
**Key Words**

Antitubercular agents  
Drug resistance  
Isoniazid  
*Mycobacterium tuberculosis*  
Rifampicin

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**Abstract**

**Objective:** Primary drug resistance to *Mycobacterium tuberculosis* has not been studied previously in Kuwait. The aim of the present study was to investigate factors associated with primary drug resistance at the Chest Diseases Hospital in Kuwait.

**Methods:** We evaluated the clinical data, radiological features and results of susceptibility tests to five antitubercular drugs between 1992 and 1995.

**Results:** Of the 582 patients admitted for newly diagnosed, previously untreated tuberculosis, 465 (79.9%) were non-Kuwaitis. Among the Kuwaitis, primary drug resistance to a single antitubercular agent was noted in isolates from 12 patients (10.3%), 7 (6.0%) for pyrazinamide and 5 (4.3%) for isoniazid. None of the Kuwaiti patients had multiple drug resistance. Regarding non-Kuwaitis, primary resistance was noted in isolates from 71 patients (15.3%). Thirty-nine patients (8.4%) were resistant to isoniazid, 29 (6.2%) to pyrazinamide, 24 (5.2%) to streptomycin, 8 (1.7%) to rifampicin, and 7 (1.5%) to ethambutol. Two drug resistance was detected in 26 patients (5.6%), and three drug resistance was noted in 5 patients (1.1%). One non-Kuwaiti patient was resistant to four antitubercular agents.

**Conclusion:** We conclude that single and multiple drug resistance is more common among non-Kuwaiti patients when compared to Kuwaitis. This is related to the fact that most of the non-Kuwaiti patients originate from countries with high incidence of tuberculosis and high drug resistance.
Introduction

Pulmonary tuberculosis (PTB) is the leading cause of infectious morbidity and mortality in many countries [1]. The rising prevalence of strains of *Mycobacterium tuberculosis* that are resistant to the most effective and widely used economic medications jeopardizes individual patients and the success of tuberculosis control programmes [1, 2]. Drug resistance can be classified into primary resistance and acquired resistance [3, 4]. Primary resistance is defined as resistance to antitubercular drugs in a patient who has never received chemotherapy. It includes infection with resistant organisms from another patient with acquired resistance, or infection with naturally resistant wild mutant [4]. Acquired resistance is defined as resistance to antitubercular agents that arises during treatment, usually due to patient non-compliance or poor drug regimen. Multiple drug resistance refers to resistance to more than one antitubercular drug [3–6]. Drug resistance varies from country to country and is a good indicator of the efficacy of the National Tuberculosis Programme [5].

During the past two decades, there has been a gradual decrease or no change in primary resistance in Western Europe [7–10] and the United States [11]. In Africa [12, 13], the Indian subcontinent [14–17], and the Kingdom of Saudi Arabia [18–20], high rates of primary and acquired drug resistance have been reported. Furthermore, the acquired immunodeficiency syndrome (AIDS) pandemic in Africa [21, 22], Asia [22, 23], and in some urban areas in the United States [24–26] has increased the prevalence of tuberculosis co-infection with AIDS. Concurrent with this upsurge of dual infection of HIV and tuberculosis is the emergence of drug-resistant tuberculosis, usually multiple drug resistant [22, 26].

The Kuwait National Tuberculosis Programme is in accordance with the World Health Organisation recommendations in emphasizing the prevention of tuberculosis and drug resistance [3, 5]. Resistance to antitubercular agents has not been studied previously in Kuwait. Based on vigorous tuberculosis control measures, single or multiple drug resistance rates are likely to be low in Kuwait, and are expected to be comparable to those reported in developed countries. However, this may not be the case, because two thirds of the Kuwaiti population is composed of non-Kuwaiti expatriate work-force. These workers originate from countries with high incidence of tuberculosis and high resistance rates [14–17, 27]. Although all the foreign workers are screened for PTB in their native countries and in Kuwait, some cases of inactive PTB may escape radiologic detection. This may be an important source of PTB cases in the non-Kuwaiti patients. Wang et al. [28] have reported that immigrants from tuberculosis endemic Asian countries had a high rate of relapse and a higher drug resistance after entry into British Columbia, Canada. We therefore assessed the factors associated with primary drug resistance in Kuwaiti and non-Kuwaiti patients admitted between 1992 and 1995.

Methods

Patients

From January 1992 through December 1995, we admitted 582 patients (117 Kuwaiti and 465 non-Kuwaitis) for newly diagnosed, previously untreated PTB at the Chest Diseases Hospital. The age range for the patients was 15–69 years (mean age, 47 years). Non-Kuwaiti patients had resided in Kuwait for a duration of 1–6 years (mean, 3 years).

All non-Kuwaiti patients were screened at the designated hospitals in their native countries for PTB. Tuberculosis screening in non-Kuwaiti patients included detailed medical history for previous PTB, clin-
ical examination and chest radiography. All the medical check-ups were supervised by specialist chest physicians from the Ministry of Health Kuwait. Residence and employment visas were not issued to any one with a history of previous PTB, or with an abnormal chest X-ray, whether due to PTB or any other chest diseases. Furthermore, on entry into Kuwait, all non-Kuwaitis had routine chest X-rays, and workers suspected of previous tuberculosis had skin tuberculin tests. Immigrants with abnormal chest X-rays or a positive tuberculin test were denied residence.

On admission, a detailed medical history regarding previous illnesses, previous PTB and medication were obtained from each patient. None of the patients had been hospitalised or treated for PTB in the past. Each patient underwent serial, clinical and radiological examinations during the course of hospitalisation. The clinical and radiological picture, and susceptibility tests were used to assess the clinical response of the patients to therapy.

**Direct Microscopy**

Three consecutive early morning sputum specimens from each patient were examined by direct microscopy for acid-fast bacilli after Ziehl-Neelsen staining. Smears were prepared after digestion, decontamination and concentration of the specimen, and examined using direct microscopy.

**Mycobacterium Culture**

The sputum was mixed thoroughly with an equal volume of 4% sodium hydroxide solution and left at room temperature for half an hour. The container was shaken every 5 min. The mixture was then centrifuged at 3,000 rpm for half an hour. Thereafter, the deposit was neutralised by 8% HCl using phenol red as an indicator. The sputum sediment was inoculated using special pipettes (one for each specimen) and distributed over the whole slope surface of the medium. The slopes were then placed in the horizontal position and left overnight at room temperature, to ensure even distribution of the sediment on the entire surface of the slope. Each cultured slope medium was examined after 4 weeks, and subsequently weekly. The colonies were counted on both the control slopes and drug-containing slopes. The number of colonies on control slopes indicated the number of culturable particles contained in the inoculum. The number of colonies on each of the drug-containing slopes indicated the number of resistant bacilli contained in the inoculum. The ratio between the second figure and the first indicated the proportion of resistant bacilli existing in the strain. The proportion of resistant bacilli was calculated using the following formula:

$$\text{Proportion of resistant bacilli} = \frac{\text{Number of colonies in drug medium}}{\text{Number of colonies in drug-free medium}} \times 100$$

Below a certain ratio of ‘critical proportion’, the strain was classified as sensitive. When equal to or above this ratio, the results were interpreted as resistant. According to Vareldzis et al. [3], the strain is resistant to SM, EMB and PZA if the proportion of resistant bacilli was 10% or above, and resistant to INH and RMP if the proportion of the resistant bacilli was 1% or above.

**Sensitivity Testing**

The sensitivity tests were performed using standard inoculum. The method used for sensitivity testing was the recently modified variant of the proportion method [3]. Each drug was incorporated in the egg-based Lowenstein-Jensen media before inspissation, and distributed in 7-ml amounts in screw-capped bottles, and then coagulated. Control media without antitubercular agents were prepared at the same time as the drug-containing media. Five front line drugs were tested including isoniazid (INH, 0.2 11 g/ml), streptomycin (SM, 4 11g/ml), pyrazinamide (PZA, 100 11 g/ml), ethambutol (EMB, 5 Rg/ml), and rifampicin (RMP, 0.2 11 g/ml). Acid media was prepared for PZA by adding N-HCl gradually and continuously shaking the media before inspissation to pH of 5.2.

The cultures were read after 4 weeks and subsequently weekly. The colonies were counted on both the control slopes and drug-containing slopes. The number of colonies on control slopes indicated the number of culturable particles contained in the inoculum. The number of colonies on each of the drug-containing slopes indicated the number of resistant bacilli contained in the inoculum. The ratio between the second figure and the first indicated the proportion of resistant bacilli existing in the strain. The proportion of resistant bacilli was calculated using the following formula:

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**Statistics**

The $\chi^2$ test was used to determine the significance of differences in proportions between groups. A $p$ value <0.05 was taken to be significant.

**Results**

The age and sex distribution of PTB patients are shown in table 1. There were more males admitted for PTB each year as com-
Table 1. Age and sex distribution of PTB patients admitted between 1992 and 1995

<table>
<thead>
<tr>
<th>Age range years</th>
<th>1992</th>
<th>1993</th>
<th>1994</th>
<th>1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>15–24</td>
<td>21</td>
<td>6</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>25–34</td>
<td>23</td>
<td>5</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>35–44</td>
<td>8</td>
<td>4</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>45–54</td>
<td>4</td>
<td>3</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>55–64</td>
<td>3</td>
<td>–</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>&gt;65</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>19</td>
<td>99</td>
<td>49</td>
</tr>
<tr>
<td>Females, %</td>
<td>24.4</td>
<td>33.1</td>
<td>20.1</td>
<td>32.4</td>
</tr>
</tbody>
</table>

Table 2. Cases of smear-positive and smear-negative PTB between 1992 and 1995

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear-positive</td>
<td>56 (71.8)</td>
<td>118 (79.7)</td>
<td>155 (89.1)</td>
<td>172 (94.5)</td>
<td>501 (86.1)</td>
</tr>
<tr>
<td>Smear-negative</td>
<td>22 (28.2)</td>
<td>30 (20.3)</td>
<td>19 (10.9)</td>
<td>10 (10.9)</td>
<td>81 (13.9)</td>
</tr>
<tr>
<td>Total</td>
<td>78 (100.0)</td>
<td>148 (100.0)</td>
<td>174 (100.0)</td>
<td>182 (100.0)</td>
<td>582 (100.0)</td>
</tr>
</tbody>
</table>

Percentages for each year are given in parentheses.

pared to females. There was also a gradual increase in the number of patients from 1992 to 1995. Table 2 shows the annual cases of direct smear-positive and smear-negative PTB admitted between January 1992 and December 1995. There was a gradual increase in the number of smear-positive, but a slight decline in the percentage of smear-negative patients admitted between 1992 and 1995.

Table 3 shows primary drug resistance among the Kuwaitis and non-Kuwaitis. Among the Kuwaitis, there were 12 cases (10.3%) of primary drug resistance: 7 (6.0%) to PZA and 5 (4.3%) to INH. Of the 465 non-Kuwaiti patients, primary drug resistance was reported in 71 patients (15.3%), including 39 (8.4%) to INH, 29 (6.2%) to PZA, 24 (5.2%) to SM, 8 (1.7%) to RMP, and 7 (1.5%) to EMB.

Table 4 shows single and multiple drug resistance. None of the Kuwaiti patients had *M. tuberculosis* isolates resistant to two or more antitubercular drugs. Among the non-Kuwaitis primary resistance to two front line antitubercular drugs was detected in isolates from 26 patients (5.6%), and resistance to three drugs was noted in isolates from 5 patients (1.1%).

Multiple drug resistance to antitubercular agents is depicted in table 5. Of the 465 non-Kuwaiti patients, resistance to two drugs was due to INH and SM (2.9%), INH and EMB (0.9%), INH and PZA (0.9%), INH and RMP (0.4%), and RMP and PZA (0.4%). Two pa-
Patients had triple drug resistance to SM, EMB, and PZA, and another 2 had resistance to INH, SM, and RMP.

**Discussion**

PTB still accounts for almost 3 million deaths annually [1, 11]. Drug resistance is a serious problem in the treatment of PTB and is a threat to a successful tuberculosis control programme [6, 29, 30]. Clinically, drug resistance is divided into two types: primary resistance and acquired or secondary resistance. Primary resistance occurs in persons who have not been treated for tuberculosis, and these persons are infected with resistant organisms [3, 4]. It is difficult to verify whether a patient has received antitubercular therapy in the past, particularly in immigrants, and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kuwaiti (n = 117)</th>
<th>Non-Kuwaiti (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>5 (4.3)</td>
<td>39 (8.4)</td>
</tr>
<tr>
<td>PZA</td>
<td>7 (6.0)</td>
<td>29 (6.2)</td>
</tr>
<tr>
<td>SM</td>
<td>–</td>
<td>24 (5.2)</td>
</tr>
<tr>
<td>RMP</td>
<td>–</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>EMB</td>
<td>–</td>
<td>7 (1.5)</td>
</tr>
</tbody>
</table>

Percentages for each drug are given in parentheses.

<table>
<thead>
<tr>
<th>Number of drugs</th>
<th>Kuwaiti (n = 117)</th>
<th>Non-Kuwaiti (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>12 (10.3)</td>
<td>42 (9.0)</td>
</tr>
<tr>
<td>Two</td>
<td>–</td>
<td>26 (5.6)</td>
</tr>
<tr>
<td>Three</td>
<td>–</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Four</td>
<td>–</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

1 Percentages of drug resistance are given in parentheses.

**Table 3.** Primary drug resistance in Kuwaiti and non-Kuwaiti patients between 1992 and 1995

**Table 4.** Frequency of single and multiple drug resistance in Kuwaiti and non-Kuwaiti patients

**Table 5.** Frequency of multiple drug resistance in Kuwaiti and non-Kuwaiti patients

<table>
<thead>
<tr>
<th>Combination</th>
<th>Antibiotics</th>
<th>Kuwaiti (n = 117)</th>
<th>Non-Kuwaiti (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two drugs</td>
<td>INH + SM</td>
<td>–</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td></td>
<td>INH + EMB</td>
<td>–</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td></td>
<td>INH + PZA</td>
<td>–</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td></td>
<td>INH + RMP</td>
<td>–</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td></td>
<td>RMP + PZA</td>
<td>–</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td></td>
<td>SM + PZA</td>
<td>–</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Three drugs</td>
<td>SM + EMB + PZA</td>
<td>–</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td></td>
<td>INH + SM + RMP</td>
<td>–</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td></td>
<td>INH + SM + PZA</td>
<td>–</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Four drugs</td>
<td>INH + EMB + PZA + RMP</td>
<td>–</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

1 Percentages of drug resistance are given in parentheses.
therefore, the term initial resistance is often used instead of primary resistance. Secondary or acquired resistance develops during tuberculosis treatment, either because the patient was treated with an inadequate regimen or due to poor compliance [3, 4].

All non-Kuwaiti patients denied receiving tuberculosis treatment in the past, and had apparently two normal chest X-rays, one taken in their native country and the other on arrival in Kuwait. Non-Kuwaitis who had a previous history of PTB, an abnormal chest X-ray or a positive tuberculin skin test were not issued residence visas.

**Primary Drug Resistance in Kuwaitis and Non-Kuwaitis**

Kuwait National Tuberculosis Programme is in accordance with the World Health Organisation recommendations, with a major
emphasis on the prevention of tuberculosis among the Kuwaiti and non-Kuwaiti expatriate manpower. All Kuwaitis receive BCG immunisation at the age of 4 years. They also have a routine pre-employment chest radiograph to exclude PTB. Non-Kuwaitis are screened with chest X-rays for PTB at designated hospitals in their native countries, and on entry into Kuwait. Based on these investigations, one can assume that all non-Kuwaitis had no active PTB at the time of entry in Kuwait.

Our findings show that single drug resistance among the Kuwaiti patients was low when compared to non-Kuwaitis. Primary resistance to INH and PZA in Kuwaiti patients was only noted in 4.3 and 6.0%, respectively. Among the non-Kuwaitis, primary resistance was reported in 71 patients (15.3%), including 39 (8.4%) to INH, 29 (6.2%) to PZA, 24 (5.2%) to SM, 8 (1.7%) to RMP, and 7 (1.5%) to EMB. Furthermore, we did not observe drug resistance to SM, RMP and EMB in the Kuwaiti patients, whereas the non-Kuwaiti resistance to SM was detected in 5.2%, to RMP in 1.7% and to EMB in 1.5% of the patients. A high incidence of drug resistance in non-Kuwaiti patients has serious implications, not only for the treatment of individual patients, but also for the supervision of contacts of these cases. Based on our tuberculosis registry, non-Kuwaiti patients with primary drug resistance had a high incidence of drug toxicity, pulmonary and extrapulmonary complications, and a higher mortality rate as compared to Kuwaiti patients.

Multiple Drug Resistance in Kuwaitis and Non-Kuwaitis

Multiple drug resistance is defined as the resistance of *M. tuberculosis* to two or more antitubercular drugs [3–6]. None of the Kuwaiti patients had resistance to two or more antitubercular drugs, indicating a good tuberculosis control programme among the Kuwaitis. However, multiple drug resistance was reported in a relatively large number of non-Kuwaiti patients. Drug resistance to two antitubercular agents was noted in 26 patients (5.6%), and to triple drugs in 5 patients (1.1%). The highest rates of two drug primary resistance was due to INH and SM combination (2.9%), INH and EMB (0.9%), INH and PZA (0.9%), INH and RMP (0.4%), and RMP and PZA (0.4%). Double drug resistance particularly to both INH and RMP or triple drug resistance is associated with much lower cure rates, approximately 60% [31]. It is not surprising for us to find a higher rate of multiple drug resistance in the non-Kuwaiti patients. Multiple drug resistance is a major public health problem in countries like Pakistan [14], India [15, 16], Bangladesh [17] and Philippines [27], from where the expatriates originate.

Although Kuwaiti patients have a low primary drug resistance, a relatively high rate of single and multiple drug resistance has been reported in the local populations in neighbouring Saudi Arabia [18–20]. Acquired resistance to RMP (9–7%) and to SM (3.3%) has been reported in indigenous Saudi Arabian populations [18–20], but not in our Kuwaiti patients. However, Zaman [19] has also shown that acquired and multiple drug resistance was more common among non-Saudis compared to the Saudis. This is in agreement with our findings, and those reported by other authors in England [8, 9] and Canada [28]. In Canada and England, for example, there is a higher rate of primary and acquired drug resistance in non-indigenous or immigrant populations.

Most of the expatriate manpower in Kuwait, Saudi Arabia and other Gulf countries originates from the Indian subcontinent and South East Asia. The higher rate of drug resistance in non-Kuwaiti patients is related to the
fact that most of our patients originate from countries with high incidences of tuberculosis [14–17, 27]. Furthermore, primary and acquired drug resistance is a major public health concern in these countries, coupled with low compliance, overcrowding and deteriorating socio-economic conditions. In India, for example, secondary drug resistance to INH is as high as 65% [15], to RMP ranges between 12 and 37.3% [15, 16], and to SM is approximately 7.4% [16]. In Pakistan, drug resistance to RMP, INH, and EMB correspond to 17.7, 14.7 and 8.7%, respectively [14]. Single and multiple drug resistance in Bangladesh [17] and Philippines [27] is also alarmingly high.

Expatriate workers are screened rigorously for PTB and other infectious diseases before entry into Kuwait. Those that meet the medical requirements are not issued visas. This is probably the main reason why the incidence rates for primary and multiple drug resistance are low in non-Kuwaiti patients as compared to those in their native countries [14–17, 27]. However, it is possible that some of the inactive PTB may escape detection during the initial radiological screening, only to be reactivated a year or so after migration. This has been shown to be true in Blackburn, England [8] and in British Columbia, Canada [28]. Foreign immigrants to these countries are diligently screened and put on surveillance. However, in Blackburn and British Columbia, it has been shown that immigrants from Asia, where PTB is still common, had a higher rate of relapse and drug resistance [8, 28]. More recently, it has also been shown that foreign-born immigrants in Germany from Africa, Asia and Turkey had a higher rate of drug resistance [10]. The medical, housing and social conditions of foreign immigrant workers may not necessarily be the same as those of the indigenous populations. Overcrowding and poor medical facilities create a potential for spread of PTB and/or reactivation.

It is concluded that primary drug resistance is rare in Kuwaiti patients but is relatively common in the migrant foreign non-Kuwaiti patients. Whether drug-resistant tuberculosis in non-Kuwaiti patients is due to recrudescence of previously undetected inactive PTB, or due to newly acquired drug-resistant PTB during short visits to their native countries, needs further investigations. The high rate of PTB relapse and drug resistance in foreign immigrants of industrialised countries necessitates surveillance and adequate treatment of tuberculosis. Tuberculin skin tests should be included in the initial screening of all immigrants suspected of previous tuberculosis or equivocal chest radiographs.

References


