LATIENT TUBERCULOSIS INFECTION DIAGNOSIS AND TREATMENT AT TWO PROVINCES OF QUANG NAM, DANANG AND RESULTS OF PUBLIC HEALTH INTERVENTIONS: INITIAL RESULTS

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Latent TB Infection (LTBI) for key affecting persons, especially household contacts with TB bacteriologically confirmed patients (household contact for short), is determined as one of the key interventions for reducing TB burden in Vietnam. The research of LTBI diagnosis and treatment at the two provinces of Quang Nam and Danang and the results of public health interventions was conducted to evaluate the results of public health interventions for individuals who are screened, diagnosed, and treated for LTBI. From 7/2017 to 6/2018, this pragmatic randomized controlled trial carried out a package of public health interventions for 1,034 household contacts at the 2 districts of Quang Nam and the 2 districts of Danang province; subjects are between 0 to 50 years old, and were determined as household contacts of the TB bacterially confirmed patients. By cascade analysis for initial data, 1,034 household contacts were listed, in which, 947/1,034 (92%) visited to district health centers for LTBI screening, 688/1,034 (66%) agreed TST (Mantoux) and returned district health centers after two days for Mantoux result, 503/1,034 (49%) continued other examinations (X-ray, sputum examination, etc.) in order to determine whether they had active tuberculosis or not, 497/1,034 (48%) completed all examinations and receives the diagnosis result, 336/1,034 (32%) was recommended to start LTBI therapy, and 320/1,034 (31%) started LTBI therapy. This result was significant higher than the baseline data of year 2016 at the same sites which only 11% of estimated household contacts were listed, and only 0.4% started LTBI therapy. At each step, the largest percentage of drops-out was LTBI screening completion. Further investigations is needed to address this issue. The data suggest that public health interventions resulted in increasing participation in all LTBI steps when compared with baseline data. And it is feasible to expand LTBI management for household contacts at age ≥ 5 years.

Keywords: Latent Tuberculosis Infection (LTBI), household contact, Mantoux testing, public health intervention, National Tuberculosis Control Program.

I. INTRODUCTION

According to the Global Tuberculosis (TB) Report 2017 by the World Health Organization (WHO), TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS.

Vietnam National Control Program has been conducted since 1957 and is considered as a "path-finder" in applying global Tuberculosis (TB) control strategies. In spite of gaining significant achievements in TB control, Vietnam still ranked at 16th out of 30 listed countries having high burden TB, and ranked 13th out of 30 countries with highest burden of MDR-TB [1]. One of the causes preventing Vietnam from TB control is high latent TB (LTBI) infection rate (around 40%) [2] where TB bacteria can become active in 5-15% of this population in their life time [3].

Aiming at global TB control, latent TB infection (LTBI) screening and treatment for high-risk group, especially household contacts with bacteriologically confirmed TB patients, is currently determined as one of the key factors recommended by the WHO [3; 4]. Up to 2017, the National Tuberculosis Control Program (NTP) has carried out a few of LTBI interventions for children aged less than 5 years old as household contacts, and the results were not as expected. The NTP data showed that there were significant percentage of drops-out at each steps of LTBI screening, treatment and treatment completion, etc [5 - 10].

With expectation of improving LTBI management capacity, the study *"LTBI diagnosis and treatment situation in the two provinces of Quang Nam, Danang and results of public health interventions"* was conducted in order to evaluate whether implementing a number of public health interventions might result in increasing the proportion LTBI detection and treatment among household contacts of patients with active pulmonary TB.

II. METHODS

1. Study design and sites

A pragmatic randomized controlled trial with community and health system interventions was selected to conduct the study. In addition, qualitative study was conducted to describe barriers of approach LTBI services, and to identify the reasons why household contacts agreed/ disagreed each period of cascade of care in diagnosis and treatment of LTBI.

The study was conducted from 7/2017 to 12/2018 in the intervention sites of the 4 districts in Quang Nam (Tam Ky, Phu Ninh) and Danang (Son Tra, Lien Chieu), and control sites of the 4 districts in Quang Nam (Nui Thanh, Thang Binh) and Danang (Thanh Khe, Hai Chau).

At intervention sites, a number of public health interventions developed by the NTP and McGill University were carried out, including (i) training health workers (HW) at district and commune levels on LTBI management, Mantoux injection skill; (ii) LTBI information, education and communication (IEC) in the community; (iii) listing household contacts; (iv) coordination to provide one-stop service (LTBI screening, diagnosis, treatment regimen decision at district health centers and then referring LTBI patients to community health stations for treatment management); (v) supplying drugs, reagent, tuberculin skin test, etc.; (vi) allowance for TB staff who successfully consulted LTBI screening and treatment; (vii) allowance for household contacts visiting district health centers for LTBI screening; and (viii) quarterly supervising and data collecting.

2. Subject and sampling

Potential participants were household contacts of index patients with newly/ relapsed diagnosed bacteriologically confirmed active pulmonary TB (smear and/or culture positive active pulmonary TB, Xpert MTB + /RIF negative). Household contacts of all ages were be considered eligible. A household contact was be defined as someone who, in the preceding 3

months, slept in the same house at least one night per week, or spent more than 1 hour per day in the house for at least 5 days per week. The house was be defined as the dwelling, or buildings, which the family unit occupies and uses regularly.

We used the randomized cluster sampling probability proportional to 2016 TB patient notifications, enhanced by stratification by the two provinces of Quang Nam and Danang. The sample size was 1,300 household contacts with bacteriologically confirmed TB patients (index patients), all ages, at the 8 districts of the two provinces. In addition, qualitative method, namely, in-depth interview and case study, was also applied for a purposive sample size including 4 district HWs, 2 commune HWs, 4 index patients, and 24 household contacts at 4 intervention sites in order to describe a number of barriers which affected LTBI diagnosis and treatment for household contacts, and also to analyze the reasons of household contacts' acceptance or non-acceptance for each steps of cascade of care in LTBI. Based on the new information collected in each in-depth interviews, sample size could be revised.

Variables or measures

The research was divided into the 3 periods: pre-intervention evaluation, intervention implementation, and post-intervention evaluation. The following variables were measured: number of household contacts (i) identified when compared with estimated ones, (ii) testing of intended for LTBI screening, (iii) completed LTBI screening and testing process, (iv) started medical evaluation, (v) completed medical evaluation, (vi) recommended LTBI treatment, (vii) started LTBI treatment, (viii) completed LTBI treatment. The collected data was compared at the time of pre- and post-intervention in the same sites, and also

at the time of post-intervention between the intervention and control sites.

3. Statistical analysis

Data collection tool and techniques

Key information to extract will include the following: 1) The number of patients diagnosed with bacteriologically confirmed active pulmonary TB (index patients), 2) The number of their household contacts who were identified as eligible for symptom screening and LTBI testing, 3) The number of who completed LTBI testing procedures - using Tuberculin Skin Test (TST), 4) The number of who were LTBI test positive, 5) The number of contacts with positive LTBI tests who had a medical evaluation to exclude active TB (e.g. medical examination, chest X-ray and sputum test if applicable), 6) The number of contacts with positive LTBI tests who completed medical evaluation and started LTBI treatment, 7) The number of LTBI patients who completed LTBI treatment. The information was abstracted from different sources, including the index case registration file, treatment cards and other sources. A standardized form was be used to record this information.

At the same time, we collected information about the problems and barriers that impede TB contact management. These were mapped onto the Cascade of care in Latent TB. The three in-depth interview questionnaires were developed for the groups of health workers, index patients and household contacts.

Data analysis

In term of quantitative study, paper data collection was uploaded into web-based mobile data collection and management system (Dacima web-based data collection developed by McGill University). All data processing and analysis was performed in SPSS 21. Descriptive statistics and bivariate analysis was used. Data of the intervention versus the control

groups was compared to evaluate intervention effectiveness; DID (Difference in differences) technique could be used.

In term of qualitative study, information from in-depth interviews was encoded, synthetized and analyzed by NVIVO 11 software.

4. Ethics

The study protocol was approved by the Ethics Review Board of the Ministry of Health, the National Lung Hospital, Viet Nam and McGill University, Canada.

III. RESULTS

Initial results of the research from July 2017 to ending June 2018 was collected and analyzed.

Baseline survey at the 4 intervention districts (Son Tra, Lien Chieu in Danang, Tam Ky, Phu Ninh in Quang Nam) showed that up to 2017, NTP policy related to LTBI management focused only on household contacts as children aged less than 5 years or 5-14 years old with HIV positive; LTBI screening and treatment was not prioritized, record of childhood TB management was insufficient related to cascade of care in LTBI for child household contacts, and LTBI testing (Mantoux or IGRA) was not routinely conducted. HWs did not pay attention to LTBI for children less than 5 years old in health practice process, did not have adequate and comprehensive understanding for LTBI, LTBI management and LTBI consultant skills in order to encourage household contacts to attend LTBI screening and treatment. As a result, household contacts with index patients did not clearly know the risk of developing TB in case of LTBI, did not understand the value of LTBI treatment, excessively worried about side-effect of LTBI treatment and therefore had a tendency towards non-acceptance of LTBI treatment recommended by HW, and only started to treatment when there are TB symptoms.

In 12-month implementation (July 2017 to June 2018), 344 index patients were registered for TB treatment, in which, HWs investigated the household contact information of 286 patients, accounted for 83%. HWs then identified 1,034 household contact in 1,032 as estimated. Analyzing cascade of care in LTBI on initial results (cumulative percentage) at the intervention sites showed that in 1,034 household contacts identified, 947 (92%) visited district health centers for LTBI consultant, 688 (66%) accepted LTBI screening, Mantoux testing, and returned to discuss the Mantoux testing result after two days, 503 (49%) started medical evaluation to determine whether had TB or not, 497 (48%) completed medical evaluation, 336 (32%) recommended LTBI treatment, and 320 (31%) started LTBI treatment (Table 1).

Table 1. Cascade of care in LTBI management for household contacts with index patients in period 1/7/2017 – 30/6/2018

	Total	Percentage (Cumulative)	Percentage (By step)
Step 1: Initial identification	1034	100%	100%
Step 2: Testing of intended for screening	947	92%	92%
Step 3: Completing screening and testing	688	66%	72%
Step 4: Starting medical evaluation	503	49%	73%
Step 5: Completing medical evaluation	497	48%	99%

	Total	Percentage (Cumulative)	Percentage (By step)
Step 6: Recommending treatment	336	32%	68%
Step 7: Starting treatment	320	31%	95%

This result was significantly higher than the 2016 baseline data at the intervention sites (only 11% household contacts identified, and only 0.4% household contacts started with LTBI treatment) (Chart 1)
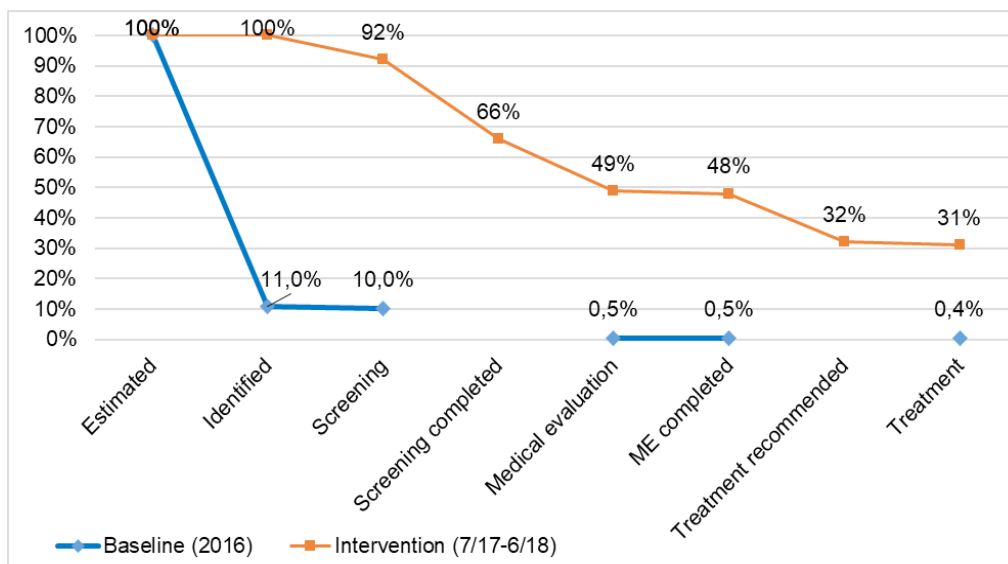

Figure 1. Cascade of care in LTBI for household contacts at the time of pre- and post-intervention

Percentage of household contacts who attended each step of cascade of care in LTBI informed that the highest drops-out was at the step of completing LTBI screening and testing (72% of household contact accepted LTBI screening and testing, 28% did not accept), therefore, it's necessary to conduct further analysis of the causes in order to recommend suitable interventions (Chart 2). In-depth interview results for 10 household contacts who did not accept LTBI screening and testing at intervention sites suggested a number of following reasons: (i) feeling no TB symptoms, so no need screening, (ii) no understanding or ambiguous understanding on LTBI treatment effectiveness, (iii) household contacts who did business were afraid of clients' discrimination in case of TB, which resulted in family income reduction, and (iv) worrying about TB detection after completing screening process which might affect jobs or relationships, etc. In according to the in-depth interviews, interviewees' knowledge on TB and LTBI was extremely limited, so it's essential to consider the HWs' responsibility and consultant skills.

Regarding step 4 (starting medical evaluation), 73% of household contact who completed step 3 (LTBI screening and testing) conducted additional examinations for TB detection, this percentage was calculated on 100% household contacts who completed step 3. However, household contacts who completed step 3 need to have the following conditions to continue to step 4: positive result

of Mantoux testing, or history of TB or LTBI, or symptoms of TB suspects while negative results of Mantoux testing, or children aged less than 5 years. Total of household contacts who had enough conditions for medical evaluation was 532; therefore, the percentage of household contact who completed step 3 and had enough conditions accepted to continue step 4 was 95% (503/532).

Regarding step 6 (recommending LTBI treatment), the reasons of drops-out percentage at 32% included (i) household contacts were diagnosed TB, so excluded LTBI treatment, or (ii) household contacts had a number of risk factors of severe side-effect in case of LTBI treatment, for example thalassemia, etc. In term of household contacts recommended with LTBI treatment, 95% started treatment, only 5% refused. The reasons of treatment refusal were (i) long treatment course (6 to 9-month isoniazid), especially for children, (ii) worrying about drug side-effects (Chart 2).
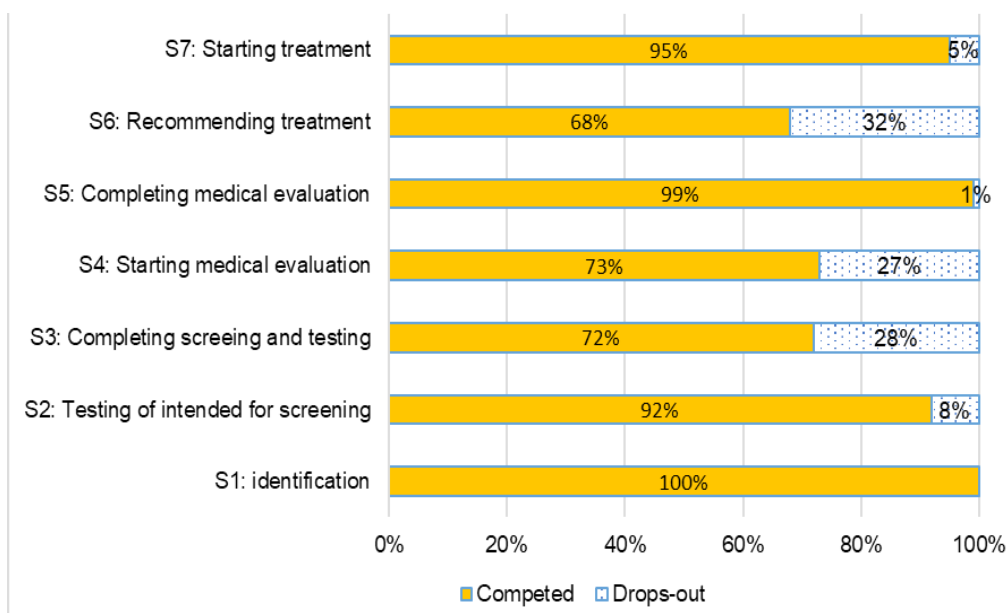

Figure 2. Household contacts' percentage attending each step of cascade of care in LTBI (7/2017-6/2018)

In comparison of data between Danang and Quang Nam, it's possible to realize that household contacts' percentage attending each step of cascade of care in LTBI in Danang is significantly higher than that in Quang Nam, especially at the step 1 – identified household contact when compared with estimated ones (117% in Danang vs. 73% in Quang Nam) (Table 2).

Table 2. Cascade of care in LTBI management for household contacts with index patients by province in period 1/7/2017 – 30/6/2018

	Danang			Quang Nam		
	Total	% (cum.)	% (by step)	Total	% (cum.)	% (by step)
Estimated household contacts	636	100%	100%	396	100%	100%
Step 1: Initial identification	746	117%	100%	288	73%	100%

Step 2: Testing of intended for screening	672	90%	90%	278	70%	97%
Step 3: Completing screening and testing	512	69%	76%	176	44%	63%
Step 4: Starting medical evaluation	390	52%	76%	113	29%	64%
Step 5: Completing medical evaluation	385	52%	99%	112	28%	99%
Step 6: Recommending treatment	255	34%	66%	81	20%	72%
Step 7: Starting treatment	246	33%	96%	74	19%	91%

Regarding LTBI treatment, results of LTBI patients related to index patients who registered in Q3/2017, 60/74 (81%) completed, 13/74 (17.5%) defaulted, 01/74 (1.5%) intendedly stopped because LTBI patients used treatment drugs (isoniazid) for suicide. Side-effects were recorded for the 02 patients, 01 patients who used drugs for suicide need be stopped, 01 patient developped rashes continued to complete the LTBI treatment course. The in-depth interview results identified the reasons of quite high defaulted percentage (17.5%) included (i) long treatment course, (ii) feeling no symptoms of TB, (iii) suspecting LTBI treatment effectiveness because of opposite information sources by other HWs.

IV. DISSCUSION

After 12-month intervention period, the percentage of completing LTBI screening and testing at intervention sites of Quang Nam and Danang (66%) was remarkably lower than that in other countries. Results from analyzing cascade of care in LTBI from 58 researches on the world for 748,572 people in period 1946-2015 showed that the percentage of completing LTBI screening and testing was 71.9% [11], meanwhile, this percentage in one cross-sectional research of LTBI management among contacts at primary care in Brazil in 2016 was 79.4% [12]. In term of LTBI treatment,

percentage of starting treatment (31%) and completing treatment in the first cohort (81%) in the two provinces of Quang Nam and Danang was quite high when compared with other countries on the world, this percentage in analysis of cascade of care in LTBI from 58 researches on the world for 748,572 people in period 1946-2015 were 30.7% and 18.8% respectively [11], and percentage in the cross-sectional research of LTBI management among contacts at primary care in Brazil in 2016 was only 24% and 16.3% in turn [12]. Research results showed that the main reasons which led to drops-out at each step of cascade of care in LTBI were (i) limited knowledge of community on TB and LTBI, and (ii) TB stigma. Responsibility of this current situation mostly belonged to HWs and health system. By survey, the stability, quantification and mindfulness of HWs who were responsible for LTBI at district level pay extremely important role; the results of LTBI management which were obviously better in Danang when compared with Quang Nam was the clear evidence for this judgment. At research sites, it's realized that commune HWs nearly had no role in LTBI management, including household contact investigation, consulting on LTBI screening and testing, although commune HWs directly delivered anti-TB drugs and TB treatment follow-up for index patients. The reasons determined were that

commune HWs must conduct so many health programs in the sites, did not have thoroughly information on LTBI, provincial and district HWs did not frequently supervised and supported.

The model of one-stop service of LTBI screening, diagnosis, treatment regimen decision at district health centers and then referring LTBI patients to commune health stations for treatment management represented more reasonable when compared with the commune-level based model of LTBI management as NTP policy, namely, all diagnosis services were provided at the same health facilities, district HWs had better consultant skills for household contacts. This re-coordination of service mode contributed an important part in increasing percentage of household contact (i) identification from 11% to 100%, (ii) attending LTBI screening from 10% to 92%, (iii) starting and completing medical evaluation from 0.5% to 48-49%, and (iv) starting LTBI treatment from 0.4% to 31%. Experience from 12-month implementation showed that encouraging household contacts to LTBI screening achieved the highest effectiveness at the time of the index patients' TB detection and registration. At this time, index patients and their household contacts were both much worrying about the TB situation and its dissemination; therefore, it's advantageous to successfully consult.

Based on the initial result of the research, it is necessary to improve IEC and consulting skills of district and commune HWs in order to increase the percentage of household contacts' LTBI treatment completion. The commune HWs' role need be paid more attention because they were close to the TB patients and their family.

One more limitation which was also detected during research implementation was that HWs were not really interested in LTBI

detection and treatment as expected, they only considered that implementation of current LTBI interventions was research activity. Therefore, it's necessary that the NTP accelerates the official expansion of comprehensive LTBI interventions as recommended by the WHO, especially, application of short-term LTBI regimen (12 doses Isoniazid and Rifapentine in 3 months). When LTBI management becomes one NTP policy with expanded target population, HWs will be more responsible

V. CONCLUSION

Public health interventions contributed on increasing household contacts to attend all steps of cascade of care in LTBI when compared with the time before interventions. However, it's essential to further strengthen IEC activities in order to improve community knowledge on LTBI management and treatment. The research results also showed that expansion of LTBI management in high-risk groups, especially household contacts at all ages, was feasible. Therefore, the NTP need accelerate the LTBI interventions with aiming at TB control on the whole country.

ACKNOWLEDGEMENTS

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