Epidemiological and cost analysis of multidrug-resistant tuberculosis in Oman

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تحليل وبائيات السل المقاوم للأدوية المتعددة وتكاليفه في سلطنة عُمان

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الخلاصة: قام الباحثون بتحليل وبائيات وتكاليف علاج جميع المرضى الثلاثة عشر الذين شُخِّصت إصابتهم بالسل المقاوم للأدوية المتعددة (11مصاباً بالسل الرئوي واثنين بالسل خارج الرئة) في سلطنة عمان في الفترة من كانون الثاني/يناير 2000 حتى تشرين الأول/أكتوبر 2005. وكان المرض ثانوياً أو مكتسباً لدى 12 من بين الـ 13 مريضاً. وتمَّ تحرِّي ما مجموعه 140 من المخالطين (بوَسَطي 10.8 مخالِطاً لكل مريض)، إلا أن تتبع المخالطين لم يكشف عن أي حالات عدوى ثانوية. وبلغ متوسط عدد الأدوية التي كانت مستفرَدات عُصَيَّات السل مقاومة لها 2.8 (المجال 2 — 5). وأُعطي وسطياً 4.7 أدوية للمرضى، وكان طول المعالجة الوسطي ثمانية أشهر. وقد شُفِيَ جميع المرضى. وكانت تكلفة الأدوية المعطاة لهذه الحالات المقاومة للأدوية المتعددة في عُمان أكثر من تكلفة النُظُم المعيارية لمعالجة عُصَيَّات السل الحساسة للأدوية، بنحو 14 إلى 29 مرة.

ABSTRACT We conducted an epidemiological and cost analysis for all 13 patients diagnosed with multaidrug-resistant tuberculosis (11 pulmonary, 2 extrapulmonary) in Oman from January 2000 to October 2005. The disease was secondary, or acquired, in 12 of 13 patients. A total of 140 contacts were screened (mean 10.8 persons per patient), but contact tracing revealed no secondary cases. The mean number of drugs that TB isolates were resistant to was 2.8 (range 2–5). A mean of 4.7 drugs were given to patients, the mean length of therapy was 8 months and all patients were cured. The cost of medications for these multidrug-resistant cases was 14 to 29 times higher than that for the standard drug-sensitive TB regimen.

Analyse épidémiologique et analyse des coûts de la tuberculose à bacilles multirésistants à Oman
RÉSUMÉ Nous avons réalisé une analyse épidémiologique et une analyse des coûts concernant les 13 patients pour lesquels le diagnostic de tuberculose à bacilles multirésistants (11 cas pulmonaires et 2 extrapulmonaires) avait été établi, de janvier 2000 à octobre 2005 à Oman. La maladie était secondaire, ou acquise, chez 12 des 13 patients. Les sujets contacts ont été recherchés, 140 au total ont été examinés (avec une moyenne de 10,8 sujets par patient) et aucun cas secondaire n'a été détecté. Le nombre moyen de médicaments auxquels les isolats provenant de patients tuberculeux étaient résistants était de 2,8 (avec des extrêmes allant de 2 à 5). En moyenne, 4,7 médicaments ont été administrés aux patients, la durée moyenne du traitement a été de 8 mois et tous les patients ont guéri. Le coût des médicaments pour ces cas de tuberculose à bacilles multirésistants à Oman était 14 à 29 fois supérieur à celui du traitement standard contre la tuberculose sensible aux médicaments.

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Introduction

Treatment for tuberculosis (TB) caused by multidrug-resistant strains of *Mycobacterium tuberculosis* is more complicated, more costly and less likely to produce favourable results than treatment for strains that are sensitive to treatment with the 1st-line drugs isoniazid and rifampicin [*1,2*]. Accordingly, multidrug-resistant TB (MDR-TB) has enhanced transmissibility and poses a greater public health risk than the drug-sensitive disease. The higher costs related to MDR-TB include longer periods of hospitalization, longer treatment with more expensive and toxic 2nd- and 3rd-line anti-TB medications, greater productivity losses and higher mortality. In a study from the United States of America, the average cost of treatment per patient who survived MDR-TB was US$ 89 594 and for those who died was US$ 717 555 [*2*].

In this study in Oman we sought to determine the epidemiological and clinical factors leading to acquisition of MDR-TB, the components of effective therapy and the economic repercussions of treatment.

Methods

We conducted a records-based retrospective review of cases of laboratory-confirmed, culture-positive MDR-TB documented and managed by the national TB control programme of the Oman Ministry of Health from January 2000 to October 2005. Demographic and clinical data extracted included: patient's age, sex and country of origin; region in Oman where disease was reported and likely location of acquiring infection; disease site (pulmonary or extrapulmonary); presence of intravenous drug use, HIV/AIDS, alcoholism or other immunosuppressive states; number of contacts screened and TB cases among contacts; previous chemoprophylaxis and/or previous treatment for TB; mean number of drugs that TB isolates were resistant to; type and estimated cost of drugs used for treatment; clinical outcome and length of follow-up.

Determination of whether MDR-TB was primary or secondary was made according to a history of previous anti-TB drug treatment and analysis of drug susceptibility data before and after initial treatment. Close contacts were defined as household members, as well as work or school colleagues having prolonged, significant contact with an index case (i.e. eating and/or sleeping in the same room). No molecular typing of *Mycobacterium* strains was performed. A simple cost analysis of treatment regimens looked only at the retail cost (taken from the published data of the Omani national formulary) and the duration of anti-TB drugs administered and not at other aspects of therapy or at the larger perspective of costs to society.

Since 1981, TB has been a notifiable disease in Oman. Newly-diagnosed cases are reported centrally to the national TB control programme at the Ministry of Health; private clinics and physicians are not allowed to treat TB, and by law they are required to refer cases to public clinics and/or hospitals for therapeutic management. This policy does not allow for under-notification, and thus the accuracy of case detection, especially for Omani nationals, approaches 100%. The Ministry of Health in Oman instituted directly observed therapy, short-course (DOTS) in 1996, and the policy is to hospitalize all sputum smear-positive cases for the initial 2 months of anti-TB drug treatment or until they achieve smear-negativity. Patients with drug-sensitive TB either self-administer their medications as outpatients or receive health centre-based DOTS, and are seen bimonthly in a local health centre where they receive their anti-TB medications free of charge. All patients

with MDR-TB are managed with DOTS on an outpatient basis, with or without an initial inpatient hospital stay, for the duration of their drug treatment.

Results

A total of 13 patients with MDR-TB were identified and the relevant data analysed. The incidence of TB in Oman during the study period ranged from 10.7 per 100 000 population in 2003 to 13 per 100 000 population in 2000. During the study period, therefore, the 13 cases of MDR-TB accounted for about 0.9% of all active TB cases (the Omani national TB control programme estimates its case detection accuracy at 100%).

The mean age of the 13 patients was 32.6 years (range 18–66 years), and the male:female ratio was 7:6. All were Omani nationals, and the geographical residence of cases by region in Oman was: Salalah (3 cases), Khabura (2 cases), and Bowsher, Khasab, Sohar, Liwa, Saham, Maabela, Al Masira and Bahla (1 case each).

Some underlying predisposing conditions included smoking (4 cases) and diabetes mellitus (1 case). There were 11 patients with pulmonary TB and 2 with extrapulmonary disease (involving lymph nodes and urinary tract respectively). There were no cases of MDR-TB related to intravenous drug use or HIV infection. Prior to their diagnosis of MDR-TB, 12 of the 13 patients had received anti-TB therapy (a past treatment history was not available for 1 patient). Thus, MDR-TB was secondary, or acquired, in at least 92% of the patients, and no patient had documented primary multidrug-resistant infection.

Contact tracing evaluated 140 household and other close contacts (a mean number of contacts screened per patient of 10.8). A total of 5 children aged less than 5 years were begun on anti-TB prophylaxis with isoniazid before drug susceptibility patterns were known. Prophylactic treatment for latent TB infection was not administered to contacts after identification of MDR-TB in index cases. There were no secondary cases of MDR-TB among the 140 contacts screened.

The TB isolates of the patients were resistant to a mean of 2.8 drugs (range 2–5). A mean of 4.7 drugs were given to the study patients. The mean length of therapy was 8 months, and after a standard follow-up period of 2 years all patients were cured. Cure was defined as clinical and radiographic stability and persistently negative post-treatment sputum cultures.

Microbiological, treatment and outcome data for all 13 patients with MDR-TB are shown in Tables 1 and 2. The cost of anti-TB drugs for MDR-TB was 14 to 29 times higher than that for drug-sensitive disease.

Discussion

The prevalence of MDR-TB varies dramatically according to geographic region, accounting for < 1% of TB cases in countries of western Europe and in Oman, and accounting for up to 27% of cases in highly endemic countries such as Latvia [*3–6*]. Primary MDR-TB refers to acquisition of infection caused by a strain of *M. tuberculosis* that is resistant to isoniazid and rifampicin. Secondary, or acquired, MDR-TB refers to drug resistance mutations occurring in a previously susceptible strain as a result of non-adherence with prescribed anti-TB treatment. At least 92% of our study cases in Oman had secondary MDR-TB, which is higher than studies in other countries where acquired resistance accounted for 66%–89% of MDR-TB cases [*3–5*]. A total

Table 1 **Microbiological, treatment, and outcome data for 13 tuberculosis (TB) patients with multi-drug resistant tuberculosis (MDR-TB) in Oman, 2000–05**

Variable	Value
Mean no. of resistant drugs per TB isolate	2.8
Drugs that isolates were resistant to (no. of patients)	
H/R	5
H/R/S	3
H/R/Z	2
H/R/E	1
H/R/E/S	1
H/R/Z/E/S	1
Mean no. of drugs used to treat MDR-TB per patient	4.7
Drugs used to treat MDR-TB (no. of patients)	
Pyrazinamide	10
Ethambutol	1
Ciprofloxacin	13
Streptomycin	8
Amikacin	5
Prothionamide	13
Cycloserine	5
Para-aminosalicylic acid	5
Surgical resection needed (no. of patients)	0
Mean treatment time (months)	8
Mean follow-up time (years)	2
Clinical outcome	
Survived	13
Died	0
Defaulted	0
Mean cost of treatment regimen per patient (Omani rials)	
Drug-sensitive TB	40
MDR-TB	540–1148

H = isoniazid; R = rifampicin; S = streptomycin; Z = pyrazinamide; E = ethambutol.

of 9 patients had been hospitalized for 2 months after their initial diagnosis of MDR-TB because of positive sputum smears, according to the national DOTS policy, and acquired resistance likely developed after these admissions as a result of subsequent non-compliance with drug therapy. Details of suspected non-adherence were not available from Ministry of Health records. The remaining 4 patients had received self-administered drug therapy entirely as outpatients or had received health centre-based DOTS for their primary TB infection.

Acquired drug resistance by *M. tuberculosis* has become one of the major obstacles to successful control of TB worldwide. Previous predictors of MDR-TB have included being foreign-born [*7–10*], having a history of previous TB [*7,11*] and HIV seropositivity [*7,11,12*], although such predisposing factors were not found in our study in Oman. Fortunately, we did not find any evidence of transmission of MDR-TB to close contacts.

Our results confirm that MDR-TB, while curable, is more complicated and more expensive to treat than the drug-sensitive disease. The duration of treatment is longer than for the drug-sensitive disease, and it is necessary to use 2nd- and 3rd-line anti-TB agents that have more adverse effects and are more expensive than the standard 1st line agents. In our study cohort, the cost of anti-TB drugs for MDR-TB was 14 to 29 times higher than treating the drug-sensitive disease.

Although previous studies have shown an increased mortality from MDR-TB compared to the drug-sensitive disease [*1,13*], our study showed a 100% cure rate. Oman's success in managing MDR-TB is most likely related to a number of factors including an excellent TB control infrastructure, diagnostic facilities for accurate culture and antibiotic susceptibility testing, active case and contact tracing by public health workers, individualized rather than standardized drug treatment, consistently available 2nd-line and 3rd-line therapeutic agents, and

Table 2 **Drug resistance and antituberculous drug regimen for 13 cases of multi-drug resistant tuberculosis in Oman**

Drugs that TB isolates were resistant to:	No. of isolates	Drug regimen	No. of doses	Cost (Omani rials)
H/R	5	Z/E/S/Pto/Cfx	1248	540
H/R/S	3	Z/E/Am/Pto/Cfx	1344	880
H/R/Z	2	E/S/Pto/Cfx/Cs/PAS	1696	802
H/R/E	1	Z/S/Pto/Cfx/Cs/PAS	1696	1148
H/R/E/S	1	Z/Am/Pto/Cfx/Cs/PAS	1792	1129
H/R/Z/E/S	1	H/Am/Pto/Cfx/Cs/PAS	1696	806

H = isoniazid; R = rifampicin; S = streptomycin; Z = pyrazinamide; E = ethambutol; Am = amikacin; Pto = prothionamide; Cfx = ciprofloxacin; Cs = cycloserine; PAS = para-aminosalicylic acid.

strictly enforced DOTS. Recent analysis of MDR-TB outcome data from large-scale series in France, Latvia, Estonia, Peru, Philippines and Russia demonstrate cure rates ranging from only 67%–76% [*3–5,14*].

In conclusion, we found a low incidence of MDR-TB in Oman (< 1%), and noted that all our cases were secondary and without previously reported risk factors such as HIV and intravenous drug use. There was no documented disease transmission among close contacts, and cure was achieved in all cases. Our data and recent literature reports demonstrate that national TB programmes employing DOTS can be effectively implemented.

From both a personal and public health perspective, prevention of MDR-TB is much more desirable than treatment of this complicated infection. Early diagnosis, enforced DOTS, and effective contact tracing of potentially exposed persons remain the most effective tools in limiting MDR-TB. Molecular epidemiology using DNA fingerprinting of recovered isolates may identify patterns of MDR-TB transmission that can further strengthen control efforts in Oman and the region.

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