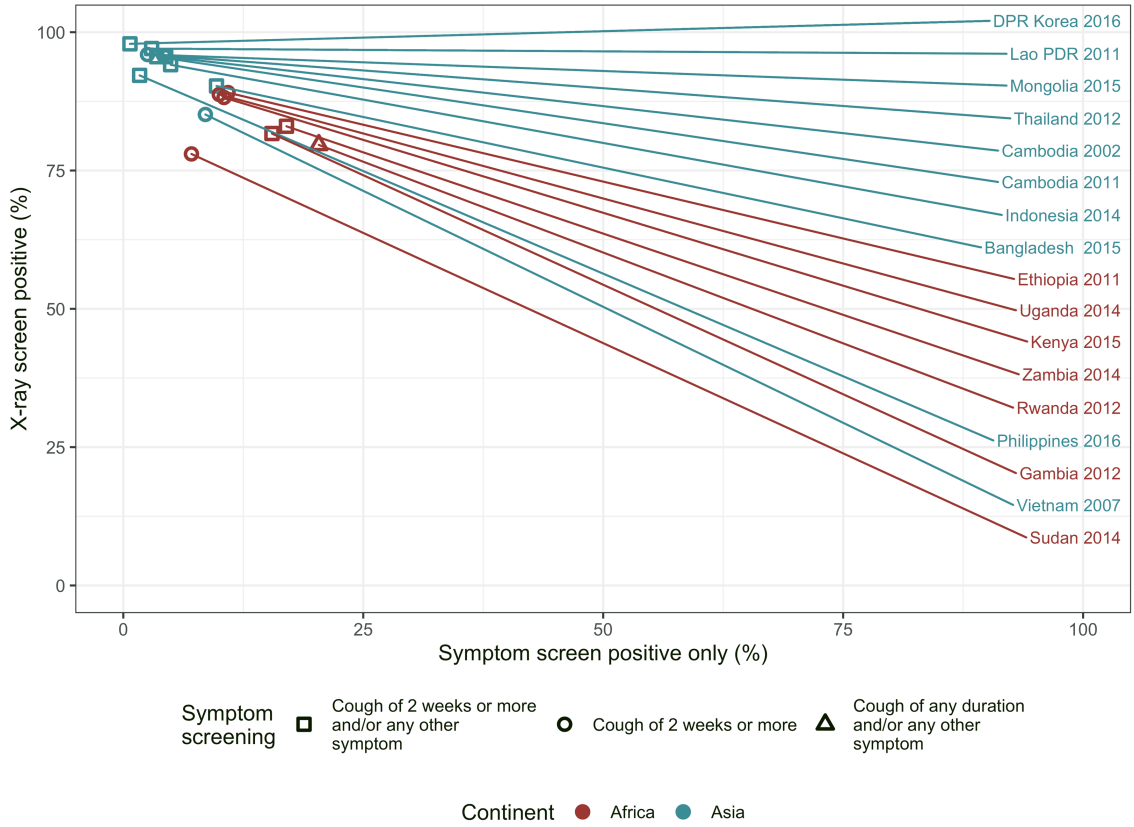

Figure 3. Screening modality for bacteriologically confirmed tuberculosis disease (TB) cases. The proportion of bacteriologically confirmed cases in prevalence surveys that screened positive on X ray (*y*-axis) or on symptom screen only (*x*-axis). Raw data are available in Table 3. Note: The Vietnam 2007 and Sudan 2014 surveys did not report symptom screening and X-ray results for TB cases who were under treatment or had a history of treatment within 2 years but did receive bacteriological examination. In the Philippines 2016 survey, 5% of bacteriologically confirmed cases were exempted from X ray (see Table 1). Abbreviations: DPR, Democratic People's Republic; PDR, People's Democratic Republic.

We found that 9 out of 10 individuals with bacteriologically confirmed TB, including those with subclinical disease, were positive on X ray–based screening, which is based on a single posterior–anterior image. We would therefore argue that X ray as a clinical screening tool needs to be reevaluated as part of the End TB Strategy [19]. Aside from its ability to detect the majority of infectious TB, rapid advancements in digitalization, portability of X-ray screening, and computer-aided X-ray reading now enable clear and consistent choices, which can be adjusted to fit the context of each country to further enhance performance [20]. It is now possible to strike a reproducible balance between the need to increase the proportion of all infectious TB found (sensitivity) and the proportion of screened individuals who are referred for bacteriological testing (positivity rate) [20], the latter of which varied between 7.1% and 24% in surveys included in our analysis. As such, X-ray screening can be optimized depending on the population screened, whether these are clinic attendees or community-based.

Prevalence surveys do not capture individuals with symptom-negative, X ray–negative, bacteriologically confirmed TB. While the data are limited, they suggest that another 0%–5% of all bacteriologically confirmed TB would be classified as subclinical [21], which means our estimates for subclinical TB would be conservative. In addition, pediatric and extrapulmonary TB are not measured in prevalence surveys.

Our results are limited to 36% of the global TB burden; therefore, key gaps remain, including China (where surveys have not reported details for bacteriologically confirmed TB cases), India, and South Africa (surveys underway). We strongly argue that surveys should report results separately by screening and bacteriological confirmation, and data could be enriched, for example, with further subdivisions by gender, urban or rural strata, and HIV status to help inform strategies to address this burden. In addition, our data reflect the proportion that is subclinical among the prevalent burden of the infectious disease, not incident disease. Finally, our study does not include data from settings with low TB incidence.

In particular, increased trends over time in the size and composition of the subclinical TB population as the overall TB prevalence changes would improve our understanding of population dynamics. Maximizing the number of repeat data points within countries would enable a within-country analysis

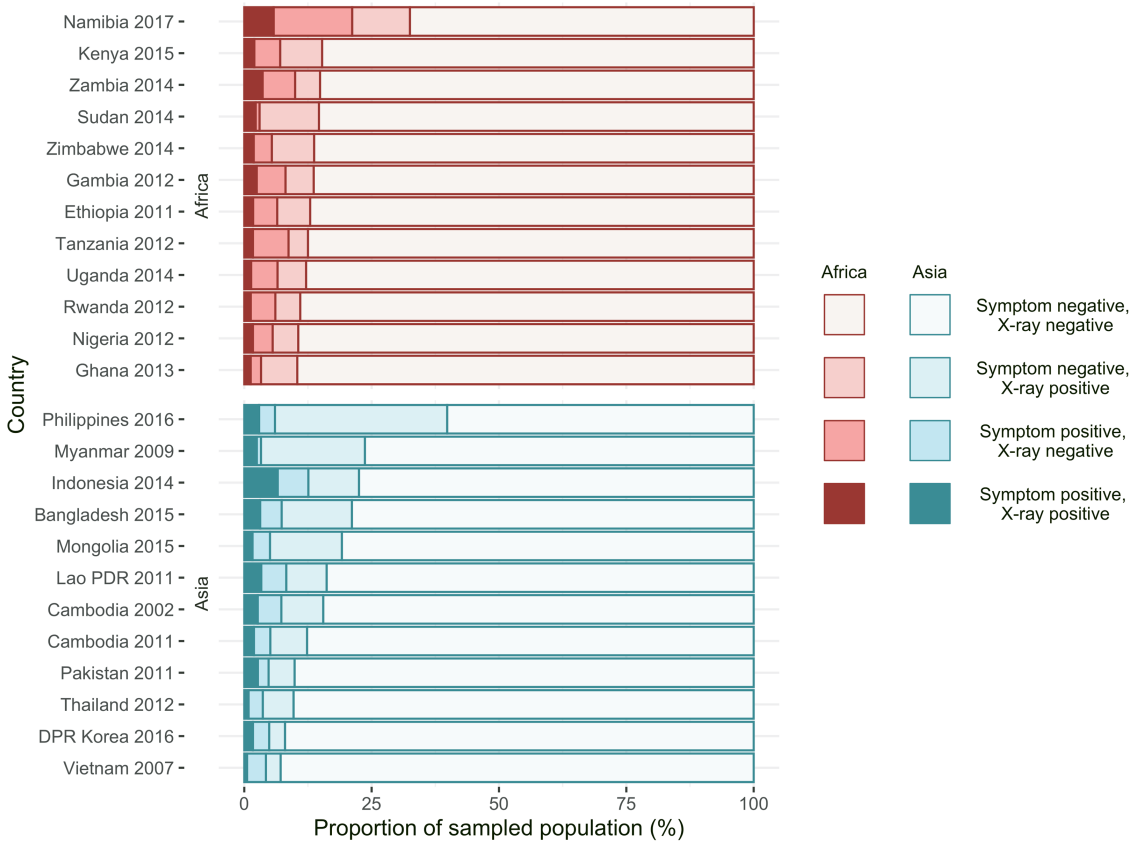

Figure 4. Population screening results. The proportion of population included in prevalence surveys that screened positive on X ray, symptom screen, both, or neither. Abbreviations: DPR, Democratic People's Republic; PDR, People's Democratic Republic.

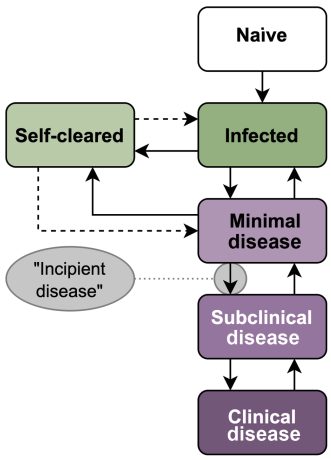

Figure 5. Model representation of the natural history of *Mycobacterium tuberculosis* (*Mtb*) infection and tuberculosis disease. Different states of *Mtb* infection (green) and tuberculosis disease are shown (purple). Infected individuals can progress and regress across the spectrum. Clinical disease: bacteriologically confirmed and symptomatic; incipient disease, transition from minimal to subclinical disease; infected, viable *Mtb* infection with potential to progress to disease; minimal disease, pathological changes caused by *Mtb*, but bacteriologically negative; naive-infected-minimal-incipient-subclnical-clinical-self-cleared, individual has cleared the *Mtb* infection and cannot progress to disease without reinfection (dashed arrows); subclinical disease, bacteriologically confirmed, negative at symptom screening.

Table 4. Survey Level Associations With the Proportion of Prevalent Tuberculosis That Is Subclinical

Variable (n Observations)	Change in Proportion of Subclinical TB (95% Confidence Interval)	*P* Value
Continent (24)		.003
Africa	Reference	
Asia	15.2% (5.6 to 24.8)	
HIV prevalence in country (24)		.34
Continuous variable	−.07% (−2.0 to .7)	
HIV prevalence in country (24)		
<1%	Reference	
1%–2%	−5.4% (−18.9 to 8.1)	.41
≥2%	−10.9% (−24.4 to 2.7)	.11
Symptom screening (24)		
Any symptom	Reference	
Cough ≥2 weeks	−5.0% (−22.1 to 12.1)	.55
Cough ≥2 weeks and/or other symptoms	−10.1% (−26.8 to 6.5)	.22
TB prevalence (23)	.01% (−.01 to .03)	.32
Patient diagnostic rate, average in the previous 5 years (22)	−8.7% (−29.8 to 12.4)	.4
Proportion of males among the cases (21)	.01% (−.8 to 1.0)	.79

Results from univariate meta-regression.

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

of the impact of program performance, including the (limited) ability to address subclinical TB. Our ecological analysis found no association between program performance and subclinical TB, likely due to unmeasured confounding factors specific to each setting. Improved reporting would also provide more data points, which may increase power for more subtle analyses, such as the proportion of subclinical TB by duration of cough, sex, or differences between continents.

We caution for overinterpretation of the evidence for a difference by continent from meta-regression (Table 4) and meta-analysis (Supplementary Materials Appendix 2), especially given that only a subset of countries for each continent is included in our study. Unmeasured confounding factors include differences in the host genetics and bacillary strains that could affect the natural history of the disease [22]. In addition, not all surveys followed the exact same protocol, not all of which was captured in our analysis. Other possible factors are related to cultural differences regarding awareness of symptoms and bacteriological confirmation criteria and techniques. Further studies are necessary to explore the causes and consequences of this result.

Despite the limitations described above, prevalence surveys offer clear advantages as a framework for analysis. First, they represent the most consistent, valid, and extensive effort for TB burden estimation of the past 3 decades [1] and aim to reflect in-country clinical practice and case definitions. As a consequence, we could address the persistent ambiguity of the definitions for subclinical TB, in particular, the precise interpretation of "asymptomatic" and "bacteriologically confirmed."

Our framework places subclinical TB as a distinct intermediary disease state, which precedes clinical (ie, symptomatic) disease and follows after a minimal disease state. Moreover, incipient disease is not a stage but, as indicated in the name, represents the flow from minimal to subclinical disease. It must be noted that the prevalence of the minimal disease state might be influenced by the limitations of X ray, and more sensitive imaging techniques, such as computed tomography scan, would be more sensitive for initial pathological changes. Progression and regression across the TB natural history spectrum has been postulated and is supported by historical and recent data [23]. The term "incipient TB" has been widely used to refer to a group of individuals who will soon progress to subclinical disease. While this makes it an attractive diagnostic target for predictive tests [24, 25], the word and concept of "incipient" implies both a transition and direction that is a flow, not be a disease state.

Our analysis and conceptual framework should enable scientific discourse and policy progress on the unaddressed burden of subclinical TB. A key consideration is how subclinical TB contributes to transmission, given that individuals do not report (prolonged) cough. However, people may not recognize cough as a symptom, and cough may not be required for effective transmission [4]. A comparison of health-seeking behavior between individuals with subclinical (asymptomatic) and clinical (symptomatic) disease could shed more light on the impact of recognizing symptoms on accessing care, but unfortunately prevalence surveys did not report the required stratified data. Another advantage is that these disease stages could help distinguish a subpopulation of patients for whom shorter treatment is both beneficial and safe [26].

A significant proportion of the global TB burden is asymptomatic and not detectable by current symptom-based screening efforts, fueling the TB epidemic through continued *M. tuberculosis* transmission [4]. Detecting subclinical TB provides an opportunity to provide care early in the disease history, which should benefit individuals by preventing extensive lung damage and the risk of post-TB sequelae [27] and benefit society by interrupting transmission. There are both historical and recent precedents to support this thesis, showing that symptom-agnostic screening through X ray [28] or Xpert [29] has near immediate impact on disease burden in high-incidence settings. The TB community needs to recognize both the challenge and opportunities of subclinical TB and develop strategies to address it. If we do so, we should have a much better chance of ending TB in our lifetime.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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