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Ministry of Health
National Center for Tuberculosis
and Leprosy Control

Report on Case-Control Study: Why smear-positive tuberculosis cases remained undiagnosed until the 2nd Cambodia National Tuberculosis Prevalence Survey 2011

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Ministry of Health

National Center for Tuberculosis and Leprosy Control

CENAT/JICA National TB Control Project

Report on a case-control study entitled;

Why smear-positive tuberculosis cases remained undiagnosed until the second prevalence survey in Cambodia

SUMMARY

OBJECTIVE: To examine what differences in demographic, socio economic and clinical characteristics there are between actively detected cases through prevalence survey and passive detected cases through routine DOTS services in Cambodia.

METHODS: A matched case-control study with 1 case to 2 controls was conducted. The cases were 103 smear-positive pulmonary TB cases identified by a prevalence survey period between December 2010 and September 2011. Controls were selected from smear-positive TB cases detected by routine DOTS services in the same commune as a case. Conditional logistic regression model was performed by univariate and multivariate analyses to examine odds ratios of being "case" compared to being "control".

RESULTS: 95 (92%) cases of 103 TB cases detected in the survey and 190 controls were interviewed. Age >= 55 years and had significantly greater odds ratio of 1.92 and smear grade >= 1+ had significantly lower odds ratio of 0.12 as well as 8 TB related symptoms by the univariate analysis. Previous TB history became significant with the odds ratio of 2.02 by the multivariate analysis. As a result of repeated multivariate analyses, 7 variables were selected as being statistically significant; age >= 55 years (3.14 odds ratio), smear grade >= 1+ (0.12 odds ratio), cough >= 28 days (0.07 odds ratio), haemoptysis (0.06 odds ratio), weight loss (0.33 odds ratio), night sweat (0.21 odds ratio) and previous TB history (50.8 odds ratio).

Conclusion: TB related symptoms are one of the greatest factors to drive TB patients to seek medical care. The NTP should strengthen case detection among the middle-aged and elderly through active case detection approach for both TB patients themselves and prevention of additional transmission of TB in the community, sustaining the current DOTS strategy.

1. Background

The second national TB prevalence survey in Cambodia was successfully conducted in 2010-2011 and identified 103 cases with smear-positive TB. The TB patients detected in the survey were referred to nearby DOTS centers for treatment. One of the research questions arisen through the survey was why TB cases detected in the survey remained undiagnosed until the survey time, while TB cases notified to the NTP passively sought medical attention in line with the conventional DOTS strategy.

To respond to this question, we conducted an additional study entitled above. The study focused on comparing between actively detected cases by the survey (cases) and passively detected cases by routine DOTS (controls).

2. Objective

The objective of the study was to examine what differences in characteristics such as age, sex, symptoms, smear grade, and other socioeconomic factors there are between the survey cases and routine DOTS cases.

3. Methods

A matched case-control study with 1 to 2 was conducted. The cases were 103 smear-positive pulmonary TB cases identified during the prevalence survey period between December 2010 and September 2011. The controls were selected from smear-positive TB cases detected through routine DOTS services in the same commune. The interview to the cases and controls was made from July to September 2012, nearly one year after the prevalence survey.

1) Cases

Cases were smear-positive pulmonary TB patients aged 18 years or over who were identified in the second prevalence survey.

2) Controls

Controls living in the same commune as a case were retrospectively selected from the time of visit to a health center within one year from new smear-positive pulmonary TB patients registered at the

health center. In case the required number of control was not met, we extended another year period back for the enrollment of controls into the study. Because the controls were limited to passively detected cases, TB cases who were registered at health center but detected by active case finding were excluded from the controls.

3) Interview

Semi-structure interview was carried out both for cases and controls by using a questionnaire, which included TB symptoms, demographic information, socioeconomic information such as possession of motorbike and charge-of-free card for medical care, and TB history of the patient and him/her family members (Annex). We used the laboratory results and symptoms information of the cases from the survey data and the laboratory data of the controls from the health center registry. In case the interviewer did not meet a case, the interview was made with one of the family members. When the interviewer did not meet a control, another control was enrolled in the study.

4) Data analysis

Distribution and frequency of smear grades, demographic characteristics, and other key variables were calculated and compared between the cases and the controls. Chi-square test or Fisher's exact test were applied to examine associations by using Epi Info 7 (Centers for Disease Control and Prevention, Atlanta, GA, USA; http://wwwn.cdc.gov/epiinfo/index.htm). In addition, to compare distributions of age and distance from house to health center, Mann-Whitney test was applied. We used conditional logistic regression to calculate odds ratios and 95% confidence intervals for the explanatory variables against the outcome variable of being a "case." This was done firstly as a univariate analysis, then as a multivariable analysis, initially including all explanatory variables then consecutively dropping the least significant one until all included variables were significant at $P < 0.05$. Mann-Whitney test and conditional logistic regression analyses were conducted with Stata 11.0 (StataCorp LP, College Station, TX).

4. Results

Of the 103 TB cases detected in the survey, 95 (92%) cases were interviewed. The 8 cases had moved out from the village with their family or died. The demographic and socioeconomic characteristics of the study subjects including 190 controls are shown in Table 1. The distribution of age was significantly different between the cases and the controls ($p < 0.0001$). There was no statistical difference in other 7 factors including age and distance from house to health center between the two groups. Table 2 shows clinical characteristics and laboratory data of the study subjects. The clinical characteristics regarding their symptoms were significantly different between the two groups, except for TB history of family and past TB history.

Table 3 shows the results of the univariate and multivariate analyses by conditional logistic regression model to examine odds ratios of being "case" compared to being "control". Age >= 55 years had significantly greater odds ratio of 1.92 and smear grade >= 1+ had significantly lower odds ratio of 0.12 as well as 8 TB related symptoms by the univariate analysis. The four symptoms of sputum, chest pain, fatigue, and fever became not statistically significant by the multivariate analysis. Previous TB history became significant with the odds ratio of 2.02 by the multivariate analysis.

As a result of repeated multivariate analyses, 7 variables shown in table 4 were selected as being statistically significant; age >= 55 years (3.14 odds ratio), smear grade >= 1+ (0.12 odds ratio), cough >= 28 days (0.07 odds ratio), haemoptysis (0.06 odds ratio), weight loss (0.33 odds ratio), night sweat (0.21 odds ratio) and previous TB history (50.8 odds ratio). When the analysis was limited to those with TB symptoms (cough >= 2wks and/or haemoptysis), the observations were similar to the above so interaction between TB symptoms and other variables were not taken into account in the analysis.

5. Discussion

The present study identified 7 variables significantly associated with being "case": age >= 55 years, smear grade >= 1+, four TB related symptoms (cough >= 28 days, haemoptysis, weight loss, and night sweat) and previous TB history by the conditional logistic regression analyses. Other socio-economic factors such as possession of user free card, motorbike or farmland, material of house, and geographic barrier to health center were not associated with being "case".

Several studies showed that actively detected cases are less symptomatic and have lower smear positivity and shorter duration of symptoms. In a community survey in South India, the patients

detected were more likely to be older, male, non-literate, and living in poor quality housing. A Bangladesh survey showed a trend in TB prevalence being associated with a lower quintile of socio economic position SEP). In the households with the lowest SEP, the prevalence of smear-positive TB was 10 times higher than the prevalence in households with the highest quintile of SEP. Although a study in Cambodia showed that active case finding approach detected older and more smear-negative patients, it did not include socio economic factors in the study.

The present study indicated lower odds ratios of possession of motorbike, farmland and user free card by multivariate analysis though they were not statistically significant. We did not find any significant association between being "case" and the distance to health center, because we selected the controls from the same commune as a case. Therefore, we have not come to conclusion whether socio economic factors or geographic barrier to health services are associated with being "case".

Older age was a significant and dependent factor for being "case" by multivariate analyses in the study. The middle-aged and elderly had higher ratio of prevalence rate to notification rate in the second prevalence survey as well. In addition, they were aware of their respiratory symptoms and took actions for seeking medical care by themselves. Take these results into consideration, one of the possible reasons for their higher prevalence notification ratio is that they have higher incidence by reactivation. In Cambodia, around two thirds of smear-positive TB cases were produced from the group with any abnormality on CXR.

The present study as well as other several studies showed that severity of symptoms of TB is one of the greatest factors to drive TB patients to seek medical care. However, currently 44% of smear-positive TB cases and only 23% of smear-negative, culture-positive TB cases complain cough 2 weeks or longer or haemoptysis. Moreover, a 5 year-follow up study for bacteriologically positive TB showed that 20% of them remained sputum-positive, who might have continued to excrete TB bacilli to others. Thus, the role of active case finding must be more importance in Cambodia for early case detection and prevention of TB transmission in the community.

According to the survey data, a certain proportion of cases (74/95) detected by prevalence survey were reported to have taken some actions of health seeking (i.e. consultation with health care providers). TB may not have been suspected by the providers because short duration and mildness of illness at the time when consultation was made. In high prevalence settings like Cambodia, it might be sensible to carry out diagnostic measures even to those with moderate symptoms which do not meet the current TB suspect criteria when they visit health facilities.

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Table 1 Demographic and socioeconomic characteristics of study subjects

Characteristics	Survey cases		Passive finding cases		p value
	N	%	N	%	
Number of cases	95	100	190	100	
Sex					
male	58	61.1	102	53.7	0.237
female	37	38.9	88	46.3	
Age					
18-34	8	8.4	35	18.4	0.005*
35-44	15	15.8	30	15.8	
45-54	20	21.1	52	27.4	
55-64	24	25.3	37	19.5	
65-	28	29.5	36	18.9	
House					
Cottage	23	24.2	50	26.3	0.979
Wood	55	57.9	101	53.2	
Brick	10	10.5	27	14.2	
Concrete	7	7.4	12	6.3	
Bicycle					
no	29	30.5	60	31.6	0.857
yes	66	69.5	130	68.4	
Motorbike					
no	49	51.6	86	45.3	0.316
yes	46	48.4	104	54.7	
Farmland					
no	24	25.3	50	26.3	0.849
yes	71	74.7	140	73.7	
User free card					
no	72	75.8	148	77.9	0.690
yes	23	24.2	42	22.1	
Distance from health center					
0 - 1.9 km	38	40.0	59	31.1	0.583*
2 - 3.9 km	19	20.0	56	29.5	
4 - 5.9 km	10	10.5	30	15.8	
6 - 8.0 km	16	16.8	30	15.8	
8.1 km-	12	12.6	15	7.9	

* : Mann Whitney's U test

Table 2 Clinical characteristics of study subjects

Characteristics	Survey cases		Passive finding cases		p value
	N	%	N	%	
Number of cases	95	100	190	100	
Smear grade					
Scanty	45	47.4	21	11.1	< 0.001
1+	23	24.2	61	32.1	
2+	12	12.6	64	33.7	
3+	15	15.8	44	23.2	
Duration of Cough					
=< 13 days	53	55.8	17	8.9	< 0.001*
14 - 27 days	29	30.5	30	15.8	
>= 28 days	13	13.7	143	75.3	
Sputum					
no	23	24.2	12	6.3	< 0.001
yes	72	75.8	178	93.7	
Haemoptysis					
no	86	90.5	120	63.2	< 0.001
yes	9	9.5	70	36.8	
Chest pain					
no	50	52.6	28	14.7	< 0.001
yes	45	47.4	162	85.3	
Weight loss					
no	44	46.3	21	11.1	< 0.001
yes	51	53.7	169	88.9	
Fatigue					
no	24	25.3	9	4.7	< 0.001
yes	71	74.7	181	95.3	
Fever					
no	24	25.3	20	10.5	0.001
yes	71	74.7	170	89.5	
Night sweat					
no	56	58.9	44	23.2	< 0.001
yes	39	41.1	146	76.8	
Family TB history					
no	82	86.3	151	79.5	0.159
yes	13	13.7	39	20.5	
Previous TB history					
no	86	90.5	180	94.7	0.276
yes	9	9.5	10	5.3	

* : Mann Whitney's U test

Table 3 Univariate and multivariate analyses (conditional logistic regression) against outcome of being cases

Variable	Cases (n = 95)		Controls (n = 195)		Univariate analysis				Multivariate analysis			
	N	%	N	%	Odds ratio	95%CI		p value	Odds ratios	95%CI		p
Sex: male	58	61.1	102	53.7	1.37	0.82	2.29	0.232	1.21	0.45	3.23	0.708
Age >= 55 years	52	54.7	73	38.4	1.92	1.16	3.17	0.011	3.70	1.32	10.34	0.013
House: brick or concrete	17	17.9	39	20.5	0.82	0.41	1.64	0.573	0.31	0.07	1.29	0.108
Bicycle	66	69.5	130	68.4	1.08	0.61	1.90	0.792	1.04	0.34	3.19	0.946
Motorbike	46	48.4	104	54.7	0.77	0.46	1.30	0.326	0.84	0.27	2.56	0.754
Farmland	71	74.7	140	73.7	1.11	0.54	2.30	0.773	0.62	0.13	2.98	0.555
Use free card	23	24.2	42	22.1	1.13	0.61	2.12	0.690	0.59	0.15	2.36	0.457
Distance >= 6 km	28	29.5	45	23.7	1.63	0.70	3.78	0.258	1.04	0.24	4.49	0.96
Smear >= 1+	50	52.6	169	88.9	0.12	0.06	0.23	< 0.001	0.11	0.03	0.36	< 0.001
Cough >= 28 days	13	13.7	143	75.3	0.05	0.03	0.11	< 0.001	0.06	0.02	0.18	< 0.001
Sputum	72	75.8	178	93.7	0.22	0.10	0.46	< 0.001	1.01	0.20	5.23	0.987
Haemoptysis	9	9.5	70	36.8	0.18	0.09	0.39	< 0.001	0.05	0.01	0.38	0.004
Chest pain	45	47.4	162	85.3	0.15	0.09	0.28	< 0.001	1.35	0.42	4.33	0.616
Weight loss	51	53.7	169	88.9	0.15	0.08	0.27	< 0.001	0.36	0.12	1.11	0.075
Fatigue	71	74.7	181	95.3	0.13	0.06	0.31	< 0.001	0.38	0.07	2.25	0.288
Fever	71	74.7	170	89.5	0.32	0.16	0.63	0.001	1.47	0.31	7.04	0.631
Night sweat	39	41.1	146	76.8	0.16	0.09	0.30	< 0.001	0.19	0.05	0.66	0.009
TB history in family	13	13.7	39	20.5	0.62	0.31	1.25	0.182	1.22	0.29	5.18	0.788
Previous TB history	9	9.5	10	5.3	2.02	0.76	5.31	0.156	67.91	6.54	704.86	< 0.001

Table 4 Final multivariate analysis (conditional logistic regression)

Variable	Multivariate analysis		
	Odds ratio	95%CI	p value
Age >= 55 years	3.14	1.26 - 7.83	0.014
Smear >= 1+	0.12	0.04 - 0.34	< 0.001
Cough >= 28 days	0.07	0.03 - 0.17	< 0.001
Haemoptysis	0.06	0.01 - 0.37	0.002
Weight loss	0.33	0.12 - 0.89	0.029
Night sweat	0.21	0.08 - 0.58	0.002
Previous TB history	50.83	6.33 - 408.30	< 0.001

Annex

Semi-structure questionnaire for Case-Control study:

1. General information:

- 2nd National Survey Participant: □Yes (case), □No (control)
- HC Name: ……., OD ……
- Date of register (dd/mm/yy……/……/……..…)
- Maximum smear grade: □Scanty, □1+, □2+, □3+
- Treatment outcomes: □ Still on treatment, □cure, □complete, □failure, □died, □default, □transfer out

2. Demographic information:

- Patient's name:.....
- Sex: □Male, □Female
- Age:.....years old (□15-24, □25-34, □35-44, □45-54, □55-64, □65-74, □75-84, □85-
- Address: Village……., Commune……,
  District……, Province……..
- Number of household members.....persons

3. Socio-economic information:

- Religious: □Buddhism, □Christian, □Muslim, □others (specify.....)
- House type: □cottage, □wooden house, □brick house, □concrete building
- Property of the household:

Bicycle: □Yes, □No

Motorbike: □Yes, □No),

Car: □Yes, □ No,

Rice/farm land: □Yes, □No)

- Do you have a card for User Fee Free? □Yes, □No, if yes - Which type?.....

4. Symptoms (at the time of TB diagnosis) and duration: □Yes, □No,

If yes please questions below:

- Cough: □yes……..days, □No
- Sputum □yes……..days, □No
- Haemoptysis: □yes……..days, □No
- Chest pain: □yes, □No
- Loss of BW: □yes, □No
- Fatigue: □yes, □No
- Fever: □yes, □No
- Night sweat: □yes, □No
- Others (specify.....)

5. Health seeking behavior (First onset of TB symptom)

First, when did your TB symptom start? (mm/yy: ……../……..)

And what did you do for it? (one choice)

- 1. □No attention
- 2. □Self medication
- 3. □Government hospital

- 4. □Health center
- 5. □Private clinic
- 6. □Private hospital
- 7. □Pharmacy
- 8. □Traditional healer
- 9. □family member
- 10. □other facility (specify.....)

If not either 3 or 4, why? (multiple choice)
- □Not sever
- □No money
- □Far distance
- □No time, busy
- □others (specify.....)

And then, where did you consult? Specify all facility in the order of your visits.
2nd……, 3rd……,4th…….
5th……..,6th……., 7th……...

How many facilities did you consult for medical care before coming to public facility?
(…… facilities excluding the current public facility)

6. TB treatment history
- □No history, □ Past history

If past history, when (Year:.....) and where? (one choice)
- □Government hospital
- □Health center
- □Private clinic
- □Private hospital
- □Pharmacy
- □Traditional healer

7. Health facility information
- Distance from patient' s house to public health facility:.....km
- Which facility (Public, private, traditional healer) do you prefer to visit first?
  why?: □convenient, □near, □cheap, □kind, etc. .....)
- Do you have any member who diagnosed as TB? □Yes, □No

if yes, where did he/she get treatment? (one choice)
- □Government hospital
- □Health center
- □Private clinic
- □Private hospital
- □Pharmacy
- □Traditional healer