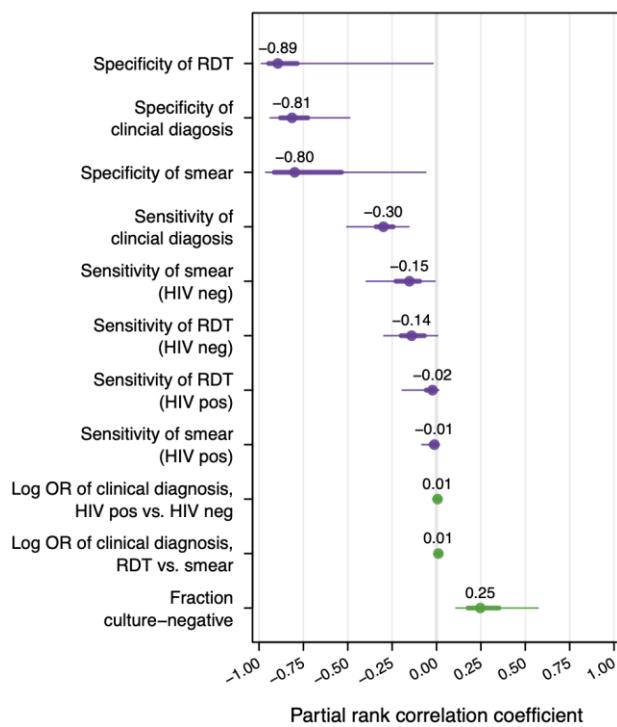


Supplementary information for “Estimating the number of incorrect tuberculosis diagnoses in low- and middle-income countries ”

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A. PRCCs for total false-positive diagnoses



B. PRCCs for total false-negative diagnoses

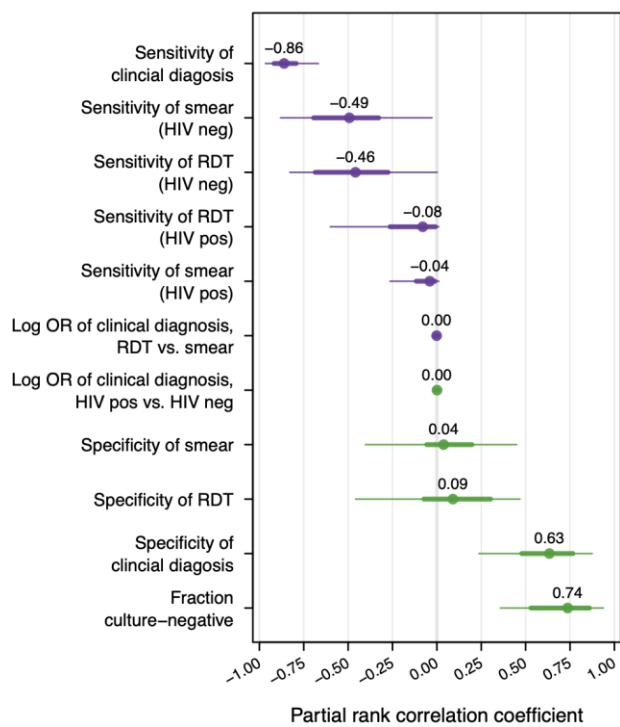


Fig. S1: Partial rank correlation coefficients (PRCCs) quantifying strength of relationship between key study outcomes and model parameters.

RDT = WHO-approved rapid diagnostic test. OR = odds-ratio. Negative PRCC values (purple bars) indicate a negative relationship between the parameter and the outcome. Positive PRCC values (green bars) indicate a positive relationship between the parameter and the outcome. PRCCs estimated for each country individually based on posterior distribution of model parameters. Values (round plotting symbol) indicate median PRCC across countries. Thick lines represent interquartile range of country-level PRCC values, thin lines represent 10th – 90th percentiles of country-level PRCC values.

Category	Countries
Included in analysis (N=111)	Afghanistan, Albania, Angola, Argentina, Armenia, Azerbaijan, Bangladesh, Belarus, Benin, Bhutan, Bolivia, Bosnia and Herzegovina, Botswana, Brazil, Bulgaria, Burkina Faso, Burundi, Cabo Verde, Cambodia, Cameroon, Central African Republic, Chad, China, Colombia, Congo, Costa Rica, Côte d'Ivoire, Cuba, Democratic People's Republic of Korea, Democratic Republic of the Congo, Dominican Republic, Ecuador, Egypt, El Salvador, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Fiji, Gabon, Georgia, Ghana, Guatemala, Guinea, Guinea-Bissau, Haiti, Honduras, India, Indonesia, Iran, Iraq, Jordan, Kazakhstan, Kenya, Kiribati, Kyrgyzstan, Lao, Lebanon, Lesotho, Liberia, Madagascar, Malawi, Malaysia, Mali, Marshall Islands, Mauritania, Mexico, Micronesia, Mongolia, Morocco, Mozambique, Myanmar, Namibia, Nepal, Nicaragua, Nigeria, North Macedonia, Pakistan, Papua New Guinea, Paraguay, Peru, Philippines, Moldova, Russia, Rwanda, Senegal, Serbia, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sri Lanka, Sudan, Suriname, Syrian Arab Republic, Tajikistan, Thailand, Timor-Leste, Togo, Tunisia, Türkiye, Uganda, Ukraine, Tanzania, Uzbekistan, Venezuela, Viet Nam, Yemen, Zambia, Zimbabwe.
Excluded from analysis due to missing data (N=8)	Algeria, Djibouti, Gambia, Libya, Niger, Samoa, Turkmenistan, Tuvalu.
Excluded from analysis due to <100 pulmonary TB notifications (N=15)	Belize, Comoros, Dominica, Grenada, Jamaica, Maldives, Mauritius, Montenegro, Palestinian Territory, Palau, Saint Lucia, Saint Vincent and the Grenadines, Sao Tome and Principe, Tonga, Vanuatu.

Table S1. Countries included and excluded from the analysis.

Table lists 134 low- and middle-income countries included in the WHO TB database.

Variable	Description
iso3	ISO 3-character country/territory code.
g_whoregion	WHO region
c_newinc	Total of new and relapse cases and cases with unknown previous TB treatment history.
new_labconf	New pulmonary bacteriologically confirmed TB cases (smear positive or culture positive or positive by WHO-recommended rapid diagnostics such as Xpert MTB/RIF). As of 2013 this also includes pulmonary bacteriologically confirmed cases with unknown previous TB treatment history.
new_clindx	New pulmonary clinically diagnosed TB cases (not bacteriologically confirmed as positive for TB, but diagnosed with active TB by a clinician or another medical practitioner who has decided to give the patient a full course of TB treatment). It also includes pulmonary clinically diagnosed cases with unknown previous TB treatment history.
ret_rel_labconf	Relapse pulmonary bacteriologically confirmed TB cases (smear positive or culture positive or positive by WHO-recommended rapid diagnostics such as Xpert MTB/RIF).
ret_rel_clindx	Relapse pulmonary clinically diagnosed TB cases (not bacteriologically confirmed as positive for TB, but diagnosed with active TB by a clinician or another medical practitioner who has decided to give the patient a full course of TB treatment).
newinc_rdx	Number of new and relapse cases notified and tested using a WHO-recommended rapid diagnostic (for example Xpert MTB/RIF) at the time of TB diagnosis (regardless of test result).
newinc_pulm_labconf_rdx	Number of new and relapse pulmonary bacteriologically confirmed cases notified and tested using a WHO-recommended rapid diagnostic (for example Xpert MTB/RIF) at the time of TB diagnosis (regardless of test result).
newinc_pulm_clindx_rdx	Number of new and relapse pulmonary clinically diagnosed cases notified and tested using a WHO-recommended rapid diagnostic (for example Xpert MTB/RIF) at the time of TB diagnosis (regardless of test result).
newinc_ep_rdx	Number of new and relapse extrapulmonary cases notified and tested using a WHO-recommended rapid diagnostic (for example Xpert MTB/RIF) at the time of TB diagnosis (regardless of test result).
newrel_hivpos	Number of new and relapse TB patients recorded as HIV-positive.

Table S2. Variables extracted from the WHO Global TB Database.

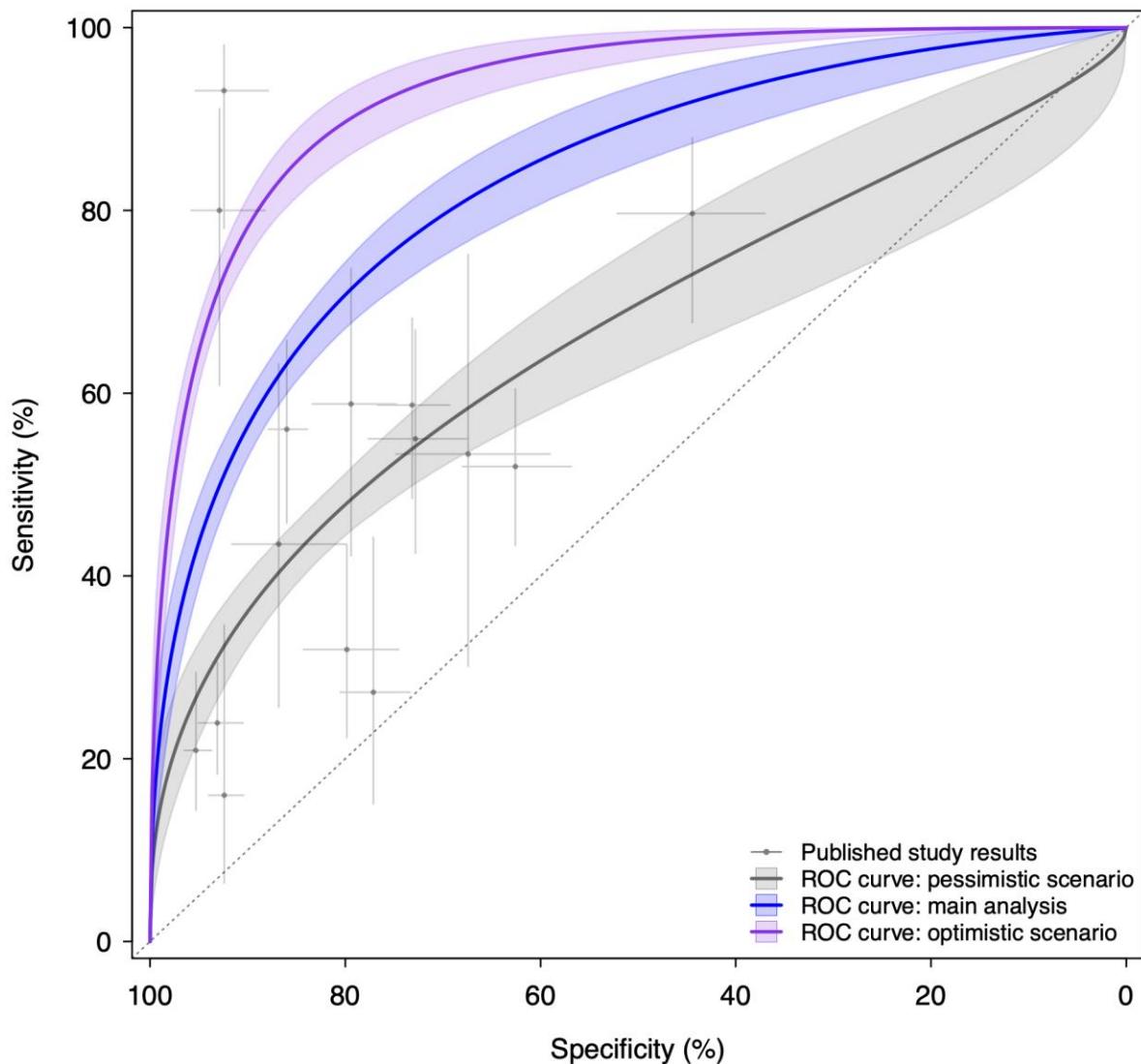


Fig. S2: Binormal ROC curves fit to results of published studies reporting sensitivity and specificity of TB clinical diagnosis.

ROC = Receiver operating characteristic. For the main analysis, we assumed one-third of clinically-positive, culture-negative individuals (as recorded in diagnostic accuracy studies of clinical diagnosis) represented culture-negative pulmonary TB (i.e., true-positive instead of false-positive). For the optimistic scenario, we assumed one-third of clinically-positive, culture-negative individuals represented culture-negative pulmonary TB. For the pessimistic scenario, we assumed no misclassification of the results of diagnostic accuracy studies of clinical diagnosis (i.e., all clinically-positive, culture-negative individuals represented false-positive diagnoses). Table S3 provides details on published studies used to derive ROC curves.

Study cohort	Study	Country	Study years	Reference tests	Sensitivity ^d	Specificity ^d	Count data available ^e	Count outcomes (number of individuals) ^f				
								True positive	False negative	True negative	False positive	Total
1	Abebe 2013	Ethiopia	2009-2011	Culture, solid media	53.3 (30.1, 75.2)	67.4 (59.0, 74.8)	Yes	8	7	89	43	147
2	Alamo 2012 ^a	Uganda	2007-2010	Culture, unspecified	80.0 (60.9, 91.1)	92.9 (88.2, 95.8)	Yes	20	5	170	13	208
3	Alamo 2012 ^a	Uganda	2008-2010	Culture, unspecified	93.1 (78.0, 98.1)	92.4 (87.9, 95.4)	Yes	27	2	183	15	227
4	Huerga 2012 ^b	Kenya	2008-2009	Culture, solid and liquid media	55.0 (42.5, 66.9)	72.8 (67.4, 77.6)	Yes	33	27	209	78	347
5	Huerga 2012 ^b	Kenya	2009-2011	Culture, solid and liquid media	31.9 (22.3, 43.4)	79.8 (74.5, 84.3)	Yes	23	49	206	52	330
6	Koole 2011	Cambodia	2008-2009	Culture, solid and liquid media	58.8 (42.2, 73.6)	79.4 (74.8, 83.4)	Yes	20	14	270	70	374
7	Siddiqi 2006	Pakistan	2003-2004	Culture, unspecified	56.0 (46.0, 66.0)	86.0 (84.0, 88.0)	No	51	40	995	162	1248
8	Soto 2011	Peru	2005-2008	Culture, solid and liquid media	23.9 (18.3, 30.6)	93.1 (90.5, 95.1)	Yes	44	140	446	33	663
9	Swai 2011	Tanzania	2000	Culture, solid media	52.0 (43.3, 60.5)	62.6 (56.8, 68.0)	Yes	66	61	179	107	413
10	Theron 2014 ^c	South Africa, Zambia, Zimbabwe	2011-2012	Culture, solid and liquid media	58.7 (48.5, 68.2)	73.2 (69.3, 76.7)	Yes	54	38	406	149	647
11	Theron 2014 ^c	South Africa, Zambia, Zimbabwe	2011-2012	Culture, solid and liquid media	27.3 (15.1, 44.2)	77.1 (73.4, 80.5)	Yes	9	24	408	121	562
12	Vassall 2011	India	2009-2010	Culture, solid and liquid media	16.0 (4.6, 32.6)	92.4 (90.5, 94.1)	No	4	21	778	64	867
13	Vassall 2011	South Africa	2009-2010	Culture, solid and liquid media	20.9 (13.8, 29.0)	95.3 (93.8, 96.6)	No	23	87	851	42	1003
14	Vassall 2011	Uganda	2009-2010	Culture, solid and liquid media	44.4 (26.2, 63.5)	86.9 (80.5, 92.2)	No	10	13	112	17	152
15	Wilson 2011	South Africa	2005-2007	Culture, liquid media	79.7 (67.7, 88.0)	44.4 (37.0, 52.1)	Yes	47	12	72	90	221

Table S3: Empirical studies used to create ROC curves for clinical diagnosis.

^a For Alamo 2012, Cohorts 1 and 2 represent results reported for the WHO 2003 and WHO 2007 algorithms, respectively. ^b For Huerga 2012, Cohorts 4 and 5 represent results prospective and retrospective cohorts, respectively. ^c For Theron 2014, Cohorts 10 and 11 represent results from smear and Xpert arms, respectively. ^d Reported sensitivity and specificity of clinical diagnosis reported with respect to culture reference standard. ^e Where count data not available, counts imputed as values that best reproduced published point estimates and confidence intervals. ^f Classification of true disease status in table based on culture reference standard.