Sputum scarcity and respiratory sample availability among children with presumptive tuberculosis in high burden countries: a systematic review and meta-analysis

Supplemental Material

Table S1. Search Strategy

PubMed	
#1	"Mycobacterium tuberculosis"[MeSH] OR "Tuberculosis"[MeSH] OR Tuberculo*[tiab] OR TB[tiab]
#2	"sputum"[MeSH] OR sputum[tiab] OR "respiratory aspiration"[MeSH] OR "gastric aspirat*"[tiab] OR "gastric lavag*"[tiab] OR "nasopharyngeal aspirat*"[tiab] OR "string test*"[tiab] OR sputa[tiab] OR expectorat*[tiab] OR phlegm*[tiab]
#3	"Urine"[Mesh] OR "Feces"[Mesh] OR "Blood"[Mesh] OR "Serum"[Mesh] OR urin*[tiab] OR stool[tiab] OR fece*[tiab] OR blood[tiab] OR serum*[tiab] OR swab*[tiab]
#4	#2 OR #3
#5	"child"[Mesh] OR "pediatrics"[Mesh] OR childhood*[tiab] OR child*[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR infan*[tiab]
#7	#1 AND #4 AND #5
#8	"2010/01/01"[PDat] : "2024/6/30"[PDat]

Embase	
#1	'Mycobacterium tuberculosis'/exp OR 'tuberculosis'/exp OR Tuberculo*:ti,ab,kw OR TB:ti,ab,kw
#2	'sputum'/exp OR 'sputum examination'/exp OR sputum*:ti,ab,kw OR aspirat*:ti,ab,kw
#3	'urine'/exp OR 'feces'/exp OR 'blood'/exp OR 'serum'/exp OR 'feces analysis'/exp OR 'urinalysis'/exp OR urin*:ti,ab,kw OR stool:ti,ab,kw OR fece*:ti,ab,kw OR blood:ti,ab,kw OR serum*:ti,ab,kw OR swab*:ti,ab,kw
#4	#2 OR #3
#5	child*:ti,ab,kw OR pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw OR infan*:ti,ab,kw
#6	#1 AND #4 AND #5
	Publication date filter: 2010-2024
	Filter: Embase only
	Filter: all categories under 18
	Filter: humans, only English

Table S2. Template for Risk of Bias assessment

Domain **Signaling Question**	**Accepted values and answers**
Domain 1: Patient Selection Could the selection of patients have introduced bias?	
1. Was a consecutive or random sample of patients enrolled?	Random → yes Consecutive → yes Convenience → no NR → unsure
2. Was a case-control design avoided?	Cohort → yes Cross-sectional → yes Case-control → no NR → unsure
3. Did the study avoid inappropriate exclusions? (e.g. previous TB, HIV, unable to provide an ERS)	Yes → yes No → no NR → unsure
Scoring: Yes on ≥ 2 questions → Low No on ≥ 2 questions → High Unsure on ≥ 2 questions → Unsure	
Domain 2: Assessment of the Outcome Is there a concern that the included participants do not match the review question?	
1. Were methods of ERS collection described in sufficient detail?	Yes → yes No → no NR → unsure
2. Were the results of ERS collection available for all, or nearly all, participants?	Yes → yes No → no NR → unsure
3. Was information on sputum quality (e.g. salivary samples) reported?	Yes → yes No → no NR → unsure
Scoring: Yes on ≥ 2 questions → Low No on ≥ 2 questions → High Unsure on ≥ 2 questions → Unsure	

Table S3. Characteristics of included studies

Study ID	Design; DTA	Country (-ies)	Clinical setting	Healthcare level	N pts	TB prevalence (%)	HIV prevalence (%)	Previous TB (%)	SAM prevalence (%)	Collection method	Number samples	Collect time	Proportion scarcity/ without sample	RoB
Ainan 2021 (1)	CSS; Yes	Tanzania	Mixed	Mixed	253	3.6	6.5	NR	NR	ES, GA	2	NR	GA: 0.04	Low, High
Bates 2013 (2)	CSS; Yes	Zambia	Inpatient	Tertiary	1037	6.2	30.5	NR	NR	ES, GA	NR	NR	ES: 0.52 GA: 0.00 ES<5: 15/663 with sample	Low, Low
Cardoso 2022 (3)	CSS; No	Brazil	Mixed	Tertiary	33	19.0	NR	NR	NR	ST	1	Spot	ST: 0.21	Low, Low
Chibolela 2023 (4)	CSS; No	Zambia	NR	Tertiary	116	11.4	23.7	NR	35.1	GA	1	NR	GA: 0.00	Low, Low
Cox 2022 (5)	CSS; Yes	South Africa	NR	Tertiary	328	30.9	19.6	7.6	29.9	IS w/suction	2	1-2 days	IS: 0.02	Low, High
Dayal 2021 (6)	CSS; Yes	India	NR	Tertiary	114	51.7	NR	NR	10.5	IS, GA	1	Spot	GA: 0.00	Low, High
Dubale 2022 (7)	CSS; Yes	Ethiopia	NR	Tertiary	152	6.7	NR	NR	35.5	ES, GA	1	NR	GA: 0.00	Low, High
Ebonyi 2020 (8)	CSS; Yes	Nigeria	Outpatient	Tertiary	103	45.6	NR	NR	68.7	ES, GA	1	Spot	ES: 0.29 GA: 0.00 ES<5: 4/58 with sample	Low, High
Hanrahan 2019 (9)	Cohort; No	South Africa	Outpatient	Primary	119	3.0	18.0	4.0	16.0	ES, NPA, IS, GA	1 ES, 2 NPA, 1 IS, 1 GA	Spot	ES: 0.41 IS: 0.02 GA: 0.23 NPA: 0.04 ES<5: 4/102 with sample	Low, Low
Hasan 2017 (10)	CSS; Yes	Pakistan	NR	Tertiary	50	18.0	NR	NR	NR	ES, GA	1	NR	ES: 0.69 GA: 0.00	Low, Low
Jaganath 2021 (11)	CSS; Yes	Uganda	Mixed	Tertiary	217	10.8	13.0	1.4	NR	ES, IS, NPA, GA	2	NR	ES: 0.54	Low, High
Kabir 2018 (12)	CSS; Yes	Bangladesh	Inpatient	Tertiary	102	15.7	NR	NR	86.2	ES, GA	1	Spot	ES: 0.64 GA: 0.00	Low, Low
Kabir 2021 (13)	CSS; Yes	Bangladesh	Inpatient	Tertiary	447	16.1	NR	2.5	41.8	IS w/ suction	1	NR	IS: 0.00	Low, Low
KasaTom 2018 (14)	CSS; Yes	Papua New Guinea	Inpatient	Tertiary	100	28.0	18.3	NR	48.4	ES, GA	2 ES, 1 GA	Spot	ES: 0.15 GA: 0.05 ES<5: 3/60 with sample	Low, Low

Khambati 2024 (15)	CSS; No	Kenya	Mixed	Mixed	300	10.5	24.3	NR	NR	GA, ST	2 each	3 days	GA: 0.02 ST: 0.03	Low, Low
Kroidl 2015 (16)	CSS; Yes	Tanzania	Outpatient	Tertiary	180	13.6	51.0	NR	NR	IS	3	NR	IS: 0.01	Low, Low
LaCourse 2018 (17)	RCT; Yes	Kenya	Inpatient	Tertiary	181	7.9	100	NR	48.1	IS, GA	2	1-2 days	GA: 0.04	Low, Low
Menon 2011 (18)	CSS; No	India	NR	Tertiary	52	36.5	0	NR	NR	GA	Up to 3	NR	GA: 0.00	Low, Low
Moore 2011 (19)	CSS; No	South Africa	NR	Primary	270	10.7	18.0	NR	NR	IS w/suction	2	NR	IS: 0.01*	Low, Low
Moore 2017 (20)	CSS; No	South Africa	Inpatient	Tertiary	920	2.9	12.5	NR	15.9	IS, GA	2	1-2 days	IS: 0.09 GA: 0.02	Low, Low
Mutabazi 2020 (21)	CSS; No	Tanzania	Mixed	Mixed	263	5.2	100	9.5	4.4	ES, GA	2 ES, 1 GA	1-2 days	ES: 0.15 GA: 0.07	Low, Low
Myo 2018 (22)	CSS; Yes	Myanmar	NR	Tertiary	231	16.5	19.0	13.0	NR	GA	1	NR	GA: 0.00	Low, Low
Nansumba 2016 (23)	CSS; No	Uganda	Mixed	Tertiary	137	10.2	31.0	NR	3.6	ST, IS w/ suction	2 each	2 days	IS: 0.08 ST: 0.16	Low, Low
Nicol 2019 (24)	CSS; Yes	South Africa	NR	Tertiary	165	24.2	10.9	NR	NR	IS w/suction	2	NR	IS: 0.00	Low, Low
Orikiriza 2018 (25)	Cohort; Yes	Uganda	Mixed	Tertiary	385	4.3	31.2	2.0	19.0	ES, IS w/suction	2	2 days	ES: 0.36 IS: 0.11	Low, High
Orikiriza 2022 (26)	CSS; Yes	Uganda	Inpatient	Tertiary	213	5.5	32.9	NR	84.0	ES, IS w/ suction, NPA, GA	2	2 days	ES: 0.22 NPA: 0.03 GA: 0.03 ES<5: 5/39 with sample	Low, High
Pang 2014 (27)	CSS; Yes	China	NR	Tertiary	211	8.1	NR	NR	NR	GA	1	Spot	GA: 0.00	Low, Low
Planting 2014 (28)	CSS; No	South Africa	Inpatient	Tertiary	843	18.6	23.8	10.4	15.6	IS w/ suction	2	1-2 days	IS: 0.02*	Low, Low
Sabi 2016 (29)	CSS; No	Tanzania	Mixed	Tertiary	192	5.2	15.1	NR	49.5	IS w/ suction	1	NR	IS: 0.03	Low, Low
Sekadde 2013 (30)	CSS; Yes	Uganda	Mixed	Tertiary	255	14.0	41.6	7.2	27.2	IS	1	Spot	IS: 0.02	Low, Low
Singh 2021 (31)	CSS; Yes	India	Outpatient	Tertiary	356	27.4	NR	NR	NR	IS, GA	2 each	2 days	IS: 0.06 GA: 0.00	Low, High
Singh 2023 (32)	CSS; No	India	Inpatient	NR	4356	2.0	0	NR	100	GA	1	NR	GA: 0.02	Low, Low
Sreedeep 2020 (33)	CSS; Yes	India	NR	Tertiary	55	13.3	11.7	NR	35.0	ES, GA	2	2 days	GA: 0.00	Low, Low
Tiwari 2015 (34)	CSS; Yes	India	NR	NR	100	36.0	NR	NR	NR	ES, GA	2 ES, 3 GA	2-3 days	ES: 0.08 GA: 0.00	Low, High
Yalamanchi 2023 (35)	CSS; No	India	Inpatient	Tertiary	255	10.2	NR	NR	NR	IS, GA	2 each	2 days	IS: 0.02 GA: 0.00	Unsure High

Yenew 2024 (36)	CSS; Yes	Ethiopia	Mixed	Mixed	896	7.6	13.2	NR	NR	ES, GA	1	Spot	GA: 0.00	Low, Low
Studies reporting results of suctioning if unable to cough after nebulization: Moore 2011: Of the 496 IS procedures, 296 (60%) samples were obtained by coughing and 200 (40%) by suctioning. Planting 2014: Of the 1257 IS procedures, 264 (21.0%) were obtained by coughing and 993 (79.0%) by suctioning.														

Legend: (abbreviations)
Design: CSS=cross-sectional study; RCT=randomized controlled trial
DTA=diagnostic test accuracy (yes, no)
Clinical setting: inpatient, outpatient, mixed inpatient and outpatient, not reported (NR)
Healthcare level: Primary, Secondary, Tertiary, mixed levels
N pts: number of participants attempting respiratory sample collection
SAM = severe acute malnutrition
Collection method: self-expectorated sputum (ES), induced sputum (IS), with suctioning if child unable to cough (w/suction), gastric aspirate (GA), nasopharyngeal aspirate (NPA), self-expectorated sputum in children <5 years (ES<5)
Number of samples attempted: 1-2, more than 2, not reported (NR)
Time of sample collection: spot, 1-2 days, 3 days or more, not reported (NR)
Risk of Bias (RoB): Patient selection, Applicability

Figure S1. Meta-analysis of proportion children under 5 years able to provide self-expectorated sputum

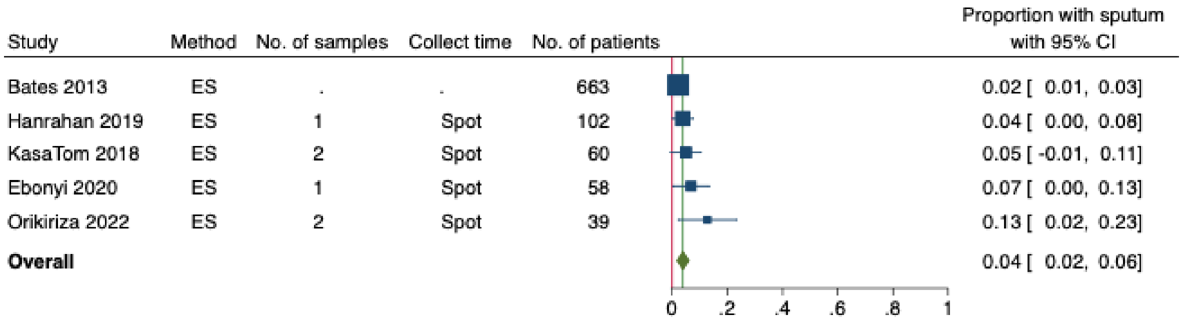


Figure S2. Meta-analysis of proportion sputum scarcity for collection of self-expectorated sputum in children 5-15 years

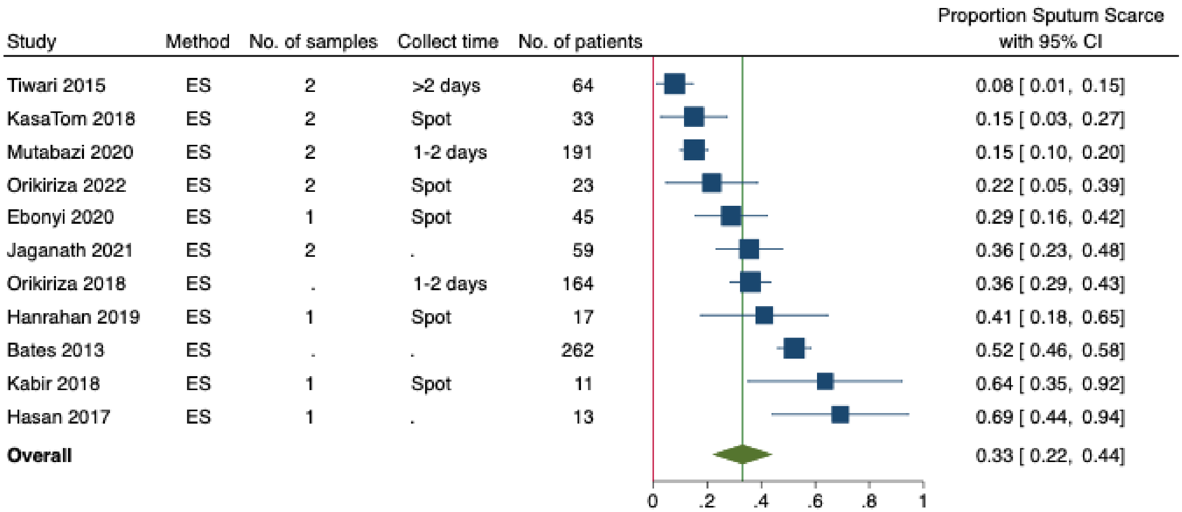


Figure S3. Meta-analysis of proportion sputum scarcity for collection of 1-2 self-expectorated spot samples in children 5-15 years

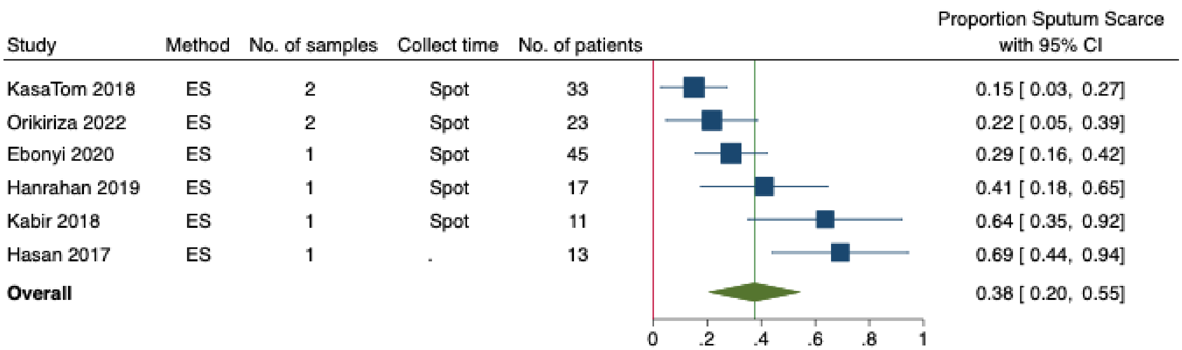


Figure S4. Meta-analysis of proportion sputum scarcity in studies with mixed HIV population for collection of self-expectorated sputum in children 5-15 years

Study	Method	No. of samples	Collect time	%CLHIV	No. of patients	Proportion Sputum Scarce with 95% CI
KasaTom 2018	ES	2	Spot	18.3	33	0.15 [0.03, 0.27]
Mutabazi 2020	ES	2	1-2 days	100.0	191	0.15 [0.10, 0.20]
Orikiriza 2022	ES	2	Spot	32.9	23	0.22 [0.05, 0.39]
Jaganath 2021	ES	2	.	13.0	59	0.36 [0.23, 0.48]
Orikiriza 2018	ES	.	1-2 days	31.2	164	0.36 [0.29, 0.43]
Hanrahan 2019	ES	1	Spot	18.0	17	0.41 [0.18, 0.65]
Bates 2013	ES	.	.	30.5	262	0.52 [0.46, 0.58]
Overall						0.31 [0.20, 0.42]

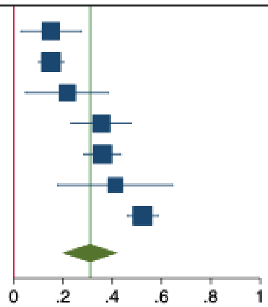


Figure S5. Meta-analysis of proportion sputum scarcity in studies with mixed SAM population for collection of self-expectorated sputum in children 5-15 years

Study	Method	No. of samples	Collect time	%SAM	No. of patients	Proportion Sputum Scarce with 95% CI
KasaTom 2018	ES	2	Spot	48.4	33	0.15 [0.03, 0.27]
Orikiriza 2022	ES	2	Spot	84.0	23	0.22 [0.05, 0.39]
Ebonyi 2020	ES	1	Spot	68.7	45	0.29 [0.16, 0.42]
Hanrahan 2019	ES	1	Spot	16.0	17	0.41 [0.18, 0.65]
Kabir 2018	ES	1	Spot	86.2	11	0.64 [0.35, 0.92]
Overall						0.31 [0.17, 0.45]

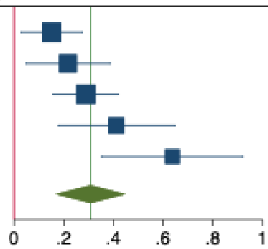


Figure S6. Meta-analysis of proportion sputum scarcity for collection of induced sputum, children<15 years

Study	Method	No. of samples	Collect time	Suction	No. of patients	Proportion Sputum Scarce with 95% CI
Kabir 2021	IS	1	.	Yes	447	0.00 [-0.00, 0.00]
Nicol 2019	IS	2	.	Yes	165	0.00 [-0.00, 0.00]
Kroidl 2015	IS	up to 3	.	NR	180	0.01 [-0.01, 0.02]
Moore 2011	IS	2	.	Yes	270	0.01 [-0.00, 0.02]
Cox 2022	IS	2	1-2 days	Yes	328	0.02 [0.00, 0.04]
Hanrahan 2019	IS	1	Spot	NR	105	0.02 [-0.01, 0.05]
Planting 2014	IS	2	1-2 days	Yes	843	0.02 [0.01, 0.03]
Sekadde 2013	IS	1	Spot	NR	255	0.02 [0.00, 0.04]
Yalamanchi 2023	IS	2	1-2 days	NR	255	0.02 [0.00, 0.04]
Sabi 2016	IS	1	.	Yes	189	0.03 [0.01, 0.05]
Singh 2021	IS	1	1-2 days	NR	356	0.06 [0.03, 0.09]
Nansumba 2016	IS	2	1-2 days	Yes	137	0.08 [0.03, 0.13]
Moore 2017	IS	2	1-2 days	NR	920	0.09 [0.07, 0.11]
Orikiriza 2018	IS		1-2 days	Yes	284	0.11 [0.08, 0.15]
Overall						0.03 [0.01, 0.05]

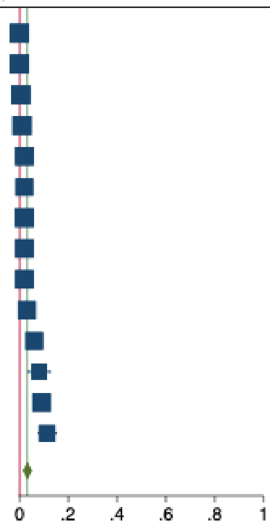
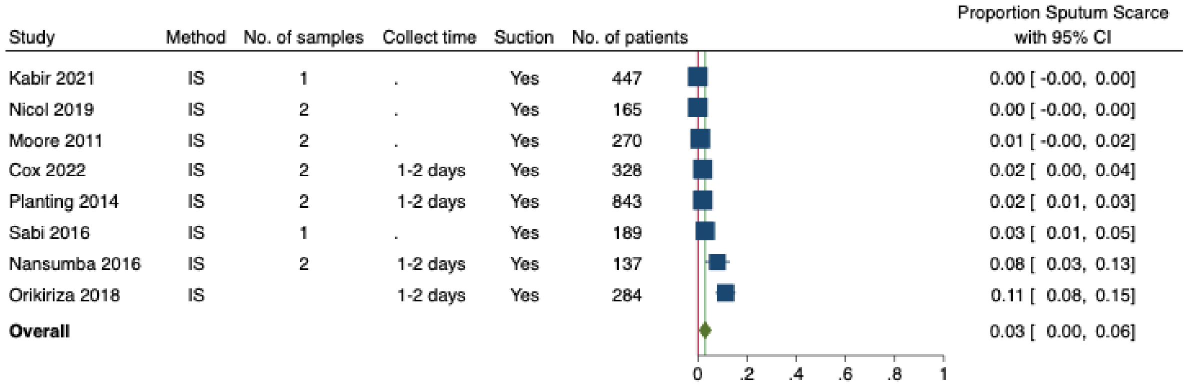


Figure S7. Meta-analysis of proportion sputum scarcity for collection of induced sputum using suctioning if children are unable to cough, children<15 years



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