Kingdom of Cambodia

Nation Religion King

Ministry of Health

Report
National Tuberculosis Drug Resistance Survey, 2006-2007

National Center for TB and Leprosy Control (CENAT)

May 2011

Contents

Foreword

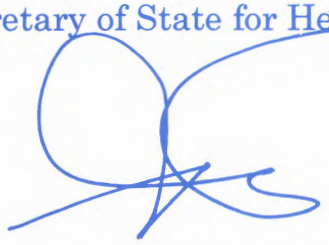
This second round of the National Tuberculosis Drug Resistance Survey (NDRS) Cambodia was conducted from September 2006 to March 2007 by the National Tuberculosis Control Program (NTP), the Ministry of Health of Cambodia. It is the result of the great collaborative efforts among partners and staff of the NTP.

The first round of the NDRS was conducted from 2000 to 2001.Five years later, in 2006, the second round of the NDRS was organized aiming at measuring the level of the Multi-Drug Resistant Tuberculosis (MDR-TB) among new TB cases and previously treated TB cases, and looking at different trend of drug resistance from the first survey. A small number of MDR-TB cases were found in the second survey, while no MDR-TB case was observed among new TB cases in the first survey. Although the NTP has extensively expanded and decentralized TB services to health center since late 2001 and thus notification rates of smear-positive cases increased to a large extent between the two survey periods, i.e. 2001 and 2006, prevalence of MDR was not yet high at the time of the second survey.

Since information from research activities become more important for the NTP, the findings of this survey will be of great significance for more effective management of MDR-TB, particularly for monitoring the trend of drug resistance after the expansion of TB services. In addition, the findings will guide the NTP to gear its efforts towards contribution to reaching the Millennium Development Goals by 2015.

Phnom Penh, 24 May, 2011

Secretary of State for Health



Prof. Eng Huot

Acknowledgments

The second round of the National Tuberculosis Drug Resistance Survey (NDRS) would not be in existence without the help of the many people who kindly assisted the NTP with their time, knowledge and expertise, and to whom we are most grateful.

On behalf of the National Center for Tuberculosis and Leprosy Control (CENAT), we would like to express our deep thanks and appreciation to all organizations and individuals for their contributions in making this survey successful.

We profoundly thank WHO, CENAT/JICA National TB Control Project, RIT/JATA US/CDC, and GFATM, and other partners for their financial and technical supports to this survey.

We sincerely hope the results of this survey will be of great benefit for the management of MDR-TB in Cambodia.

Phnom Penh, 24 May, 2011

National Center for TB and Leprosy Control
Director

Dr. Mao Tan Eang

Abbreviations

CDC/GAP: the Global AIDS Program of the United States Centers for Disease Control and Prevention
CENAT: National Center for Tuberculosis and Leprosy Control
CI: Confidence Interval
DEFF: Design Effect
DOTS: directly observed treatment, short-course
DRS: Drug Resistance Survey
DST: Drug Susceptibility Test
GFATM: Global Fund to fight AIDS, Tuberculosis and Malaria
IUATLD: International Union Against Tuberculosis and Lung Disease
JICA: Japan International Cooperation Agency
LPA: line probe assay
MDR-TB: Multi-Drug Resistant Tuberculosis
MOTT: Mycobacterium other than tuberculosis
NDRS: National Drug Resistance Survey
NTP: National Tuberculosis Control Program
OD: Operational District
PSU: Primary Sampling Unit
RIT/JATA: Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association
SRL: Supranational Reference Laboratory
TB: tuberculosis
VNTR: Variable Numbers of Tandem Repeats
WHO: World Health Organization

E: EB, ethambutol
H: INH, isoniazid
R: RFP: rifampicin
Z: PZA, pyrazinamide
S: SM, streptomycin

Executive Summary

Cambodia, a country with around 14 million population, has been ranked 21st of the 22 countries with a high-burden of tuberculosis (TB) by the World Health Organization (WHO). The National Tuberculosis Control Program (NTP) had initially adopted Directly Observed Treatment, Short-course (DOTS) at hospitals nationwide since 1994, and then since late 2001, it has successfully expanded and decentralized DOTS into health center, followed by community levels.

Between 1994 and 2004, the NTP used the eight-month regimen with rifampicin (RFP), the most potent anti-TB drug, only for initial two months. However, to shorten the duration of the treatment and to improve cure rate, the program has introduced the six-month with RFP throughout since 2005. This transition, among others, posed a concern to the NTP that prevalence of multidrug-resistant TB (MDR-TB), a strain of TB bacilli resistant to both isoniazid (INH) and RFP, and thus is much more difficult and costly to be treated, may have possibly increased from the levels observed in 2001 when the first national drug resistance survey (NDRS) was conducted. The second NDRS was conducted from September 2006 to March 2007, to assess the prevalence of MDR-TB among new and previously treated TB cases.

Sputum samples were collected from 30 clusters of operational districts across the country chosen with sampling probability proportionate to the number of the cases notified in 2005. Drug susceptibility was tested for the four drugs: INH, RFP, ethambutol (EB) and streptomycin (SM), according to an internationally recommended method for drug resistance surveillance.

A total of 781 samples: 725 from new and 56 from previously treated cases, were available for drug susceptibility testing. Ninety-nine (13.6%, 95% confidence interval (CI) 10.7-17.3%) of the new cases, 12 (20.8%, 95%CI: 11.3-35.1%) of previously treated cases, and 111 (14.1%, 95%CI: 11.3-17.6%) of the combined cases (i.e. new and previously treated cases) showed drug resistance to at least one of the four drugs. Prevalence rates of drug resistance to INH and RFP among new cases were 7.4% and 1.8%, respectively. There were 16 (2.0%, 95%CI: 1.2-3.2%) MDR-TB cases in total (combined cases): ten (1.4%, 95%CI: 0.8-2.5%) among new and six (10.0%, 95%CI: 4.8%-19.6%) among previously treated cases.

Despite the decentralization of TB services and the introduction of the current regimen in 2005, the prevalence of MDR-TB among new cases was still reasonably low and the regimen should successfully be able to cure almost all the new cases. It is, however, strongly recommended that the third NDRS be conducted after 2011. It is also recommended that NTP should set up a sentinel surveillance system in which trend of drug resistance, at least RFP, among previously treated cases is monitored.

I. Background

Directly Observed Treatment, Short-course (DOTS) is a proven intervention for treatment of tuberculosis (TB), based on accurate diagnosis and patients taking a full course of a cocktail of anti-TB drugs, which include isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA), streptomicin (SM), and ethambutol (EB). DOTS hinges on government commitment, detection, treatment, uninterrupted supply of anti-tuberculosis drugs and a monitoring and reporting system to evaluate treatment outcomes for each patient.

Cambodia, a country with a 14 million population, has been ranked as 21st of the 22 countries with a high-burden of TB by the World Health Organization (WHO).The national tuberculosis control program (NTP) had adopted DOTS at hospitals since 1994 and reached nationwide coverage in 1999. Since late 2001, it has been extensively expanding and decentralizing DOTS through the initiative of "DOTS Expansion to all health centers by 2005."DOTS at HC covered 100% by end 2004.

Prevalence of multidrug-resistant (MDR)-TB among new and previously treated cases was 0.0% (95% confidence interval [CI]: 0-0.6%) and 3.1% (95%CI: 0.6-8.9%), respectively,[1] shown by the first round of National Tuberculosis Drug Resistance Survey (NDRS), which was conducted from October 2000 to April 2001 as a part of the Global TB Drug Resistance Surveillance initiated by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD). Moreover, no MDR case was detected out of 245 bacteriological positive cases in the National TB Prevalence Survey conducted in 2002,[2] with a small prevalence of mono-resistance to INH (4.5%) and SM (2.4%), even though Cambodia had a high prevalence of TB with a rate of 269/100,000 population for new smear-positive TB. This was partly due to the fact that, between 1994 and 2004, NTP used the eight-month regimen (2HRZE/6HE) with INH and EB in the continuation phase.

Since 2005, the NTP has introduced the six-month regimen (2HRZE/4HR), which includes INH and RFP in the continuation phase, to shorten the duration of TB treatment and to improve cure rate. This transition might have some shortcomings, one of which would possibly be increase in prevalence of MDR-TB, if DOTS is not properly applied and defaulter rate is high. A patient with MDR-TB is much more difficult to be treated and costly to be cured. Therefore, it is essential for the NTP to monitor the trend of prevalence of MDR-TB in the country.

The second round of NDRS was expected to determine the level of drug resistance and steps to be taken by the NTP of Cambodia to address the issues related to MDR-TB, including the development of strategies for the management of MDR-TB.

II. Objectives

The objectives of this survey are: primarily to measure the level of MDR-TB among new TB cases, and secondary, to measure the level of MDR-TB among previously treated TB cases.

III. Organizations

The National Center for Tuberculosis and Leprosy Control (CENAT) took overall leadership for NDRS. The central and provincial TB supervisors provided supervision to maintain the quality of implementation of NDRS. CENAT and the Battambang Provincial TB Laboratory performed primary culture of the specimens, and the isolates were then sent to CENAT for identification and drug susceptibility testing (DST). The Research Institute of Tuberculosis (RIT) supported the NDRS as the designated Supranational Reference Laboratory (SRL), in terms of developing protocol, providing technical advice and quality assurance and control of DST. WHO assisted in reviewing the protocol and provided technical advice to the protocol. WHO, CENAT/JICA (Japan International Cooperation Agency) National TB Control Project, and RIT provided with support for data analysis, report writing, and dissemination workshop of the results.

Fund was provided by Global Fund fight against AIDS, Tuberculosis, and Malaria for operational and implementation cost, while JICA supported for technical experts, laboratory equipment and consumables, including DST medium, support for CENAT laboratory personnel. The Global AIDS Program of the United States Centers for Disease Control and Prevention (CDC/GAP) also provided support for laboratory equipment for the survey. CENAT provided human resource and logistic support for implementation of the survey.

IV. Methods

4.1 Survey Sesign

(1) Target population and operational definitions

The target population in the study was newly registered smear-positive cases. A smear-positive pulmonary TB case was defined by the presence of either two or more positive smears, or one positive smear plus an abnormal chest X-ray result consistent with TB judged by a medical officer at the diagnosis of TB. A new case was defined as a patient who had never had TB treatment or who had taken anti-TB drug for less than a month, and a previously treated case was a patient who had been treated for TB for one month or more.

(2) Sampling design

A two stage sampling method was adopted, considering the simplicity of sampling and estimating the prevalence of drug resistance in the country.

The primary sampling units (PSUs) were systematically selected from a list of operational districts (ODs) with sampling probability proportionate to the number of smear-positive cases notified to NTP in 2005, allowing selecting the same PSUs more than once. This could serve as proxy to Proportional Population Sampling with replacement, which can produce self-weighted samples. The systematic sampling has nature of stratification. The PSUs were selected from ODs, because of less fluctuation of notified cases than at diagnostic center level. The same number of clusters (30) as the first NDRS was adopted, because the design effect in the first NDRS was low as shown below.

At the second stage, each PSU (i.e. OD) sequentially enrolled eligible cases regardless of treatment centers in the OD to which the patient first consulted from the date designated by the OD until the accumulated number of enrolled cases reached a certain number (33).

(3) Sampling frame

As mentioned above, as the sampling frame a list of ODs was used with the total number of smear-positive TB cases (consisting of new and previously treated cases) newly registered a year before the NDRS (i.e. 2005). The use of the number of newly registered cases rather than that of new or previously treated cases has the advantage of being more robust against fluctuation and inaccuracy of case categorization in notification. It is another advantage that the combined prevalence can also be estimated directly from the collected sample.

(4) Study sites and subjects

The NDRS was conducted nationwide, except three remote ODs (Stung Treng, Mondulkiri, and Ratanakiri OD) where the numbers of cases were quite small, accounting only for 1.0% of the total notified smear-positive TB cases of the country each year. A subject was defined as a smear-positive pulmonary TB patient who was diagnosed and had not yet put on treatment at the selected study sites (Table 1 and Figure 1). Cases were included in the study until the accumulated number of smear-positive cases had reached 33 in each cluster. TB patients who refused to sign the informed consent form were excluded.

(5) Sample size of cases with DST results

The sample size was set as 700, based on the assumption that any resistance to RFP was 1% among new cases and the upper limit of 95% confidence interval (CI) was 2.0% or less. The sample size of 700 was considered appropriate, as well, to be able to produce 95%CI narrow enough for inference of MDR and any drug resistance among new cases. It was decided that the sample size should be based primarily on prevalence of RFP resistance rather than that of MDR, because in the last survey, no MDR was found among new cases and the NTP is now more concerned with RFP resistance, the prevalence of which was 0.63% in the first NDRS.

Since the prevalence of RFP resistance was relatively small, a logit transformation method was adopted in estimating 95% CI, instead of a normal approximation method, which might not be appropriate for a small proportion. There are several ways to estimate CI for such a small number. The decision was made, because we used the Stata version 11 (StataCorp, Texas, USA) for data analysis and it has the "*svy*" commands, in which the above said method is employed.

The design effect (DEFF) was estimated as 1.0 for the prevalence of RFP resistance and as 1.2 for any drug resistance. In the first NDRS, DEFF for resistance to RFP was 0.9, which was interpreted as no design effect (DEFF = 1), and for any drug resistance 1.15. For the prevalence of any drug resistance, it was expected that DEFF as high as that was observed in the first NDRS (1.2) might be seen.

With the sample size of 700, and when DEFF was 1.0 and 1.2, the upper limit of 95%CI for 1% prevalence of RFP resistance would be 2.15% and 2.3%, respectively. Under the same assumption, 95% CI for 10% prevalence of any drug resistance, which was observed in the first NDRS, would be 7.3-12.9%

with DEFF of 1.2. If prevalence of MDR was 0.5% or less, the probability of not being able to detect MDR would be 3% (one side 95% confidence limit for zero prevalence of MDR in 700 cases would be 0.43%) with no design effect.

(6) The number of cases enrolled

The following assumptions were adopted to decide the number of cases to be enrolled to obtain the sample size of 700 with DST result available. It was presumed culture recovery rate would be 90%, as was observed in the prevalence survey conducted in 2002, because the laboratory procedure was the same. In the prevalence survey, out of 84 smear-positive cases, 75 cases had primary culture positive (recovery rate of 89%). The proportion of previously treated cases was set as 15%, based on the experience in the first NDRS, in which it was 13.7%. In the routine case notification reports, it is 4-5%, however, in the first NDRS, it increased by 10%, probably because of more in-depth interview of treatment history. Also, an 8% safety margin was adopted to secure the result. Under these assumptions, the number of cases to be enrolled was:

$$700 \times (1/0.9) \times (1/0.85) \times (1/0.92) = 990$$

Therefore, it was decided that each cluster would enrol 33 (990 cases /30 clusters) smear-positive cases.

(7) Duration of enrollment

It was initially expected that it would take less than five months to enrol 33 smear-positive pulmonary cases at each cluster, however, the actual intake period was from September 2006 through March 2007.

4.2 Procedures of Collection of Data and Sputum Specimens, Transportation, Supervision

(1) Data collection and procedures

At each cluster, the OD TB supervisor and medical doctors in charge were assigned as the focal point for NDRS. Once the designated diagnostic center, either the Provincial or the OD Referral Hospital or former district hospital (TB Unit), detected a smear-positive TB case, the smear test result was communicated to the designated focal point and the staff of the health center to which the patient consulted. The health center staff then obtained an informed consent (Annex 1) and collected the morning (the first) sputum specimen at the health center. The patient was further asked to go to the diagnostic center to submit "on the spot" (the second) sputum specimen. The interview was also made by the interviewer, which was a trained medical doctor, to collect social-demographic and health information from the patient, including past history of TB treatment based on the semi-structured

questionnaire (Annex 2).

The final decision on whether the case is categorized as a new case or a previously treated case was made by the OD TB supervisor responsible for the OD concerned, after the interview by the medical doctor. The OD supervisor fills out the registration list of the eligible subjects (Annex 3).

Sputum containers were labelled with the specimen number such as xx-00-1 or 2, in which the xx denoted the OD code, the 00 the patient code, and the 1 or 2 the serial number of sputum specimens of the patient, i.e. the first sputum specimen was labelled as [1] and the second as [2]. Both sputum specimens were taken prior to taking the first dose of anti-TB drugs. All the numbers were pre-stamped on labels and study forms at CENAT before the implementation of the study to avoid mistakes in the field.

(2) Transportation of sputum specimens

The sputum specimens were transported together with the sputum transportation form (Annex 4), being kept in an icebox at 4-8 °C from the interview sites to the designated culture center on the same day of the interview.

There are two culture centers: CENAT was responsible for 12 provinces, i.e. Phnom Penh (1OD and 4 hospitals), Kampong Speu (2ODs), Kandal (3ODs), Svay Rieng (2ODs), Kampong Chnang (1OD), Kampong Thom (2ODs), Takoev (2ODs), Kampot (2ODs), Prey Veng (3ODs), Sieam Reap (3ODs) , Kratie (1OD) and Kampong Cham (3ODs); and Battambang for three provinces, i.e. Pursat (1OD), Bantey Meanchey (2ODs) and Battambang (1OD).

(3) Supervision of the diagnostic centers

The Provincial or Central supervisors visited each clustered-OD once a week at the beginning and every two weeks thereafter to validate diagnostic and interview results with the supervision checklist (Annex 5). Some of the patients involved in the survey were re-interviewed by Provincial and Central supervisors to obtain more accurate information on his/her treatment history.

4.3 Laboratory examinations

The same procedures recommended by WHO/IUATLD[3] were employed in the study. The laboratory examinations, including primary culture, identification test for *M. tuberculosis*, DST, and quality control of DST, were almost the same as the ones in the first survey. The only exception was the part of pre-treatment of primary culture in which we did not use 1% CPC (Cetylpyridinium Chloride) in this study; however, CPC was used to avoid

putrefaction in the first survey. After the completion of primary culture, all isolates grown at Battambang culture center were sent to CENAT laboratory once a month for identification and DST (Please See the report[1] of the first NDRS for more information).

4.4 Analysis

The sampling weight proportional to reciprocal of the number of cases with DST results in each cluster is given because the proportion of previously treated is small. As mentioned before, the Stata verion 11 (StataCorp, Texas, USA) was used for data analysis. If the number of drug-resistance cases is less than five, the binomial exact method was used. For test of difference, if the expected number of drug-resistance cases is less than five, the binomial exact method without sampling weight for test of difference in proportions was used.

4.5 Ethical Issues

The protocol of the study was submitted to the Ethics Committee of Ministry of Health of Cambodia and has been approved. Informed consent was obtained from the participants to the study.

V. Results

5.1 Sample collection and laboratory tests

Out of the 30 clusters, one cluster enrolled 32 cases and the others enrolled 33 cases, thus 989 eligible cases were enrolled in total, of which, two patients did not receive the interview and thus were excluded from the analysis; one had INH mono-resistance and the other had no growth of subculture. Of the remaining 987, 870 (88.1%) had primary isolates recovered, 17 were contaminated and 100 were culture negative. Out of the 870 culture positive samples, two were MOTT, seven had less than five colonies, and 20 were failed in subculture. Thus, these 29 cases were also excluded from further examination. Isolates were obtained from 841 cases out of the remaining 861, and then they were stocked for DST (Figure 2).

Since the isolates for 60 cases had no subculture recovered from the stock, the isolates for remaining 781 cases were eventually examined for DST, of which 725 were new and 56 were previously treated cases. The proportion (7%) of previously treated cases among study subjects with DST was slightly higher than the proportion of re-treatment cases nationwide in 2006 (4%). Among the 781 cases, 53% were male and 47% were female. About 70% of the cases belonged to age category between 15 and 54 years old. The age and sex distributions of new smear-positive cases were similar to those of national TB

statistics[4] in 2006 as shown in Table 2.

5.2 Prevalence of Drug Resistance

The distribution of anti-TB drug resistance was summarized in Tab. 3. Out of the 725 new cases, 99 were the cases with resistance to any drug (13.6%, 95%CI: 10.7-17.3%). Resistance to RFP was found in 19 cases (2.4%). Prevalence of resistance to RFP by treatment history was 1.8% (13/725) (95%CI: 0.8-2.5%) for new cases and 10.0% (6/56)(95%CI: 4.8-19.6%) for previously treated cases.

There were 16 strains of MDR-TB, resistant to both RFP and INH, in total (2.4%, 95%CI: 1.5-3.7%). Prevalence of MDR-TB by treatment history was 1.4% (10/725), (95%CI: 0.8-2.5%) for new cases and 10.0% (6/56)(95%CI: 4.8-19.6%) for previously treated cases. Previous treatment history was significantly associated with the prevalence of MDR. However, previous treatment history was not significantly associated with prevalence of any drug resistance, although the point estimate was higher in previously treated cases than in new cases.

5.3 Examination of factors associated with any drug resistance

The sampling size was not designed to detect any association of potential risk factors with prevalence of drug resistance; however, factors, such as age group, sex, location of diagnostic centers, and type of facilities were examined for association with drug resistance among new cases (Tab. 4).

There was significant difference between age group and drug resistance, and it seems that those aged 55 years old or more had lower prevalence of any drug resistance, there was no clear trend between age and prevalence of drug resistance. In the subgroup without treatment history, prevalence of resistance to any drugs was still lower in those aged 55 years old or older. Sex was not significantly associated with prevalence of any drug resistance. Prevalence of any drug resistance and MDR was higher in diagnostic centers located in provincial capital cities (including Phnom Penh) than in those in other areas, although the association was not statistically significant. Prevalence of any drug resistance and MDR was not significantly associated with type of facilities, either; however, the point estimates were slightly higher in hospitals than in health centers. There were only two cases with non-Cambodian nationality, and both of them had any drug resistance.

VI. Discussion

6.1 Main Findings

The second round of NDRS conducted in 2006-2007 has shown prevalence rates of MDR-TB as 1.4% among new cases and 10.0% among previously treated cases, a slightly but significantly higher rate among new cases and a higher rate among previously treated cases than had been indicated in the first NDRS in 2000 (0.0% and 3.1%, respectively). The Survey was conducted carefully based on an internationally recommended method and the samples should be representative and reflective of the situation at the time of the implementation. The prevalence of MDR-TB among new cases was still reasonably low, and thus the rifampicin based standard regimen should be able to successfully cure almost all the newly enrolled TB cases.

It appears that prevalence of MDR in Cambodia is no longer very rare, though still lower than some other Asian countries: prevalence of MDR among new and previously treated cases was 3.8% and 22.1%, respectively, in the Philippines in 2003, and 2.7% and 19.3%, respectively, in Viet Nam in 2006.[5] The low MDR-TB prevalence in Cambodia was partly due to the facts that RFP was initially introduced nationwide in mid 1990s and then in 2005, NTP introduced the six-month regimen, replacing the eight-month regimen which did not contain RFP on the continuation phase, thus until recently emergence of RFP resistance had been successfully maintained low. Assuming that it may take a decade or two for MDR-TB to emerge, particularly among new TB cases, after RFP-based regimen was introduced nationwide, it is speculated that the first survey in 2000-2001 may have been too early to observe emergence of RFP resistance among new cases, so may as well the second survey. In future years, prevalence of MDR may gradually increase, particularly more than five years after the introduction of the six-month regimen. Therefore, it is strongly recommended that NTP should continuously monitor the trend of drug resistance in the country by 1) a sentinel surveillance for MDR among previously treated cases and 2) a third round of NDRS, which should more focused on new cases.

6.2 Assessment of Potential Limitation

(1) Influence of failure of subculture

Primary recovery rate (88%) of the second survey was compatible with that of the first survey. In the second survey, however, 60 isolates (7.1%) stocked for DST could not be examined due to failure of recovery from stock. To assess potential influence of this failure of subculture for a part of isolates on

prevalence of drug resistance, line-probe assay (LPA) was carried out for the 60 cases at RIT. Of which, 55 reacted successfully with LPA and only one isolate, from a previously treated case, was categorized as RFP resistance. Therefore, the failure of subculture was less likely to cause underestimate MDR prevalence among new cases in this survey.

(2) Assessment of possibility of cross-contamination of MDR isolates

Five of 16 MDR isolates were inoculated on slants on the same day at the same laboratory. To assess any possibility of cross-contamination, Variable Numbers of Tandem Repeats (VNTR) of these isolates were examined at RIT. The results showed that only two of the five isolates had the same VNTR pattern, suggesting that cross-contamination did not occur to a significant extent which affected the survey result.

(3) Assessment of enrollment of cases

In some clusters, eligible cases were not enrolled consecutively according to the order of diagnosis dates. This may have been that TB cases diagnosed more delayed and thus fewer cases were enrolled at health centers than at hospitals (TB units). However, even so, it did not at least lead to underestimation of MDR prevalence, because the survey results indicated that the cases at TB units had higher MDR rates than those at health centers as shown later, although it is not statistically significant.

(4) Classification of treatment history of MDR cases

While either the first NDRS or the first National Prevalence Survey did not observe any MDR cases among new cases, there were MDR cases among new cases in the second NDRS. Table 5 shows the results from the first and the second survey for major patterns of drug susceptibility. There may be previously treated cases categorized falsely as new cases, because the proportion of previously treated cases in the second survey (7.2%) was much lower than that of the first survey (13.1%), possibly leading to overestimation of MDR prevalence among new cases. However, since all the MDR cases detected in the second survey except one case were re-interviewed for their TB treatment history, the classification of MDR cases should be accurate.

6.3 Assessment of Factors Associated with Drug Desistance

(1) Previous treatment history

Difference in prevalence of any drug resistance between new cases and previously treated cases was not large (13.6% vs. 20.8%, p = 0.178) and was lower in Cambodia than in other countries[3] with reports. One of the most probable reasons is its sampling variability due to the small number of

previously treated cases. Another reason may be misclassification of previous treatment history. However, it may be also attributable to low prevalence of resistance to SM in previously treated cases.

As observed in the first survey, the difference in the prevalence of drug resistance to SM between new cases and previously treated cases was very small (8.0% vs. 8.6 %) while that for INH and RFP are larger (7.4% vs. 17.3% and 1.8% vs. 10.0% for INH and RFP, respectively). Information on the time of previous treatment was available for 44 out of the 56 previously treated cases and the majority (39 cases) received their previous treatments after 1995, indicating most of the cases categorized as previously treated did not actually receive SM during the TB treatment, because SM has not been included in the regimens for new cases: Category-I and III, since 1994. Therefore, most of resistance to SM in new cases was presumed to have acquired through the transmission of TB with resistance to SM.

The prevalence of MDR was significantly higher among previously treated cases than among new (1.4% vs. 10.0%, $p < 0.001$), as was expected.

(2) Location and types of diagnostic centers

Although the point estimate of prevalence of any drug resistance in cases in urban areas was higher than that in rural areas, the difference was either not large or statistically significant. However, in the first survey, the difference was statistically significant (15.8% in urban and 7.8% in rural, $p < 0.05$). The contradictory observations in the two surveys may be due to difference in survey design; in the first survey, one site consisted of only one diagnostic center, while in the second survey, one site usually consisted of a diagnostic center and some health centers. The difference in prevalence of drug resistance between cases in urban and those in rural may have been reduced. This speculation might be plausible if there was historically difference in access to TB treatment between urban and rural areas and the population in rural areas had had better access to TB treatment. However, it is difficult to conclude whether it is correct or not with only two data points available.

(3) Age groups and sex

The point estimates of any drug resistance increased among younger cases while decreased among elderly cases, though, the numbers of cases were too small to assess the differences between the two surveys with statistical significance. However, caution should be given in an increase in proportion of resistant TB cases among young patients because it would reflect recent transmission of drug resistance TB.

There was no significant association between sex and any resistance or MDR although the point estimates indicated lower prevalence of any resistance or MDR among female than among male.

6.4 Planning of future surveys and surveillance

The current DOTS program of Cambodia is characterized by ambulatory DOT at health center and community levels while in the past it was hospital DOTS. The second NDRS was carried out a couple of years after DOTS expansion into health centers was totally completed in 2004. It is necessary to carry out the third round NDRS to monitor whether prevalence of MDR increases or not several years after the decentralization of TB services because routine DST for all cases will not be implemented within a few years.

In addition to a series of national cross sectional surveys, the NTP should consider routine monitoring of drug-resistance TB in some selected spots, such as high TB/HIV prevalent areas. It would also be useful to introduce a sentinel surveillance system in some selected hospitals where DST at least for RFP is regularly examined, particularly for previously treated cases.

VII. Conclusion

The second round of NDRS was successfully conducted from 2006-2007 showing recent prevalence of TB drug resistance in Cambodia. This second survey revealed that there existed MDR cases even among new cases as well as among previously treated cases. The MDR prevalence was not yet high and almost all the newly enrolled TB cases should be able to be cured with the current standard regimen. However, caution should be taken to follow the trend of MDR prevalence among previously treated cases by a sentinel surveillance system as well as by periodical NDRSs focusing on new cases.

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Tables and Figures

Table 1 Operational Districts selected by population proportionate cluster sampling and TB facilities involved in the survey

No of newly registered smear positive cases = 21,808

No of clusters = 30, Cluster interval = 21,808 / 30 = 727

Areas				Population	Number of TB cases registered				TB facility		
No	Province	No	Operatinal District		New	ReTt	S(+)	Cumulative	RH/ FDH	HC	Total
1	*KANDAL*	1	TAKMOV	234,450	316	16	332	332	2	14	16
		2	KOH THOM	153,016	266	4	270	942	1	10	11
		3	MOUK KAMPOL	85,382	91	6	97	1,554	1	5	6
2	*SVAY RIENG*	4	SVAY RIENG	299,963	769	56	825	2,805	2	16	18
		5	ROMEAS HEK	130,825	179	4	183	2,988	1	9	10
3	*CENTRAL HOSPITAL*	6	4 hospitals (CENAT, Mettapheap K/S, Preah Ketmealea, Hope Center)	-	455	85	540	3,878	4	0	4
4	*PHNOM PENH*	7	WEST	316,538	200	7	207	4,547	1	6	7
5	*PURSAT*	8	BAKAN	136,965	243	5	248	5,308	1	10	11
6	*BATTAMBANG*	9	THMAR KOUL	193,940	223	9	232	5,918	2	16	18
7	*BANTEAY MEANCHEY*	10	MONGKOL BOREI	232,771	423	19	442	6,969	2	13	15
		11	OCHROV	178,431	291	5	296	7,507	1	4	5
8	*SIEM REAP*	12	SIEM REAP	271,429	414	15	429	8,183	1	14	15
		13	SOTNIKUM	251,687	546	22	568	9,295	1	15	16
		14	KRALANH	113,581	358	6	364	9,659	1	5	6
9	*KOMPONG THOM*	15	KG THOM	284,254	537	11	548	10,476	1	16	17
		16	STUNG	134,764	317	7	324	11,274	1	9	10
10	*TAKEO*	17	DAUNKEOV	199,424	466	11	477	11,751	1	14	15
		18	PREY KABAS	161,302	395	21	416	12,467	2	12	14
11	*KOMPONG SPEU*	19	KOMPONG SPEU	335,000	598	24	622	13,599	1	14	15
		20	KARNG PISEY	124,873	546	12	558	14,157	1	12	13
12	*KAMPOT*	21	KAMPOT	142,016	255	0	255	14,633	1	6	7
		22	CHHOUK	181,066	280	12	292	15,367	1	7	8
13	*PREY VENG*	23	PREY VENG	206,296	615	30	645	16,399	1	16	17
		24	PEARING	191,236	400	17	417	17,089	2	24	26
		25	PREAH SDACH	114,196	254	9	263	17,783	1	5	6
14	*KOMPONG CHHNANG*	26	KG. CHHNANG	298,115	519	18	537	18,588	1	19	20
15	*KRATIE*	27	KRATIE	156,948	200	5	205	19,059	1	10	11
16	*KOMPONG CHAM*	28	KRAUCH CHMAR	114,228	131	2	133	19,739	1	5	6
		29	SREY SANTHOR	161,071	184	6	190	20,504	1	5	6
		30	ORAING OV	100,136	108	2	110	21,246	1	6	7
								Total number of TB facilities involved	39	317	356
	PHNOM PENH		National Pediatrique	-	2	0	2				
	STUNG TRENG		STUNG TRENG(OD)	-	123	2	125				
	MONDLKIRI		SEN MONORUM(OD)	-	16	4	20				
	RATTANAKIRI		BANHUNG(OD)	-	78	2	80				
				Sub-total	219	8	227	1.0%			

Figure 1 Map of 30 Clusters Surveyed

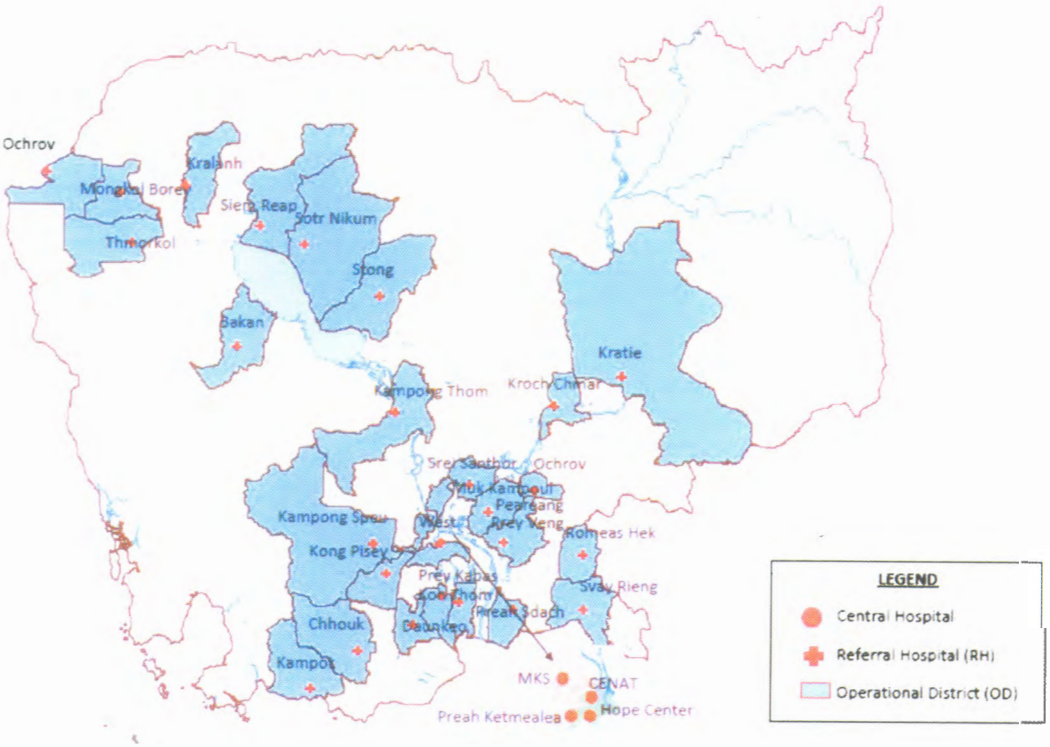

Figure 2 Results of culture examination

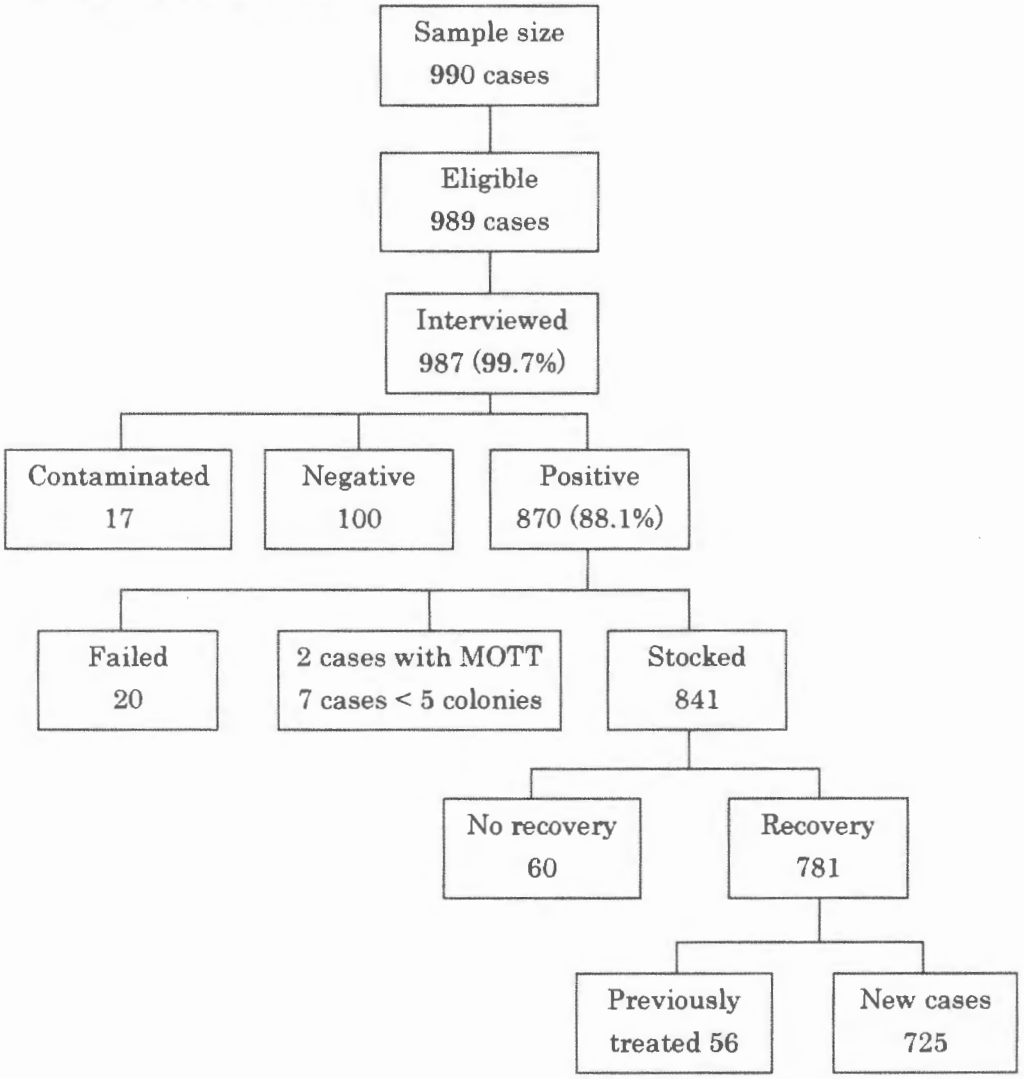

Table 2 Age and Sex distribution of new smear-positive case

2006 Notification (New Smear-positive)

	0-14	15-24	25-34	35-44	45-54	55-65	65+	Total	%
Male	50	791	1486	2205	1902	1689	1665	9788	50.7%
Female	44	749	1330	1839	2072	1915	1557	9506	49.3%
Total	94	1540	2816	4044	3974	3604	3222	19294	
%	0.5%	8.0%	14.6%	21.0%	20.6%	18.7%	16.7%	100.0%	

2006-2007 NDRS (New Cases with DST results)

	0-14	15-24	25-34	35-44	45-54	55-65	65+	Total	%
Male	0	26	86	90	63	63	51	381	52.6%
Female	1	33	42	71	64	69	64	344	47.4%
Total	1	59	128	161	129	132	115	725	
%	0.1%	8.1%	17.7%	22.2%	17.8%	18.2%	15.9%	100.0%	

Table 3 Drug susceptibility patterns

	New				Previously Treated				Combined			
	n°	%(*)	95% CI(**)		n°	%(*)	95% CI(**)		n°	%(*)	95% CI(**)	
Total number of strains tested	725				56				781			
SENSITIVE TO ALL 4 DRUGS	626				44				670			
ANY RESISTANCE	99	13.6%	10.7%	17.3%	12	20.8%	11.3%	35.1%	111	14.1%	11.3%	17.6%
Isoniazid (NH)	50	7.4%	5.4%	9.9%	10	17.3%	9.8%	28.5%	62	8.0%	6.1%	10.6%
Rifampicin (RMP)	13	1.8%	1.1%	3.0%	6	10.0%	4.8%	19.6%	19	2.4%	1.5%	3.7%
Ethambutol (EMB)	8	1.1%	0.5%	2.2%	5	8.1%	3.7%	16.8%	13	1.5%	0.8%	2.8%
Streptomycin (SM)	59	8.0%	5.8%	11.1%	5	8.6%	3.1%	21.6%	64	8.1%	5.9%	11.0%
MONORESISTANCE	42				3				45			
Isoniazid (NH)	33	4.7%	3.0%	7.4%	3	5.6%	1.8%	16.5%	36	4.8%	3.1%	7.3%
Rifampicin (RMP)	3	0.4%	0.1%	1.2%	0	0.0%	0.0%	6.4%	3	0.4%	0.1%	1.2%
Ethambutol (EMB)	3	0.4%	0.1%	1.2%	0	0.0%	0.0%	6.4%	3	0.4%	0.1%	1.2%
Streptomycin (SM)	3	0.4%	0.1%	1.2%	0	0.0%	0.0%	6.4%	3	0.4%	0.1%	1.2%
MULTIDRUG RESISTANCE	10	1.4%	0.8%	2.5%	6	10.0%	4.8%	19.6%	16	2.0%	1.2%	3.2%
NH + RMP	1	0.1%	0.0%	1.1%	2	3.5%	0.8%	13.4%	3	0.4%	0.1%	1.2%
NH + RMP + EMB	3	0.4%	0.1%	1.6%	2	3.1%	0.8%	11.8%	5	0.5%	0.1%	2.3%
NH + RMP + SM	1	0.1%	0.0%	0.8%	0	0.0%	0.0%	6.4%	1	0.1%	0.0%	0.7%
NH + RMP + EMB + SM	5	0.7%	0.2%	1.6%	2	3.6%	0.4%	12.3%	7	0.9%	0.4%	1.8%
OTHER PATTERNS												
NH + EMB	0	0.0%	0.0%	0.5%	0	0.0%	0.0%	6.4%	0	0.0%	0.0%	0.5%
NH + SM	9	1.2%	0.7%	2.2%	0	0.0%	0.0%	6.4%	9	1.2%	0.0%	0.5%
NH + EMB + SM	0	0.0%	0.0%	0.5%	0	0.0%	0.0%	6.4%	0	0.0%	0.0%	0.5%
RMP + EMB	0	0.0%	0.0%	0.5%	0	0.0%	0.0%	6.4%	0	0.0%	0.0%	0.5%
RMP + SM	0	0.0%	0.0%	0.5%	0	0.0%	0.0%	6.4%	0	0.0%	0.0%	0.5%
RMP + EMB + SM	0	0.0%	0.0%	0.5%	0	0.0%	0.0%	6.4%	0	0.0%	0.0%	0.5%
EMB + SM	0	0.0%	0.0%	0.5%	0	0.0%	0.0%	6.4%	0	0.0%	0.0%	0.5%

*: Weighted average. Weights are given according to the explanation in method section
**: CI for patterns with resistant cases less than 5 is calculated by binomial exact method.
Other CIs are calculated by logit transformation.

Table 4 Association of factors with any drug resistance and MDR

A. Assessment of association of previous treatment with drug resistance

	Total	Any Drug Resistance	%	95%CI	p-value	MDR	%	95%CI	p-value (***)
New Cases	725	99	13.7%	10.7%-17.3%		10	1.4%	0.8%-2.6%	
Previously treated cases	56	12	20.8%	11.3%-35.11%	P = 0.1781	6	10.0%	4.8%-19.6%	p < 0.001

B. Assessment of association of factors with resistance among New Smear-positive cases

	Total	Any Drug Resistance	%	95%CI		MDR	%(*)	95%CI(**)	p-value (***)
non Capital of Province	408	51	12.1%	8.7%-16.4%		4	1.0%	0.4%-2.4%	
Province Capital	317	48	15.7%	11.0%-21.9%	p= 0.2537	6	2.0%	0.9%-4.2%	P = 0.346
Health Center	460	57	12.3%	8.8%-16.8%		5	1.1%	0.4%-2.5%	
Hospital	265	42	16.1%	11.7%-21.7%	p= 0.2015	5	2.0%	0.6%-4.3%	P = 0.510
Male	381	60	15.9%	12.0%-20.9%		7	1.8%	0.7%-3.7%	
Female	344	39	11.1%	8.0%-15.4%	P = 0.0524	3	0.9%	0.2%-2.5%	p=0.347
0-	60	13	20.7%	12.6%-31.3%		0	0.0%	0.0%-6.0%	
25-	128	18	13.0%	6.5%-24.0%		5	3.9%	1.2%-8.9%	
35-	161	22	14.0%	10.1%-19.1%		3	1.9%	0.4%-5.3%	
45-	129	28	22.5%	13.4%-35.2%		0	0.0%	0.0%-2.8%	
55-	132	11	8.9%	4.6%-16.3%		1	0.8%	0.0%-4.1%	
65-	115	7	6.1%	2.6%-13.7%	p = 0.0203	1	0.9%	0.0%-4.7%	p= 0.136(**)

*: unweigted, **: binomial exact ***: Fisher's exact

Table 5 Major drug susceptibility patterns of the first and the second survey				
	New			
	1st survey	95%CI	2nd survey	95%CI
No of cases examined	638		725	
Any resistance	10.1%	7.7%-13.0%	13.60%	10.70%-17.26%
INH	6.1%	4.3%-8.4%	7.40%	5.4%-9.9%
RFP (*)	0.6%	0.2%-1.6%	1.80%	0.9%-3.1%
MDR(*)	0.0%	0.0%-0.6%	1.4%	0.7%-2.6%
	Previously Treated			
	1st survey	95%CI	2nd survey	95%CI
No of cases examined	96		56	
Any resistance	16.6%	11.2%-24.0%	20.81%	11.3%-35.1%
INH	15.8%	10.4%-23.3%	17.25%	9.8%-28.5%
RFP (*)	3.1%	0.6%-8.9%	10.00%	4.8%-20.4%
MDR(*)	3.1%	0.6%-9.0%	10.00%	4.8%-20.4%
	Combined			
	1st survey	95%CI	2nd survey	95%CI
No of cases examined	734		781	
Any resistance	10.8%	8.5%-13.7%	14.10%	11.3%-17.6%
INH	7.4%	5.62%-9.73%	8.0%	6.1%-10.6%
RFP (*)	1.0%	0.4%-2.0%	2.40%	1.5%-3.7%
MDR(*)	0.4%	0.1%-1.2%	2%	1.2%-3.3%
*: confidence interval is calculated by Stata command for binomial exact method				

Annex

Annex 1: **Informed Consent Form for Participant**

Study title: Drug resistance surveillance

I,_____ after reading or having explained to me the content and procedure of this study, fully understand what expected of me as a subject and agree with participating in this study.

I understand

1. The purpose and procedure of the study
2. That I will not face any discomfort or harm
3. That I could withdraw at any time without giving reason
4. That information provided by me will be kept confidential
5. That the result of the study will be used for the further case management related to drug resistance.

Name Signature

Age sex

Date:

Address

I, _____ interviewer, certify that I have explained to the above subject the content and procedure of the study according to the attached information sheet. I have covered all points listed above.

Name Signature

Age sex

Date:

Name of facility:

If you have any questions and suggestion please contact National Center For Tuberculosis and Leprosy Control, St 278&95 Sangkat Boueng Keng Kang II Chamkarmorn , Phnom Penh, Cambodia :Tel : 023 219 274

Contact person:

Dr.Mao Tan Eang Tel: 012-916503

Dr.Koeut Pichenda Tel: 012-839647

Dr. Khun Kim Eam, Tel:, 012-856146

Dr.Poeu Satha Tel: 012-988868

Dr. Saint Saly, Tel: 017-522360

Annex 2: Clinical Information Form

Patient

Questionnaire of National Drug Resistance Surveillance

Please fill in this question form about all S(+) TB ***before starting TB treatment***.

OD:..... Province:.....

Interviewer: .....

Date of Interview:.....

Place of interview:.....

A) Patient' s Identification

Patient's name : .....Age.....years, Sex : Male ( ) Female ( )

Nationality : Cambodian ☐ Others:..... ☐

Place of TB treatment:.....

Day Mo Yr

TB register number : .....Date registered : / ____/ _____/ _____/

Date of first treatment / ____/ _____/ _____/

B) *Ask the patient about his/her* disease history

B1 Patient's history:

1. How l ong have you been sick ?

Cough:(.....) Chest pain(.....) Hemoptysis(.....)

2. Did you have the same symptoms prior to this episode? Yes ( ),No ( )
3. Did you have other symptoms of lung disease? Yes (symptom?) No ( )
4. Did you have chest X- ray examination prior to this episode? Yes ( ), No ( )
5. Did you have sputum examination prior to this episode? Yes ( ), No ( )
6. Did you have ***any drug treatment for one month or more?*** Yes ( ), No ( )

   If yes, please ask the patient to show medical prescription, TB treatment form or drugs remained what was the name of the drugs? ( ).
7. Did you ***receive injections for one month or more*** ? Yes ( ), No ( )

   If yes, please ask the patient to show medical prescription, TB treatment form or drugs remained what was the name of the drugs? ( ).
8. Did you have red urine during using those drugs? Yes ( ) , No ( )
9. Have you ever got previously TB treatment? Yes ( ) go to B2 , No ( ) go to

B1-1

B1-1: After the answer above did the patients receive previous treatment for TB? (Judgment of Interviewer)

Yes ( ) go to B2, No ( ), go to C

B2 Information about the previous TB treatment

1. Where was the patient treated? .....

Public facility (National H, RH, HC)

Private clinic ( )

Others (specify)

2. When was the patient treated? .....(Month Year)

3. How long has the patient been treated?

Less than one month ( ), One month or more (Months)

4. The outcome of the last treatment according to patient's answer?

Cured ( ) Not cured ( ) Unknown ( )

C) MEDICAL RECORDS

After extensive question and checking TB register or other documents, did you discover that the patient has been registered for TB treatment?

Yes (register No), No (why?)

If he/she was registered for TB treatment in OD, (OD responsibility), in Province (Province responsibility), out of province (CENAT responsibility)

C-1 If yes, how long has the patient been treated?

Less than one month ( ), One month or more (Months)

C- 2 ***If yes***, what was the outcome of the last treatment?

Cured ( ) Completed ( ) Defaulted ( )

Failed ( ) Transferred out (where)

Please collect 2 sputum specimens for culture. And then register the patient.

Date of sputum collection : (day) (month) (year)

First sputum : ..... / / / (Early morning)

Second sputum:... .... / / / (Spot)

Facility register number :

... Date registered : / / /

Date of first treatment / / /

Name of interviewer .....

D) FINAL DECISION by OD supervisor

D1 Examine on the answer above on the questionnaire , Has the patient ever got TB treatment one month or more?

- Yes **Previously Treated Case** ( )
  (answer to the question B2-3 or or C1 was 'One month or more')
- No **New Case** ( ) (answer to the question B1-1 and or C1 was No, or to the question B2-3 or C1 was 'Less than one month')

Note: if you can not decide Yes or No, please ask your supervisor

D2 If "Yes", what was the outcome of previous treatment?

1) Cured/ treatment completed ☐
2) Failed ☐
3) Defaulted ☐
4) Chronic ☐
5) Relapse/defaulter not distinguishable ☐
6) Unknown ☐

Note: 1)-3): the outcome of previous treatment

4): already 'chronic' at that time of the previous treatment

5): we can not know whether the outcome of previous treatment was cured/completed (= currently relapse) or defaulter.

6) unknown outcome of previous treatment

Name of OD supervisor ..... .

Annex 3: Registration List

OD name: _____ Province name: _____

Duration: from ___/____/2006 to ___/____/2006

N	Name	ID #	Name of TB unit / HC	Age		New/ Previous	Date of sputum collection	Date of sending Sputum	Remarks
				M	F				

*Please specify the total of number of new case.

New Case	Previously treated

Signature:_____ OD supervisor name:_____

Annex 4: Sputum Transportation Form

Code:

TB Unit: ..... OD: .....

1. Patient's identification

Name: ..... Sex: ☐ Male ☐ FemaleAge: .....years

Facility name: ..... (National Hosp, RH, HC)

Register number: ..... Date of register: dd...../mm...../yy.....

2. Sputum examination

Laboratory register number: ..... Date of examination: dd...../mm...../yy.....

Result: 1st sputum ( ) 2nd sputum ( ) 3rd sputum ( )

3. Sputum collection for surveillance

Date of sputum collection: **First:** dd...../mm...../yy..... **Second:** dd...../mm...../yy.....

TB Unit staff: ..... Signature: .....

Date of receiving sputum at Culture Center: dd...../mm...../yy.....

Name and signature: .....

Note: TB unit staff must cooperate with 2nd interviewer to fill the above form, especially 1st and 2nd point.

Annex 5: Supervision Checklist

Name of OD:..... Code.....Province.....
Date of last visit: .....
Date of visit: :.....
Name of supervisor: ..... Position .....

1. Check documents

Check the record of laboratory register, OD TB register, transfer sheet (Patient' s Transferring IN and OUT) and surveillance sheets.

Then fill up the charts below:

1.1 Laboratory register

a) Number of new detection, BK+ recorded in laboratory register within the previous and current supervision.

1.2 OD TB register

b) Number of BK+ cases diagnosed in the OD within the previous and the current supervision
c) Number of BK+ case diagnosed before patient did not receive any treatment from other OD and transfer in their unit within the previous and the current supervision.

1.3 Surveillance sheet

d) Number of BK+ cases included in surveillance within the previous and the current supervision.

	New cases	Relapse	Failure	Return After Defaulted	Others	Total
a)						
b)						
c)						
d)						

2. Verify the diagnosis

Please check sheet-1 and verify whether the results of 2 times or 3 times sputum examination are positive or not. If there is something unclear, please ask them the procedure of diagnosis being as smear positive case (sputum examination positive 1 time including X-ray abnormal).

Abnormal case: .....

.....

3. Verify the intake of patients

3.1 If has any lost case(s) (b plus c unequal d), please record missing case(s) with TB Registration #, registered date, the type of disease and the reason of missing.

Name of TB patient	TB Register number	Date of registration	Type of patient (New, Relapse)	Reason

3.2 Recheck the registered cases in the surveillance:

If, some case is not correct being intake in surveillance case, please record the number of survey (surveillance code) and the reason.

No.	Surveillance code	TB register number	Name of TB patient	Reason
1				
2				
3				
4				

4. Check the forms

If there are unclear or missing items, please tell the responsibility person to fill up.

5. Verify the form comparing to the number recorded on sputum container

Please make sure that TB register number, surveillance code and name are correct in each items.

No.	**Surveillance code**	TB register number	Name of TB patient	Reason
1				
2				
3				
4				

6. Check *drug taking* history

Select some patients to interview about the previous TB drug taking history.

No.	Surveillance code	TB register number	Name of TB patient	Correct	Not correct
1					
2					

7. **Verify the sputum collection by meeting patient**

7.1 Identify patients who are registered in this surveillance including hospitalization, ambulatory and DOTS at home.

7.1.1 Number of patients included in the surveillance and met you at the time of supervision.

	Number of patients registered in surveillance	Number of patients who you see during supervision
TB unit		
HC		

7.1.2 If you don't see some patients, write down the number of surveillance and TB register of those missing during supervision and mention the reason (Example: died or just absence)

No.	Surveillance code	TB register number	Name of TB patient	TB Unit	HC	Reason
1						
2						

Then ask the question existing in 7-1- 3 and collect sputum from him/her as the procedure written in 7-1-4.

Serial number	Surveillance number	TB register number	Hospitalization	Ambulatory	Reason
1					

ការបោះពុម្ពត្រូវបានឧបត្ថម្ភដោយ
អង្គការ US-CDC

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