

To editor:

We have read with interest the editorial on "It is a necessity, not a luxury, to obtain sputum TB culture and susceptibility from all tuberculosis patients in Thailand"(1). The efforts taken by the authors to recommend sending the sputum culture and sensitivity tests from every tuberculosis patients in this country.

As all of us are fully aware that tuberculosis continues to be a very major problem throughout the world: in the early 1990 as many as 16 million cases of tuberculosis have been reported with, each year, 8 million new cases and 3 million deaths due to the disease (2). A very conservative estimate of the total number of new cases each year is 5.5 million, of which 74% occur in Asia and another 12% in Africa (2). In Thailand 47,767 (79 per 100,000) new tuberculosis cases were reported in 1994, of which half were highly infectious (3). However, appreciable under-reporting is likely, and estimates of the true burden of tuberculosis suggest that between 75,000 and 100,000 new cases occur annually (3).

Concerning with this magnitude of problems, the Anti-tuberculosis Association of Thailand had released the guideline for management of tuberculosis in the mid 1996 (4). These guidelines were introduced with an aim to be use as a reference by clinicians in day to day practices to improve tuberculosis care at the general and district hospitals in Thailand.

The guidelines indicated that the microscope is the first step in the search for acid-fast bacilli in the laboratory. Drug sensitivity testing is obviously the logical complement of *M. tuberculosis* isolation. However, newly diagnosed, previously untreated patients are usually started on therapy well before pretreatment drug susceptibility results are known. Thus systematic drug sensitivity tests can not be considered a prerequisite or even a need (4), particularly in country like Thailand where a standard regimen is recommended by national programmes. In this region of the world with a high incidence of tuberculosis but with limited health care resources, the major role of the medical services is to detect infectious cases and to treat them.

The culture of specimens for mycobacteria is much more expensive than microscopy. It requires incubators, facilities and materials for preparation of media and the necessary skilled staffs to undertake decontamination, inoculation of media and detection of positive culture. Nevertheless, it serves their major purposes. Firstly, it detects patients whose sputum contains insufficient bacilli for them to be seen microscopically. Secondly, culture enables a definite identification of the bacillus to be made. This is not so important in area such as Thailand where tuberculosis is very common as the great majority of isolates will be *M. tuberculosis*. Thirdly, culture is an essential prerequisite for drug susceptibility.

No one would argue that ideally it would be superb to recommend obtaining sputum TB culture and susceptibility from all tuberculosis patients in Thailand. If we guide the clinicians in this way, it was estimated that more than 300,000 specimens will be submitted to the tuberculosis laboratories each years. At the moment, only limited number of laboratories in Thailand (approximately 2-3) can provide the culture services and they can not take such a burden. It would be naive if we advise the policy that the physicians in this country can not follow.

The Anti-tuberculosis Association of Thailand is now pushing very hard to set up the Reference Laboratories for tuberculosis in this country in order to promote the high technical level and quality control of every form of tuberculosis bacteriology including the cultures and sensitivity test. In the near future we may be able to recommend routinely obtaining sputum culture and sensitivities test for tuberculosis in all patients.

Judging on the above reasons, we suggested that drug susceptibility is mandatory only in suspected drug-resistant tuberculosis and those who relapse after completing chemotherapy.

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In response to Prof. Banyat Priyanonda et al:

It is truly an honor for our article to get an immediate response from the authorities of the Anti-tuberculosis Association of Thailand. Their arguments are very well taken. We fully understand the reasons behind the official recommendation which are based on the enormous number of TB patients, limited budget and inadequate laboratory facilities. The question is should we follow our national guideline which deemed to be effective for many developing countries or should we try something new in view of the change in epidemiology of drug resistant TB, in particular primary rifampicin resistance.

As practicing physicians we have often seen many patients mishandled by our medical colleagues elsewhere because they followed the recommendation in not performing TB culture and susceptibility. In our private hospital we found the prevalence of primary rifampicin, isoniazid resistance and MDR tuberculosis in new patients to be 17, 19 and 12 percent respectively and acquired rifampicin, isoniazid resistance and MDR in retreated patients to be 35, 35 and 28 percent respectively. This is an unexpectedly high prevalence of drug resistant tuberculosis in any private hospital. Recently Dr. Charoen Chuchottaworn from Central Chest Hospital (1) reported a prevalence of primary resistant strain to rifampicin, isoniazid and MDR to be 14.3, 15.7 and 8.8 percent respectively in new cases of tuberculosis coinfecting with HIV, an alarming increase from 8.9, 13.8 and 2.7 percent respectively in his previous study done during 1988-1993. The preliminary report of the national drug resistance surveillance project covering 46 provinces from TB Division of Ministry of Public Health reveals the prevalence of primary rifampicin resistance and MDR-TB in 1997 to be 9.2 and 3.48 percent respectively. According to WHO/IUATLD global surveillance project (2) the rate of primary resistance to rifampicin among many countries ranged from 0 to 3 percent (median rate 0.2%). In Beijing, China the primary rifampicin resistance rate was 0-0.8 percent and our neighbor Malaysia had only 1 percent. **Thailand probably has the highest primary rifampicin resistance rate in the world.** This means we are in a very serious trouble. Being chest and infectious disease physicians ourselves we feel obliged to voice our serious concern on this matter.

We agree in principle with Prof. Banyat Priyanonda colleagues that drug susceptibility is only mandatory in suspected drug resistant tuberculosis and those who relapse after completing chemotherapy. **The question here is which Thai patients have suspected drug resistant TB.** As mentioned in their letter to the editor about 100,000 new cases may occur annually and half of them have positive AFB smear. Based on this data we may assume that each year at least 13,000 new TB patients harbor dangerously rifampicin resistant and MDR-TB. These mycobacteria will resist to the standard short course anti-tuberculous therapy, therefore these TB patients behave as dangerous spreaders in the community for a long time especially to their innocent family members and even the personnels of the health clinics and hospitals all over the country. Not to mention another group of dangerous spreaders of TB as well as excellent receptors themselves, these are many hundreds of thousands of HIV-infected patients residing all over the country. Therefore **all Thai TB patients should practically be suspected to have drug resistant TB** and drug susceptibility should be mandatory. In fact, for many years CDC of America has recommended drug susceptibility in all TB patients who come from Southeast Asia (3).

It seems that our medical authorities are not, at least publicly, too much concerned about this alarming statistics. Some even lump together the primary INH and rifampicin resistance as if they were the same. The major difference between the two is that the standard short course chemotherapy is effective only in INH resistant,

not in primary rifampicin resistant TB. The high rate of primary rifampicin resistance in Thailand obviously reflects the failure of non-supervised standard short course rifampicin containing regimen. It is probably too late to implement DOT and standard short course regimen. It might have worked if DOT had been applied more than a decade ago when the level of rifampicin resistance was still low. Today drug susceptibility has as much therapeutic as well as preventive implication as DOT. We can not afford not to do it, as we already see the serious consequence of inadequate control of TB in Thailand, the alarmingly increasing incidence of primary rifampicin resistant and MDR-TB. The success rate in treating MDR-TB by alternative drug regimen is rather low, at best 65 percent (4) and very costly beyond the means of most Thai patients.

We realize that under the present situation it is impossible to obtain culture and susceptibility in every TB patient and we agree that the AFB staining is the most practical and appropriate method for the diagnosis of active pulmonary tuberculosis in our country. Nevertheless we must change the concept of all practicing physicians that they must try their best to get the culture and susceptibility test done in all tuberculosis patients. **The needs will dictate the availability of the facilities.** At the present time to be cost saving and to focus on those who are highly infectious, we may have to be selective by submitting sputa for culture and susceptibility only from 50,000 new cases with positive AFB smear and those who relapse after completing the chemotherapy. It is very important to keep patients on four drug regimen while waiting for the result which sometime might take as long as 3 months. Once the result of susceptibility testing returns, the four drug regimen can be modified. We should be able to expand the capacity of existing laboratories to cope with the increasing number of specimens. It is not that difficult to recruit and train additional lab technicians. We have already had experience and known how to run the reliable solid media TB laboratories for many years. It is technically simple and not very costly. We would like to ask the health authorities to seriously look into this problem before it will be too late, otherwise the rate of primary rifampicin resistance and MDR-TB will keep going up. It is a real challenge for all involving parties to see through it that we can control our man-made problem of drug resistance.

We are very pleased to learn that the Anti-tuberculosis Association of Thailand is striving to set up the reference laboratories and we humbly request the experienced and respectable committee members of the Association to reconsider and modify the existing recommendation so that we will have some weapon to fight back the rapidly spreading primary rifampicin resistant TB. **The time is now, we can not wait any longer as it is almost too late!**

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Addendum: It is truly amazing that we learn of the prevalence of primary drug resistance in Thailand from the recent issue of New England Journal of Medicine. Thailand is one of the countries which participated in the study of global surveillance for antituberculosis-drug resistance, 1994-1997 (1). Dr. Panyanandana is the principal investigator who supplied the survey result done countrywide in Thailand during 1996-1997. Prior to this publication, this data is inaccessible to most of Thai physicians. According to this report, indisputably Thailand has the highest rate of primary rifampicin resistance in

the world. The prevalence of primary resistance to rifampicin alone was 6.9 percent and primary resistance to rifampicin with or without resistance to other drugs was 16.8 percent. The median rate of primary mono-resistance to rifampicin and resistance to rifampicin with or without other drugs in 32 countries was 0.2 percent and 1.8 percent respectively. The threat of primary rifampicin resistant tuberculosis in Thailand is real. It is this abnormally high rate of primary rifampicin resistance that justify the mandate why we have to obtain drug susceptibility in all new sputum smear positive pulmonary tuberculosis.

Manoon Leechawengwong, M.D.
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June 16, 1998.

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To whom it may concern,

The guidelines for the diagnosis and treatment of tuberculosis cases in Thailand as issued by the Ministry of Public Health state that diagnosis should primarily rely on the results of sputum smear examinations, with additional aid from X-rays. The performance of sputum cultures and susceptibility tests is reserved for exceptional cases who fail to respond to both the standard and the retreatment regimens. These guidelines are directly criticised by the authors of this editorial, who state their "strong belief" that cultures and susceptibility tests should be performed for *all* patients. Unfortunately, the authors fail to provide any rational explanation for their belief in this article.


The authors cite very high levels for primary INH and rifampicin resistance in Thailand. It must be noted that the first and only representative study of countrywide resistance to tuberculosis drugs is currently underway, and final results will be available by the end of 1998. Before this date, speculations about resistance levels have to be viewed as unfounded, especially if they are, as in this case, provided without any reference.

The authors correctly state that Thailand may have a risk of comparatively high drug resistance levels, and they also provide the correct explanation: low patient compliance with short-course regimens that have been available in Thailand for more than a decade. Given this explanation, the solution to the problem is clear: to ensure full patient compliance with standard regimens throughout the duration of treatment. This is what the revised National Tuberculosis Programme promotes through the use of directly observed treatment (DOT) for all patients. Worldwide evidence shows the substantial reductions of previously existing drug resistance levels if this policy is strictly adhered to (1,2). It remains unclear what the authors instead want to achieve with a policy of susceptibility testing for all patients without addressing the fundamental problems. Even if they would detect large numbers of cases with drug resistance: do they expect that these patients would comply better with complicated second line regimens if compliance with standard regimens is generally low?


The most unsettling point about this article is that the authors completely avoid to mention the cost implications of their proposal. Facilities for susceptibility testing currently exist only at the central level within

the public health structure in Thailand. To do such tests for all patients would require the purchase of new equipment for all district hospitals, followed by immense recurrent costs for the required diagnostic supplies. One may well assume that the required expenditures would exceed all funds that are currently available for the training and supervision of staff to reliably deliver standard drug regimens under observation. In other words, all current program improvements would have to be stopped. The result would be an ever increasing problem of drug resistance. Is this in the interest of the authors, since at least they will be able to detect all resistant cases?

The authors make their proposal at a time when this country is in a severe financial crisis, all the more requiring that the government spends existing funds for cost-effective interventions with the greatest benefits for the population. Short-course chemotherapy for tuberculosis under direct observation is one of these priority interventions (3). Its good reputation could easily be ruined if irresponsible suggestions would be followed, such as those made in this article.



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In response to Drs. Panyanandana and Sawert:

The above argument with those authoritative strong words are welcomed. We are happy to read a response from the directly responsible department from the Ministry of Public Health and his WHO consultant. It is ironic that the TB Division dismissed our claim and called our statement regarding high prevalence of drug resistance, especially primary rifampicin resistance, a speculation. Already having the preliminary data on the level of drug resistance in 1997 (1) on hand, instead of acknowledging the alarmingly high level of primary rifampicin (9.2%), the TB Division turned a blind eye to their own data and preferred to wait for the final result at the end of 1998. We predict that the result will not be any better; it will only get worse as years go by.

We would like our readers to understand the fundamental problem of primary rifampicin resistance. More than a decade ago the primary rifampicin resistant TB was exceedingly rare throughout the world. It was demonstrated at that time by Dr. Mitchison (2) that the response to modern short course chemotherapy in patients with initial rifampicin resistance was poor. He wrote in his article that if rifampicin resistance became widespread, it would threaten the success of short course chemotherapy. This statement has recently been affirmed by Dr. Richard O'Brien of WHO (3). Since most low income countries, including Thailand have had very high prevalence of primary INH resistance for several decades, it is imperative that, from the outset, all resource-poor countries must prevent the loss of rifampicin, the most effective drug we have left. This is done by adhering to the principle of protecting rifampicin throughout the entire course of treatment and through retreatment. First, rifampicin must never be given without direct supervision. Second, rifampicin must always be given in the initial intensive phase with at least two drugs to which the patient's organisms are most likely susceptible and rifampicin is never given with INH and pyrazinamide because this will pose an unacceptable risk of losing rifampicin if patients have primary INH resistant TB.

Looking at hindsight, our previous national TB programme which was endorsed by WHO, was not prudent enough in term to protecting rifampicin. We have been giving the short course chemotherapy 2HRZE/4HR for more than a decade without direct supervision. Only 2HRZ/2HR has been given to TB patients with negative smear; this risks the loss of rifampicin if patients have primary INH resistant TB. This regimen must be

immediately abandoned and replaced by four drug regimen. The retreatment regimen for treating the relapse 2SHRZE/1HRZE/5HRE is also poorly conceived because it only adds one more drug to a failing regimen. It is no wonder why we have such a very high rate of primary rifampicin resistance. Our highest rate of primary rifampicin resistance in the world reflects the imprudent previous national TB programme. We are now paying the hefty price for the past mistake in term of increasing programme cost and larger burden of patients.

Let us compare our previous national TB programme with those of African countries. Their initial intensive regimen of 2HRZE is given under direct supervision followed by non-supervised 6 months of INH and thioacetazone. Their policy has not led to an appreciable increase in the rate of primary rifampicin resistant TB. Retreatment of African patients who relapse after the above regimen with the 2SHRZE/1HRZE/5HRE guarantees a successful outcome without having to do susceptibility even though the TB organisms are resistant to INH and thioacetazone, as long as the organisms remain susceptible to rifampicin.

It is obvious that we, clinicians and the public health authorities have different focuses. Our focus is directed toward individuals and our treatment is based upon the result of susceptibility. The public health authorities focus on the entire TB population. They organize and formulate the empiric national TB regimen based upon the probability that the organisms will be susceptible to it. Thailand has followed the previous national TB guideline for more than a decade; nonetheless, we found out that TB in Thailand has only been partially controlled at the expense of massive increase in level of primary rifampicin resistance. The spreading of primary rifampicin resistant TB poses a serious threat to all individuals. We, clinicians have to call for an action that has been carefully thought through. We agree wholeheartedly with DOTS to prevent further loss of rifampicin. With the present high level of primary rifampicin resistance, in other words, the horse is already out of the barn, DOT and short course chemotherapy can not control the existing rifampicin resistant TB.

What we want to accomplish in our suggestion on obtaining susceptibility in all patients is to identify the cases with primary rifampicin resistant TB and treat them successfully with 18 months of INH, ethambutol and pyrazinamide. In so doing we can contain the spreading of rifampicin resistant TB in Thailand. We do not intend to detect a large number of MDR-TB as we agree MDR-TB in poor Thai patients are most likely incurable. **The benefit of interruption of transmission of primary rifampicin resistant TB should outweigh the cost of performing drug susceptibility.** A successful treatment of primary rifampicin resistant TB the first time is more cost effective than waiting to find out and retreat them at the end of short course chemotherapy. As we already stated that we would not need an in-house TB laboratory in every hospital. The sputa can be sent or mailed to the existing TB laboratories. It should not be a big investment as the existing lab can be expanded to cope with the increasing number of specimens. The cost of performing TB culture/susceptibility in Thailand is not that expensive. It probably costs less than 3 US dollars per specimen not that costly as in industrialized countries.

The expenditure in performing susceptibility in all TB patients is minuscule comparing to the loss of 39 billion US dollars in our foreign reserves in a futile attempt by central bank of Thailand to protect our baht. During this economic downturn, if we manage and allocate our limited budget well, we can spare 200,000 US dollars per year to spend on susceptibility testing. This amount of money would be well worth spending for all Thais and our future generation. In the past we spent lavishly on many unnecessary items. Just to cite one example, the amount of 74.5 million US dollars, the deposit being kept by the US, for eight F/A - 18 jet fighters will be more than enough to establish the laboratory facilities and purchase anti-tuberculous drugs for all patients in Thailand. Even in the Ministry of Public Health there are still some expensive pieces of medical equipment lying idle in some corners of the hospitals and health centers.

Primary rifampicin resistant TB is not only a threat to Thais. Once it emerges, it becomes a global threat. This is analogous to the present Asian financial crisis which originated first in Thailand and spread to other Asian countries. We may need help from rich countries to fight the drug resistant TB.

It is an irony that our suggestion has been branded irresponsible. The public health authorities who organized and endorsed the previous national TB guideline should themselves be held responsible for the massive increase in rifampicin resistant TB. Our Thai society will be much better off if someone have enough courage to speak up against the establishment when they have good reasons to believe that authorities are not doing the right things. We ought to have brains to think for ourselves; otherwise we only have ourselves to blame. The

short term WHO consultant will come and go, but we and our Thai children are here to stay. We hope we have clarified ourselves; however we would like to apologize to our public authorities if we unintentionally create any animosity as we have no ulterior motive and absolutely nothing to gain in our suggestion. We have been using the best evidence and the reasoning to express the different opinion. We will rest our argument right here and let our readers use their own judgment in considering this matter.

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