

# A Study of Primary Drug Resistance in Pulmonary Tuberculosis in West Malaysia 1984-1987

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## Summary

Eight hundred and fifty-six strains of *Mycobacterium tuberculosis* from previously untreated patients with pulmonary tuberculosis from various states in West Malaysia were studied during the period 1984 to 1987. All the strains were tested for *in vitro* susceptibility to the anti-tuberculosis drugs isoniazid (INH), streptomycin (SM), rifampicin (RMP) and ethambutol (ETB).

One hundred and twenty-one of the isolates (14.18%) were resistant to 1 drug while 17 (1.97%) were resistant to 2 drugs. No strain was found to be resistant to more than 2 drugs. The prevalence of primary resistance to INH was 4.20%, SM was 7.59%, RMP was 0.95% and ETB was 1.44%. In 1.86% of isolates, resistance was noted to both INH and SM, while 0.11% were resistant to both RMP and ETB. There was no significant difference in distribution of resistant bacilli between the sexes ( $p > 0.01$ ).

**Key words:** Primary anti-tuberculosis drug resistance, pulmonary tuberculosis, West Malaysia.

## Introduction

The National Tuberculosis Control Programme was introduced in 1961. As a measure of the success of its implementation, tuberculosis is no longer one of the 10 major causes of medically-certified deaths in Malaysia<sup>1</sup>. Nonetheless, it remains a significant health problem both locally and worldwide<sup>2</sup>.

Primary drug resistance occurs when the initial population of *Mycobacterium tuberculosis* contains a large percentage of organisms resistant to 1 or more anti-tuberculosis drugs<sup>3</sup>. Information regarding the local prevalence and type of resistance aids the clinician when faced with a treatment decision in an individual patient with tuberculosis<sup>4</sup>. It is also a reflection of the effectiveness of the control programme. This is because resistance emerges as a result of infection with a strain which originates from another patient who had acquired resistance due to inadequate or inappropriate chemotherapy (secondary drug resistance)<sup>5,6</sup>.

The objective of this study was to determine the prevalence of primary resistance to isoniazid (INH), streptomycin (SM), rifampicin (RMP) and ethambutol (ETB) in Malaysia.

### Materials and Methods

The states of Kelantan, Terengganu, Kedah, Penang, Perak and Melaka, together with the National Tuberculosis Centre, Kuala Lumpur, were chosen for the study, which was carried out between 1984 and 1987. Bacteriologically positive patients with no previous history of tuberculosis were selected. A careful inquiry was made to ensure that these patients had not had any form of anti-tuberculosis chemotherapy. The findings were verified by checking with the Central Tuberculosis Registry. Any patient who had been previously registered was excluded. In all, 856 patients who met the required criteria were enrolled.

All positive cultures from the selected patients were sent to the National Tuberculosis Centre for drug sensitivity testing. Two cultures from each patient were screened. Drug susceptibility tests were carried out using the absolute concentration method based on WHO/TB/Techn.Guide/67.7. Lowenstein-Jensen media were incorporated with drugs as shown in Table I. The drug-incorporated media were inspissated at 80°C for 50 minutes. The bacterial suspension (inoculum) used had about 2,000 colony-forming units (CFU). Incubation was at 37°C and the final reading was taken after 4 weeks of incubation. H37 RV strain of *Mycobacterium tuberculosis* was used as a standard reference (control).

Strains showing growth of greater than 1% or more than 20 colonies were classified as resistant. All strains selected were also subjected to the niacin test and the nitrate reduction test. All strains showed positive reactions to both the tests and were therefore classified as *Mycobacterium tuberculosis* (as opposed to other atypical mycobacteria).

The calibration of drug sensitivity testing is done periodically, using isolates from new cases. The drug concentrations are prepared in series and minimum inhibitory concentration (MIC) determined. The concentration where the majority of strains are sensitive is taken as the MIC. These tests were done in July 1985 and again in 1988. The MIC did not change significantly. Cultures of known drug sensitivity pattern were also sent to Japan to have them retested. There was good correlation between the results obtained.

**Table I**  
Concentration of anti-tuberculosis drugs in Lowenstein-Jensen media

Drug	Concentration (microgram/ml)
Isoniazid	5
Streptomycin	20
Rifampicin	50
Ethambutol	3

**Table II**  
The prevalence of primary drug resistance to 1 drug

Drug	Number tested	Number resistant	% resistant
Isoniazid	856	36	4.20
Streptomycin	856	65	7.59
Rifampicin	835	8	0.95
Ethambutol	826	12	1.44

## Results

Of the 856 strains studied, 735 (85.82%) were sensitive or susceptible to all 4 drugs. One hundred and twenty-one of the isolates (14.18%) were resistant to 1 drug (Table II). The drug with the highest prevalence of primary resistance was SM (7.59%), while RMP had the lowest rate (0.95%). Seventeen strains (1.97%) were resistant to a combination of 2 drugs. None showed resistance to more than 2 drugs (Table III).

Of the 536 male patients, 11.19% had primary resistant strains, while 10.94% of 320 females had such strains. There was no significant difference in distribution of resistant bacilli between the sexes ( $p > 0.01$ ).

## Discussion

In Malaysia, the current standard anti-tuberculous regimen consists of a combination of INH, RMP, pyrazinamide (PZA) and either SM or ETB. RMP and ETB were introduced into the regimen with the implementation of short-course chemotherapy in 1984. In our study, it was found that primary resistance to SM (7.59%) and INH (4.20%) were higher than to ETB (1.44%) or RMP (0.95%). This is consistent with the findings of Janowiec *et al*, that the longer a drug has been used, the higher would be the prevalence of primary resistance<sup>7</sup>. As in the study by Trivedi and Desai<sup>8</sup>, the majority of our cases were resistant to only 1 drug while multiple drug resistance was uncommon.

Earlier studies have shown very infrequent primary resistance to RMP<sup>7,9</sup>. Trivedi and Desai suggested that there is a loss of virulence in the RMP resistant strains<sup>8</sup>. However, with greater use, recent studies have demonstrated an increase in primary resistance to this drug<sup>4,10</sup>. A high prevalence of INH and SM resistance may be responsible for the emergence of RMP resistance. Prior resistance to INH, a drug included in all common anti-tuberculosis regimens, may provide the basis for the emergence of RMP resistance<sup>8</sup>.

In our study, we found no significant difference in distribution of resistant bacilli between the sexes. This was also shown in the study of Trivedi and Desai<sup>8</sup>. No relationship has also been found between primary drug resistance and age<sup>6,8</sup>. In a study by Ben-Dov and Mason, patients with cavitary pulmonary disease were, however, noted to have a higher prevalence of primary drug resistance<sup>3</sup>. This may be attributed to the higher bacillary population, which is bound to harbour a higher number of resistant mutants.

Factors that may contribute to an increase in prevalence of primary drug resistance include international travel and migration<sup>10</sup>. Ormerod reported that there was no primary drug resistance among whites in the United Kingdom while the prevalence was between 8% to 13% among Indians<sup>11,12</sup>. In the United States of America, Asian immigrants had a higher prevalence of primary drug resistance than 'native' Americans<sup>4</sup>. These findings may be relevant in the local context in view of the significant number of immigrants present here. They may bring into this country characteristics of drug resistance peculiar to their country of origin. Patients with the Acquired Immunodeficiency Syndrome (AIDS) present the clinician with a new subgroup to manage. Due to

**Table III**  
The prevalence of primary drug resistance to drug combinations

Drug combination	Number tested	Number resistant	% resistant
INH and SM	856	16	1.86
RMP and ETB	835	1	0.11
SM and RMP	835	0	0
Total		17	1.97

INH=Isoniazid; SM=Streptomycin; RMP=Rifampicin; ETB=Ethambutol.

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their immunocompromised status, they may present with more fulminant disease and harbour a larger population of bacilli. They may also have a different rate and pattern of primary drug resistance.

In conclusion, the present prevalence of primary drug resistance in tuberculosis in West Malaysia is comparatively low<sup>6,8,10</sup>. We should, however, continue monitoring patterns as an integral part of the control programme. If proper vigilance is not maintained, tuberculosis may once again become a major cause of morbidity and mortality in Malaysia.

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