Clinical Practice Guideline Number 3
Diagnosis, Treatment and Control of Tuberculosis

THE PHILIPPINE CLINICAL PRACTICE GUIDELINES ON THE DIAGNOSIS, TREATMENT AND CONTROL OF PULMONARY TUBERCULOSIS

Report of the Task Force on Tuberculosis
2000

This guideline is intended for use by a broad range of healthcare professionals including medical specialists, clinical practitioners, administrators, policy workers and nurses.

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PREAMBLE

The purpose of these guidelines is to provide the practicing physician with a rational and manageable approach to the diagnosis, treatment and control of pulmonary tuberculosis in the Philippines. By their very nature, these guidelines cannot encompass all eventualities. Care has been taken to confirm the accuracy of the information presented and to describe generally accepted practices. However, the authors, editors and publishers disclaim any and all liability for errors or omissions or for any consequences from application of the information in this text and make no warranty, expressed or implied, with respect to the contents of this publication. Under no circumstances will this text supervene the experienced clinical judgment of the treating physician.

BACKGROUND

Rationale

Infectious diseases continue to be among the leading causes of morbidity and mortality in the Philippines. Antimicrobial agents are employed in the management of these diseases in a wide variety of patient conditions and clinical situations. The proliferation of newer antibiotics, diagnostic technology and therapeutic modalities exerts pressure on the physician to keep up with new knowledge. Unfortunately, the demands of clinical practice leave the majority of health professionals little time to critically appraise developments. Consequently, patients are exposed to wide variations in clinical care even for similar conditions and with great potential for irrational management. Thus, the impact of irrational medical practice, both in health and economic terms, can be substantial.

One way of addressing the problem is through clinical practice guidelines (CPGs) utilization. This will potentially minimize practice variations and irrationality of management decisions. Unfortunately, for the same clinical condition, there are different CPGs developed by different professional societies and hospitals using different techniques and methodologies. Thus, there is potential confusion among the target users.

One of the challenges is to harmonize the CPGs, develop a common standard for all, and collectively advocate for its utilization. The Philippine Society for Microbiology and Infectious Diseases (PSMID) had been active in CPG development for a number of years. Recently, PSMID focused its efforts in harmonizing its CPGs with other societies, and synergizing activities with them. In addition, of primary concern is to approach these efforts in a more methodical and systematic fashion by following defined and scientifically acceptable processes and standards. The impetus for this is the desire to embrace the evidence- based concept, create effective partnership with appropriate collaborators, broaden the base of stake- holders, enhance education and training, and strengthen effective negotiation skills as strategies for CPG utilization. Through the initiative of PSMID, a consortium of collaborating societies and agencies organized the Philippine Practice Guidelines Group in Infectious Diseases (PPGG-ID) on 24 August 1997 with a whole-day seminar workshop. Representatives of this consortium signed the Memorandum of Agreement on 21 December 1997.

PPGG-ID is composed of 16 professional societies/agencies. The Coordinating Council is the governing arm, with PSMID acting as the Secretariat. Initially, five multidisciplinary Task Forces were created to tackle five common infections, namely, community- acquired pneumonia (CAP), urinary tract infections (UTI), bacterial meningitis, pulmonary tuberculosis (PTB), and sexually transmitted disease (STD). Work immediately began earnestly in December 1997.

The Philippine College of Chest Physicians (PCCP) had been equally active in the area of pulmonary infections. It has found comrnonality of aspirations with PSMID. PCCP and PSMID for the last three years were prime movers in the CPG project and had been collaborating closely in these activities.

Objectives

The objective for PPGG- ID is for the member sectors/societies to develop a common CPG based on the evidence-based approach and consensus-development techniques, and bring the whole effort of CPG development to its full cycle, i.e., including dissemination, implementation and impact-assessment.

Methods Employed

The evidence-based approach and formal consensus techniques (nominal group technique and the Delphi technique) were employed in the CPG development. Each Task Force membership was multidisciplinary with representatives coming from two or more society partners, including clinical epidemiology practitioners. Expert panel members were either representative of a society or an acclaimed expert in the discipline. The stakeholders were broad to include representatives from the pharmaceutical industry, educators, administrators, policy-makers and key influentials. Each of the following phases had specific output in the end. Task Force and Expert Panel members, respectively, had series of meetings or encounters within each phase to achieve their tasks.

Phase 1: Preparation of the Evidence. Based Report (EBR)

The Task Force identified problems and clinical issues. These were prioritized and formulated into agenda for action. They then systematically reviewed and assessed the scientific literature electronically or through ancestry technique. Members tracked, retrieved and appraised current evidence pertaining to the diagnosis, management and prevention of the infectious disease in question. Recommendations were graded according to a scale modified from the IDSA Quality Standards for Infectious Diseases (1994) [Appendix 1]. Please refer to Appendix 1 for quality filters in assessing evidence from the scientific literature. The resulting draft was the EBR.

Phase II: Preparation of the Interim Report (IR)

The Interim Report was the result of review and discussion of the EBR by the same Task Force members. In most instances, Phases I and II were indistinguishable. The nominal group technique was employed. Consensus was defined as 70% of votes cast, either by written ballots or by raising of hands.

Phase III: Preparation of the Draft Guidelines (DG)

The Draft Guidelines was the result of Expert Panel review of the IR using the modified Delphi technique. Expert Panel was composed of Task Force members plus additional experts. All were again requested to vote on the issues until a consensus was reached (70% agreement for each issue; maximum of three circulation) . This was done in a meeting, by mail or both.

Phase IV: Preparation of the Final Guidelines (FG)

The Final Guidelines considered the comments and feedback of stakeholders (non-panelists). A list of stakeholders was prepared and the DG was sent to them for review. Feedback was either written or verbal during a presentation in a public forum. Due consideration was given if these were based on sound clinical evidence.

The completion of this Final Guidelines is just one of the milestones. It is the commitment of PPGG- ID to bring the CPG into the utilization phase. Afterall, "Guidelines do not implement themselves" (Australian National Health and Medical Research Council). Effort for dissemination, implementation, monitoring and impact assessment is planned (Phases V- VII). Additionally, appropriate research issues and knowledge gaps were identified and will be acted upon.

INTRODUCTION

Tuberculosis Problem in the Philippines

According to the World Health Organization (WHO), the Philippines is one of the 22 countries in the world, which account for 80% of the world's TB cases. Routine reporting systems consistently place tuberculosis among the top 5 causes of morbidity and mortality in the country. The rates for 1994 were 244.5/100,000 for morbidity and 39.81/100,000 for mortality. It is important to note that these figures, particularly morbidity, do not include the TB patients exclusively going to the private sector.

The 1997 National Prevalence Survey showed that there are 213,600 cases of tuberculosis nationwide. Based on the Annual Risk of Tuberculous Infection (ARTI), there are 138 new cases of smear positive individuals per 100,000 population. This translates to a total of 103,118 new cases added to the existing pool of TB cases every year in the entire country.

Comparing the 1997 National Prevalence Survey with one done in 1983, the adjusted rates per 100,000 population for AFB smear positivity were 3.1 and 6.6, and for culture positivity were 8.1 and 8.6 for the 1997 and 1981-1983 surveys, respectively. The ARTI in 1997 was 2.3% versus 2.5% in 1981-1983. This comparison shows a slow and inadequate decline of TB cases in the country. Prevalence rates in urban and rural areas do not differ significantly. However rates among the males are higher and rates of TB increase with age with the highest prevalence occurring in the productive age group.

Rationale for the Creation of TB Consensus Statements 1999

It has been approximately ten years since the formulation of the 1st National Consensus on Tuberculosis in the Philippines. Since that time, new data have been generated in relation to the diagnosis and management of tuberculosis. The methodology for coming out with more evidence-based but pragmatic consensus statements or practice guidelines has evolved. Thus in mid 1997, the TB Council of the Philippine College of Chest Physicians (PCCP) together with the Philippine Society for Microbiology and Infectious Disease (PSMID) and the Department of Health (DOH) initiated the formulation of these TB Consensus Statements with the following objectives: (a) to update the consensus statements on the diagnosis and treatment of tuberculosis in the Philippines; (b) to address critical issues in the overall control of TB in the country; and (c) to come out with more pragmatic, yet evidence-based (whenever possible) recommendations addressing the above issues in order to reduce the burden of tuberculosis in the country at an adequate and faster rate.

The following steps were followed in the formulation of the consensus statements: (a) formulation of core group from PCCP, PSMID and DOH and advisers; (b) selection of topics (diagnosis, treatment and control strategies and prevention) and formulation of committees covering the topics; (c) selection/invitation of stakeholder societies in tuberculosis (e.g. family medicine, nursing association, NGOs) to be members of the committees; (d) selection of specific questions to be addressed by each committee; (e) searching the literature; (f) grading the evidence (Please see Appendix 1); (g) formulation of the draft; (h) seeking feedback from advisers and members of other committees; (i) critical review of the draft by members of different societies; and (j) formulation of final paper.

The consensus statements in their final form are truly the work of the people with the common goal of controlling tuberculosis in the Philippines. And as such, these consensus statements will continually evolve and change to address pressing and relevant issues utilizing current, available data and resources. The National Consensus on Tuberculosis is truly a big step forward in realizing our dream of achieving TB control through concerted and unified action.

The consensus statements are to be disseminated to concerned physicians and other health workers nationwide basically through interactive patient-base small group discussions. Evaluation of the process and impact of the consensus statements is also to be carried out.

The TB Consensus Statements are aimed at all health workers and physicians (generalists/specialists and private/government) who manage or are involved in the care of TB patients and in the control of tuberculosis in the country.

RECOMMENDATIONS

Recommendations made by the working groups on Tuberculosis addressed issues on diagnosis, treatment and control of pulmonary tuberculosis. The summary of evidence after each recommendation serves as the basis for the consensus statements. Whenever appropriate, recommendations for research were also given.

DIAGNOSIS OF PULMONARY TUBERCULOSIS

Questions Addressed:

Clinical Diagnosis:

1. What clinical signs and symptoms should make one suspect PTB?
2. Can any specific sign or symptom discriminate between PTB and non-TB respiratory disease?
3. Can a patient with no symptoms have PTB?
4. Can any specific clinical sign or symptom be used to monitor response to anti-TB treatment?

Laboratory Diagnosis:

5. What is the most important test to request for a patient with clinical signs and symptoms of PTB?
6. How should I advise my patient to collect sputum?
7. How many sputum specimens should I instruct my patient to submit to the laboratory?
8. What is a significant rnicroscopy result?
9. When should I request for sputum TB culture and sensitivity tests?
10. What should I do for patients unable to bring up sputum?
11. For smear negative patients and patients unable to produce sputum even after sputum induction, are there other options to obtain a bacteriologic diagnosis?
    a. What is the role of bronchoscopy in the diagnosis of PTB?
    b. What is the role of the PCR technique in the diagnosis of PTB?
12. What is the role of serologic tests, such as ELISA, in the diagnosis of PTB?

Radiologic Diagnosis:

13. Do radiologic features of PTB correlate with disease activity?
14. In smear negative patients, can the chest x-ray results be used as a basis for initiating treatment and monitoring treatment response?
15. What is the value of routine chest x-rays for PTB screening?
16. What is the value of a chest CT scan for diagnosing PTB?

Clinical Diagnosis

Question 1: What clinical signs and symptoms should make one suspect PTB?

Consensus Statement:

A chronic cough, significant weight loss, sweats and chills, fatigue and body malaise, and fever are found in over half of patients suffering from PTB. These clinical signs and symptoms should raise the possibility of PTB. In contrast to common perception, fever is intermittent in PTB and does not commonly occur in the afternoon. Hemoptysis is more associated with non-TB respiratory disease than PTB. (Recommendation Grade: D)

Summary of Evidence:

A review of the literature yielded at least 3 studies relevant to this question with patients diagnosed to have PTB based on positive culture results (1-3). Approximately 75% of the patients complained of a chronic cough and significant weight loss. Sweats and chills, fatigue and body malaise, and fever were less consistently reported (about half of the patient population). Only about 25% of the patients complained of hemoptysis. Anorexia was not consistently reported. In these studies, the reported fever was intermittent. Another study evaluated the timing of fever in relation to the presence or absence of radiographic findings compatible with PTB (4). Fever occurred with equal frequency in patients with and without radiographic findings compatible with PTB. Among those with suggestive radiographic findings and fever, only 12% specifically reported afternoon rises of temperature. A more recent study compared TB and non-TB patients. Their diagnosis was based on positive cultures for MTB (5). Their results indicate that hemoptysis is more significantly associated with a non-TB respiratory disease. (Level of Evidence: 6)

Question 2: Can any specific clinical sign or symptom discriminate between PTB and non-TB respiratory disease?

Consensus Statement

Only a chronic cough consistently indicates PTB over non-PTB respiratory disease. No other sign and symptom is discriminative for PTB (Recommendation Grade: B)

Summary of Evidence:

To determine if a specific clinical sign and symptom can discriminate for a disease, its occurrence in a group of suspect patients must be studied. The suspect population should mimic that seen in clinical practice and should include both patients with and without the disease. Two clinical studies evaluated signs and symptoms in such a population (5, 6). PTB was diagnosed by smear and/or culture in the study of Cohen (6). Diagnosis was by culture in the study by Samb (5). There were no significant differences in the occurrence of anorexia, weight loss, fever and dyspnea between patients with PTB and those with non-TB respiratory disease. In Cohen's study, sputum production was more frequent in PTB patients. This was not confirmed by Samb's study. In both studies, a chronic cough occurred with significantly greater frequency in PTB patients. Both studies were well designed and would have rated as "Level 1' evidence, except for a lack of the requisite number of 50 patients per diagnosis group. (Level of Evidence: 2)

Research Recommendation:

Conduct a large-scale, clinic-based study on the presenting clinical signs and symptoms of patients suspected of having PTB. Outcome must be defined in terms of diagnoses established from test results of respiratory specimens (e.g., sputum GS/CS, AFB smear and culture, KOH smear and fungal culture, biopsy results.) All tests must be done in all patients recruited.

Question 3: Can a patient with no symptoms have PTB?

Consensus Statement:

PTB does not have to be symptomatic. Even among culture proven PTB patients, a small percentage (5-14%) may have no symptoms. Asymptomatic PTB is more frequently observed in older age groups. (Recommendation Grade: D)

Summary of Evidence:

The National Prevalence Survey of 1997 (7) interviewed 9, 286 randomly selected persons aged 20 years or above. The individuals were queried on symptoms of a chronic cough (> 2 weeks), hemoptysis of any duration, chest and/or back pain (> 1 month), and fever (> 1 month). 4.7% of asymptomatic individuals had radiographic findings suggestive of PTB. In the study by Barnes (1), 5 % of 188 culture proven PTB cases had no symptoms. In an earlier study by MacGregor (2), 14% of culture proven cases were asymptomatic. The overall rates of smear and/or culture positivity among asymptomatics in the National Prevalence Survey were 0.2 and 0.7 per 1000 individuals, respectively. In the Prevalence Survey, radiographic findings suggestive of PTB were more common in asymptomatics aged 50 years or more. Smear and/or culture positive PTB was more common in asymptomatic aged 60 years and above. (Level of Evidence: 6)

Research Recommendation:

Conduct a community-based mass screening study for PTB. A standardized questionnaire on clinical signs and symptoms, a chest x-ray, and sputum AFB studies should he administered to all patients without discrimination.

Question 4: Can any specific clinical sign or symptom be used to monitor response to anti-TB treatment?

Consensus Statement:

There are no specific studies correlating the resolution of clinical signs and symptoms with bacteriologic response to treatment. Limited evidence indicates that the resolution of a chronic cough takes longer than the resolution of other possible signs and symptoms of active PTB. (Recommendation Grade: D)

Summary of Evidence:

A local study comparing treatment outcome using 3 and 4 drugs performed a Kaplan-Meier analysis on symptom relief with treatment (8). The time to disappearance of symptoms averaged 14-16 weeks for cough, and 4 weeks for both fever and hemoptysis. Resolution of other clinical signs and symptoms was not reported. (Level of Evidence: 6)

Research Recommendation:

Prospectively evaluate smear and/or culture (+) PTB patients to document the initial occurrence and resolution of symptoms with treatment as compared with eventual treatment outcome.

Laboratory Diagnosis

Question 5. What is the most important test to request for a patient with clinical signs and symptoms suggestive of PTB?

Consensus Statement:

Sputum examination for acid-fast bacilli (AFB) or direct microscopy is the most important diagnostic test to request for a patient clinically suspected to have PTB. (Recommendation Grade: A)

Summary of Evidence:

In the clinics, sputum smears for AFB bacilli are less commonly requested than chest X- rays. This practice is not uncommon. A national survey of physicians' knowledge, attitudes and practices for TB diagnosis and monitoring was conducted

in Botswana (8). Senior District Medical Officers of the government were the most likely to adhere to guidelines on the use of sputum examination for diagnosis (87%) and follow-up (50%). Private practitioners were the least likely to follow the same guidelines (53% and 10%, respectively). It is accepted, however, that a chest radiograph can only suggest the possibility of PTB (See following section on Radiologic Diagnosis). Definitive diagnosis is established by tests for acid- fast bacilli (AFB) in sputum specimen (9).

Sputum microscopy for AFB is simple and easy to perform, even by a non-specialist. It is economical and may be made available even in remote areas where a microscopy center could he organized. Studies through the years have established its high specificity at 97.5-99.8% (10-15). The major disadvantage of the test is its low sensitivity (51.8-53.1%). It is estimated that a positive test result requires the presence of at least 10^4 bacilli per ml of specimen. In one study, pairs of sputum specimens obtained pre-treatment from 166 smear-positive patients with PTB were examined by direct smear, culture on Lowenstein-Jensen medium, and by quantitative colony counting on selective 7H11 medium. Although there was overlap between specimens with negative and positive direct smears, a specimen count of 10^4 cfu/ml or more was likely to have a positive smear while a negative smear was likely if the count was lower (16). In the clinics, a positive test result for a specific patient warrants a presumptive diagnosis of active PTB.

The role of sputum rnicroscopy is basic in countries, such as the Philippines, where the prevalence of PTB is high. The stronger evidence in its favor was provided by the local study of Mendoza and Narciso (13). The sputum smear was correlated with mycobacterial culture for 1046 specimens. The resulting sensitivity and specificity was 51.8% and 97.5%, respectively, with an overall correlation of 91.5%. Computed positive predictive value (PPV) and negative predictive value (NPV) were 76.3% and 93.0%, respectively. The likelihood ratio was 21.58. The acid-fast smear remains valid for the diagnosis of pulmonary tuberculosis even in low prevalence situations (7). (Level of Evidence: 1)

Research Recommendation:

Conduct a large-scale survey on tuberculosis diagnostic practices among physicians in the Philippines.

Question 6: How should I advise my patient to collect sputum?

Consensus Statement:

Patients must be made aware of the importance of sputum quality. They must know that a good specimen comes from the lungs. Mucus from the nose and throat and saliva from the mouth are not good specimens. To obtain a good specimen, instruct the patients to follow the following steps:

1. **Clean and thoroughly rinse the mouth with water.**
2. **Breathe deeply 3 times.**
3. **After the third breath, cough hard and try to bring up sputum from deep in the lungs.**
4. **Expectorate the sputum into a clean container with a well-fitted cap.**
5. **Collect at least 1 teaspoonful.**
6. **Examine the specimen to see that it is not just saliva. Repeat the process if necessary.**

The chances of obtaining a good specimen are better when patients are supervised either by their doctor or by laboratory personnel. (Recommendation Grade: C)

Summary of Evidence:

Studies on sputum quality and yield point out the importance of obtaining a good specimen. McCarter and colleagues studied 724 consecutive specimens and sub-analyzed 172 specimens which were positive for tuberculosis. Of 51 smear positive, 92.2% were from specimens with neutrophils. Of 121 culture positive specimens, 90.1% were cultured from specimens with neutrophils (18). In a study on sputum induction for the diagnosis of tuberculosis, specimens were more likely to be smear positive or culture positive if they had a predominance of polymorphonuclear (PMN) cells. There was a direct correlation between sputum quality (i.e., the number of PMNS) and culture positivity. The presence of PMN cells in the specimen was indicative of sputum, in contrast to epithelial cells, which originate from saliva (19). Highlights from the Core Curriculum on Tuberculosis of the US Department of Health and Human Services and the Center for Disease Control and Prevention, USA emphasize the importance of sputum collection (20). The steps recommended here are modified from their recommendations. It is

emphasized that coaching patients individually on how to expectorate can facilitate sputum collection. Unsupervised patients are seldom successful in providing an adequate specimen, especially the first time. (Level of Evidence: 3)

Research Recommendation:

1. Spot laboratory survey on the adequacy of submitted sputum specimens for direct microscopy.
2. Survey how many patients are adequately instructed on sputum collection.
3. Survey of patient and laboratory collection practices.

Question 7: How many sputum specimens should I instruct my patient to submit to the laboratory?

Consensus Statement:

At least three sputum specimens should be submitted for direct microscopy. Ideally, the specimens should be submitted to the laboratory within 24 hours from the time of collection. (Recommendation Grade: D)

Summary of Evidence:

Traditionally, physicians are trained to order sputum AFB for three consecutive mornings. This is based on old data from Kubica et al in 1975 (21) where sputum culture for TB done on 201 patients yielded only 30% in the first sputum sample, increasing with the second and third samples to 38%. From the fourth to the tenth sample however, the rise in yield was not significant anymore.

1970 and 1975 reports from the National Tuberculosis Institute of India indicated a better yield of 52.9% from the first sputum specimen (N=194 patients) (22). In their reevaluation of sputum rnicroscopy and culture for the diagnosis of PTB, Levy and colleagues had similar results (12). In 53.7% patients, the sputum was positive on the first smear. Increasing yields were obtained from the second, third and fourth smears (60.2%, 63.9% and 65.7%), respectively. In the Philippines, Cruz and colleagues studied sputum from 2012 patients at the Quezon Institute. The examinations increased the yield to 32% and 36.53% for the second and third sputum specimens, respectively (23).

Current recommendations from the WHO (24), International Union Against Tuberculosis and Lung Disease (25) and the Philippine Department of Health (DOH) in the 1997 Technical Guidelines of the New Tuberculosis Program (26) specify that three samples be sent for microscopy.

In areas where the microscopy center is easily accessible to the patient, patients are advised to submit sputum specimen for examination on three consecutive mornings. However in situations where this is not practical, the DOH schedule as follows is a reasonable alternative:

First Specimen: Spot specimen collected at the time of consultation
Second Specimen: Early morning specimen collected by the patient as instructed by health care worker or physician.
Third Specimen: Spot specimen collected when patient comes back to submit second specimen.

Specimens collected at home should be sent to the microscopy center or laboratory as soon as possible. Otherwise, it is important to refrigerate the closed specimen container and/or make sure it is not exposed directly to sunlight until it can be brought to the center. At the latest, sputum specimens should be submitted within 4 days from the time of collection. (Level of Evidence: 6)

Research Recommendation.

Determine the cumulative AFB-positive yield of sequential sputum specimens.

Question 8: What is a significant microscopy result?

Consensus Statement 8A:

In areas where laboratory personnel are well trained and where quality assurance policies are routinely practiced, the finding of AFB (+) in any of one or more sputum specimens submitted

for examinations is significant. This constitutes a presumptive diagnosis of PTB. (Recommendation Grade: A)

Summary of Evidence:

The very high specificity of sputum microscopy for detection of acid-fast bacilli implies a low rate of false negatives. Mendoza and Narciso documented a test specificity of 97.5% using fluorescent microscopy at the Lung Center of the Philippines (13). A more recent study from the same institution supported these findings and showed good correlation between the smear results and positive culture yields. All specimens read as AFB (+++) or (++++) yielded a positive growth on BACTEC medium. In addition, 94% of all specimens read as AFB (+) or (++) grew M. tuberculosis on culture (27). (Level of Evidence: 1)

Consensus Statement 8B:

In areas where quality control at microscopy centers is less than optimal, caution is recommended in the interpretation of smears reported as AFB (+) or less. If only 1 of 3 specimens is read as AFB (+), a second set of 3 sputum specimens should be submitted for repeat examination by direct microscopy. (Recommended Grade: B)

Summary of Evidence:

The above recommendation is based on DOH guidelines and seeks to decrease the likelihood of false positive smears when only a few acid-fast bacilli are seen. The recommendation is supported by documented over-reading of AFB smears in 16 randomly chosen field microscopy centers of the National Capital Region (28). AFB positivity was 16.6% at the health center level. However, positivity was only 10%, when the same smears were read by a reference microscopist at the Philippine General Hospital Medical Research Laboratory. (Level of Evidence: 2)

Research Recommendation:

Evaluate the local diagnostic accuracy of currently recommended reporting methods for direct smear microscopy in reference to MTB culture.

Question 9: When should I request for sputum TB culture and sensitivity test?

Consensus Statement:

At the very least, sputum culture and sensitivity testing for *Mycobacterium tuberculosis* should be done whenever possible in the following situations:

1. **Smear (-) patients with a strong clinical possibility of PTB and suggestive chest X-rays.**
2. **Smear (+) or (-) patients suspected of multi-drug resistant PTB.**
3. **Smear (+) patients demonstrating the 'rise fall' phenomenon.**
4. **All cases of relapse**
5. **All cases of re-treatment**
6. **All cases of treatment failure**

Summary of Evidence:

The diagnosis of pulmonary tuberculosis becomes definitive when one is able to isolate Mycobacterium tuberculosis by culture. It is ideal to confirm all smear positive cases with culture. However, in lieu of the cost of culture and the prevailing limited technical facilities, sputum culture for TB cannot be feasibly recommended as part of a routine evaluation. The clinical situations cited above constitute special situations where a sputum culture for TB is necessary for proper case management.

There are, however, identified clinical situations where TB cultures are not only ideal but necessary. Patients who would benefit from sputum culture for TB generally fall into two categories: smear negative patients and those suspected of multidrug resistant TB (MDR-TB).

The 1997 National TB Prevalence Survey reported an MDR rate of 3.6% (3 of 55 isolates) (7). MDR rates from referral centers are expected to be much higher. In a larger study at the Philippine General Hospital, only 17% of 299 M.

tuberculosis isolates were fully susceptible to all drugs tested. 38% of isolates showed multiple drug resistance. Two of the identified risk factors for multi-drug resistance were: (1) a previous history of treatment for TB (odds ratio [OR] 2.44) (95% CI, 1.49-4.01); and (2) a previous treatment period longer than 3 months but less than 6 months (OR 4.6, p=0.0001) (29).

In Brazil, MDR-TB was associated with such unfavorable outcomes as failure to sterilize the sputum during treatment, death and abandonment of therapy (p=0.002). Patients who failed with the first and second line drugs had a 33% and 65% rate of MDR-TB, respectively. Failure was defined as an outcome in which the sputum smear remained positive for AFB after 5 months of treatment or became positive after initially clearing during treatment (30).

Research Recommendation:

Document the local yield of sputum culture and sensitivity testing in the situations outlined in the consensus statement.

Question 10: What should I do for patients unable to bring up sputum?

Consensus Statements:

Supervised nebulization with a warm, sterile, hypertonic saline (3%) solution is useful for obtaining specimens from patients highly suspected of having PTB. It should be attempted for all cooperative patients who are smear-negative or unable to expectorate sputum spontaneously. (Recommendation Grade: A)

Summary of Evidence:

Sputum induction using hypertonic saline (3%) is an alternative means of obtaining specimens from the lower respiratory tract (31). No significant differences have been found in the microbiologic yields of induced and spontaneous sputum samples for mycobacteria (32). In Malawi, sputum was successfully induced in 73 of 82 patients with clinically suspected tuberculosis (89%). The patients were either expectorating negative sputum or had unproductive cough. Smears and/or cultures of the induced sputum were positive in 30 patients. These patients constitute roughly 36% of the original population in whom bacteriologic confirmation would not otherwise have been obtained. Acid-fast bacilli were detected in subsets of both patients initially smear-negative or had unproductive cough (33). Similar data are reported in children. A recent study successfully induced sputum in 29 of 30 children who were suspected of having PTB. In all, the diagnosis was confirmed in 8 of these 29 children (4 by AFB microscopy, 4 by TB culture) (19).

Sputum induction avoids unnecessary invasive procedures when successful. It should be performed for all patients who are highly suspected of having PTB but are smear-negative or unable to expectorate sputum. (Level of Evidence: 1)

Research Recommendation:

Local study comparing the microbiologic yield from identically processed induced and conventional sputum samples for *Mycobacterium tuberculosis*. Culture of MTB should serve as the reference end-point.

Question 11: For smear-negative patients and patients unable to produce sputum even after sputum induction, are there other options to obtain a bacteriologic diagnosis?

Sub-Question 11a: What is the role of bronchoscopy for diagnosing PTB?

Consensus Statement:

Bronchoscopy has a limited role in the diagnosis of PTB. The procedure may be considered in selected situations:

1. **High-risk patients who are unable to produce sputum either spontaneously or by induction, e.g. immunocompromised host.**
2. **Patients in whom the probability of another or concomitant disease is high, e.g. malignancy. (Recommendation Grade: A)**

Summary of Evidence:

The Mayo clinic reviewed their experience with bronchoscopy over a 5-year period. During this period, 209 patients had culture proved M. tuberculosis, from specimens taken from various sources. Bronchoscopy was performed on 34 (16%) of the 209 patients. A total of 32 patients (94%) were subsequently documented to have MTB, either from cultures of bronchoscopic washings or secretions (N=26) or from the cultures of sputa or gastric aspirates obtained after bronchoscopy (N=6). In the latter 6 patients, bronchoscopic instrumentation was considered instrumental in producing the subsequent positive cultures. There were 174 patients with culture-proved atypical mycobacteriosis from various sources. Forty (23%) underwent bronchoscopy. Bronchoscopic cultures of secretions or washings or both were positive for atypical organisms in 38 cases (95%). The authors concluded that there is a high degree of sensitivity of bronchoscopic cultures in patients with typical or atypical mycobacterial disease or colonization (34).

In a smaller study, the records of 56 patients clinically suspected of having active TB, with an abnormal chest radiography consistent with TB, who had 3 negative sputum smears or an ability to produce sputum, and who had undergone fiber optic bronchoscopy and transbronchial biopsy were reviewed. Evaluations were diagnostic in 29 of the 56 patients (52%) either by culture of bronchial specimens, histopatology of transbronchial biopsy material, or post-bronchoscopy sputum cultures. Mycobacterial infection was diagnosed in 22 and other disease processes in 11 patients. These authors concluded that fiberoptic bronchoscopy and transbronchial biopsy were useful procedures for evaluating highly suspect TB patients in whom a diagnosis cannot be established from sputum specimen (35).

Other studies conducted in smear-negative PTB reported a high yield from brush smears obtained from caseous material visible during bronchoscopy (36,37).

The literature establishes the utility of bronchoscopy for diagnosing mycobacterial disease particularly in situations where sputum specimens are non-diagnostic. However, sputum induction is much less invasive and must be attempted prior to considering bronchoscopy. In a prospective Canadian study, 101 consecutive sputum-smear negative patients referred for evaluation of possible active PTB underwent sputum induction with hypertonic saline between 2 and 48 hours before bronchoscopy. Sputum induction was well tolerated and produced adequate specimens in 93 patients. The sensitivity and negative predictive value of culture from bronchoscopy specimens was 73% and 91% compared with 87% and 96%, respectively for sputum induction when a specimen was obtained. The authors concluded that sputum induction is a well tolerated, low cost procedure that provides the same, if not better, diagnostic yield compared with bronchoscopy in smear-negative PTB (38).

In communities with a high prevalence of tuberculosis, bronchoscopy is unlikely to reveal any specific etiology, other than tuberculosis, in immunologically competent patients who have 'typical' x-ray pictures of tuberculosis (39). Bronchoscopy is therefore not recommended for the routine diagnosis of PTB in our setting. For smear-negative patients, who are unable to produce specimen even after sputum induction using hypertonic saline, bronchoscopy should be considered only in selected clinical situations. For example, in a critically ill immunocompromised host there may be an urgent need to establish the etiology of a pulmonary infiltrate on the chest radiograph after other standard diagnostic approaches have failed. Bronchoscopy could also be of value in cases where the presence of another or concomitant disease, e.g., malignancy is considered. (Level of Evidence: 1)

Research Recommendation:

Most studies evaluating the diagnostic utility of bronchoscopy in PTB were carried out in low prevalence populations. It is conceivable that the yield may be higher in high prevalence populations. It may be worthwhile evaluating the utility of bronchoscopy in our setting as applied to smear-negative patients from whom specimens cannot be obtained even by induction. Such a study would necessarily include patient populations other than those included in the consensus statement.

Sub-Question 11b: What is the role of the polymerase chain reaction (PCR) technique for diagnosing PTB?

Consensus Statement 11b-A:

The PCR is a highly sensitive technique for the detection of Mycobacteria in sputum specimens. It is capable of detecting *M. tuberculosis* even in culture negative specimens, such as those obtained from patients already on anti-tuberculosis medications. However, PCR should not be used for monitoring treatment response because even non-viable *M. tuberculosis* will be detected. (Recommendation Grade: A)

***Summary of Evidence**:*

Since its first application in the diagnosis of TB in 1989 by Brisson-Noel, the PCR has become the most widely used technique for amplifying nucleic acids from Mycobacteria. The objectives of the technology are to reduce the time necessary to detect the pathogen in clinical specimens, to increase the sensitivity and specificity of diagnosis, and to simplify the test by automation and incorporation of non-isotopic detection formats (40).

A large body of level I evidence exists establishing the utility of the PCR for the detection of M. tuberculosis in sputum and other respiratory specimens. Moore and Curry in 1995 studied 1009 sputum specimens and obtained a sensitivity of 99% and 66% for smear positive-specimens, respectively. The PCR detected M. tuberculosis in 27 culture-negative specimens from patients on anti-tuberculosis therapy. However, the technique failed to identify 28 culture positive specimens with low colony counts (< 100 CFU per ml.) The recomputed sensitivity and specificity of the PCR was reported at 85% and 99.6%, respectively. In comparison, sputum culture has a sensitivity and specificity of 87% and 100%, respectively. The positive and negative predictive values of the PCR were 0.986 and 0.966, respectively. The likelihood ratio was computed at 283 (41). More recent data report a range of 97-99% sensitivity for PCR. One study on 109 smear negative patients reported a sensitivity of 97.8%. Specificity, however, was low (27%) (42).

One of the advantages of the PCR technique is speed. The assay can be completed in 8 hours and results can be available within 10 hours from specimen submission. In addition, M. tuberculosis can be identified even in culture-negative specimens. Studies compared the sensitivity and specificity of the PCR with that of the conventional microscopy and culture. The method has been found to be fast and sensitive. The reported sensitivity of the PCR, culture and staining was 97%, 88% and 65%, respectively. The specificity was 100% in all cases (43-45). (Level of Evidence: 1)

Consensus Statement 11b-B:

Despite the excellent data, the performance of the PCR requires a high level of technology. The PCR must be performed only in experienced referral laboratories that possess the appropriate expertise, personnel, and laboratory infrastructure, as well as contamination control measures. In addition, the technique is expensive to perform. For this reason, the PCR is not recommended for routine diagnosis of PTB. (Recommendation Grade: C)

***Summary of Evidence**:*

Based on the cited data, if both PCR and acid-fast staining are used to screen every sputum specimen, PCR will detect at least 83% of positive specimens while the flourochrome smear technique will detect only 51% of positive specimens. Unfortunately, the added cost in laboratory fess will amount to P2000 (USD 50). This amount is not nominal or economically feasible given prevailing local economic conditions. (Level of Evidence: 3)

Research Recommendations:

It may be useful to evaluate the utility of the PCR for patients highly suspected of relapse in cases where sputum studies obtained are non-diagnostic.

Question 12: What is the role of serologic tests, i.e., ELISA in diagnosing PTB?

Consensus Statement:

The interpretation of single positive ELISA test is difficult because of the high prevalence of TB infection. The test is not recommended for routine use in the diagnosis of PTB. The test may be of value in smear-negative patients with negative ELISA test results. For these patients, consideration of non-TB disease is warranted.

There are other potential uses of the test that may be considered on a case-to-case basis:

1. **Considerations of presumptive treatment for highly suspected PTB cases with negative sputum tests and elevated antibody titers.**
2. **Initiation of re-treatment in suspected cases of relapse who have negative sputum smears, elevated antibody titers, and who had received adequate treatment more than 2 years previously. (Recommendation Grade: C)**

Summary of Evidence:

Sero-diagnosis involves detection of serum antibodies and mycobacterial antigens from clinical specimens. Interest in serologic tests stems from the need to establish a diagnosis in smear and/or culture negative patients highly suspected of having tuberculosis and in cases of extra-pulmonary tuberculosis where the utility of conventional laboratory tests are limited. In addition, serologic tests are generally rapid, minimally invasive, inexpensive and simple to perform (45). Among serological tools, immunoassays based on the enzyme-linked immunosorbent assay (ELISA) has been the method of choice because of its high sensitivity, simplicity, reproducibility and versatility in screening a large number of specimens (47). Using highly purified mycobacterial antigens, ELISA measures IgG antibody levels. At present there are two antigens available in the Philippines, the Pathozyme test using the 58kDA and the Mycodot using LAM.

In China, the utility of the 38-kDA antigen for the diagnosis of TB was evaluated in 152 PTB patients. The controls consisted of healthy individuals and patients with non-TB respiratory disease. Antibody was detected in 89% (54/61) of sputum (+) and 74% (67/91) of sputum (-), clinically diagnosed patients. Only 3% (1/30) of healthy controls and 9% (5/56) of patients with non-TB respiratory disease had detectable antibody levels. The overall test values were reported at 93% for specificity and 95% for positive predictive value (47%).

At the Lung Center of the Philippines, the 38-kDa antigen was evaluated in 49 cases suspected of PTB but with negative acid-fast smears to determine its clinical utility in this subset of patients. Of the 49 subjects included, 18 were classified as active PTB, 22 had inactive PTB, and 9 had non-tuberculous conditions. The ELISA test was positive in 72%, 31% and 12% of the active, inactive, and non-PTB cases, respectively. A positive test was predictive of the presence of TB (active or inactive) in 95% while a negative test was predictive of the absence of active TB in 92% (48). These data mirror those reported in China.

In another study, 201 patients with PTB and 67 patients with extrapulmonary TB were evaluated. Test specificity values using the 38 kDa antigen were 92% for sputum (+) and sputum (-) cases of PTB as well as for cases of extrapulmonary TB. Positive predictive values of the test were 84%, 87% and 80% for sputum (+), sputum (-) and extrapulmonary cases, respectively. Only 2% (1/44) of the healthy control BCG-vaccinated subjects gave weak positive signals in the assay. The authors concluded that the rapid serological assay is a valuable aid in clinical diagnosis for both pulmonary and extrapulmonary TB (50).

The researchers at the Lung Center further evaluated the change in antibody levels with treatment. Antibody levels of patients with active TB decreased with chemotherapy, although the time of seroconversion varied. Some patients remained seropositive up to 10 months into the follow-up period. For inactive PTB, serology titers remained negative in all cases where it was initially negative while in those with positive tests, the antibody levels gradually decreased (48). In India, a study on CSF samples from patients with TB meningitis similarly demonstrated a progressive drop in antibody levels over a 6-week period to follow-up (50). A study conducted in London reported that serological tests become negative within 2.5 years of successful treatment. Furthermore, their results suggest that there may be value in reporting the actual antibody titers with titers above a certain value suggesting active tuberculosis (51). Studies measuring MTB-specific antibodies in pulmonary tuberculosis suggest that a rise in antibody titers occur if bacteriologic relapse occurs during treatment (52).

It has been reported that even under optimal conditions, the ELISA method does not offer any advantages in terms of diagnostic test characteristics to sputum smears. Using a prevalence of 4.2/1000, the ELISA test utilizing 38-kDa antigen has a high specificity (100%) but a poor sensitivity. The PPV and NPV are computed at 69% and 77% respectively. Given the high prevalence of PTB in the Philippines, interpretation of spot tests will be difficult. As such, serological tests are not recommended for routine use in the diagnosis of PTB

What then are the potential roles of a serological test, such as an ELISA using the 38-kDa antigen? Researchers at the Lung Center proposed an algorithm for use of the ELISA test (48). The following are based on this algorithm plus data from the literature.

1. For patients suspected of PTB but with negative sputum smear results, negative test results suggest the absence of antibodies to MTB. In these patients, a non-TB respiratory disease should be considered.

2. The test may be of value in cases highly suspected of PTB based on clinical and radiologic findings but with negative sputum tests even after sputum induction. An initially elevated titer would strengthen the case for presumptive treatment.

3. Antibody titers are also reported to increase with relapse. For suspected cases of relapse who are sputum smear (-), no treatment is recommended if adequate treatment was received within the past 2 years. This is based on data suggesting that antibody titers should have normalized by this time. If more than 2 years has elapsed since adequate treatment was received, re-treatment is recommended. (Level of Evidence: 3)

Research Recommendations:

1. Follow-up patients with active TB and inactive TB with positive ELISA readings to determine the longest time interval to seroconversion.
2. Evaluate the utility of antibody-titer 'cut-offs' in differentiating active from inactive PTB.
3. Evaluate the utility and validity of the recommended applications of the ELISA test in a clinical setting.

Radiologic Diagnosis

Question 13: Do radiologic features of PTB correlate with disease activity?

Consensus Statement:

Most of the available evidence indicates that no radiologic feature correlates well with disease activity. One good study indicated that hilar or mediastinal lymphadenopathy and diffuse reticulonodular infiltrates may individually correlate with active PTB in the presence of a respiratory or constitutional symptom suggestive of respiratory disease. The study was limited to hospitalized patients. Additional studies are needed to verify their findings. (Recommendation Grade: B)

Summary of Evidence:

Varied radiographic features of PTB are reported in the literature (3,20,53-56). These studies were mainly retrospective in design and used sputum microscopy or culture as a basis for determining tuberculosis disease activity. As much as 15-20% of chest radiographs in two studies were read as normal, despite the presence of disease (53,57). Two of the largest studies demonstrated that cavitary lesions had higher positive sputum (57%) and culture yields (96%) when compared with noncavitary lesions (12-32% and 70%, respectively) (10,55). Overall, however, no radiologic finding was noted to consistently correlate, with activity. Incorrect appraisal of disease activity based on radiographs was a common cause of misdiagnosis.

Unusual or atypical features are noted as much as 34% of individuals with positive sputum findings (53). Many adult patients (14-25%) have chest X-ray features consistent with primary tuberculosis (54,55). These include isolated pleural effusions, military infiltrates, and isolated unilateral or bilateral hilar adenopathy. Fibroproductive (fibronodular or fibrocalcific) lesions are conventionally thought to signify inactivity. However as many as 18% of patients with these lesions have positive sputum yields. A larger review has demonstrated that disease activity cannot be based solely on chest x-rays features (56).

Older studies reporting on the utility of chest radiographs for diagnosing active tuberculosis suffered from patient selection bias and lack of adequate controls (57-59). Sensitivities were reported at 68-75% with positive predictive values of 51% (as a single test) and 67% (when combined with symptoms) (61). Symptoms of activity are likewise non-specific (4,53-55). If the chest x-ray was used to make a presumptive diagnosis, the clinical symptoms that strongly correlated with a suggestive radiograph were hemoptysis, dyspnea, cough severity and degree of weight loss. A scoring system was proposed correlating clinical symptoms and chest radiographic findings (4).

More recent studies are better designed. In 1996, 101 consecutively referred suspected PTB cases were evaluated to identify symptom and radiographic predictors of smear-positive TB. A 'typical' x-ray was defined as one with nodular, alveolar, or interstitial infiltrates above the clavicle or in the upper zones of the lung. Growth of MTB on culture was used as the gold standard for diagnosis. No significant differences were found in the frequency of a 'typical' chest x-ray between TB and non-TB patients. Chest x-ray test characteristics were reported at 73% sensitivity, 63% specificity, 60% positive predictive value, and 75% negative predictive value (6).

A larger study combined data from 2 parallel studies on hospitalized patients. Included in the study were patients aged 15 years or above, with pulmonary or constitutional symptoms suggestive of a respiratory disease, and an abnormality on the chest radiograph. Reticulonodular infiltrates and hilar or mediastinal lynphadenopathy were found to discriminate between patients with TB (N=4) and patients with non-TB respiratory disease (N=141). A pleural effusion, cavitation, patch infiltrates and consolidation were non-discriminative. The specificity of reticulonodular infiltrates and adenopathy was reported at 89 and 94%, respectively. Sensitivity was reported at 39 and 24%, respectively (5). The authors suggested the conduct of a similar study among outpatients. (Level of Evidence: 2)

Research Recommendation:

1. Validation of a scoring system on the correlation of chest x-ray and clinical findings.
2. Prospective studies that would adequately assess the sensitivity and specificity of chest radiograph in indicating active tuberculosis.

Question 14: In smear (-) patients, can the chest X-ray be used as a basis for initiating treatment and monitoring treatments response?

Consensus Statement:

At current levels of evidence, it appears acceptable to base a presumptive diagnosis of PTB on the chest x-ray findings. This may be sufficient enough to initiate treatment. The clinical response to treatment should be closely monitored and ideally documented with radiographs over the next 3 months. The stability of a lesion can only be confidently assessed by comparing chest x-rays taken 6 months apart. (Recommendation Grade: D)

Summary of Evidence:

Sputum examination is accepted as the preferred method for definitive diagnosis of PTB. However, its limitations are widely recognized (4,54-55). The yield of AFB smear is dependent on many factors. As such, authorities suggest testing of at least three sputum samples in individuals highly suspected of having tuberculosis. Induced sputum with heated aerosol of saline solution has yields of 28-57% (54).

Only 50% of adult primary TB cases are AFB positive (1). In post-primary cases, less than 20% have positive yields on smears (4,55). The incidence is generally low (31%) even with cavitary lesions on chest x-ray (4). In one study, half of all AFB smear-negative patients (N=139) were eventually judged to have active TB. MTB was cultured in 12% of patients and 36% of cases had clinical and radiographic improvement with empiric therapy (61).

Given the above statistics and considering the high prevalence of TB in the Philippines, it appears justified to make a presumptive diagnosis of PTB in patients with compatible clinical presentations and a suggestive chest radiograph. In highly suspected cases, this may be sufficient to initiate treatment despite failure to obtain immediate sputum confirmation. The consequences of delaying therapy cannot be ignored. Retrospective studies report that a delay in initiating proper treatment can be as long as 4-6 weeks in situations where tuberculosis was not entertained on initial presentation (54-55,57).

The diagnosis of PTB in the absence of bacteriology is reasonable in certain situations. For patients with a suggestive clinical presentation and a compatible chest radiograph, a trial of chemotherapy may be indicated. Response to treatment should be monitored over the following three months to monitor for changes in the radiographic lesion (1,54,55,61). Considering the absence of pathognomonic features for active disease, serial roentgenograms (6 months apart) are recommended before deciding that a lesion is inactive (57). (Level of Evidence: 5)

Research Recommendation:

1. Prospective studies on the outcome of patients with a presumptive diagnosis of PTB based on chest radiograph.
2. Diagnostic studies to evaluate AFB smear negative patients suspected of having PTB.
3. An algorithm or guidelines in the proper sequential approach to patients above.

Question 15: What is the value of routine chest x-rays for PTB screening?

Consensus Statement:

The evidence suggests value in performing routine chest x-rays in clinical settings with a high prevalence of tuberculosis. Test sensitivity is low (68%-75%) but the consequences of missing the diagnosis remain significant enough to support the practice. (Recommendation Grade: D)

Summary of Evidence:

Two review articles evaluated the risk-benefit ratio of routine chest x-rays as part of annual or periodic examinations, pre-employment evaluations, or initial test on admission. These studies covered populations with a low prevalence of tuberculosis. The authors concluded that the cumulative radiation risk were substantially higher than previously appreciated and recommended abandonment of such a practice as it does not contribute to enhanced patient care. In the two articles, a good history and physical examination was considered essential to identify individuals who would potentially benefit from a chest x-ray examination (58,59). Similar conclusions were reported in a special article addressing the impact of routine chest x-ray films during admission (62)

However, the data differ in populations with a high prevalence of PTB. One study revisited the utility of routine chest x-rays on admission in a subset of patients with subsequent culture-proven tuberculosis. Of 58 patients whose chief complaints were unrelated to PTB, the chest x-ray suggested tuberculosis in 90% of cases (52/58). Furthermore, 31% of patients with no suggestive symptoms were eventually culture positive. The authors concluded that routine admission chest x-rays are useful in populations where tuberculosis is still common. They further indicated that the probability of detecting AFB on sputum smear is greatly influenced by the roentgenographic finding (1). Khan and colleagues reported parallel results. Among patients with

culture-proven tuberculosis or caseating granulomas on biopsy 20% were asymptomatic but presented with abnormal chest radiographs (53).

Remember that the effectiveness of any diagnostic test is directly related to the prevalence of the disease sought for in the test population. Considering this and the available evidence, there appears to be value in doing routine chest radiographs to detect tuberculosis in high prevalence settings such as that of the Philippines. The sensitivity of the chest x-ray for this purpose is relatively low (68-75%) (57-59). However, the consequences of missing the diagnosis remain significant enough to warrant this practice. (Level of Evidence: 5)

Research Recommendation:

1. Prospective local studies on the outcome of routine chest x-ray examinations for detecting PTB.
2. Further studies documenting the risks and potential possible radiation hazards of routine chest X-rays.
3. Cost-analysis study on chest X-rays for asymptomatic individuals or individuals with complaints unrelated to PTB.

Question 16: What is the value of a chest CT scan for the diagnosis of PTB?

Consensus Statement:

The use of chest CT scans for routine diagnosis of PTB cannot be recommended, as the cost is prohibitive. In selected situations, the chest CT scan has a limited role as an adjunctive tool to rule out disease entities that may mimic PTB or co-exist with a TB infection, e.g., unusual radiographic presentations (mass lesions, atypical infiltrates). (Recommendation Grade: D)

Summary of Evidence:

The large studies on computed tomography for pulmonary tuberculosis were reviewed in relation to chest radiographs. The studies are mainly descriptive in nature focusing on the various patterns with which the disease might present (56,63).

In one prospective study, CT findings of active disease as well as sequential changes to treatment were documented in 41 patients. Centrilobular lesions (nodules or branching linear structures 2-4 mm in diameter) around the small airways were reported to be the most characteristic CT scan feature of early active tuberculosis. These lesions were not evident on the chest radiograph and were postulated to be reliable criterion for indicating disease activity. Most of these lesions were observed to disappear within 5 months after the start of treatment (64).

High-resolution CT detects 98% of patients with evidence of endobronchial spread (a common complication of cavitation). The rate is notably high when compared to the pick-up rates of basic chest radiographs (15-48%) (56). Other studies have established acceptable accuracy values for CT scans with respect to localizing lesions within the pulmonary lobule. These authors conclude that certain diseases, including tuberculosis, can be differentiated from other similar entities based on peculiar patterns of involvement and distributions in the lobule (63). A very recent study correlated cytokine levels in bronchoalveolar lavage fluid with the extent of disease extension as defined by high-resolution CT scan. The correlation between cytokines and high-resolution CT scan total scores were better than those observed with individual radiologic findings (65). These findings are understandable in the light of the hypersensitivity reaction induced by MTB in the lung and the greater sensitivity of CT scan for detecting anatomic abnormalities.

CT has further identified differences in pulmonary parenchymal involvement for subsets of patients with PTB. A study comparing conventional and high-resolution CT scans in patients with and without underlying diseases suggest that multiple cavities within a given lesion and a non-segmental distribution are more common in immunocompromised patients and patients with diabetes (66). HIV-seropositive patients have been found to have a higher prevalence of disseminated disease on CT and a lower prevalence of localized parenchymal disease as compared with HIVseronegative patients (67).

While a CT scan can provide more information and greater detail than a chest radiograph, its cost remains prohibitive. As such, the routine use of CT scans for the diagnosis of PTB cannot be recommended. CT scan may have a limited role for diagnosis in situations where similar or co-existing disease entities are highly considered, e.g., granuloma vs. malignancy.

CT-scans could be of value in cases where PTB is highly suspected but the chest radiographic features are atypical in presentation. The utility of CT-scans for the latter purpose remains to be established. (Level of Evidence: 6)

Research Recommendation:

Evaluate the cost-benefit ratio of performing CT scans in the limited situations outlined in the consensus statement.

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TREATMENT OF TUBERCULOSIS

Questions Addressed:

1. What is the drug treatment of choice for newly diagnosed PTB in the Philippines?
2. Is there a difference between 2 and 3 drugs in the maintenance phase of short-course treatment for PTB?
3. What is MDR versus multi-drug resistant (non-MDR) TB?
4. What are primary (initial) drug resistance and secondary drug resistance?
5. What is the rate of MDR-TB in the Philippines?
6. Is there a correlation between bacteriologic drug resistance seen in vitro with treatment response of patients?
7. How does one interpret the results of drug testing for mycobacteria?
8. What is the risk of failure for MDR-TB vs. multiple drug resistant (non-MDR) drug resistant TB?
9. Is there a difference in treatment response between primary (initial) drug resistance and secondary drug resistance?
10. What are the predictors of MDR-TB?
11. How is drug resistance avoided?
12. What is the empiric therapy for MDR-TB suspect?
13. What is the role of adjunctive treatment for MDR-TB?
    a. Surgery
    b. Interferon gamma
    c. M. vaccae
14. What is the treatment for TB in special situations?
    a. TB in pregnancy and lactation
    b. TB in patients with hepatic disease
    c. TB in patients with renal disease
    d. TB in the elderly
    e. TB in HIV/AIDS
    f. Extrapulmonary TB
    g. Monitoring and management of adverse reactions to anti-TB drug
15. What is the recommended secondary chemoprophylactic regimen in the Philippines?
16. Who should get secondary chemoprophylaxis?
17. Should secondary chemoprophylaxis be adopted by the National TB Control Program in the Philippines?

Question 1: What is the treatment of choice for newly diagnosed PTB in the Philippines?

Consensus Statement:

Based on level 1-2 evidence from a meta-analysis of 6 randomized controlled trials and community-based nationwide in-vitro resistance surveys, a minimum of 3 drugs (2RHZ/4RH) is recommended for the intensive phase treatment of newly diagnosed PTB. (Recommendation Grade: A)

In urban areas and most places in the Philippines where drug resistance is high as shown in surveys, 4 drugs (2RHZE(S)/4RH or 2RHZE/4R3H3) is the preferred drug regimen. (Recommendation Grade: C)

Better compliance using DOTS and other adherence-enhancing measures must be propagated to ensure better treatment outcomes.

Individual evaluation, taking into account the bacterial burden, resistance rates in area, affordability of drugs, availability of drugs and compliance should be done by the health care provider. Mandatory sputum culture and sensitivity testing should be done for patients highly suspected with MDR.

Summary Evidence:

The highest levels of evidence are provided by meta-analysis (1,2). A meta-analysis of the use of 3 versus 4 drugs in the intensive-phase of short course therapy of newly diagnosed PTB was done which incorporated the results of 6 RCTs (2 local, 4 foreign studies) using Revman version 3. A summary of the included studies is shown in Table 1 (3,4,5,6,7). Similarities in settings and resistant rates in these countries made the comparison more credible (Philippines, Thailand, South Africa, Pakistan and Poland).

Table 1: Included RCTs in the meta-analysis

STUDY	SETTING	Treatment regimens		Number of subjects		INH**
		Treatment	Control	Treatment	Control	resistance (%)
Khan 1981	Pakistan	2RHZS/4RH	2RHZ/4RH	29	30	27***
Snider1984*	Poland	2RHZS/$4R_2H_2$	2RHZ/$4R_2H_2$	78	135	1.9
Cowie 1990	South Africa	4RHZE	4RHZ	81	69	NS[@]
Punnotok 1995	Thailand	2RHZE/4RH	2RHZ/6HT	102	97	7.5
Hipol 1998	Philippines	2RHZE/4RH	2RHZ/4RH	44	42	45.7
Yu 1998*	Philippines	2RHZE/4RH	2RHZ/4RH	117	111	20.9
Total				45	484	

*Multicenter studies; **at least to INH; ***drug resistance for hospital; [@] not stated

For most of the treatment outcomes to clinicians (relapse rates at 1, 2 years, AFB conversion rates at 2 and 6 months, x-ray improvement and relief of symptoms at 6 months) results were heterogenous with no evidence for a difference between the 2 treatment groups except for AFB smear conversion at 2 months where all 5 RCTs showed a trend favoring 3 drug therapy (odds ratio1.6 with 95% CI, 0.99-2.60) and a trend favoring 4 drugs in smear conversion and symptom relief at 6 months but this was not statistically significant with wide 95% CIs. For these outcomes, assessment of results is level 2-consistent with Grade B Recommendations.

The quality of individual studies based on Hatala et al. (8) in this meta-analysis can be seen in Table 2. Most of the studies included are of relatively good quality (ranging form 0.75-0.92) providing level 1-2 evidence.

For adverse drug reactions, over-all odds ratio was 2.53 (95% CI, 1.42-4.53) in favor of 3 drugs and for compliance rates, the OR was 0.66 (95% CI, 0.45-0.98), in favor of 4 drugs (2 out of 4 studies showing better compliance used streptomycin in place of ethambutol). This constitutes Level 1 (homogenous) evidence for a meta-analysis. Summary of over-all results and evaluation of 11 important treatment outcomes is shown in Figure 1. While these individual RCT studies may be criticized for various problems (i.e. drop-outs, lack of blinding, at least 1 with possible conflict of interest from funding source) they still constitute the best evidence so far compared to the other uncontrolled open trials and anecdotal studies from which the previous groups had to work on. The 6 RCTs showed that there was no difference in treatment outcomes between 3 and 4 drugs except for adverse outcomes and compliance rates. Figure 1 shows summary of the treatment outcomes for the meta-analysis. There were other local open trials on this including those cited in the 1989 PCCP consensus but these studies were either clinical case series forming level 5 evidence (10, 11,12,13,14).

An unpublished local cost-benefit analysis (15) (CBA) on 3 versus 4 drugs (1994) showed that 4 drugs was more cost-beneficial than 3 drugs but this analysis incorporated data from non-randomized controlled studies and incorporated local data from non-RCTs and foreign data. An ongoing CBA is presently being done to incorporate the results of these recent studies.

Table 2: Methodological Quality Scores (MQS) of individual studies Included in the meta-analysis

Study	Randomiztion	Follow-up	Blinding of assessor	Intention-to-treat	Inclusion and exclusion criteria	Intervention	Compliance	Blinding of patients	Defined outcome	MQS*
Khan	2	1	2	1	1	1	1	0	1	0.83
Snider	2	2	2	0	1	1	1	0	1	0.83
Cowie	2	1	2	1	1	1	0	0	1	0.75
Punnotok	2	1	2	0	1	1	1	0	1	0.75
Hipol	2	1	2	1	1	1	0	0	1	0.75
Yu	2	2	2	1	1	1	1	0	1	0.92

*MQS = assessment of trial's methodologic quality, obtained by dividing sum score by the maximum attainable score of 9

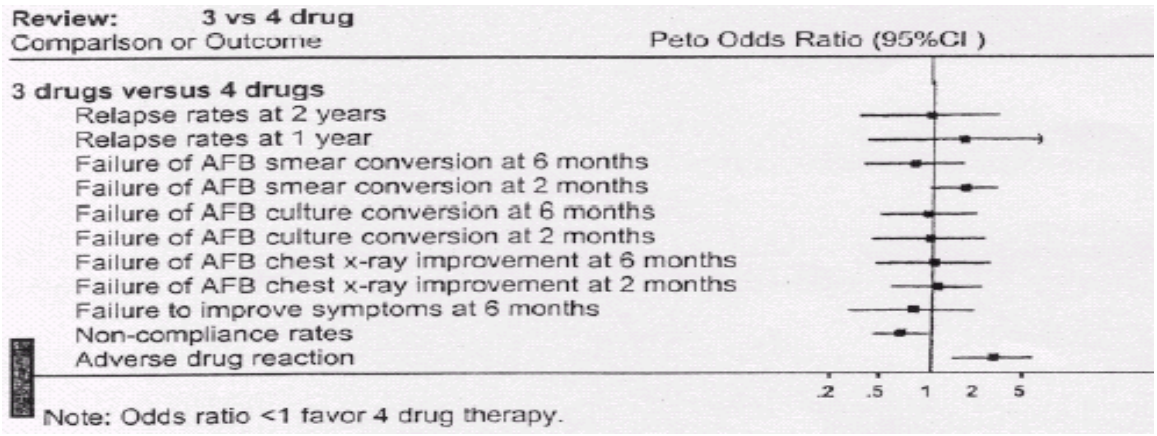

Figure 1: Meta-analysis of 6 RCTs on 3 vs 4 drugs for treatment

Evidence provided by–vitro resistance surveys

For this, the Committee relied more on multi-centered surveys and studies provided by 3 of the latest available: the 1997 National Prevalence Survey (covering all regions), the 1997 MDR Sentinel Surveillance Site (4 regions, NCR, Zamboanga, Cebu and La Union) (16) and the multi-center TB study of the comparison of 3 vs 4 drugs covering 7 regions (Dagupan, Pampanga, NCR-Lung Center, Cavite, Cebu, Palawan and Davao). These are shown in Table 3. The MDR rates (defined as resistance to both INH and Rifampicin) was 4.3% in the National Prevalence Survey, 5% for the MDR Site (6.2% over-all with 95% CI, 3-9.4%) and 9.7% for the multi-center TB study. All these results are quite far from the hospital based in vitro studies done before 1979-1995 showing rates of 13.6-30.5%. Data from hospital based surveys from 1990 to 1996 at 3 large tertiary hospitals covering 1904 cultures showed ranges of fully sensitive organisms at a very low 16.7-28.7%, single drug resistance at 16.3-30.5% and MDR of 13.6-58.9%) probably reflecting the tertiary referral bias of these studies (also these surveys did not distinguish between initial and acquired drug resistance). Most of these patients probably belong to re-treatment cases and those with previous intake of medications.

Correlation between initial INH drug resistance and treatment response

Previous consensus statements had recommended at least a 4 drug initial drug regimen if the prevalence of INH resistance in a community exceeded 4%. All large scale studies mentioned previously showed rates between 14.9% (Tupasi) to 16.9% (Tan-Torres) and initial INH resistance (i.e. those with no previous treatment) to be 11.5% (Tupasi) to 20.9% (Yu).

The analysis of the 6 randomized controlled studies on 3 versus 4 drugs in the intensive phase treatment of newly diagnosed PTB, showed that 5 of the RCTs did not look at the correlation of initial INH drug resistance and treatment response. The only study (Yu) in which the data are available seems to suggest that treatment response to 3 or 4 drugs did not correlate with initial INH resistance (over-all initial INH drug resistance for both groups was a high 20.9%).

Table 3: Summary of multi-center community-based in-vitro surveys

Study	Fully Sensitive	INH resistance (%)	> 2 drugs (%)	MDR (%) (at least RH)
1997 NPS *(Tupasi)				
combined data (n=188)	82.4	14.9	8.0	4.3
initial drug resistance (n=30)	86.6	11.5	5.4	1.5
acquired (n=26)	74.3	22.9	14.3	14.3
1997 MDR Sentinel Site Study (Tan-Torres)				
combined data (n=395)	71.1	14.4	13.2	6.2 (3-9.4, 95% CI)
initial drug resistance				5.0
NCR (latest data)(n=287)				7.0 (3.5-10.5, 95% CI)
initial resistance (n=168)				5.0
Acquired (n=33)				7.0
1998 Multi-center study (Yu)				
Initial resistance (n=62)	76.9	20.9	16.1	9.7

*National Prevalence Survey

Recommendations:

At the present time, there is a lack of current evidence or clear trends in favor of efficacy and superiority of 4 drugs over 3 in newly diagnosed PTB in a meta-analysis. The committee maintains the recommendations in the 1989 TB Consensus Report and adopted by WHO in most countries with some qualifications in urban areas like the National Capital Region. However, this is based at best on level 3 evidence (Grade C recommendation). The use of four drug 2RHZE(S)/4RH) daily in the intensive phase treatment adds an additional assurance against treatment failure should there be unexpected drug resistance and assuming adherence to the treatment regimen, also helps the loss of additional drugs (17). This is especially true for those patients who live in areas of known high drug resistance like the urban areas of the National Capital Region (NCR), Cebu, Davao, Zamboanga and Pampanga. Drug affordability should also be taken into account. In program conditions, where budget limitations, lack of steady supplies as well as adherence to treatment is not guaranteed, prudence dictates that the program manager as well as the individual physician exercises sound judgement by weighing the risks and benefits of recommending 3 vs 4 drugs.

The health care provider must take into consideration the following:

1. Bacterial load/burden (i.e. cavitary, AFB+4 smear versus, non-cavitary, active radiologically, smear-negative - in the latter, 3 drugs may suffice if in low resistance areas)
2. The probable resistance rates in his community
   a. In known areas of high resistance (NCR, Cebu, Davao, Zamboanga, Cavite, Pampanga), 4 drugs is the treatment of choice.
   b. In areas where surveys have shown relatively low resistance (Palawan and cities like Dagupan and Puerto Princesa and particularly in the rural areas), the 3 drug regimen (2 RHZ/4RH) may still be used in new patients coming from these areas, but strict adherence to treatment (like DOTS) must be followed to reduce the risk of relapse and the emergence of resistant strains.
   c. It also recommended that in communities where resistance rates are not known, 4 drugs can be used empirically and in-vitro resistance using a reputable TB reference laboratory be done if patient is suspected to have resistant PTB or history of previous intake is unknown.
3. The affordability of the drugs (if the patient will procure it himself)
4. Availability of drugs (if taken from the local health center) and above all

5. Compliance

Evidence seems to suggest better compliance if one were to include streptomycin as the 4th drug but this has to be weighed against the increased risk of adverse drug reactions. Anti-TB drugs must be used with caution among the elderly population.

It must be reiterated that these recommendations are based on confirmed PTB cases (bacteriologically confirmed by positive AFB smear or culture, extensive radiologic lesions) and not based on x-rays of doubtful readings. ***Neither 3 nor 4 drugs will work in newly diagnosed PTB unless strict compliance is assured.*** The on going sentinel sites and surveys may also be used to guide clinicians. Intermittent regimens (fully and in the follow-up phases of treatment) should be encouraged although results for the former are still being fully evaluated.

Question 2: Is there any difference between 2 and 3 drugs in the maintenance phase of short-course treatment for PTB?

Consensus Statement:

At the present time, a minimum of 2 drugs (4RH) given for 4 months is required for the maintenance phase of short-course chemotherapy. There are currently no randomized controlled trials addressing this issue at the present time and the meta-analysis previously mentioned all dealt with a 2-drug maintenance regimen.

Additional drugs (i.e. ethambutol) maybe recommended depending on the results of susceptibility testing. (Recommendation Grade: C)

Question 3: What is MDR-TB versus multiple drug resistant (non-MDR) TB?

Multiple drug resistance is considered to be present when TB bacilli are resistant to two or more first line drugs (H, R, S, Z, E) (18). Consistent with current definition, the phrase multi-drug resistant tuberculosis (MDR-TB) implies infection by strain of *M. tuberculosis*, which shows in vitro resistance to at least isoniazid and rifampin, the 2 most potent ant-TB drugs, with or without resistance to other drugs (19).

Question 4: What are primary (initial) drug resistance and secondary drug resistance?

WHO/IUALTD defined Primary (initial) Drug Resistance as the presence of resistant strains of *M. tuberculosis* in a patient who, in response to direct questioning denies having had anti-tuberculosis treatment for more than a month and in countries where adequate documentation is available, no evidence of such history exist.

In surveys and clinical practice, it is not easy to differentiate primary resistance and undisclosed acquired resistance since the patient may not know or may deny that he had previous tuberculosis treatment (20). Toman therefore recommended that if it is impossible to obtain from a new drug-resistant patient a reliable history of previous chemotherapy, it is better to use the term *Initial Drug Resistance*. It could cover primary as well as undisclosed acquired resistance.

Acquired (Secondary) Drug Resistance exists among patients diagnosed with tuberculosis and started on anti-tuberculosis treatment whose bacilli then developed drug resistance to one or more of the medications used during treatment (19).

Question 5: What is the rate of MDR-TB in the Philippines?

Multi-drug resistant tuberculosis has been found most frequently in those with previous intake of anti-TB drugs for at least a month. Thus, MDR-TB is primarily an iatrogenic problem.

Previous studies of susceptibility patterns of Mycobacterium isolates came from tertiary care referral hospitals and reported rates as high as 32% for MDR-TB (21).

TABLE 4. Susceptibility patterns of Mycobacterium isolates

Category	QI* 1976 n=2,722	QI* 1980 n=934	NPS 1983 n=156	ASTER 1986 n=130	LCP* 1989 n=100	LCP* 1992 n=223
Fully Susceptible	86	34	62	20	38	14
Resistant						
1-drug	5.4	38	26.9	27.0	24	15
MDR	7.9	29	14.0	53.0	38	71

*Referral centers **MDR referred to > 2 drug resistance (not RH)

Recently, community-based data have become available. The sentinel site surveillance, utilizing health centers in the provinces where the regional TB laboratories were established has documented a 6.2% (95% CI, 3.0-9.4) MDR rate for the National Capital Region.

This came from a total of 224 isolates collected during 1995-96 (16). Data from other sentinel sites are still forthcoming. Dr. Tupasi in the 1997 National Prevalence Survey documented an MDR rate of 8.3% from 60 isolates of patients enrolled in a clinical trial run in seven sites in the Philippines. It is important to note that lower rate seen by Dr. Tupasi is a result of the sampling for the National Prevalence Survey. Patients, whether symptomatic or not were asked to produce sputum if their chest x-rays were positive. In the sentinel site surveillance and in Dr. Yu's study, these are TB symptomatics presenting for care at the health center or private clinics.

Question 6: Is there a correlation between bacteriologic drug resistance seen in-vitro with treatment response of patients?

This question assumes that the mycobacteriology laboratory is reporting bacteriologic drug resistance accurately. Drug sensitivity testing for *Mycobacterium tuberculosis* is an elaborate and difficult procedure to perform and requires considerable expertise and experience (22,23). It is important when interpreting the results of sensitivity testing that one is assured of adequate quality control in the mycobacteriology laboratory.

Results of conventional sensitivity testing are usually available 6-8 weeks after submission of the specimen to the laboratory. At this time, the patient is already expected to have manifested a clinical response to his empiric therapy. Four possible situations can occur.

1. Results show that the mycobacterium is sensitive to the drugs currently being given and a clinical response is demonstrated. Continue with current treatment.
2. Results show that the mycobacterium is sensitive to the drugs currently being given but no clinical response demonstrated. Assess the compliance of the patient with drug treatment. If the patient is not under directly observed therapy, assume that the patient is non-compliant, continue current treatment and institute DOT.
3. Results show that the mycobacterium is not sensitive to the drugs being given and no clinical response has been demonstrated. Revise current therapy depending on the sensitivity results.
4. Results show that the mycobacterium is not sensitive to some of the drugs being given but a clinical response has been observed. In general, the risk of treatment failure is expected to increase with the number of drugs being reported as resistant. Determine the number of drugs to which the mycobacterium is still sensitive. Assess their bactericidal activity. In general, if the mycobacterium is still sensitive to three or more drugs, one can continue the current treatment and monitor the sputum smear positivity. If only one or two drugs are active, weigh the patient's risk of developing adverse effects if a second line drug is used. In this case, one can choose to continue with current management and follow-up the patient closely or one can

add a second-line drug. It is best that the situation is explained to the patient and his preferences are elicited.

These recommendations are based mostly from expert opinion and from subgroup analysis of results from clinical trials. (Recommendation Grade: D)

TABLE 5. Multi-drug resistant tuberculosis (T. Tan-Torres, M. Mendoza, C. Ang. National Capital Region)

Pattern	Number	%
Fully Susceptible	65	73.7
One Drug Resistance	32	14.3
Isoniazid (INH)	17	7.6
Rifampicin (RIF)	4	1.8
Ethambutol (EMB)	9	4.0
Streptomycin	2	0.9
Two Drug Resistance	18	8.0
INH-RIF	6	2.7
INH-EMB	4	1.8
INH-STREP	3	1.3
RIF-EMB	2	0.9
RIF-STREP	2	0.9
EMB-STREP	1	0.4
Three Drug Resistance	6	2.7
INH-RIF-EMB	2	0.9
INH-RIF-STREP	3	1.3
INH-EMB-STREP	0	0.0
RIF-EMB-STREP	1	0.4
Four Drug Resistance	3	1.3
INH-RIF-EMB=-STREP	3	1.3
TOTAL	**224**	**100.0**

Question 7: How does one interpret the results of drug sensitivity testing for Mycobacteria?

1. Accuracy of drug sensitivity testing for *Mycobacterium tuberculosis*

It is widely accepted that drug sensitivity testing for *Mycobacterium tuberculosis* is an elaborate procedure and difficult to standardize even in the best laboratories. It requires considerable expertise and experience (22, 23). At present, there is no data on the quality of sensitivity testing in the Mycobacteriology laboratories in the Philippines. There is at present no designated national reference laboratory. Under these conditions, it is best to interpret results of drug sensitivity testing while considering the patient's clinical response and sputum AFB smear results.

2. Relationship of resistance and treatment response

Treatment response varies depending on the type of resistance (initial or acquired, multidrug resistance or multiple drug resistance) present. Most of the data have been reported as group data. For example, Shimao (24) reports the ff:

Prevalence of Initial INH resistance (%)	Failure and Relapse Rates (%)
0	10
10	12.5
20	15
30	17.5
40	20

From the above, it is clear that as the prevalence of single drug resistance rises, the risk of failure also increases but it is not a direct correlation. This is understandable because chemotherapy of tuberculosis consists of multiple drugs. Also, the risk of rifampicin resistance is low if there is no history

of previous drug intake as in patients with initial resistance. Thus, even with INH resistance, rifampicin is usually effective as bactericidal drug (23).

In a local clinical trial (21) using an 8-month largely intermittent therapy in a population with a high rate of drug resistance (mostly acquired), the efficacy rates were:

Fully sensitive	85%
One-drug resistance	76%
Two drug resistance	53%
Three drug resistance	28%
4 or 5 drug resistance	no success

In patients with a history of drug intake of more than one month, the risk of acquired multidrug resistant tuberculosis is increased. Documented resistance with both INH and rifampicin guarantees failure of standard anti-TB regimens because of the loss of the bactericidal action.

Question 8: What is the risk of treatment failure for MDR-TB versus multiple Drug resistant (non-MDR) TB?

Initiation of drug therapy in patients with proven multidrug resistant tuberculosis requires assessment of the history of treatment as well as efficient laboratory studies to characterize the susceptibility of the specific strain. The optimal duration of re-treatment has not been clearly identified. Different periods recommended are general projections. However, multiple drug resistance where isoniazid and rifampicin are not involved together, duration of treatment is at the range of 6-12 months (26), with good results. But when resistance to both drugs occurs, the prospect of successful chemotherapy is greatly diminished. In that case, the period of treatment is from 12-24 months after sputum conversion (25,26,27,28). In a cohort study of 171 immunocompetent patients, Gable and colleagues reported 56% response to therapy, defined by negative sputum cultures for 3 months. In general, only approximately 50% of people with combined isoniazid and rifampicin resistant disease respond favorably even to aggressive treatment (25,26,29).

A tuberculosis re-treatment regimen should always include at least 3-4 (25,26) but possibly as many as six or seven drugs. The number of drugs used varies depending on the extent of disease and the potency of the available agents. Therapy should be initiated in the hospital to permit observation of toxicity intolerance, which would allow a change in regimen, and for rigid supervision.

The treatment of MDR patients is straightforward. They should be placed on a regimen using 1st or 2nd line drugs based on susceptibility test, using at least three sensitive drugs (30) including an injectible agent (26). Various drugs and regimens have been recommended for treating patients with MDR-TB and their close contacts. However, none of the proposed regimens has been tested in randomized clinical trials (19). Regimens should be tailored by experts using three to five drugs the patient has not previously received and to which drug sensitivity test results show no resistance; a single drug must never be added to a failing regimen. Treatment must be given daily and under direct supervision. Once the patients' sputum has converted to consistently negative microscopy, weaker or more toxic drug can be withdrawn. Treatment shall then be continued for 18 additional months (29). Good data, however, are not available on the relative effectiveness of various regimens and the necessary duration of treatment. Based on available data, although limited, amikacin, quinolones and long acting rifamycins are commonly being used as second line drugs.

These conclusions and recommendations are based mostly form descriptive, prospective and retrospective clinical trials with level 3 of quality of evidence and from expert opinions as cited. (Recommendation Grade: C-D)

Question 9: Is there a difference in treatment response between primary (initial) drug resistance and secondary drug resistance?

Treatment response of primary resistant cases has a better outlook than secondary resistant cases. Based on prospective and retrospective clinical trials with level 3 quality of evidence and expert opinions (Recommendation Grade: C-D)

Toman states that there is adequate evidence that with standard chemotherapy, the prognosis for patients with primary resistance to one drug is almost as favorable. as that for patients with susceptible organisms. The study in Hong Kong by BMRC published in Tubercle, 1974 led to the conclusion that changing treatment on the basis of sensitivity tests had results which, when compared to disregarding these finding and just giving standard chemotherapy, came up with only very marginal differences. Such study actually included only the subjects with initial drug resistance and not chronic patients who often have multiple resistances after irregular course of chemotherapy. A closer look into the study also shows increasing failure rates-18, 28 and 60% with resistance to 1, 2 and 3 drugs respectively.

On the other hand, the efficacy of re-treatment for failure cases, is in general, worse than in the original treatment as cited in same study, comparing daily and intermittent rifampicin plus ethambutol in re-treatment of INH resistant cases. This too was evident in the outcome of chronic cases of pulmonary tuberculosis followed up for 5 years by the Tuberculosis Research Committee of Japan. Out of 513 cases, 262 (51%) died during the follow up period and 159 (31%) were still in the hospital, majority still bacteriologically positive.

Although treatment response of primary resistant cases in general, cannot be said to be as good as that of sensitive cases, there are reasons that prognostically, primary resistance has a better outlook that secondary resistance. First, previously treated TB patients not only have MDR more frequently than new patients, but the degree of resistance is much higher (i.e. higher MIC, especially for INH). Furthermore, the drug resistant strains harbored by previously treated patients are usually resistant to a single drug compared to only 26% of cases with primary resistance (19).

Question 10: What are the predictors of MDR-TB?

The most powerful predictor for multi-drug resistant organism in all studies is a history of treatment of tuberculosis. Irregular and inadequate therapy is the most common means by which resistant organisms are acquired and patients with previous history of treatment should be presumed to harbor drug resistant organisms until proven otherwise (2). Patients whose treatment fails after 2 course of the standardized regimen (the second being supervised) are likely to harbor MDR-TB (29).

Based on descriptive and prospective clinical trials with level 3 quality of evidence and expert opinions. (Recommendation Grade: C-D)

Costello et al. found in their study of 4,017 TB patients with 41% drug resistance that the percentage of the drug resistance strains increased with increasing duration of previous treatment.

Patients with cavitary and bilateral lesions on chest X-rays have a high frequency of resistance, presumably because they harbor greater number of TB bacilli (27,31).

With increasing number of cases, TB patients with HIV infection or AIDS consistently produce drug resistant strains (25,26,28,30,43,44).

Salomon gave positive HIV infection as one of the main predictors in their prospective study involving 84 TB patients. Of the 14 (17%) MDR-TB cases identified, 13 were HIV infected.

Mendoza et al. of PGH, in a prospective study involving 299 cases concluded that the high rate of MDR-TB was associated with previous anti-TB treatment. The chance of developing MCR-TB was significantly increased when inadequate prior treatment was given for more than 3 months.

Duration of previous chemotherapy is a guide to the likelihood of finding drug resistance. In the study on prevalence of resistance in Quezon Institute by Manalo et al., data showed that previous history of treatment less than one month yielded 30% resistance to one or more drugs while those with the history of as short as 1-3 months harbored 68% resistance strains. With a history of 6 or more months of previous chemotherapy, drug resistance was almost invariably present. Data also showed that the total number of patients with 1, 2 or 3-drug resistance was higher in re-treatment cases at 67% against 62% among primary treatment cases.

Question 11: How is drug resistance avoided?

Drug resistance can be avoided by countrywide standardization of anti-tuberculosis regimen using directly observed treatment short course (DOTS) strategy to ensure completion of treatment and cure for the majority of patients.

This has been associated with protection against the development of drug resistance. Avoiding resistance therefore is treating all cases adequately.

However, based on critical reevaluation of several studies, MDR-TB incidence falls only in settings where patients with active MDR-TB are treated effectively. In no setting in the world with an already established MDR problems have case rates fallen even when DOTS was introduced. Therefore, further transmission of MDR-TB strain (primary resistance) may still occur in DOTS-based countries (23).

Resistance is a function of big bacillary numbers. The bigger the bacillary population, the greater the number of resistant mutants. Basically monotherapy, improper drug combination and inadequate doses and therapy are circumstances that promote emergence of secondary resistance and must be avoided (19).

Question 12: What is the empiric therapy for MDR-TB suspect?

Basic Principles: (taken from the Guidelines for the Management of Drug-Resistant Tuberculosis-WHO)

1. MDR-TB patients will often require the use of at least some second-line drugs. These drugs are less effective and have more side effects than the present standard essential drugs. It must be made clear to the patient and staff that meticulously taking the prescribed reserve regimen is all that stands between the patient and death. The patient must try to tolerate any unpleasant side effects in order to achieve survival. He/she must agree to remain under direct observation, with each dose supervised, at least until the sputum is negative. The patient must receive clear and complete explanations before treatment, and permanent psychological support and attention.
2. In designing a regimen, do not aim to keep drugs in reserve. That is the way to lose one battle after another.
3. Prescribe drugs, which the patient has not previously taken. The bacilli are fairly certain to be sensitive to these. The practice of adding isoniazid to these drugs confers no advantage.
4. If, on the evidence, it is possible that the bacilli remain sensitive to a "standard" drug (Strep/ PZA/EMB) in spite of the patient having received it in an unreliable combination, you may add it to the regimen in case it is still useful but do not rely on it to prevent further resistance; if tests later show resistance to that drug, you may have failed to protect the newly introduced drugs. On the other hand, if the bacilli turn out to be still sensitive to it, it will give an additional effect. This may, after you have the results of resistance tests, permit you safely to withdraw weaker second-line drug, which is causing the patient side effects, but still leave an effective regimen, which will prevent further resistance.
5. The initial regimens should consist of at least three drugs, preferably four or five, to which the bacilli are likely to be fully sensitive, i. e. drugs not previously used for that patient. Among those drugs, desirable to use in combination an injectible aminoglycoside (according to the rank of choice) and pyrazinamide (even if previously used, because resistance is usually unlikely). This combination has a good bactericidal activity.
6. When the patient's sputum has converted to negative, you can withdraw one or more drugs, preferably a weaker drug, which is causing side effects.
7. The treatment with these weaker regimens should be continued for at least 18 months after sputum conversion to prevent elapse.
8. In any regimen chosen, especially when weaker drugs are used, the treatment should be given daily and should be directly observed. It is also mandatory to monitor bacteriological results (smear and culture monthly from the second month until the sixth month and then quarterly until the end of treatment)

Recommendations are based on expert opinions (Recommendation Grade D).

Question 13: What is the role of adjunctive therapy for MDR-TB?

Consensus Statement:

At the present time there is no clear evidence for the beneficial effects of current adjuvant therapy in the treatment of MDR-TB. Of the adjuvant therapies reviewed, surgery showed some promise (Recommendation Grade: B) while *M. vaccae* from RCTs showed no benefit for MDR-TB. (Recommendation Grade: A)

A. Surgery

Surgery is rarely used for the treatment of TB. However, the most common recent indication for operative intervention in patients with tuberculosis has been MDR-TB for whom drug therapy alone could not provide an enduring cure.

The WHO 1997 guidelines for the management of drug resistant tuberculosis consider surgery for a patient with bacilli resistant or probably resistant, to all except two or three relatively weak drugs. If the patient has large localized cavity, with little other disease, reasonable lung function and only two or three (weak) drugs available, surgery should be seriously considered. To avoid serious, and potentially fatal tuberculosis complications of surgery, operate when the bacillary population is likely to be at its lowest. If only a very weak regimen is available, experience has shown that the most favorable time is after two months of treatment. After surgery, the same regimen should be continued for at least 18 months (29).

The bases for this recommendation are the studies of Iseman and colleagues (32,33) that looked at the therapeutic efficacy of surgery. Of 99 MDR-TB patients 27 had surgery and 25 remained sputum culture negative for a mean duration of 36 months (combination of surgery and medical therapy) (32). The other study (33) involved 57 patients. Thirty four required pneumonectomies and 23 had lobectomies. Of 50 surviving patients, 49 remained culture negative for M tuberculosis. The retrospective study of Leuven et al. reviewed 62 patients who underwent pulmonary resection for drug resistant strains of M tuberculosis. Eighteen of 24 patients (75%) who were persistently sputum positive at the time of operation immediately converted to negative sputum smear and culture. For all patients who were sputum negative after operation, 80% remained relapse-free. However, given the advanced stage of lung damage typical of such patients, the intervention entailed overall morbidity of 23% (34).

In most of the studies reviewed (32-38), the primary indication for surgery is failure to convert despite an adequate drug regimen. Van Leuven et al. (34) had a second indication and this is for patients who have already, in the course of treatment, converted to a sputum negative state. The operation is pre-emptive to hopefully prevent relapse. In this group the indication for operation is less clear-cut and subject to controversy.

The length of postoperative drug therapy remains controversial. Operation may ablate the major reservoir of the bacilli, but the 'cure' resides with the completeness of the antibiotic course. Iseman and colleagues (32, 33) suggest continuation of therapy for 18 to 24 months while the WHO guidelines suggest 18 months (29).

TABLE 6. Indications for surgery among MDR-TB cases

Group	Indication	Criteria
A	Failure to convert	Sputum smear culture positive despite at least 4-6 mos. treatment with an adequate drug regimen
B	Previous relapse	Previous history of two or more TB relapses and/or one or more relapses during the MDR-TB treatment course
C	High profile on drug resistance	Infection with strains of M. tuberculosis resistant to four or more drugs
D	High or potential risk for relapse	Patients not falling in the previous categories but considered likely to relapse despite conversion as gauged by the presence of a destroyed lung or lobe.

Literature reviewed indicated level 2 quality of evidence on which recommendations are made (Recommendation Grade: B)

B. Interferon-Y (IFN-Y)

The role of IFN-Y in the adjunctive treatment of MDRTB infection, as well as the optimum doses and duration of therapy should be further investigated in prospective, randomized trials.

IFN-Y has been shown to activate monocytes and macrophages against *Mycobacterium tuberculosis* in vitro. It has been used successfully with conventional anti-mycobacterial therapy in the treatment of refractory atypical mycobacterial infections such as those due to *Mycobacterium avium* complex.

Raad et al. described the used of IFN-Y in a patient with leukemia in whom IFN-Y and GCSF (granulocyte colony stimulating factor) were used successfully as adjunctive therapy for refractory MDR-TB infection of the brain and spine (39).

Preliminary data suggest that aerosol IFN-Y is a well-tolerated treatment that may be useful as adjunctive therapy in patients with MDR-TB who are otherwise not responding well to therapy. In five patients with advanced MDR-TB, IFN-Y via aerosol was associated with improvement in the following parameters: sputum AFB smears became negative in all patients, stabilization of weight gain and lengthening of the time to positive culture of M. tuberculosis from sputum sample (40).

Based on the two papers noted on the use of IFN-Y as adjunctive therapy, the recommendation merited a grade of C and a level 3 quality of evidence.

C. *Mycobacterium Vaccae*

The role of *M vaccae* in the adjunctive treatment of MDRTB infection should be further investigated.

A controlled and blinded study was carried out in Gambia in 1979, which involved 280 patients with active TB, where one group received immunotherapy with M vaccae in addition to the usual TB regimen. It was found out that significantly more patients survived who received immunotherapy than those who received placebo. In Nigeria, a randomized controlled but open study was also carried out where patients with pulmonary TB received whatever chemotherapy they can afford, which varies from several months to none al all. Small numbers received either M. vaccae or placebo at the time of diagnosis or after 7, 14, or 21 days of chemotherapy. The time of giving immunotherapy hastened clearance of bacilli from the sputum, reduced ESR, increased body weight and improved patient well-being. The follow-up on this study after 10-12 months showed that 41 of 42 patients receiving the immunotherapy were alive and well whereas 19 of the 47 given placebo had died (p>0.0001). Those in the immunotherapy group bought an average of 2.9 months of chemotherapy, whereas those in the placebo group purchased a mean of 6.5 months of chemotherapy (41).

Early results are very encouraging and show some treatment failure patients becoming sputum negative for the first time after immunotherapy. From studies in Mashad, Iran, which were the subject of a letter published in the Lancet, 11 of 41 patients with multiple drug resistant tuberculosis became well and consistently sputum negative after 1 to 5 doses of M vaccae at about 2 months interval. In India, 5/9 patients became sputum-negative; in both Kuwait and Romania, 2/2 became sputum negative; in UK, a young patient made an unexpected and dramatic clinical recovery after 1 or 2 doses; and in Vietnam, 10/21 treatment failure patients became sputum negative for AFB after a single dose (41).

The prospective randomized study by Montoya et al. in the Philippines involving both susceptible and resistant M. tuberculosis concluded that M. vaccae is potentially useful and effective immunotherapeutic agent in the management of tuberculosis. However, little benefit is seen when M. vaccae is used for cases of multidrug resistant TB (42).

Question 14: What is the treatment of tuberculosis in special situations?

This part addresses the available data on the treatment of tuberculosis in special situations such as:

a. TB in pregnancy/lactation
b. TB in patients with hepatic disease
c. TB in patients with renal disease
d. TB in the elderly
e. TB in HIV/AIDS
f. TB in immunocompromised states other than HIV/AIDS
g. Extrapulmonary TB
h. Monitoring and management of adverse reactions to anti-TB drugs

a. Tuberculosis in pregnancy and lactation

Question 14. a1: Who should be treated?

Consensus Statement:

A woman who states she is pregnant or menstruation is >2 weeks late, or there is possibility that the woman is pregnant, and who presents with sign and symptoms highly suggestive of PTB.

Question 14. a2: What treatment regimen should be initiated?

i. for sputum AFB smear (+) and/or TB culture (+) with/without CXR evidence of PTB
= For HIV (-) without risk for HIV, immunocompetent

Consensus Statement:

The regimen should consist of rifampicin, isoniazid and ethambutol for at least nine months or at lest six months beyond culture conversion whichever is longer (43,44). However, if the organisms are proven sensitive to both rifampicin and isoniazid, ethambutol could be instituted during the initial three months only.

The use of pyrazinamide must be avoided except in situations where resistance to rifampicin or isoniazid is highly suspected and resistance to pyrazinamide is unlikely (45, 46). If ever it is to be utilized, it must be given after the first trimester of pregnancy.

Streptomycin should not be used as previously stated in the National TB Consensus Part I because it is potentially hazardous not only during the first trimester but throughout gestation. It induces ototoxicity (43,46,47,48).

Summary of Evidence:

Pyrazinamide is used as a bactericidal drug in most first-line regimens. It is essential to short course chemotherapy because of its potent and early bactericidal activity (45,49). It works very well at the intracellular environment (within human macrophages) and at an acidic pH (49,50,51). Moreover, a 5-year follow-up of a controlled trial of five to 6 month regimens of chemotherapy for PTB showed that the total relapse rates for patients with drug susceptible strains pretreatment were 3.4% for the pyrazinamide series compared with 10.3% for the non-pyrazinamide series ($p<0.001$) (52). However, in pregnancy, it must be used with caution because there are no controlled studies to prove its safety during pregnancy. Moreover, there is inadequate data concerning its teratogenicity (43-46,52-56).

Streptomycin is the only anti-tuberculosis drug that has been shown to cause fetal malformation. In 40 pregnancies, 17% of the babies had eight nerve palsies deficits ranging form mild hearing loss to bilateral deafness (4). Snider, et al. reported that one of six fetuses born to mothers treated with streptomycin developed some hearing loss or vestibular defects (47,56).

= HIV (+), with risk for HIV, immunocompromised

Consensus Statement:

In this particular group, treatment consisting of rifampicin, isoniazid and ethambutol must be extended to at least twelve months or at least nine months beyond culture conversion, whichever is longer. Pyrazinamide may be utilized but should be instituted after the first trimester of pregnancy.

Summary of Evidence:

In HIV-infected pregnant patients, treatment must be extended for at least 12 months. This is supported by the randomized controlled trial conducted among HIV-infected patients in Zaire which compared 6 vs 12 month therapy consisting of rifampicin, isoniazid, ethambutol and pyrazinamide daily followed by 4 or 10 months of rifampicin and isoniazid administered

twice weekly. The study showed increased relapse rate (9% vs. 1.9%) in those who received 6-month course of therapy vs. those who received 12 months treatment. However, no difference in survival was noted between the two groups (57).

In several other studies, increased pathogenicity of tuberculosis among HIV-infected individuals was observed preventing the containment of initial infection, allowing reactivation and failure to confer long-term immunity (46,58,59). Moreover, patients were noted to have marked increased rates of progression from infection to fulminant disease (46,60-62).

=MDR-TB suspect

Consensus Statement:

Treatment would rely mainly on the use of second-line drugs. However, their use during pregnancy must be weighed against the risk to the fetus and the mother.

ii. For CXR (+), sputum AFB smear (-) and/or TB culture (-)
=HIV (-) without risk for HIV, immunocompetent

Consensus Statement:

For non-cavitary disease, treatment should consist of rifampicin, isoniazid and ethambutol for nine months. For cavitary disease, treatment should be extended to 12 months using the same regimen.

Summary of Evidence:

In pregnant patients with cavitary disease, treatment should be extended to 12 months simply because the regimen does not contain pyrazinamide or streptomycin. The summary of evidence of pyrazinamide has been stated earlier.

Streptomycin is the most effective anti-tuberculosis drug available for rapidly metabolizing organisms at the neutral pH of the extracellular environment, such as within pulmonary cavities.

=HIV (+), with risk for HIV, immunocompromised

Consensus Statement:

For non-cavitary and cavitary disease, treatment should consist of rifampicin, isoniazid and ethambutol for twelve (12) months.

Summary of Evidence:

(See above summaries)

Question 14. a3: What are the precautions to take and how should treatment be 'monitored?

A pregnant woman who is taking isoniazid as part of her anti-tuberculosis regimen should be placed on Vitamin B6 at 25mg/day to prevent peripheral neuropathy.

The following should likewise be assessed on a monthly basis:

a. Clinical condition of the patient
b. AFB smears and TB culture
c. Liver enzymes
d. Visual acuity and color vision while on ethambutol (45,48,52)

Question 14. a4: Should pregnant women suspected to have TB infection receive chemoprophylaxis?

Consensus Statement:

Pregnant women who are <35 years of age and are TB asymptomatic with (+) PPD and normal chest radiographs (45,46,53,56) are candidates for chemoprophylaxis. However, in general therapy should be delayed 3-6 months after delivery except in the following situations:

a. (+) PPD (>15mm) with no previous treatment
b. (+) PPD (>10mm) from high prevalence areas or workplace
c. (+) PPD (>10mm) with CXR suggestive of inactive TB disease
d. (+) PPD (> 5mm) in an immunocompromised or HIV (+) patient
e. recent converters (within 2 years)
f. close contacts persons with active TB disease

Women greater than 35 years of age with a PPD <15 mm induration should not receive chemoprophylaxis during pregnancy or the immediate postpartum period unless they are immunocompromised or have established close contacts with persons having active TB disease

Summary of Evidence:

The recommendation that preventive therapy, except in special situations, must be delayed until after delivery is based on the observation that pregnancy does not seem to increase the risk of developing active tuberculosis (45,55). Moreover, the risk of isoniazid-induced hepatitis is higher among pregnant women (20 of 1000 cases) with deaths varying form 0.001% to 4.6% (53,55,56,64,65). A 2.5 fold increase in the risk of isoniazid associated hepatitis was also noted among pregnant and postpartum Hispanic women.

Situations wherein therapy cannot be delayed include those with HIV and other immunocompromised states. The risk of tuberculin-positive person with HIV infection may be as high as 8% per year (58,62). Though not well quantified, persons with other medical conditions that increase the risk of tuberculosis include those with adrenocorticosteroid, those on immunosuppresive therapy, those with hematological and reticuloendothelial disease, injection drug users known to be HIV sero-negative, end stage renal disease and clinical situations associated with substantial rapid weight loss or chronic undernutrition (45).

The risk of developing tuberculosis in close contacts of persons with newly diagnosed infectious tuberculosis is high, 2-4% for the first year, with persons who have a (+) PPD having the greater risk. Furthermore, persons who do not develop disease in the period immediately following infection are at some risk for the remainder of their lives.
Age is considered a consistent risk factor for the development of isoniazid induced hepatotoxicity. Relative risk of hepatitis is 5.2/1000 in patients taking INH therapy for one year; the risk was 2.8/1000 in those patients <35 years old, and 7.7/1000 in those more than 35 years old (15,27). Black et al. noted the risk of isoniazid-induced hepatitis to be lowest in patients younger than 20 years and the greatest among patient's 50-64 years old (15,28). Van den Brande et al. Found a greater incidence of transaminase elevation among patients > 60 years of age as compared to the young (38% vs 18%). A transaminase index (the ratio of the highest transaminase value over the baseline value) of at least 5 was found in 22% of elderly compared with 8% of the young (48,66).

Question 14. a5: What preventive therapy or chemoprophylaxis should be given to those pregnant women?

Consensus Statement:

Preventive therapy or chemoprophylaxis consists of a single daily close of isoniazid (INH) at 5mg kg BW (usually 300 mg) with 50 mg of pyridoxine daily for 6-12 months (average of 9 months) (45,46,53,55,56).

In situations where primary resistance to isoniazid is high, ethambutol can be added to the regimen (44,45).

Summary of Evidence:

Preventive therapy presumably acts by diminishing or eradicating the bacterial population in "healed" or radiographically invisible lesions. Follow-up studies have demonstrated that the beneficial effect of 12 months of isoniazid preventive therapy given to persons with a positive tuberculin skin test reaction persists for as long 20 years (45,63).

Question 14. a6: How safe is breast-feeding while taking anti-TB drugs?

It is quite safe. In fact, most authorities believe that it is unnecessary to substitute formula feeding for breast milk in the light of the absence of reports of adverse effects among infants of nursing mothers and the relatively small doses that infants receive (52,53,56,69). However, if both mother and infant are taking INH, the drug may reach supra-therapeutic doses in the nursing infant. In this circumstance, bottle-feeding is recommended. Supplemental pyridoxine should given to an infant who is taking INH or whose mother (who is breast feeding) is taking INH. Pyridoxine deficiency may cause seizures in the newborn (55,56,69).

b. Patients with liver disease or past history of liver disease

Protocol applies to a patient with liver disease and who presents with signs and symptoms highly suggestive of PTB

Question 14. b1: What treatment regimen should be initiated?

i. Patients with hepatitis virus carriage or a past history of acute hepatitis or excessive alcohol consumption without clinical evidence of chronic liver disease
These patients can receive the usual short course chemotherapy regimen (70).

ii. Patients with established chronic liver disease
Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of 8 months (2SHRE/6HR).
An alternative regimen is streptomycin plus isoniazid plus ethambutol in the initial phase followed by isoniazid and ethambutol in the continuation phase, with a total treatment duration of 12 months (2SHE/10HE).

iii. Patients with hepatic failure
It is recommended that streptomycin and ethambutol be given. If a third drug is needed, isoniazid or rifampicin can be given cautiously in lowered doses.

iv. Patients with acute hepatitis unrelated to TB or anti-TB treatment
In this case, clinical judgement is necessary. In some cases it is possible to defer TB treatment until the acute hepatitis has resolved. In other cases, when it is necessary to treat TB during acute hepatitis, the combination of streptomycin and ethambutol up to a maximum duration of 3 months is the safest option until the hepatitis has resolved. The patient can then receive a continuation phase of 6 months isoniazid and rifampicin (3SE/6HR).

Precautions and monitoring

Since liver injury is the major toxic effect of pyrazinamide, especially in higher doses, great caution should be observed in patients with pre-existing hepatic abnormalities (71), and should not be given in patients with chronic liver disease.

Liver function tests should be monitored closely in patients being given hepatotoxic drugs. Treatment regimens should be re-evaluated if there is:

a. an increase in liver enzymes by 5x the normal value
b. further deterioration in liver function in patients with hepatic failure (72).

c. Patients with renal insufficiency/renal failure

Protocol applies to patients with renal failure and who presents with signs and symptoms highly suggestive of TB.

Question 14. c1: What treatment regimen should be initiated?

Consensus Statement:

Isoniazid, rifampicin and pyrazinamide, which are eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds, can be given in normal dosages in patients with renal failure (70,72).

The safest regimen to be administered in patients with renal failure is 2HRZ/6HR.

Precautions and monitoring:

Drugs that are nephrotoxic or are cleared by the kidneys should be avoided, i.e. streptomycin, ethambutol, kanamycin, capreomycin, cycloserine and thiocetazone. If drug resistance or toxicity requires the use of any of these drugs, they should be given in normal dose size but a longer than normal intervals.

If drug resistance or toxicity requires the use of any of these drugs, they should be given in normal dose size but a longer than normal intervals.

Where facilities are available to monitor renal function closely, it may be possible to give streptomycin and ethambutol in reduced doses

In severe renal failure, patients should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy.

Summary of Evidence:

Little data are available regarding the use of isoniazid in chronic renal failure or in patients undergoing dialysis. A trend towards prolonged T ½ attributed to acetylation phenotype rather than to the degree of renal function impairment found in several studies (73,74) was not proven in some (75). Isoniazid is dialyzable, with reported dialysance ranging from 24 to 49 ml/min (76); 73% of the total isoniazid dose was reported to be removed by a 5-hour hemodialysis (74). Andrew et al recommended that patients receiving long-term hemodialysis be treated with INH 300 mg daily, with the dose administered after dialysis days (77). They also recommended that liver function tests and neurologic examination be performed at regular intervals to screen for drug toxicity.

Ethambutol is largely dependent on renal function for excretion with 54 to 60% recovered in the urine primarily unchanged within 24 hours after administration of a single dose (78). The renal clearance of the drug is significantly in excess of the GFR, and dosage modification is necessary when renal function is impaired (79,80). In patients with end stage renal disease, the component of hepatic metabolism of ethambutol may be significant. Ethambutol is removed by both hemodialysis and peritoneal dialysis. Dosage recommendations in patients undergoing dialysis are varied: 5 mg/kg/day, 8 to 10 mg/kg /day to 18-23 mg/kg/day (9).

The metabolism and excretion of rifampicin are not dependent on renal function, thus, it can readily be used in patients with tuberculosis undergoing dialysis.

Few data are available concerning the use of PZA in renal insufficiency or the effects of dialysis on drug removal. Renal excretion may be significant. The dose should be modified from the usual 20 to 35 mg/kg/day to 12 to 20 mg/kg/day. Routine monitoring of hepatic function is necessary in patients with normal renal function and especially in those with renal failure.

d. TB in elderly patients

Protocol applies to patients over the age of 65 and who presents with signs and symptoms suggestive of TB.

Question 14. d1: What treatment regimen should be initiated?

Consensus Statement:

The combination of rifampicin and isoniazid in standard doses for 9 months is generally well-tolerated and quite effective (9RH). Few elderly persons harbor tubercle bacilli that are resistant to any of the drugs in use today because most of the disease is the result of recrudescence

of an infection acquired many decades before. For this reason it is generally not necessary to add a third drug, as one would do when treating a younger person in a large city where drug resistance is common (81).

e. Tuberculosis in HIV Seropositive Patients

Question 14. e1: What treatment regimen is recommended for HIV seropositive patients diagnosed to have PTB with available susceptibility tests ?

Consensus Statement:

Patients who are HIV seropositive and who have sputum (+) AFB smears should be started on the following medications (pending sensitivity results):

INTENSIVE PHASE (1st 2 months)

Isoniazid	**300mg/ day (add pyridoxine 25 mg/day)**
Rifampicin	**450 mg/day for patients <50kg**
	600 mg/day for patients >50kg
Ethambutol	**25 mg/day - may be discontinued after 2 months for as long as sensitivity studies show that the patient is susceptible to INH, rifampicin and PZA**
PZA	**20-30 mg/kg/day**

MAINTENANCE PHASE (4-7 months)

Isoniazid and rifampicin at above dosages

** Drug regimen may be altered depending on the culture and sensitivity results of the patient.
** Directly observed therapy should be used whenever possible, with an initially daily treatment regimen eventually being switched to an intermittent twice or thrice weekly regimen as soon as possible.
** Fixed drug combinations should be used whenever possible so as to avoid the use of monotherapy.

Summary of Evidence:

Chemotherapy of tuberculosis using the currently available agents is highly effective, even in HIV seropositive patients. The presence of seropositivity should not make the physician alter the drug regimen being used in the treatment of pulmonary tuberculosis, presuming that there is no reason to suspect drug resistance (82).

Quadruple anti-TB therapy using the usual drugs (isoniazid, rifampicin, pyrazinamide, ethambutol or streptomycin) is still recommended for the 1st 2 months of treatment, to be followed by INH and rifampicin for 4 to 7 months maintenance treatment (83,84,85,86).

As much as possible, rifampicin-based chemotherapy should be given to decrease both the relapse rates and the treatment failure rates. It has been documented in several studies that the absence of rifampicin from the treatment regimen leads to higher relapse and even treatment failure rates.

Question 14. e2: How long should treatment be given?

A six-month course of quadruple (in the intensive phase) anti-TB medications may be given if the following conditions are met:

a. **If the sputum cultures reveal complete sensitivity to all 4 drugs used in the intensive phase**
b. **If there is evident clinical response**
c. **If there is sputum conversion after 2 months of treatment**
d. **If there is improvement in the chest X-ray findings**

An 18-month course is recommended if both INH and rifampicin cannot be used in the regimen (83). Most studies, however, recommend a 9-month minimum treatment period or at least

6 months treatment after sputum conversion is documented. This would be especially true for those instances wherein there is resistance to one or more of the primary drugs being used.

Summary of Evidence:

Again, there has already been much documentation of the success in curing TB in HIV positive patients with the standard short course chemotherapy using 4 drugs in the initial phase and 2 drugs in the continuation phase. However, the length of time that the treatment will be given may still vary, depending on the drug regimen being used as well as the incidence of resistance to drugs, particularly INH and rifampicin (87, 88).

Question 14. e3: What regimen is recommended for HIV seropositive patients diagnosed to have PTB without available susceptibility test?

When susceptibility tests are not available, and the individual has no cavitary disease. INH, rifampicin, ethambutol and pyrazinamide should be continued for 9 months, under a strict DOT program, and for at least 6 months after culture conversion, whichever is longer. Fixed dose combinations are again recommended. If the patient has cavitary TB on chest x-ray, treatment with 4 drugs is recommended for 12 month (89, 91).

Question 14. e4: Should the serological or immune status alter the course of therapy for tuberculosis in HIV patients?

Similar cure rates were found between HIV seropositive patients as well as HIV seronegative patients irrespective of serological or immune status. Although a lower CD4 count in the HIV patients did result in greater mortality, the cure rates did not differ significantly between the HIV seropositive and HIV seronegative patients (92, 93).

Question 14. e5: How do we treat HIV seropositive patients suspected to have MDR- TB?

General Principles:

a. Use at least 3 drugs to which the organism is susceptible
b. Avoid drugs previously administered to the patient
c. Tailor the regimen to avoid additive toxicities
d. Monitor closely for compliance and response to treatment

Summary of Evidence:

All HIV seropositive patients should have sensitivity studies done on their sputum specimens. Although the incidence of resistance does not differ significantly between HIV seropositive and seronegative patients, the sensitivity studies are still a vital part of the treatment plan of the patient failure or success (94-96).

Maneuvers that may increase compliance should also be done. Intermittent therapy has been successful in some studies. Directly observed therapy likewise plays a big role in the management not just of MDR-TB in HIV (+) patients but of PTB per se (97).

f. Treatment for Extrapulmonary Tuberculosis

Question 14. f1: What is the appropriate treatment for patients with extrapulmonary tuberculosis?

Consensus Statement:

Extrapulmonary tuberculosis should be managed according to the drug regimen outlined for pulmonary tuberculosis. (Recommendation Grade: C)

Intensive phase (first 2 months)		
Isoniazid (H)	Adult (any weight)	300 mg
	Children	5 mg/ kg
Rifampicin Adult	< 50 kg	450mg
	≥ 50 kg	600mg
	Children	10mg/kg
Pyrazinamide (Z)	Adult <50 kg	1.5 g
	50-74kg	2.0 g
	> 75 kg	2.5 g
	Children	35mg/kg
* Streptomycin (S) (by intramuscular injection once daily)		
	Adult below ages 40 yr	
	<50 kg	0.75 g
	>50 kg	1.0 g
	Age 40-60 yr	0.75 g
	Age >60 yr	0.5 g
	Children	10mg/kg (but not over 0.75g)
or		
* Ethambutol (E) (by mouth in a single dose day)		
	Adults or children	25 mg/kg

Maintenance phase (next 4-7 months)
Isoniazid and rifampicin given in same dosages as mentioned.
* Should be included in the initial regimen until the results of drug susceptibility studies are available

Summary of Evidence:

As a general rule, regimens that are adequate for the treatment of pulmonary tuberculosis is adults and children will also be effective in extrapulmonary tuberculosis since the mycobacterial burden is usually considerably smaller in the latter. The lesions may be numerous but individual lesions contain small population of organism easily reached by the drugs. (Level of Evidence: 3)

Children who have miliary tuberculosis, bone/joint tuberculosis or tuberculosis meningitis should receive a minimum of 12 months therapy (2,8,9). (Level of Evidence: 4)

Question 14. f2: Is it necessary to give corticosteroid (prednisone) to those who have extrapulmonary tuberculosis?

Consensus Statement:

Prednisone may be of benefit among patients who have miliary tuberculosis, tuberculous meningitis or tuberculous pericarditis. An initial regimen of 60 to 80 mg of prednisone per day (in children the dose is 13 mg/kg) has been used, with tapering over 8 to 11 weeks. Steroid metabolism is increased when rifampicin is co-administered, and the dosage may need to be increased. (Recommendation Grade: D)

Summary of Evidence:

Fulminant miliary TB may be associated with the adult respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC). In such cases, corticosteroid treatment is indicated. Many also advise the use of corticosteroids in severely ill persons with delayed initial response to chemotherapy. But it is dangerous to use prednisone unless you are sure of the diagnosis (in case you are suppressing the patient's defenses against some undiagnosed infection you are not treating). (Level of Evidence: 4)

In cases of tuberculous meningitis, many authorities advocate the use of corticosteroid in patients who are initially confused, stuporous, or have focal neurologic deficits, dense paraplegia or hemiplegia, opening pressure greater than 300 mmHg or CNS block. Cerebral edema evidenced by CT scan is considered an indication for corticosteroid therapy. Corticosteroids have been shown to help manage cerebral edema, are associated with fewer long-term complications, and are used almost routinely in childhood meningitis and, by some, in adult meningitis.

Data for the role of corticosteroids in tuberculosis pericarditis are less well defined but indicate that these agents may be beneficial in the acute phases of the disease. Corticosteriods appear to enhance resorption of the pericardial fluid and lessen (but not eliminate) the risk of pericardial related mortality in acute disease. They also do not affect long-term constrictive complication. (Level of Evidence: 4)

Question 14. f3: Is there a role for surgery in treatment of extrapulmonary tuberculosis?

Tuberculous meningitis

Neurosurgical intervention is often requested to relieve the hydrocephalus that complicates most cases of tuberculous meningitis. Neurologic improvement following ventricular decompression may be dramatic, particularly in children. However, the surgery is not without risks, such as shunt malfunction, bacterial superinfection, and the more theoretical concern of disseminating mycobacteria elsewhere in the body.

Tuberculous lymphadenitis

Adjuvant surgical intervention should be reserved for lymph nodes that do not resolve with chemotherapy, for symptomatic relief (rare in adults), for drainage of persistent fluctuant lesions, or for diagnosis if the FNA is non-diagnostic or not available. Aspiration of abscesses should be avoided if possible because sinuses may develop in the needle track. It is better to make a small surgical incision and let out the pus.

Renal tuberculosis

Surgery is indicated only for intractable pain, persistence of non-tuberculous infection from obstruction or serious, persisting hematuria.

Tuberculosis of the Female Genitourinary Tract

The role of surgical excision of the uterus, tubes and ovaries is indicated for chronic pelvic pain, recurrent disease after medical management, pelvic TB in postmenopausal woman and persistent fistulous tracts.

Tuberculosis of the epididymis and testes

Epididymectomy or orchiectomy is indicated only if there is lack of clinical response.

Pericardial tuberculosis

Invasive or surgical procedures are generally recommended for three groups of patients (1) patient with cardiac tamponade; (2) patients on medical therapy with recurrent or progressive pericardial effusion or pericardial thickening; and (3) patients with constrictive pericarditis. Early surgical intervention has also been advocated when close follow-up of patients is difficult or impossible. Interventions for cardiac tamponade include pericardiocentesis, pericardiostomy and limited or extensive pericardiectomy.

Osteoarticular tuberculosis

In the early stages of disease of the knee, before there is substantial loss of bone or cartilage, operative intervention is necessary only to drain large abscesses and to obtain synovial tissue for biopsy. External immobilization is used only to correct fixed deformities since early mobility is necessary after adequate debridement. In later stages of the disease, arthrodesis and joint replacement have been advocated when there is loss of the joint space and osseous architecture with radical debridement of all avascular tissue and the juxtaposition of viable cancellous bone at the time of the arthrodesis. Treatment of active tuberculosis of the hip, in which the joint space has been destroyed, consists of a radical decompression, drainage of the abscess and removal of all avascular tissue. The second stage of treatment after a high dose of multiple anti-tuberculosis chemotherapy (with clinical and hematological evidence that the disease has been eradicated) involves either an arthrodesis of the hip in a young patient or a hip arthroplasty without cement in an older patient.

Spinal tuberculosis (Pott's disease)

Criteria for surgical management of Pott's disease: neurologic deficit (includes Acute neurologic deterioration, paraparesis and paraplegia); spinal instability/deformity (more than 50% vertebral body collapse or destruction; spinal deformity of more than 15 degrees); unresponsiveness to medical therapy (development or progression of neurologic deficits, spinal deformity intractable pain and progression of disease), and noncompliance with medication.

g. Adverse effects of common anti-tuberculosis drugs and their corresponding therapy

Isoniazid (INH)-associated hepatitis:

Hepatic toxicity/hepatitis is the most well known and studied adverse effect associated with INH administration (111,124-126). It occurs mainly through conversion of the monoacety hydrazine metabolite via cytochrome p450 induction (111,126). The incidence is equal among slow (Americans) and fast acetylators (Chinese and Japanese) (111,124-126).

Question 14. g1: What factors enhance toxicity?

Age, female sex, alcoholism, concurrent use of rifampicin and other hepatotoxic drugs, and endemicity for viral hepatitis.

Summary of Evidence:

The incidence of INH-associated hepatitis is increased in older patients (>35 years old) (11,112,120-123,131). Women particularly during pregnancy and the immediate postpartum period are also prone to develop toxicity (111-113,123,131-133). Snider and Caras noted that of the 161 patients who died from INH-associated hepatitis, 69% were females (113). Moulding and colleagues likewise found an increased rate of hepatitis among women of childbearing age, with 16 of 20 deaths occurring in women (112). In a study made to determine the risk assessment between African-American men and women in developing INH-associated hepatitis, the risk was noted to be 1.6/1000 among men and 11.1/1000 among women (123).

Ethanol increases metabolism of isoniazid thereby enhancing production of toxic metabolites.

Rifampicin, when administered together with INH, is hypothesized to induce cytochrome p450 oxidation causing increased production of the toxic metabolites from monoacetyl hydrazine (111,130). It was also demonstrated that rifampicin increases the metabolism of INH alone and 1.6% for those receiving INH together with other anti-tuberculosis drugs but for rifampicin. When taken together with rifampicin, the incidence rises to 2.55% (114).

In developing countries, the incidence of INH-associated hepatitis was noted to be increased in areas highly endemic for viral hepatitis (115,128).

Other toxic manifestations of INH include peripheral neuropathy and hypersensitivity reaction consisting of rash, urticaria, fever, leukocytosis and eosinophilia. Rarely, it can induce seizures (except during an acute overdose), optic neuritis,

arthralgias, vasculitis, shoulder-hand syndrome, and agranulocytosis. Lately, it was hypothesized to cause alopecia in five Canadian-born white people with pulmonary tuberculosis (129).

TREATMENT

1. drug withdrawal particularly when liver enzymes become elevated to >3x the normal (113,116); 2. pyridoxine (111) and 3. for acute overdose, stabilization of airways and hemodynamics, gastric lavage activated charcoal.

Rifampicin-associated hepatotoxicity

The incidence of clinical hepatitis in patients taking rifampicin is about 1.1% (113). Hepatotoxicity occurs during the first 8 weeks of therapy, and the incidence increases with age, in patients with previous liver disease, in those taking INH, and in disease conditions that slow down inactivation of the drug.

Rifampicin mainly produces an elevation of the alkaline phosphatase and bilirubin (cholestatic pattern) and induces only minimal elevations in serum transaminases. The drug gives orange-red color to body secretions, which, although concerning, is benign in nature and does not require withdrawal of the drug [1,6]. Other adverse reactions include rash, fever, myalgia, arthralgia, anemia, thrombocytopenia, DIC, vomiting, diarrhea, pseudomembranous colitis, hepato-renal syndrome and acute renal failure (111).

TREATMENT

Same as in INH therapy but for the use of pyridoxine

Pyrazinamide-associated hepatotoxicity

Pyrazinamide likewise induces hepatotoxicity. It is reported to occur in up to 10% of patients and contributes an additional 1-5% chance of developing hepatotoxicity in those receiving INH, rifampicin and pyrazinamide combined. The development of hepatitis is dose-related and is associated with a high degree of mortality.

Other toxic effects include fever; arthralgia (gout-like) due to interference with urate excretion, nausea, vomiting and myoglobinuric renal failure.

TREATMENT

Drug withdrawal, supportive therapy and activated charcoal for acute overdose.

Ethambutol-associated optic neuritis

Ethambutol produces optic neuritis, which is most often retrobulbar. Its incidence varies from 6% at a dose of 25 mg/kg or less to a high of 15% at a dose of 35 mg/kg BW. It is often mild and reversible but occasionally can become severe and irreversible. Its hallmark signs are decreased visual acuity, loss green color perception, central scotomas and peripheral field defect (111,132).

Other reactions associated with therapeutic use of ethambutol include anaphylaxis, peripheral neuritis, thrombocytopenia and gouty arthritis.

An acute overdose can result in abdominal pain, mental confusion, fever and visual hallucinations.

TREATMENT

Drug withdrawal, supportive therapy and activated charcoal for acute overdose [1].

Streptomycin-associated ototoxicity

Ototoxicity is the most common adverse effect of streptomycin (111,116,119,131,133). It is related to the dose and duration of therapy. Renal toxicity, though less common, also occurs.

Other less common side effects include neuromuscular blockade and hypersensitivity reactions like fever, rash, urticaria, anaphylaxis and cytopenia. Quinolones, ciproflolaxin and ofloxacin are the mainly utilized anti-tuberculosis drugs. The commonly known adverse effects are gastrointestinal upset, dizziness, photosensitivity and skin rash.

Monitoring for Adverse Reactions

1. Evaluate patients for adverse reactions at least monthly
2. Perform baseline tests of one or more of the following (according to risk involved):
   - Hepatic enzymes
   - Bilirubin
   - BUN and/or creatinine
   - CBC
   - Platelet count (qualitative or quantitative)
   - BUA (if pyrazinamide is used)
   - Hearing function (if ethambutol is used)
3. Instruct patients taking INH, rifampicin or pyrazinamide to report immediately any symptoms any symptoms suggesting hepatitis such as:
   - Loss of appetite
   - Malaise
   - Unexplained fever for 3 or more days
   - Nausea
   - Vomiting
   - Abdominal tenderness
   - Persistently dark urine
   - Yellowish discoloration of the skin (116)

Symptom-based approach to adverse effects of anti-TB drugs

Side-effects	Drug(s)probably responsible	Management
Minor		
Anorexia, nausea, abdominal pain	Rifampicin	Give drugs last thing at night
Joint pains	Pyrazinamide	Aspirin/NSAIDS
Burning sensation	Isoniazid	Pyridoxine 100 mg daily
Orange-red urine	Rifampicin	Reassurance
Deafness (no gross abnormality on otoscopy)	Streptomycin	Stop Streptomycin, use Ethambutol
Dizziness (vertigo and nystagmus)	Streptomycin	Stop Streptomycin, use Ethambutol
Jaundice (other causes excluded)	Most anti-TB drugs (especially isoniazid, rifampicin, and pyrazinamide)	Stop anti-TB drugs
Vomiting and Confusion	Most anti-TB drugs	Stop anti-TB drugs(Suspect drug-Induced acute liver Failure) Urgent liver function Test and prothrombin time
Visual impairment (other causes excluded)	Ethambutol	Stop Ethambutol
Shock, purpura acute renal failure	Rifampicin	Stop Rifampicin

Re-introduction of Anti-TB Drugs Following Drug Reaction

Drug	Likelihood of Causing a Reaction	Challenge Doses		
		Day1	Day 2	Day 3
Isoniazid	least likely	50 mg	300mg	300mg
Rifampicin		75 mg	300mg	full dose
Pyrazinamide		250mg	1000mg	full dose
Ethambutol		100mg	500mg	full dose
Streptomycin	most likely	125mg	500mg	full dose

If the initial reaction is severe, smaller initial challenge should be given (approximately 1/10 of the doses given for Day 1).

The idea of drug challenge is to identify the drug responsible for the reaction. Drug challenge starts with the anti-TB drug least likely to be responsible for the reaction (i.e., isoniazid). The idea of starting with a small challenge dose is that if a reaction occurs to a small challenge dose, it will not be such a bad reaction as to a full dose. The dose is gradually increased over 3 days. The procedure is repeated, adding in one drug at a time. A reaction after adding a particular drug identifies the drug as the one responsible for the reaction. There is no evidence that this challenge process gives rise to drug resistance (117).

In the event that adverse reaction to a drug is confirmed, the offending drug must be replaced with another drug. It may be necessary to extend the treatment regimen. The start of the resumed regimen is then considered as a new start of treatment. This prolongs the total time of anti-tuberculosis therapy, but it reduces the risk of recurrence (117,118)

Occasionally, patients develop hypersensitivity to the two most potent anti-TB drugs, isoniazid and rifampicin. Since these drugs from the cornerstone of short-course chemotherapy, it may be necessary to refer these patients to allergologists for desensitization process (117,118). If and when this falls, one may opt to use second-line drugs in addition bearing in mind the risk of greater side-effects, treatment failures and relapses.

Question 15: What is the recommended secondary chemoprophylaxis regimen in the Philippines?

Consensus Statement:

The recommended secondary chemoprophylactic regimen is isoniazid 300 mg daily in a single dose (10 mg/kg daily for children) for 6 to 12 months. Treatment for 12 months is advised for persons with HIV infection or other major forms of immunosuppression as well as for those with stable abnormal appearing chest radiographs suggestive of past tuberculosis. (Recommendation Grade: A)

For persons who are at high risk for tuberculosis whose adherence to therapy is in doubt, supervised preventive therapy is indicated when possible, and if resources to provide daily supervised therapy are not adequate, an alternative to daily treatment is isoniazid given twice weekly at a dose at 15 mg/kg.

In situations where infection with isoniazid-resistant strain is suspected, prophylaxis should be provided with rifampicin if the organism is sensitive to it. In those situations where the infecting strain is resistant to isoniazid and rifampicin and perhaps to other anti-tuberculous drugs, there is no agreement regarding the best course of action to be taken and there are no data from controlled trials. If the organism is sensitive to ethambutol or pyrazinamide, these drugs can be used. If the subject is healthy and not immunocompromised, defer giving any preventive treatment, and choose instead to provide close clinical observation.

Summary of Evidence:

Many excellent trials involving more than 125,000 subjects have been done to evaluate the effectiveness of secondary chemoprophylaxis. The results indicate that isoniazid prophylaxis given to tuberculin reactors can reduce the risk of active tuberculosis by as much as 90% in those who complete a full course of treatment, and in children, the reduction in risk approaches 100% (136,137,138) (Level 1 Evidence). Protection is most marked during the medication period. However, it persists after treatment; it persisted throughout the observation period of the various trials and among Alaskan villagers, protection persisted for as long as 19 years (139,140).

Isoniazid also can be effective in preventing reactivation of previously untreated tuberculous disease; a number of controlled trials involving more than 35,000 subjects have been reported (141,142,143). Among those for whom the medication was given for at least 1 year, the reduction in tuberculosis due to isoniazid was 66% and the reduced risk persisted throughout the observation period. Giving isoniazid to persons with healed tuberculosis who previously received adequate chemotherapy provides no additional protection. Isoniazid given to symptom-free persons who are seropositive for HIV reduces the risk for tuberculosis and increases the time for development of symptomatic HIV disease and the acquired immunodefiency syndrome (AIDS) (142,144).

Fear that isoniazid given alone for prophylaxis might allow the emergence of tubercle bacilli resistant to isoniazid has not been substantiated; indeed those persons for whom chemoprophylaxis fails and in whom culture-positive tuberculosis subsequently develops have been found to harbor isoniazid-sensitive organisms with same frequency as those persons who have never received isoniazid (142). This observation is in keeping with the fact that persons selected for preventive treatment are almost certain to harbor relatively few viable tubercle bacilli (<100,000 organisms) and this means that the possible presence of an isoniazid-resistant mutant is very remote (145).

Isoniazid preventive therapy carries with it the risk of side effects, some of which are very serious. The most important toxic effects are on the liver. The drug is well tolerated by most persons, particularly children, but 2 or 3 percent of adults over age 50 develop chemical evidence of liver injury and this can lead to chemical hepatitis if the drug is not stopped when these tests indicate the condition. A review of available case reports of fatal hepatitis possibly associated with isoniazid indicates that careful attention to signs and symptoms of developing isoniazid toxicity has decreased the frequency of this problem since the early 1970's (146). Factors that can increase the risk of isoniazid hepatitis are alcohol or drug abuse, previous hepatitis, simultaneous use of hepatotoxic drugs, and the postpartum state. These risks for toxicity together with some deaths have generated dispute among experts over balancing the risks and benefits in low-risk populations that has not been resolved.

Question 16: Who should get secondary chemoprophylaxis?

Consensus Statement:

There are four situations in which secondary chemoprophylaxis might be considered in the Philippines.

1. **Childhood contacts of infectious cases (Recommendation Grade: A)**
2. **Patients who have positive skin test and have the following medical risk factors for tuberculosis: diabetes mellitus, on immunosuppresive treatment, hemodialysis and with fibrotic lesion (Recommendation Grade: A) (For preventive treatment in pregnancy, please see section on tuberculosis and pregnancy).**
3. **Patients who are being routinely screened for tuberculosis by tuberculin skin testing and skin test converts from negative to positive (e.g. hospital worker).**
4. **Patients with HIV infection who are also at risk for tuberculosis.**

Summary of Evidence:

Household contacts of infectious sputum (smear positive) cases are likely to have been recently infected and have a risk of developing tuberculosis of up 5% during the two years following infection. The risk of disease, and especially severe disease, among very young children is specially great. Therefore, tuberculin positive contracts of infectious cases are candidates for preventive therapy. In addition, young tuberculin-negative children who have been in contact with an infectious case within the past three months are candidates for preventive therapy until a repeat tuberculin skin test is done three months after the last contact with the infectious source. If the repeat skin test is positive, therapy should be continued. If the reaction remains negative, therapy need not be continued unless there is continuing exposure to an infectious source-case. If skin test is not available in the TB program, World Health Organization recommends isoniazid preventive therapy for all childhood contacts of infectious cases.

Patients who have positive skin test and have medical risk factors for tuberculosis (e.g. diabetes mellitus, immunosuppresive treatment, hemodialysis and fibrotic lesions) should be given preventive therapy. The medical conditions that have been reported to increase the risk of active tuberculosis in infected persons are shown in Table 7:

TABLE 7. Risk factors for tuberculosis following infection with M. tuberculosis (147,148,149).

Risk Factors	Absolute/1000 person years	Relative risk
Infection > 7 years past	0.7	
Infection < 1 year past	10.4	
Fibrotic lesion	2.0-13.6	
Immunosuppresive treatment		11.9
Hemodialysis		10-15
Diabetes mellitus		20.-3.6

Other medical risk factors for tuberculosis that have been quantified include prolonged therapy with adrenocorticosteriods (e.g. the equivalent of at least 15 mg of prednisone daily over four weeks), some hematological and reticuloendothelial malignancies, which are associated with suppressed cellular immunity (e.g. leukemia and Hodgkin's disease), and other conditions associated with substantial rapid weight loss or chronic undernutrition (e.g. chronic peptic ulcer disease, chronic malabsorption syndromes, chronic alcoholism).

Because voluntary HIV testing is not readily available in many developing countries, opportunities to implement preventive therapy for this indication are limited. However, tuberculosis screening and the provision of preventive therapy should be considered for any site where voluntary HIV testing is available. Feasibility studies are needed to assess the cost, demand for the services, sustainability and potential impact.

Question 17. Should secondary chemoprophylaxis be adopted by the National TB Control Program in the Philippines?

Consensus Statement:

National TB Programs lacking resources to provide short-course chemotherapy cannot consider a general preventive therapy program. However, when resources are available for case finding and treatment, preventive therapy of high-risk persons, especially children living in households with infectious cases and HIV-infected persons, should be considered.

Summary of Evidence:

The main arguments against the use of chemoprophylaxis in the tuberculosis program of a resource-limited developing country are the large cost of preventive therapy and the concern about promoting drug resistance. However, data on drug resistance from the US Public Health Service studies indicate that among cases of tuberculosis in the contact studies, isoniazid resistance was no more common among placebo recipients (141).

Another potential limitation to use of preventive therapy is that it would not prevent disease associated with re-infection after the completion of therapy. This concern is of particular relevance in developing countries with high incidence rates infection like the Philippines (150). This situation needs to be further explored and evaluated.

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TB CONTROL-STRATEGIES AND PREVENTION IN THE PHILIPPINES

Questions Addressed:

1. What is the state of tuberculosis in the Philippines?
2. What are the reasons why tuberculosis remains uncontrolled in the Philippines?
3. Overall, what can be done to improve TB control in the Philippines?
4. What can be done to improve TB disease prevention efforts?

Introduction

The statements and recommendations in this section were mainly based on the following : (a) TB Control Service (DOH) data and Philippines Health Statistics; (b) National Prevalence Surveys in 1997 and 1981-83; (c) World Health Organization data; (d) focused group discussions among health workers; (e) HPSR recommendations on tuberculosis; (f) data derived from MEDLINE search and (g) local and foreign experts opinion.

Question 1: What is the state of tuberculosis control in the Philippines?

Consensus Statement:

Tuberculosis remains a major health problem in the Philippines. Seventy five Filipinos die of tuberculosis each day; approximately 200,000 to 600,000 Filipinos are spreading the disease and infecting 10 other individuals annually; approximately 15 million Filipinos are infected with tuberculosis; and there has been little change in the state of the TB problem for the past 14 years.

Summary of Evidence/Discussion:

Philippine Health Statistics

Philippines Health Statistics for 1994 (1), which is based on routine reporting systems and thus may have problems with underreporting and non-uniformity in diagnostic criteria, places TB among the top 5 causes of mortality (with a rate of 39.8/100,000). It is estimated that 75 Filipinos die of tuberculosis each day. Compared to the summary statistics in the 5 years prior to 1994, the rate and ranking have not significantly changed. (It is important to note these figures do not reflect the TB patients to the private sector).

National Prevalence Surveys

The 1997 National Prevalence Survey (2), which included 21,960 individuals, has provided representative detailed epidemiologic information on the state of the tuberculosis problem in the country that is not limited by problems of underreporting and lack of standardization. The study showed the following results:

a. The prevalence of culture positive tuberculosis extrapolated to the total population is 8.1/1000 (95% CI, 6.35-9.81) and the prevalence for smear positive tuberculosis is 3.1/1000 (95% CI, 1.24-5.10). These figures imply that in the population of approximately 74 million, *there are approximately 200,000 to 600,000 Filipinos who are harboring the live TB bacilli in their sputum and may each be infecting 10 persons per annum.* The 1981-83 National Prevalence Survey (3) figures were 8.6/1000 for culture positive and 6.6/1000 for smear positive tuberculosis.

b. The overall prevalence of tuberculin sensitive (induration of >8 mm to 2 TU) among unvaccinated individuals was 63% (this roughly reflects a 17% increase from the 1981-83 survey of 54%). Since BCG vaccine does not protect against the natural TB infection (4) and since (+) PPD reaction from previous BCG vaccination wanes in 5-10 years, the 63% positive tuberculin reaction can be applied to the whole adult population. *This translates to 14.8 million or 21.6 infected Filipinos.*

c. The annual risk of infection (ARI), which is a measure of the risk to the population from infectious TB cases in the community and which can be considered the most informative index of the magnitude of the TB problem, is 2.3%. The 1981-83 National Prevalence Survey's figure for ARI was 2.5%. For every 1% ARI, Styblo's group claimed that there should be around 60 smear (+) cases per 100, 000 population (4). *Applying this relationship to our population of 74 million, an ARI of 2.3% translates to about 103,118*

new positive smear cases annually. Using the benchmark of Clancy (5) (Table 1), our 115/100,000 incidence of smear positive cases places the Philippines in the category of high risk for TB.

Economic Burden of TB

At the moment, there is little explicit data on the economic burden of illness attributed to tuberculosis in the country. An International Labor study showed that tuberculosis was ranked number 2 in terms of claims for compensation from the Social Security System. A 1993-95 data from one industrial clinic showed that among 1244 consecutive applicants for local and overseas employment, 37% had chest x-ray findings compatible with TB and 42% did not resolve with antibiotic treatment. Seventy-nine percent were rejected for employment because of definite or suspected TB. In an annual examination for employees, 193 out of 619 (31%) had chest X-ray findings compatible with TB (6).

In the Department of Education and Culture TB Program in 1987-1992, 25.4% of 269,012 elementary and secondary teachers were found to be positive for chest x-ray findings consistent with TB and /or sputum AFB smear. Due to inadequate resources, only 33% were treated with short course chemotherapy (7).

Table 1. Benchmark for tuberculosis (n rates/100, 000/ year)

ARI	Risk for TB
> 1000	Epidemic TB
> 100	High Risk for TB
< 10	Low Risk for TB
< 1	TB programs entering elimination phase
0.1	TB eliminated

A comparison of the results of the National Prevalence Surveys reported in 1981-83 and 1997 is shown in Table 2.

Table 2. Comparison of the results of the 1981-83 and 1997 National Prevalence Surveys on Tuberculosis

Outcome Measures	1997	1981-83
Prevalence of smear positive (per 1000)	3.1	6.6
Prevalence of culture positive (per 1000)	8.1	8.6
Prevalence of radiographic abnormalities suggestive of tuberculosis (ages > 10 years)		
Total	4.2%	4.2%
Minimal	3.49%	2.50%
Moderate or far-advanced	0.71%	1.70%
Cavitated disease	0.26%	0.47%
Proportion of patients with BCG scars	66%	40%
Among those without BCG scars, prevalence of tuberculous infection	63.4%	54.4%
Annual risk of infection	2.3% (high risk)	2.5% (high risk)

MDR-TB

Multi-drug resistance, defined by WHO as resistance to both isoniazid and rifampicin, occurs most frequently in those with previous intake of anti-TB drugs for at least one month. Early studies in the Philippines from tertiary care referral hospitals have reported MDR rates as high as 32% (8). However, community-based surveys have documented an MDR rate of only 6.2% (95% CI, 3.0-9.4) in the sentinel site study in national Capital Region (9), 3.6% in the 1997 National Prevalence Survey and 8.3% in seven sites in the Philippines (10). Nevertheless, to put these figures in perspective one must look at the recently published Global Surveillance for Antituberculosis-Drug Resistance conducted by WHO from 1994-1997 (11). In this worldwide countrywide-based study, some countries reported to have particularly high

prevalence of acquired multi-drug resistance include Argentina with rate of 22.2 (95%CI, 17.6-27.7), the Dominican Republic with 19.7 (95%CI, 13.1 – 28.2) and the Soviet Union with 27.3 (95% CI, 13.9 – 45.8) and Latvia with 54.4 (95% CI, 47.7 – 60.9). The Philippines with a rate ranging from 3.6% to 8.3% can still be considered as a low prevalence area for MDR tuberculosis. However, the hospital data are alarming and unless factors contributing to its occurrence are neutralized soon, the community-based figures may rise in the near future.

WHO Assessment of TB in Philippines

The 1998 World Health Organization Global Tuberculosis Report has cited the Philippines as one of the 22 countries in the world which accounted for 80% of the world's TB cases and , therefore, is also one of the countries that would determine whether the battle against tuberculosis will be lost or won.

Question 2: What are the reasons why tuberculosis remains uncontrolled in The Philippines?

Consensus Statement:

The reasons why tuberculosis remains uncontrolled in the Philippines are: inadequate case finding (both in the private and public sector), poor case holding (due especially to physician's and patients' nonadherence), and deficient TB prevention programs.

Summary of Evidence/Discussion:

Inadequate Case Finding

The 1997 government NTP targets 70% of the expected smear (+) cases annually. In its latest report, the DOH claimed to have achieved 90% of the target. It can be assumed that the remaining cases representing 35% of the total smear (+) cases and the missed 10% of the 70% targeted by the NTP may not be undergoing treatment at all or are seeing the more popular private MDs.

The reasons for poor case-finding include (a) inadequate laboratory facilities and poor quality control leading to low or non-availment of these facilities by patients and health providers; (b) socio-behavioural issues including the TB stigma and poverty; and (c) non-availability of adequate guidelines on the diagnosis/management of TB in children.

(a) Inadequate laboratory facilities and poor quality control

A major reason for the inadequate case finding is the scarcity of sufficiently equipped and properly manned laboratory facility for sputum examination. In the 1998 HPSR study (12), it was concluded that numerous deficiencies exist in AFB smear diagnosis of TB. Foremost are the lack of adequately functioning microscopes (13,14), lack of sufficient quantities of supplies used in sputum collection and smear preparations (15), inadequate training and supervision of microscopists (14,16) and lack of quality control for smear collection and recording of results (17).

Compounding the effects of problems in the laboratory is the inappropriate usage and in many instances actual non-availment of the laboratory facilities for AFB smear examination, a highly specific test for TB, is rarely requested by private MDs. Cost seems to be not the real issue since country-wide free AFB smear is offered through NTP. In many cases though the turn around of results may take 1-2 weeks because each government medical technologist commonly has 2-3 municipality assignment. Nonetheless there is over-reliance on chest radiography which is not a relatively cheap diagnostic test and which, as a single test, cannot determine disease activity. In addition, chest radiography accuracy is dependent on several factors that my not be present at all times under field conditions, namely, the

competence of the technician, the freshness of the developer and the availability of an experienced radiologist.

(b) Socio-behavioural issues

The 1997 National Prevalence Survey of 1, 805 TB symptomatics showed that 49% of them did nothing of their illness. This is similar to the finding in the 1981-83 NPS (35.1% of 1,5,17). Half of the action takers self medicated. Of the remainder who sought medical help, more went to the private MDs rather than to the NTP service. Overall, only a small minority of 6.5% availed of the government health service. The reasons of the non-action takers include ignorance, the TB stigma, inconvenience, inadequacy and unacceptability of the source of relief, and poverty (3,19). Others did not regard their symptoms as serious. For some, it was a matter of mental shortfall or inability to relate ideas, while for others it was their coping mechanism or 'psychological block'. Those patients who perceived themselves to be poor were significantly more likely to delay the first consult (17).

Despite the free medications offered by government health centers, more patients tended to seek private medical consultation. The reason is not dissatisfaction with the health center personnel but with the unavailability of anti-TB drugs. A study in Camiguin showed that patients who consulted the government health centers were satisfied with the services offered by the center in terms of accessibility, human aspect area and information delivery (18). This finding is confirmed by the study in Malabon where respondents assessed competence and friendliness of the health center staff satisfactory (17). However, there were major problems in the availability of drugs in the center. A study by Sarmiento showed that as much as 27.3% of patients were asked to wait for drug supply while 63% were placed under standard regimen (15). Patients who failed to get the free medications became bitter, resentful and cynical about public health services. In other settings, patients who consulted a private physician were not aware of availability of free drugs in the government health centers (17)

(c) TB in children

As a disease, TB in children is much harder to diagnose. Signs and symptoms are non-specific and, individually, are not pathognomonic of TB. Most of the diagnosis of childhood TB is based on the radiographic findings of hilar lymphadenopathy, with or without a parenchymal focus. However, radiography alone cannot be used for diagnosis. Hilar adenopathy has only 83% sensitivity and 35% specificity (22). The information that has the best diagnostic value is the presence of a household member who is smear (+) for AFB.

Because of the difficulty in accurately diagnosing tuberculosis in childhood, figures for its incidence in childhood are open to doubt. It has been estimated that in 1989, 1.3 million cases of tuberculosis occurred in the world and that 450,000 deaths resulted (21). A more accurate reflection of the incidence of childhood tuberculous meningitis while trends in infection can be best determined by the annual risk of infection.

Between 90 and 95% of tuberculosis in children are non-infectious and pre-adolescent children play little role in the spread of tuberculosis. Consequently, they are given little consideration in tuberculosis programs. Nevertheless, particularly in high incidence areas, a considerable burden of disease will result from childhood tuberculosis and its effect upon the health services will be compounded by the difficulty surrounding the accurate diagnosis of tuberculosis in children and the uncertain boundary between infection and disease (20).

Poor Case Holding

An evaluation of the NTP by WHO in 1993 found serious problems in case holding in the peripheral units visited. Cohort analysis showed that cure rates in the NTP ranged from 67.0 in 1987 to 78% in 1997 (23). It is also important to note that in 1996, 28% of patients were re-treatment cases, which

indicate that case holding is indeed faulty and that patients are coming back for re-treatment (12). The major reasons for poor case holding are: (a) inadequate drugs and poor drug distribution; (b) patients' non-adherence; (c) physicians' non-adherence; and (d) low motivation of health workers.

(a) *Inadequate drugs and poor drug distribution*

Despite increase in funding for TB started in 1986, the NTP drugs procured were only enough for 65% of the expected smear (+) cases. Drug distribution was also faulty with many health centers not getting their allocations and others piling up expiring inventories. When drug supply stops, even if temporally, the patient under NTP is generally unable to secure a 'bridge' supply of medication. Treatment stops prematurely and patient resorts to monotherapy.

(b) *Patients' Non-Adherence*

Worldwide, the most common factor blamed for failure of anti-TB therapy is patient non-adherence. Taking multiple drugs tends to produce side effects. Also, taking drugs for a period way after the resolution of original symptoms is indeed against Filipino norms. In the National Capital Region, the active completion rate of NTP patients, as reported averages 78%. While data are not available, the adherence rate among private patients is estimated to be no better (expert panel). Compliance building measures like patient education (26), pill counts and urine spot check are only marginally effective in improving compliance.

(c) *Physicians' non-adherence*

It has become evident in the last few years that more important than poor patient adherence, the major reason for poor case holding is poor physician adherence (both government and private physicians) to proper diagnosis and treatment of tuberculosis in the country. In many cases, the regimen prescribed by the health provider is not potent enough. Under the NTP, this occurs only when the free drugs run out. In the private clinics, this is rampant. This phenomenon, which is not unique in the Philippines stems from the fact that private MDs are trained to be independent and are in no obligation to follow treatment guidelines. It has been shown by a recent local study that although 70% of private MDs initially follow the WHO prescribed regimen for treatment of TB, these physicians have been prone to make substitutions in the prescribed regimen resulting in more than 100 variations in regimens when differences in dosages and duration were considered (25). It was also shown that 8.2% of these studied physicians still use rifampicin and isoniazid alone as initial treatment.

It can be deduced from this observational study and 'expert panel' that a number of physicians continue to practice the medicine they were taught decades ago, albeit, with modifications from biases they acquired through the years. Monotherapy continues to be prescribed as well as bad combination drugs.

(d) *Low motivation of health workers*

Motivation of the health personnel is an important factor in carrying out TB control. In 1993, when health personnel in the periphery were devolved with consequent reduction in rank and take home pay, a noticeable rise in TB mortality rate was noted.

Question 3: Overall, what can be done to improve case holding and case finding?

1. **It is proposed that a top-level commission or superbody with the sole mandate to control TB be organized.** It will be staffed by dedicated people of complementary expertise (medical, public health, program management, legislation and others) who will re-energize the NTP. This commission should

be able to coordinate well the activities in the private and government sectors. The commission shall be armed with police powers to enforce new and existing regulations like those on regulating anti-TB drugs sales to purely prescription basis, mandatory confinement of non-complaint patients particularly those with MDR organisms. It should ensure compliance of the practitioners in getting TB provider accreditation and in reporting TB to the proper office.

2. **The government should reassess its program. High yield activities like the pilot programs of DOTS should be supported and expanded quickly.** Directly Observed Treatment Strategy is the only strategy that has been consistently found to improve case holding and thereby cure rates in control programs (27,28). The DOTS strategy involves the following: (a) priority detection and cure of infectious smear positive patients through sputum microscopy; (b) observation of patient by health service staff worker or trained community worker (or family member) to ensure that the correct dose of medication is taken daily; (c) proper monitoring of patient during the course of the patient; (d) standardized short-course chemotherapy with uninterrupted drug supply; and (e) political commitment to the above.

   DOTS was started in 1996 by TBCS in 3 pilot areas, namely, Iloilo City, Antique and Batangas, which covered only 2% of the population. In 1987 DOTS was expanded to cover 8% of the population. DOTS was done at least for the intensive phase with the health center or house of village health worker or patient as the place of treatment. Treatment partners were village workers, 65.6% of the time; health center staff, 29.2% of the time; and family members, 5.2%. Cure rate achieved was 80% in 435 patients, which is higher than the national figure of 75%. By December 1999, 50% of the population will be covered by DOTS and by year 2001, it is projected that 100% will be under DOTS.

   A recent study by Dye and colleagues in the WHO utilized an age-structured mathematical model to forecast the effect of improved case finding through DOTS on the TB epidemic for the 6 WHO regions. Their study concluded that in countries where the incidence of TB is stable and HIV is absent, control program that reaches WHO targets of 70% of case detection and 85% cure rate would reduce incidence rate by 11% per year and death rate by 12% per year (29).

   Ineffective components should be scrapped and modified. Monitoring and evaluation should put more emphasis on the proper detailed implementation of the program. Control of TB will take time and will happen in stages. A statutory fund allocation for TB control over the next 10 years or so should be passed obviating the current need for DOH to competitively beg for NTP funding year after year.

3. **The government should prioritize allocating enough funds for anti TB drugs, TB being one of the most cost-effective diseases to treat (WHO). In parallel, an efficient system of procurement, storage and distribution must be in place to minimize inventory losses.**

4. **A national registry is essential. Laws for mandatory supervised treatment appropriate for the public hazard that TB really is, should be passed. If resources are available, quarantine may have to be imposed in those proven to have MDR TB.**

   When a patient defaults or transfers out, this is not readily recognized both in the present private clinic setting and in many occasions in the NTP. The absence of a registry makes tracing of these defaulters difficult. Follow-up efforts cannot be done to entice them to go back to the program. Unlike countries that are serious in achieving TB control, no statutory provisions exist in the Philippines that will make patients complete their regimen and impose quarantine procedures to resistant cases.

5. **It should be mandatory that all physicians treating TB cases undergo an intensive refresher course on TB.** A national consensus in treating TB applicable to both the public and private settings should be formulated. It should be actively disseminated to all caregivers in urban and rural areas. Again techniques of academic detailing and interactive small group, patient based discussion with content experts in tuberculosis should be used. Measures to ensure MD compliance to the consensus should be in place.

6. **A refresher course on proper laboratory testing procedure is needed to educate the health providers. A mass media campaign may have to be launched also since patients themselves may not like the sputum test and insist on certain actions not consistent with the program.**
7. **Since the government health workers are the actual implementers of the NTP, incentives should be provided to them possible prorated to the accomplishments.** Some effective non-monetary incentives, which may be included, can consists of constant feedback on their accomplishments with corresponding recognition and some form of training for their further development as health workers. Also, access to transportation and communication facilities should be assured since these are crucial for proper program supervision
8. **It is recommended that the DOH, PAFP and PIA must lead a market segmentation health information campaign to encourage patients to seek medical help.** In case this is done, the NTPs capacity should be beefed up to be able to handle the expected surge in service demands. If the patients come to the health centers and there are no enough drugs, mass information campaign can backfire.
9. **Also to protect the potent anti-TB drugs available, the BFAD should enforce the non-OTC nature of anti-TB Drugs.** Support of the Pharmacy Association of the Philippines should be secured.
10. It is recommended that an educational drive by the Philippine Pediatric Society disseminating the content of its newly published consensus Childhood Tuberculosis should be done. The proven techniques for changing behavior of physicians like academic detailing and interactive small group, patient-based discussions with content experts in tuberculosis should be used.

Question 4: What can be done to improve TB prevention efforts?

Consensus Statement:

It is proposed that, in addition to supporting a high profile trimedia campaign emphasizing health promotion practices as general prevention strategies for TB, both the government and the private sector jointly endorse specific guidelines on contact tracing and prophylactic therapy to be implemented whenever funding is available.

Summary of Evidence/Discussion:

Disease prevention is always a major approach to public health conditions like tuberculosis. Active preventive intervention for tuberculosis involves treatment of the infective source case and treating those infected. Aggressive case detection and prompt treatment because of the perceived cost for chemoprophylaxis, about US $17, 000 per case prevented (31). National program lacking the resources to provide short-course chemotherapy cannot consider a general preventive therapy program. However, when resources are available for case finding and treatment, preventive therapy of high-risk persons, e.g., children living in households of infectious patients, should be considered. The National TB Program should provide the guideline on contact tracing and the most effective chemoprophylactic regimen to be used in areas where funds are available. The private sector, which has its own endogenous source of funds should be encouraged to do contact tracing and provide chemoprophylaxis.

Research Recommendations:

1. Survey the health seeking behavior of TB symptomatics at the start, the middle and at the end of treatment; identify the determinants of the behavior seeking pattern of the patients, including reasons for going to the private or public provider.
2. Evaluation of the techniques for effectively changing physician's behavior, e.g. academic detailing, in the local setting.
3. Regular monitoring of the MDR problem in the country
4. Determination of most cost effective way of implementing DOTS nationwide.

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APPENDICES

Appendix 1

Grading System for Recommendations

Grade A: The recommendation is based on one or more studies at Level 1
Grade B: The best evidence is at Level 2
Grade C: The best evidence is at Level 3
Grade D: The best evidence is lower than Level 3 (included are experts' opinion and clinical experience)

Appendix 2

Levels of Evidence for Rating Studies on Accuracy of Diagnostic Tests

Level 1: All 5 of the following criteria are satisfied
a. There was an independent interpretation of the result of the diagnostic test (without knowledge of the result of the gold standard)
b. There was an independent interpretation of the result of the gold standard (without knowledge of the result of the diagnostic test)
c. The study patients consisted of patients suspected (but not known) to have the disorder of interest.
d. The diagnostic test and gold standard are both described in sufficient detail to allow reproducibility
e. The study population consists of at least 50 patients with, and 50 patients without the disorder of interest.

Level 2: 4 of the 5 criteria are met
Level 3: 3 of the 5 criteria are met
Level 4: 2 of the 5 criteria are met
Level 5: 1 of the 5 criteria is met
Level 6: none of the 5 criteria are met

Appendix 3

Levels of Evidence for Rating Studies on the Effectiveness of Treatment

Level 1: A randomized controlled (RCT) that demonstrates a statistically significant difference in at least one major outcome e. g. survival
OR
If the difference is not statistically significant, an RCT of adequate sample size to exclude 25% difference in relative risk with 80% power, given the observed results

Level 2: An RCT that does not meet the Level 1 criteria
Level 3: A non-randomized trial with concurrent controls selected by some systematic method (i. e., not selected on the basis of perceived suitability for one of the treatment options)
Level 4: Before-after study or case series (at least 10 patients) with historical controls or controls drawn from other studies.
Level 5: Case series (at least 10 patients) without controls

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