Where are the missing people affected by tuberculosis? A programme review of patient-pathway and cascade of care to optimise tuberculosis case-finding, treatment, and prevention in Cambodia

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Teo AKJ, *et al. BMJ Global Health* 2023; 8:e010994. doi: 10.1136/bmjgh-2022-010994

Categorisation of facilities based on the levels of care provided

Supplementary Table 1: Facility levels

Levels	Description
0	Basic and community-level care. Laboratory and diagnostic services are generally unavailable on-site, but treatment may be administered (pharmacies). This study also considered those who sought advice from traditional healers and family members and self-medicated as level 0.
1	Primary health care services, commonly outpatient care with essential diagnostic services. Services are provided by clinically trained staff such as nurses and doctors (health centres and private clinics).
2	Primary health and more advanced care. Diagnostic, treatment and in-patient services are provided with limited specialised care. Examples included district referral hospitals and facilities operated by NGOs. As the types of government/private hospitals were not further defined in the prevalence survey, we could not distinguish the levels of care provided. In Cambodia, hospitals operated by private entities and NGOs are primarily located in major urban cities. Hence, we considered government and private hospitals reported in the prevalence survey as level 3 facilities.
3	Facilities that provide specialized care with greater inpatient, diagnostic, and treatment capacities (government and private hospitals, including those operated by NGOs).

Non-governmental organisations; NGOs

Estimates in each column of the patient pathway analysis

Supplementary Table 2: Estimated proportions in each column of the patient pathway analysis

		Place of initial care-seeking (public)			Place of initial care-seeking (private)				Place of initial care-seeking (non-medical)				Coverage of diagnostics (public)		Coverage of types of diagnostics (public)			Coverage of types of diagnostics (public)			Access to diagnostics (public)		Coverage of treatment (public)		Access to treatment (public)		Notification location			Treatment outcome
	% of total population living in urban settings in each province	Government hospital	Health center	**Total public**	Private hospital	Private clinic	Pharmacy	**Total private medical**	Traditional healer	Family member	Self-medicating	**Total private non-medical**	Government hospital	Health center	Government hospital microscopy	Government hospital Genexpert	Government hospital culture	Health center microscopy	Health center Genexpert	Health center culture	Government hospital	Health center	Government hospital	Health center	Government hospital	Health center	**Public**	**Missing**	**Private/non-medical**	**Treatment completed/cured**
		Level 3	Level 1		Level 3	Level 1	Level 0		Level 0	Level 0	Level 0		Level 3	Level 1	Level 3	Level 3	Level 3	Level 1	Level 1	Level 1	Level 3	Level 1	Level 3	Level 1	Level 3	Level 1				
		%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	**%**
National		4.16	37.58	41.74	2.75	14.48	36.65	53.89	0.70	0.52	3.16	4.37	84.96	8.50	83.46	54.14	2.26	8.50	0.00	0.00	3.53	3.20	97.74	100.00	4.07	37.58	63.00	37.00	0.00	94.43
Sub-national																														
Banteay Meanchey	33.7	1.58	58.79	60.37	1.32	8.52	21.44	31.28	0.44	0.88	7.03	8.35	77.78	4.35	77.78	44.44	0.00	3.00	0.00	0.00	1.23	2.56	100.00	100.00	1.58	58.79	na	na	na	94.82
Battambang	22.3	5.73	16.17	21.90	3.94	23.69	45.64	73.27	0.36	0.95	3.52	4.83	71.43	9.09	71.43	57.14	14.29	8.00	0.00	0.00	4.09	1.47	100.00	100.00	5.73	16.17	na	na	na	94.49
Kampong Cham	14.6	2.99	48.62	51.61	1.92	21.92	17.23	41.07	1.34	1.16	4.82	7.32	100.00	3.30	100.00	55.56	11.11	3.00	0.00	0.00	2.99	1.60	100.00	100.00	2.99	48.62	na	na	na	90.79
Kampong Chhnang	9.1	2.96	41.11	44.07	3.90	4.91	43.84	52.65	0.47	0.47	2.34	3.28	100.00	8.89	100.00	100.00	0.00	4.00	0.00	0.00	2.96	3.65	100.00	100.00	2.96	41.11	na	na	na	94.74
Kampong Speu	10	3.38	24.65	28.03	0.94	29.58	40.11	70.64	0.61	0.39	0.33	1.33	100.00	3.51	100.00	75.00	0.00	2.00	0.00	0.00	3.38	0.87	100.00	100.00	3.38	24.65	na	na	na	95.80
Kampong Thom	9.7	2.84	41.61	44.44	0.39	14.03	40.35	54.77	0.39	0.32	0.08	0.79	100.00	12.73	100.00	100.00	0.00	7.00	0.00	0.00	2.84	5.30	100.00	100.00	2.84	41.61	na	na	na	92.16
Kampot	10.4	4.13	59.24	63.37	5.76	5.33	23.59	34.67	0.76	0.11	1.09	1.96	100.00	4.55	100.00	60.00	0.00	3.00	0.00	0.00	4.13	2.69	100.00	100.00	4.13	59.24	na	na	na	95.86
Kandal	31.1	3.39	14.45	17.83	5.33	15.62	53.95	74.90	0.27	0.45	6.55	7.27	100.00	0.93	100.00	72.73	0.00	1.00	0.00	0.00	3.39	0.14	100.00	100.00	3.39	14.45	na	na	na	93.81
Kep	54.7	9.58	46.71	56.29	0.30	3.89	37.72	41.92	0.30	0.90	0.60	1.80	100.00	0.00	100.00	100.00	0.00	0.00	0.00	0.00	9.58	0.00	100.00	100.00	9.58	46.71	na	na	na	100.00
Kratie	11.7	2.02	12.79	14.81	2.02	33.33	41.41	76.77	3.37	1.35	3.70	8.42	80.00	5.13	80.00	40.00	0.00	2.00	0.00	0.00	1.62	0.66	100.00	100.00	2.02	12.79	na	na	na	99.27
Pailin	51.6	4.93	35.62	40.55	1.37	28.77	26.85	56.99	1.10	0.82	0.55	2.47	100.00	0.00	100.00	100.00	0.00	0.00	0.00	0.00	4.93	0.00	100.00	100.00	4.93	35.62	na	na	na	97.09
Phnom Penh	89.9	4.53	13.00	17.53	5.08	9.37	64.57	79.02	0.18	0.48	2.78	3.45	47.62	4.35	47.62	33.33	4.76	2.00	0.00	0.00	2.16	0.57	85.71	100.00	3.89	13.00	na	na	na	96.27
Preah Sihanouk	55	15.46	11.67	27.13	5.99	8.20	58.68	72.87	0.00	0.00	0.00	0.00	100.00	13.33	100.00	100.00	0.00	2.00	0.00	0.00	15.46	1.56	100.00	100.00	15.46	11.67	na	na	na	98.17
Preah Vihear	12.4	1.99	77.41	79.40	0.00	11.63	7.31	18.94	1.00	0.66	0.00	1.66	100.00	40.00	100.00	50.00	0.00	12.00	0.00	0.00	1.99	30.96	100.00	100.00	1.99	77.41	na	na	na	97.94
Prey Veng	5.2	2.73	45.25	47.98	2.08	19.29	22.84	44.21	1.04	0.66	6.12	7.81	84.62	3.51	76.92	23.08	0.00	4.00	0.00	0.00	2.31	1.59	100.00	100.00	2.73	45.25	na	na	na	98.22
Pursat	16	3.82	56.83	60.65	0.59	6.17	26.43	33.19	1.03	0.29	4.85	6.17	100.00	5.00	100.00	50.00	0.00	2.00	0.00	0.00	3.82	2.84	100.00	100.00	3.82	56.83	na	na	na	94.11
Ratanak Kiri	19.3	0.54	94.61	95.15	0.00	0.54	4.04	4.58	0.27	0.00	0.00	0.27	100.00	29.63	100.00	50.00	0.00	8.00	0.00	0.00	0.54	28.03	100.00	100.00	0.54	94.61	na	na	na	89.47
Siem Reap	29.5	6.00	42.65	48.65	1.21	6.65	42.28	50.14	0.88	0.09	0.23	1.21	100.00	8.42	80.00	60.00	0.00	8.00	0.00	0.00	6.00	3.59	100.00	100.00	6.00	42.65	na	na	na	94.59
Svay Rieng	16.1	1.65	56.60	58.25	0.78	13.50	25.92	40.19	0.97	0.00	0.58	1.55	66.67	13.64	66.67	50.00	0.00	6.00	0.00	0.00	1.10	7.72	100.00	100.00	1.65	56.60	na	na	na	95.80
Takeo	4.9	12.13	42.45	54.58	8.29	6.56	20.67	35.52	0.12	0.25	9.53	9.90	100.00	7.41	100.00	71.43	0.00	6.00	0.00	0.00	12.13	3.14	100.00	100.00	12.13	42.45	na	na	na	93.24
Tboung Khmum		5.29	22.70	27.99	2.56	8.53	58.87	69.97	1.37	0.34	0.34	2.05	100.00	1.41	100.00	71.43	0.00	1.00	0.00	0.00	5.29	0.32	100.00	100.00	5.29	22.70	na	na	na	92.03

Calculations of the steps in the TB disease care cascade

Supplementary Table 3: Key parameters, data sources, and the calculations involved to arrive at the best estimate (rows highlighted in grey) used in the construction of the cascade of care for TB disease

Steps in the cascade of care	Parameters	Best estimate	Lower bound	Upper bound	Formulas	Remarks	Sources/ references
1. Estimated incidence of TB	Total number of incidence TB cases (all-forms) in 2019	**47000**	**31000**	**68000**		Most appropriate data available for this indicator	WHO global TB database 2020[1]
2. Accessed TB tests	Smear or GeneXpert® MTB/RIF positive:						
	- The proportion of individuals tested using smear microscopy (%)	*35.0*	*34.0*	*36.0*	Formula: step 3 cascade value/1 – the proportion of smear-positive who went undiagnosed The proportion of smear-positive who went undiagnosed = proportion of individuals who failed to provide a second sputum specimen x The incremental yield of a second sputum smear	Proportions obtained from the entire cohort of cases notified in 2019. Lower and upper bounds were presented as Clopper-Pearson confidence intervals for binomial proportion.	NTP
	- The proportion of individuals tested using GeneXpert®MTB/RIF (%)	*65.0*	*64.0*	*66.0*			NTP
	- The proportion of individuals who failed to provide a second sputum specimen (%)	*5.8*				Uncertainty/confidence intervals unavailable	WHO policy statement 2011[2]
	- The incremental yield of a second sputum smear (%)	*11.9*				Uncertainty/confidence intervals unavailable	Mase et al. 2007[3]
	Smear positive = Step 3 value (11006.3) x 0.35 / 1 – (0.058 x 0.119) *Lower bound* *= Step 3 value (10801.2) x 0.35 / 1 – (0.058 x 0.119)* *Upper bound* *= Step 3 value (11317) x 0.35 / 1 – (0.058 x 0.119)*	**3879.0**	**3698.0**	**4102.3**			
	GeneXpert® MTB/RIF positive = Step 3 value (11006.3) x 0.65 *Lower bound* *= Step 3 value (10801.2) x 0.65* *Upper bound* *= Step 3 value (11317) x 0.65*	**7154.1**	**6912.8**	**7469.0**		We assumed that a small percentage of all sputum samples (~1%) returns with an invalid result. So, it was deemed reasonable to assume that there were no GeneXpert® MTB/RIF-positive who went undiagnosed.	

	Retreatment positive = Step 3 retreatment value (117.1) x the estimated proportion of retreatment smear-positive in Cambodia (0.264)/1 – (0.058 x 0.119) *Lower bound* *= Step 3 retreatment value (114.9) x the estimated proportion of retreatment smear-positive in Cambodia (0.264)/1 – (0.058 x 0.119)* *Upper bound* *= Step 3 retreatment value (120.4) x the estimated proportion of retreatment smear-positive in Cambodia (0.264)/1 – (0.058 x 0.119)*	**31.2**	**30.6**	**32.1**	Formula: step 3 retreatment value x the estimated proportion of retreatment smear-positive in Cambodia/1 – the proportion of smear-positive who went undiagnosed		
	Smear negative and previously treated excluding relapse cases:						
	- The ratio of smear-positive to negative	*0.4*	*0.5*	*0.3*	Formula: step 2 cascade value for smear or GeneXpert® MTB/RIF positive / ratio of smear-positive to smear-negative	Smear microscopy diagnosed 3689 smear-negative TB in 2019 and after accounting for its sensitivity, 8579 (3689/0.430) true smear-negative would have reached TB diagnostic facilities and were evaluated. Therefore, the ratio of smear-positive to smear-negative, in this case, would be 0.349 (2998 smear-positive/8579)	NTP
	- The ratio of GeneXpert® MTB/RIF-positive to negative	*1.7*	*1.8*	*1.5*		GeneXpert® MTB/RIF diagnosed 3835 smear-negative TB in 2019 and after accounting for its sensitivity, 4428 (3835/0.860) true smear-negative would have reached TB diagnostic facilities and were evaluated. Therefore, the ratio of smear-positive to smear-negative, in this case, would be 1.664 (7419 GeneXpert® MTB/RIF positive/4428)	NTP
	- Sensitivity of smear microscopy (%)	*43.0*	*32.0*	*55.0*		Lower and upper bounds were presented as Clopper-Pearson	National TB prevalence

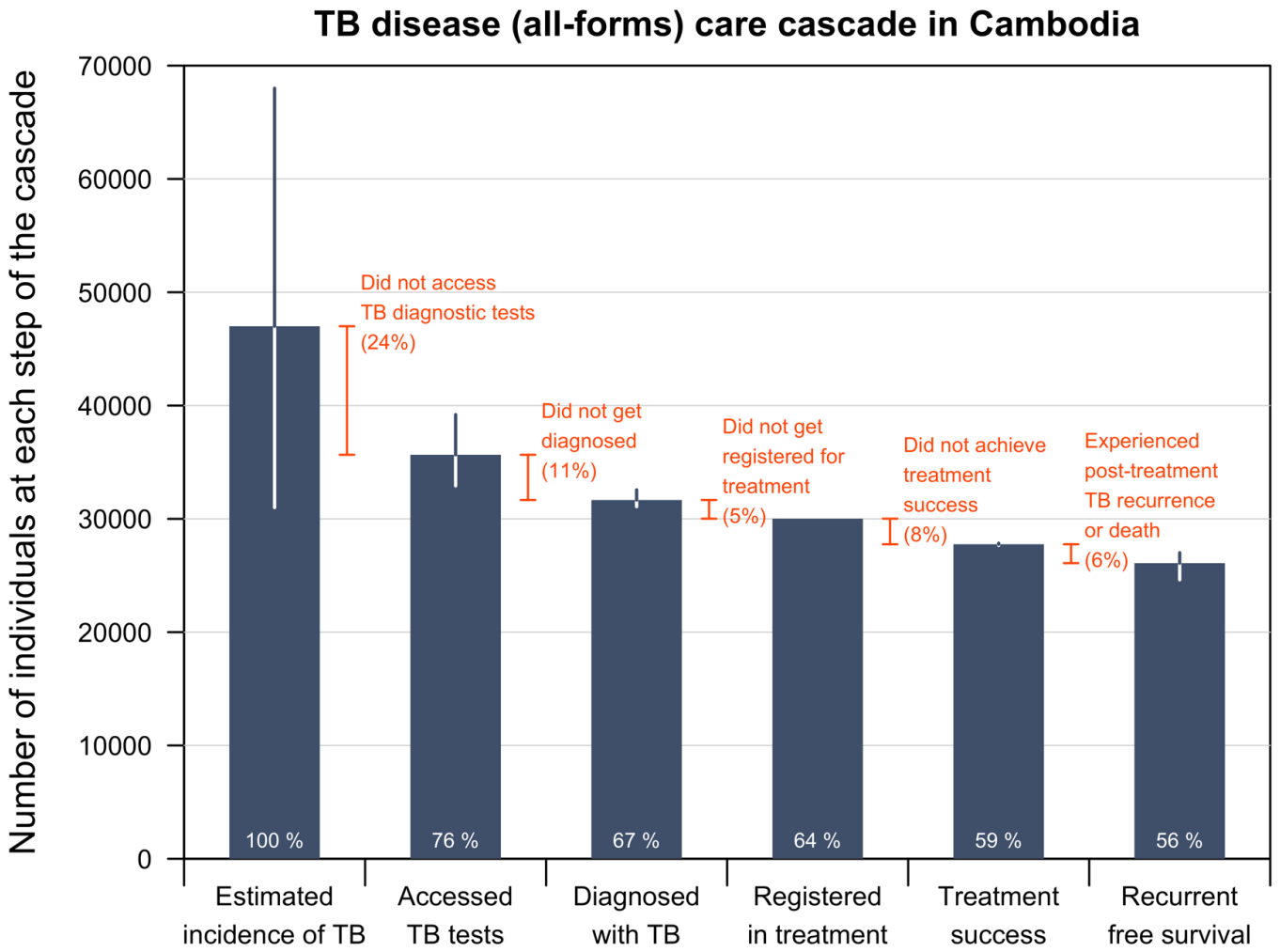
						confidence intervals for binomial proportion	survey 2011[4]
	- Sensitivity of GeneXpert® MTB/RIF (%)	*86.0*	*76.0*	*92.0*			Steingart et al. 2014
	Smear negative = Step 2 value for smear negative (3879) / 0.349 *Lower bound* *= Step 2 value for* smear negative *(3698) / 0.447* *Upper bound* *= Step 2 value for* smear negative *(4102.3) / 0.260*	**11101.4**	**8274.2**	**15776.4**			
	GeneXpert® MTB/RIF negative = Step 2 value for GeneXpert® MTB/RIF negative (7154.1) / 1.664 *Lower bound* *= Step 2 value for GeneXpert® MTB/RIF negative (6912.8) / 1.780* *Upper bound* *= Step 2 value for GeneXpert® MTB/RIF negative (7469) / 1.470*	**4299.7**	**3883.7**	**5079.6**			
	Retreatment smear-negative = Step 3 retreatment value (117.1) x the estimated proportion of retreatment smear-negative (0.736) x proportion of individuals tested using smear microscopy (0.35) / 0.349 *Lower bound* *= Step 3 retreatment value (114.9) x the estimated proportion of retreatment smear-negative (0.736) x proportion of individuals tested using smear microscopy (0.34) / 0.447* *Upper bound* *= Step 3 retreatment value (120.4) x the estimated proportion of retreatment smear-negative (0.736) x proportion of individuals tested using smear microscopy (0.36) / 0.260*	**86.3**	**64.3**	**122.6**	Formula: step 3 retreatment value x the estimated proportion of retreatment smear-negative in Cambodia x the proportion of individuals tested using smear microscopy / ratio of smear-positive to smear-negative		

	Retreatment GeneXpert® MTB/RIF negative = Step 3 retreatment value (117.1) x the estimated proportion of retreatment smear-negative (0.736) x proportion of individuals tested using smear microscopy (0.65) / 1.664 *Lower bound* *= Step 3 retreatment value (114.9) x the estimated proportion of retreatment smear-negative (0.736) x proportion of individuals tested using smear microscopy (0.65) / 1.780* *Upper bound* *= Step 3 retreatment value (120.4) x the estimated proportion of retreatment smear-negative (0.736) x proportion of individuals tested using smear microscopy (0.65) / 1.470*	**33.6**	**30.9**	**30.1**	Formula: step 3 retreatment value x the estimated proportion of retreatment smear-negative in Cambodia x the proportion of individuals tested using GeneXpert® MTB/RIF / ratio of GeneXpert® MTB/RIF positive to negative		
	Extrapulmonary TB:						
	- The average the proportion of undiagnosed smear-positive (0.007) and the proportion of undiagnosed smear-negative TB (0.366) (%) *Lower bound* *= the average the proportion of undiagnosed smear-positive (0.007) and the proportion of undiagnosed smear-negative TB (0.362) (%)* *Upper bound* *= the average the proportion of undiagnosed smear-positive (0.007) and the proportion of undiagnosed smear-negative TB (0.378) (%)*	*18.7*	*18.5*	*19.3*	<u>The proportion of undiagnosed smear negative</u> <u>Formula:</u> step 2 smear negative value - step 3 smear negative value / step 2 smear negative estimate <u>Proportion of smear-positive patients presenting to TB diagnostic facilities who remain undiagnosed because of failure to provide a second sputum smear</u> <u>Formula:</u> proportion of individuals who failed to provide a second sputum specimen x the incremental yield of a second sputum smear	We assumed that extrapulmonary TB (EPTB) is more challenging to diagnose than smear-positive pulmonary TB. However, it is assumed that EPTB is easier to diagnose than smear-negative TB. Therefore, the proportion of undiagnosed EPTB is assumed to be the average of the proportions of undiagnosed smear positive and smear negative TB.[5]	
	Extrapulmonary TB = Step 3 extrapulmonary TB (11322)/1 - the average the proportion of undiagnosed smear-positive and the proportion of undiagnosed smear-negative TB (0.204) *Lower bound* *= Step 3 extrapulmonary TB (11111)/1 - the average the proportion of undiagnosed smear-*	**14226.4**	**13049.3**	**16020.7**			

	positive and the proportion of undiagnosed smear-negative TB (0.149) *Upper bound* *= Step 3 extrapulmonary TB (11641)/1 - the average the proportion of undiagnosed smear-positive and the proportion of undiagnosed smear-negative TB (0.273)*				Formula: Step 3 extrapulmonary TB/1 - the average the proportion of undiagnosed smear-positive and the proportion of undiagnosed smear-negative TB		
3. Diagnosed with TB	Pre-treatment loss to follow-up rate (%)	*5.2*	3.4	7.8	Formula: Step 4 value / 1 – pre-treatment loss to follow-up rate		Mao et al. 2012[6]
	Smear positive = Step 4 value (10434) / (1 - 0.052) *Lower bound* *= Step 4 value (10434) / (1 - 0.034)* *Upper bound* *= Step 4 value (10434) / (1 - 0.078)*	**11006**	**10801**	**11317**			
	Smear negative = Step 4 value (8739) / (1 - 0.052) *Lower bound* *= Step 4 value (8739) / (1 - 0.034)* *Upper bound* *= Step 4 value (8739) / (1 - 0.078)*	**9218.4**	**9046.6**	**9478.3**			
	Retreatment = Step 4 value (111) / (1 - 0.052) *Lower bound* *= Step 4 value (111) / (1 - 0.034)* *Upper bound* *= Step 4 value (111) / (1 - 0.078)*	**117.1**	**114.9**	**120.4**			
	Extrapulmonary TB = Step 4 value (10733) / (1 - 0.052) *Lower bound* *= Step 4 value (10733) / (1 - 0.034)*	**11322**	**11111**	**11641**			

	Upper bound *= Step 4 value (10733) / (1 - 0.078)*						
4. Registered in treatment	Total number of people with TB registered in treatment in 2019 New and relapse smear positive: 10434 New and relapse smear negative: 8739 Retreatment: 111 Extrapulmonary TB: 10733	**30017**				Directly observed information (total number of people notified to the NTP)	WHO global TB database 2020[1]
5. Treatment success	Total number of people with TB who achieved treatment success in 2019	**27758**	**27667**	**27847**		Uncertainty bounds were presented as Clopper-Pearson confidence intervals for binomial proportion	NTP
6. Recurrence-free survival	The proportion of TB survivors who remained alive and TB-free (%)	*94.0*	*89.0*	*97.0*	Formula: Step 5 value x the proportion of TB survivors who remained alive and TB-free	Lower and upper bounds were presented as Clopper-Pearson confidence intervals for binomial proportion	Primary data
	Recurrence free survival = Step 5 value (27758) x the proportion of TB survivors who remained alive and TB-free (0.94) *Lower bound* *= Step 5 value (27667) x the proportion of TB survivors who remained alive and TB-free (0.89)* *Upper bound* *= Step 5 value (27847) x the proportion of TB survivors who remained alive and TB-free (0.97)*	**26093**	**24624**	**27012**			

TB; tuberculosis, NTP; National TB program, MTB/RIF; Mycobacterium tuberculosis/resistance to rifampin, WHO; World Health Organization



Supplementary Figure 1: TB disease care cascade in Cambodia. Proportions (in white) refer to the percentage of people at each step of the cascade compared to the first step (estimated TB incidence). Proportions (in orange) refer to the percentage attritted at each step compared to the previous step (% difference). Step 2 of the cascade incorporated the sensitivity of smear microscopy (Ziehl-Neelsen method) derived from Davis et al.[7] The treatment success rate presented in the care cascade differs from PPA despite representing 2019's outcomes because of the denominator used. We used the preceding step to treatment outcome in the care cascade as the denominator resulting in a treatment success rate of 92%. We obtained the treatment success rate in PPA (96%) from the WHO database, and it was based on the total number of persons evaluated in 2020 as the denominator. Abbreviation: TB, tuberculosis

Community Mobilization Initiatives to End Tuberculosis (COMMIT) project and the derivation of parameters from the TB preventive therapy intervention

To achieve the end TB strategy goals[8], the challenges of treating TB infection reservoir need to be addressed, and programmatic management of LTBI must be scaled up to combat tuberculosis.[9,10] COMMIT is collaborating with the NTP and partners to implement the TB infection guidelines targeting both people living with HIV (PLHIV) and household contacts (children <5 and all ages) of persons with bacteriologically confirmed TB in 10 operational districts in Cambodia.

COMMIT aims to reduce TB transmission and progression by targeting TB contacts, and PLHIV engaged through the different case-finding models in the community and the health facilities for TB preventive therapy (TPT). During active case finding and community TB screening, PLHIV and household contacts were evaluated for eligibility for TPT. The criteria included the absence of TB disease (determined through TB symptoms screening) and other contraindications such as active hepatitis, heavy alcohol consumption, symptoms of peripheral neuropathy, and known hypersensitivity to TPT.[11] Those who were eligible were referred to the health facilities for TPT initiation and follow-up. People who started on TPT were followed-up and supported by health centre staff and community health workers to ensure completion of treatment.

We used TPT program data between June 2020 and March 2021 to derive relevant parameters for the construction of TB infection and the TPT care cascade.

Supplementary Table 4: Number and proportions of household contacts who were screened, eligible for, and started TPT

Evaluation	**All ages**	**<5**
Total household contacts of BK+ screened for TB	3761	329
Total household contacts of BK+ during the specific period	4259	359
% of household contacts of BK+ screened for TB	88.3%	91.6%
Total household contacts of BK+ eligible for TPT	3052	272
Total household contacts of BK+ screened for TB	3761	329
% of household contacts of BK+ eligible for TPT	81.1%	82.7%
Total household contacts of BK+ eligible for and started TPT	1900	194
Total household contacts of BK+ eligible for TPT	3052	272
% of household contacts of BK+ eligible for and started TPT	62.3%	71.3%

TB; tuberculosis, TPT; TB preventive therapy, BK+; bacteriologically confirmed TB

Supplementary Table 5: Number and proportions of household contacts who initiated and completed TPT

Treatment	**All ages**			**<5**		
	6H	**3RH**	**3HP**	**6H**	**3RH**	**3HP**
Total household contacts of BK+ completed TPT	142	286	188	8	55	9
Total household contacts of BK+ eligible for and started TPT	172	333	211	10	60	10
% of household contacts of BK+ completed TPT	82.6%	85.9%	89.1%	80.0%	91.7%	90%

TB; tuberculosis, TPT; TB preventive therapy, BK+; bacteriologically confirmed TB, 6H; 6-months isoniazid, 3RH; 3-months (once daily) isoniazid and rifampicin, 3HP; 3-months (once weekly) isoniazid and rifapentine

Calculations of the steps in the TB infection and TB preventive therapy care cascade

Supplementary Table 6: Key parameters, data sources, and the calculations involved to arrive at the best estimate (rows highlighted in grey) used in the construction of the cascade of care for TB infection and TPT

Steps in the cascade of care	Parameters	Best estimate						Remarks	Sources
		2019			2020				
		Best estimate	Lower bound	Upper bound	Best estimate	Lower bound	Upper bound		
PLHIV									
1. Estimated number of PLHIV	PLHIV (all ages)	76000	68000	83000	75000	67000	83000		UNAIDS[12]
2. Number of PLHIV who know their HIV status	PLHIV who know their status	62320	49640	74700	63000	50250	76360		UNAIDS[12]
3. Number of PLHIV on antiretroviral therapy who are eligible for TPT	PLHIV who are eligible for TPT	60980			61672			Uncertainty/confidence intervals unavailable	National HIV Program
4. Number of PLHIV who initiated TPT	PLHIV who initiated TPT (any course)	28669			34839			Uncertainty/confidence intervals unavailable	National HIV Program
5. Number of PLHIV who initiated TPT and completed the course	PLHIV who initiated and completed TPT (any course)	20319			21109			Uncertainty/confidence intervals unavailable	National HIV Program
Household contacts (children <5 years)									
1. Number of household contacts (children aged <5) of persons with bacteriologically confirmed TB	Point estimate of the annual contacts (children aged <5) needing evaluation	9245	8985	9510	9245	8985	9510	We assumed that the point estimate and its uncertainty intervals to be the same in 2019 and 2020	Yuen et al. 2016[13]
2. Number of household contacts (children aged <5) of persons with bacteriologically confirmed TB evaluated for TB disease and infection	The proportion of household contact (children <5) who were evaluated for TB disease and infection* (%)	*91.6*	*88.3*	*94.3*	*91.6*	*88.3*	*94.3*	We applied the same % to 2019 and 2020. Lower and upper bounds were presented as Clopper-Pearson confidence intervals for binomial proportion	TPT program database (COMMIT)
	Step 3 value x the proportion of household contact (children <5) who were evaluated for TB disease and infection (0.916)	5019.5	4756.5	5302.2	4910.3	4643.3	5549.3		
3. Number of children aged <5 who were TB negative and eligible for TPT	The proportion of household contact (children <5) who were eligible for and initiated TPT (%)	4600	4200	5000	4500	4100	4900		WHO global TB database 2020[1]

4. Number of children aged <5 who initiated TPT	Number of children aged <5 who initiated TPT	3033			3778			Directly observed information (total number of children <5 years who initiated TPT). Uncertainty intervals unavailable	National TB Program and WHO
5. Number of children aged <5 who initiated TPT and completed the course	The proportion of household contact (children <5) who completed TPT (%)	*80.0*	*44.0*	*98.0*	*80.0*	*44.0*	*98.0*	We used the treatment completion rates of the six-month Isoniazid regimen in both instances, as it was the predominant TPT regimen used in Cambodia in 2019 and most of 2020. It was also a more conservative and plausible assumption. Lower and upper bounds were presented as Clopper-Pearson confidence intervals for binomial proportion. The wide intervals were due to small sample size.	TPT program database (COMMIT)
	Step 4 value x the proportion of household contact (children <5) who completed TPT (0.80)	2426.4	1334.5	2972.3	3022.4	1662.3	3702.4		
Household contacts (all ages)									
1. Number of household contacts (all ages) of persons with bacteriologically confirmed TB	Number of persons with new and relapse bacteriologically confirmed pulmonary TB	10434			10426			Uncertainty/confidence intervals unavailable.	WHO global TB database 2020[1]
	Estimated average household size	3.68	3.65	3.72	3.68	3.65	3.72	The estimated average household size was 4.68 (95% CI 4.65-4.72). As we are interested in household contacts, we considered 3.68 (95% CI 3.65-3.72) by excluding the source case in the household.	Demographic and health survey 2014[14]
	Number of persons with new and relapse bacteriologically confirmed pulmonary TB x estimated average household size (3.68)	38397	38084	38814	38368	38055	38785		
2. Number of household contacts (all ages) of persons with bacteriologically confirmed TB evaluated for TB disease and infection	Number of household contacts (all ages) evaluated for TB disease and infection*	18938			27542			Directly observed information (total number of household contacts evaluated for TB disease and TPT). Uncertainty intervals unavailable	National TB Program and WHO
3. Number of household contacts (all ages) who were TB negative and eligible for TPT	The proportion of household contact (all ages) who were healthy and eligible for TPT (%)	*60.0*	*30.0*	*90.0*	*80.0*	*40.0*	*100.0*	Upon consultation with the NTP, we assumed that 60% and 80% of the household contacts were TB-free and eligible for TPT in 2019	National TB Program

	Number of household contacts (all ages) evaluated for TB disease and infection x The proportion of household contact (all ages) who were healthy and eligible for TPT	11363	5681	17044	22034	11017	27542	and 2020, respectively. The difference in eligibility proportions could be attributed to the expansion of coverage and activities in 2020, which included eligible household contacts of all ages (beyond children <5) for TPT. However, due to the lack of precision in approximating the proportions of household contacts eligible for TPT, we assumed the lower and upper bounds to be within 50% of the estimates.	
4. Number of household contacts (all ages) who initiated TPT	Number of household contacts (all ages) who initiated TPT	3218			14449			Directly observed information. Uncertainty/confidence intervals unavailable.	National TB Program
5. Number of household contacts (all ages) who initiated TPT and completed the course	The proportion of household contact (children <5) who completed TPT (%)	*82.6*	*76.0*	*88.0*	*82.6*	*76.0*	*88.0*	We used the treatment completion rates of the six-month Isoniazid regimen in both instances, as it was the predominant TPT regimen used in Cambodia in 2019 and most of 2020. It was also a more conservative and plausible assumption. Lower and upper bounds were presented as Clopper-Pearson confidence intervals for binomial proportion.	TPT program database (COMMIT)
	Step 4 value x the proportion of household contact (children <5) who completed TPT (0.826)	2657	2446	2929	18191	10981	12701		

PLHIV; people living with HIV, UNAIDS; Joint United Nations Programme on HIV/AIDS, TPT; tuberculosis preventive therapy, TB; tuberculosis, COMMIT; Community Mobilization Initiatives to End TB (USAID funded project in Cambodia)

*Evaluation to rule of TB disease (clinical symptoms-based screening and might include chest radiography), and potential contraindications to TPT, such as liver disease and known allergies to TPT

Dissemination workshop

A dissemination workshop was organised by the National Center for Tuberculosis and Leprosy Control (CENAT), World Health Organization (WHO) Western Pacific Regional Office, KHANA, and the National University of Singapore on the 16th of September 2022.

The primary purpose of this workshop was to share key findings from this study, discuss the recommendations, and develop an action plan for implementation. The workshop was held in a hybrid mode with 96 participants representing the following institutions:

National TB Programme

1. National Center for Tuberculosis and Leprosy Control

WHO, non-governmental organisations, and academic institutions

1. World Health Organization Western Pacific Regional Office Cambodia
2. KHANA Cambodia
3. National University of Singapore
4. HIV/AIDS Coordinating Committee (HACC)
5. The United States Agency for International Development (USAID)
    a. TB Data, Impact Assessment and Communications Hub (TB DIAH) project
    b. Sustaining Technical and Analytical Resources (STAR) project
6. FHI 360
    a. Infectious Disease Detection and Surveillance (IDDS) project
7. Population Services International (PSI) Cambodia
8. Clinton Health Access Initiative (CHAI)
9. Operation ASHA (Op-ASHA)
10. Cambodian Health Committee (CHC)
11. Health and Social Development (HSD) Cambodia

Sub-national representatives

1. Provincial and operational districts TB supervisors, operational districts directors, and health care workers (primary health centres and referral hospitals) from the following provinces
    a. Battambang
    b. Siem Reap
    c. Kampong Cham
    d. Kampot
    e. Takeo
    f. Kampong Speu

We adopted a nominal group technique to develop consensus on the solutions and establish priorities for action.[15] First, the key findings from this study, including a list of eight broad recommendations synthesised by the core project team, were introduced and explained. Next, the broad recommendations were ranked by all the participants using Mentimeter (mentimeter.com, Stockholm, Sweden) based on their perceived level of importance (1; most important, 8; least important).

1. Improve accuracy of TB diagnosis
2. Bring quality TB diagnostic services closer to communities
3. Design context-specific interventions to improve treatment initiation and adherence
4. Address health system and socio-economic barriers to TB services
5. Scale up TB preventive therapy using shorter regimens, including the incorporation of systematic monitoring and evaluation system
6. Enhance data generation, management, and utilisation to inform policies and programs
7. Revitalise and contextualise the public-private engagement through the nationwide implementation of the new public-private mix strategy
8. Further understand post-TB health and wellbeing

Workshop participants were asked to deliberate on locally tangible solutions and action plans for each broad recommendation. Subsequently, they were divided into two groups where individual ideas were shared and

discussed. The groups reconvened, and the specific action plans were presented and discussed. Group consensus on the action plans was reached through the voting and ranking process. The National TB Programme reputed these priorities to be instrumental in informing programs and policies at the national and sub-national levels. The results are summarised in **Table 6**.

Supplementary Table 7: Recommendations and action plans

Recommendations	**Current status/gaps**	**Action plans***
Improve accuracy of TB diagnosis		
Scale-up GeneXpert MTB/RIF testing at diagnosis (analyse under-utilization of GeneXpert MTB/RIF, strategic deployment of GeneXpert MTB/RIF, availability of lab tech)	• Insufficient machines to meet demand • Modules are broken/not functioning most of the time • Test cartridges out of stock • Difficult to handle and maintain the machines	1. Training and capacity building to operate and maintain GeneXpert MTB/RIF 2. Review the diagnostic algorithm in ensuring supply meets demand 3. Encourage people with presumptive TB to visit facilities with TB diagnostics 4. Increase availability of GeneXpert MTB/RIF, including strategic deployment to facilities with increasing demand
Interventions to improve quality of specimen (production, storage, and transportation)	• Significant number of samples could not be used (e.g., containing only saliva) and the proportion varies across provinces • No standard storage equipment and procedures for transportation • No proper storage equipment in laboratories	1. Provide standard equipment and procedures for storage in the facilities and during transportation 2. Scale-up specimen transport mechanisms
Improve access to x-ray especially for asymptomatic high-risk populations (mapping of functioning x-ray machines and radiologist, use of artificial intelligence)		1. Enhance x-ray film reading ability through training and the use of artificial intelligence
Utilise robust screening and diagnostic algorithms where resources permit		
Bring quality TB diagnostic services closer to the communities		
Scale-up systematic screening in high-risk populations (e.g., community-based ACF, facility-based ACF)	• Systematic screening of high-risk groups required • ACF remains limited and frequency	1. Increase frequency and intensity of ACF
Strengthen household contact investigation	• ACF's location was often not where they live. Hence, it was difficult to perform contact investigations • Some people with TB became uncontactable after being notified of their diagnosis	1. Engage local health centres through robust referral system (community ACF to health centres) to follow-up people with TB closely 2. Engage family members from the beginning to assist with follow-up and contact investigation

		3. Provide information to people with TB on the importance of contact investigation to their family members and the community
Design context-specific interventions to improve treatment initiation and adherence		
Design and implement interventions to address patient-related factors	• Limited health education and awareness-raising activities in the community	1. Organise community and social events to raise awareness 2. Educate people affected by TB and public on disease transmission and infection control regulations through community and social events, including the use of social media
Design and implement interventions to address condition/therapy related factors		1. Establish and improvise procedures for the management of adverse effects and co-morbidities, including the establishment of patient support group
Design and implement interventions to address health system related factors		1. Train health care staff, distribute information, education, and communication materials, and improve referral mechanism
Address health system and socio-economic barriers to TB services		
Enhance social protection to address financial barriers	• Not all people with TB have access to IDPoor programme[†]	1. Establish policy dialogue with relevant sectors in ensuring all people with TB be automatically included in the IDPoor system
Strengthen multi sectoral response (poverty reduction, nutritional interventions etc.)	• No existing structure such as the multisectoral accountability framework (MAF)[‡] for TB	1. Establish MAF-TB for Cambodia
Capacity building of healthcare staff and improve referral pathway to TB lab	• Lack of exposure to the social determinants of health in medical and allied health curriculum • Lack of continuous medical education and capacity building activities to improve health care delivery processes such as referral mechanisms	1. Include TB and social determinants of health in medical and allied health curriculum 2. Conduct regular training to improve healthcare delivery processes
Scale up TPT using shorter regimens, including the incorporation of systematic monitoring and evaluation system		
Ensure guidance, resources and tools are available to provide TPT in the routine setting	• Lack of funding to support TPT activities • Drugs (TPT) shortage at the hospitals, particularly newer shorter regimens (3HP over 6H)	1. Conduct regular training courses for health care workers 2. Advocate and source for funding to support TPT activities

	• Lack of guideline to inform TPT practices	
Conduct research to better understand the best regimen option and facilitators/barriers of TPT uptake/completion, and design appropriate interventions	• Loss to follow-up during treatment could be due to the differences between each regimen and pill burden (3RH) • Unwanted adverse drug events led to poor adherence and loss to follow-up • Lack of preferred regimen (e.g., 3H) leading to poor adherence and eventual loss to follow-up	1. Drugs of choice e.g., 3HP/6H should be made available 2. More studies and systematic documentation of the TPT side effects and their impact on the recipients 3. Conduct frequent home visits to evaluate wellbeing of people on TPT and adverse drug events (if any)
Ensure household contact investigation activities are always linked to assessment of TPT eligibility and TPT uptake (an integrated search-treat-prevent approach)	• Lack of screening activities for TPT	1. Ensure TPT is considered during household contact investigation
Ensure the availability of recording and reporting tools and systems for TPT		1. Improve and develop the ability to record the data
Enhance data generation, management and utilization to inform policies and programs		
Improve the quality of data usage, and evaluation		1. Further develop and improve the ability to use data for monitoring and evaluation activities through training and capacity building of relevant personnel at the national and subnational levels
Revitalise and contextualise the public-private engagement through the nationwide implementation of the new public-private mix strategy		
Discuss and formulate relevant policy and regulatory support mechanisms required for the implementation of public-private mix (PPM) strategy at national level (mandatory notification policy, workplace policy, etc.)		Workshop participants opined that this workshop was not a suitable platform for this discussion because: - It involves other sectors beyond health and TB who were not present - A separate symposium specific to PPM will be held after this workshop
Discuss, explore, and pilot PPM models proposed in the new PPM strategy at operational level	• The current model still lacks cooperation and communication between the relevant sectors and parties. After the revitalization of PPM, it has covered 34 operational districts to date. Yet, even within the 34 ODs, the progress is not optimal.	1. Increase the coverage of PPM and encourage more involvement from the private sectors 2. Provincial and operational district health departments should conduct frequent technical site visits 3. Schedule regular update meetings to streamline communications
Further understand post-TB health and wellbeing		

Further understand post-TB health and wellbeing	• There are people with TB who passed post treatment. Thus, it is important to determine whether this was caused by TB and to prevent this from happening	1. Conduct more studies on post-TB health and wellbeing 2. At least 2 visits to the health facilities should be implemented within 1 year post TB treatment to evaluate the health and wellbeing of TB survivors

MTB/RIF; Mycobacterium *tuberculosis*/Rifampicin resistant, ACF; active case finding, 6H; 6-months isoniazid, 3RH; 3-months (once daily) isoniazid and rifampicin, 3HP; 3-months (once weekly) isoniazid and rifapentine, PPM; public-private mix

*Ranked by workshop participants in ascending order, with 1 being the most important

†IDPoor is Cambodia's national poverty identification system that allows its recipients to access social assistance programmes in health, nutrition, water and sanitation, agriculture, and education[16]

‡Multisectoral accountability framework is a tool for achieving and assessing progress towards the implementation of political commitments and targets to end TB[17]

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