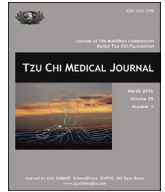




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## Case Report

# Outbreak of multidrug-resistant tuberculosis in an aboriginal family in eastern Taiwan



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## ABSTRACT

Spread of multidrug-resistant tuberculosis (MDR-TB) strains in the general population presents a serious threat to public health and severely threatens existing control efforts. Techniques such as spoligotyping and *Mycobacterium* interspersed repetitive units—variable-number tandem-repeat typing of mycobacterial isolates have been employed to confirm familial outbreaks of MDR-TB. We diagnosed and traced four MDR-TB cases in a family via genotyping. Despite aggressive treatment, the index case remained culture positive, but the other patients were cured. This is the first documentation of a familial MDR-TB outbreak affecting human immunodeficiency virus-seronegative patients in eastern Taiwan. Molecular techniques are important in the identification of sources of MDR-TB infections. The adult index case in our study developed MDR-TB due to poor compliance with the drug regimen (acquired resistance), followed by transmission of MDR-TB to his children in close household contact. This emphasizes the importance of an effective drug delivery program, such as directly observed treatment, to improve drug compliance and prevent the emergence of drug-resistant cases.

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## 1. Introduction

The World Health Organization estimated that the incidence of multidrug-resistant tuberculosis (MDR-TB), defined as isolates with resistance to at least isoniazid and rifampicin, was 220,000–400,000 cases (best estimate, 310,000) in the year 2011. MDR-TB has become an important issue in the management of TB [1]. The spread of MDR-TB strains in the general population presents a serious threat to public health and severely threatens existing control efforts, because the treatment of MDR-TB is prolonged (18–24 months), less efficacious (success rate <60%), more toxic, and much costlier [2] than that of drug-susceptible tuberculosis.

MDR-TB can result from new transmission of a resistant strain (primary transmission) or poor management of a patient infected with drug-susceptible organisms (acquired resistance). Outbreaks

of MDR-TB have occurred in health care facilities and institutional settings, primarily involving patients infected with the human immunodeficiency virus (HIV) [3–5]. A combination of epidemiologic investigation and genotyping has been used to find the origin of outbreaks and track dissemination of MDR-TB strains. In this report, we describe four HIV-seronegative MDR-TB cases in an aboriginal family in eastern Taiwan.

## 2. Case Reports

## 2.1. Case 1

The index case (Case 1) was an aboriginal man who was a tunnel worker. He lived in the village of Wan-Rong, Taiwan which had a TB incidence of 512.5 cases per population of 100,000 in 2006. He was first diagnosed with pulmonary TB in November 2000, when he was 43 years old. Sputum smears were positive for acid-fast bacilli, and sputum cultures grew *Mycobacterium tuberculosis*. This isolate was sensitive to all first-line drugs. The patient was cured after 8 months of standardized treatment, but due to a relapse in February 2002, antituberculosis treatment was restarted.

Conflicts of interest: none.

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During the second treatment course, the patient showed poor compliance with the treatment regimen. Sputum cultures were again positive in April 2004, and chest radiography revealed worsening of left lung infiltrations and cavitations (Fig. 1A). The results of a drug-susceptibility test (DST) of the sputum culture 2 months later revealed resistance to isoniazid (H) and rifampicin (R), so the patient's regimen was changed to ethambutol (E), pyrazinamide (Z), streptomycin (S), prothionamide (Pto), and moxifloxacin (Mfx). In September 2005, sputum cultures still grew *M. tuberculosis*, and repeated DST showed resistance to HERS.

The patient was enrolled in a directly observed therapy program (DOT-plus) in 2007, and continued treatment with E, Z, Pto, Mfx, para-aminosalicylic acid, and rifabutin (Rfb). However, this sputum cultures remained positive. Despite the use of Group I–V antituberculosis drugs, the patient's sputum cultures remained positive at the time of this report. He was diagnosed to have chronic MDR-TB in 2009 and was placed in long-term isolation in a negative-pressure room.

### 2.2. Case 2

Case 2 is the third daughter of the index case. In 2002, she was diagnosed with pulmonary TB at the age of 19 years. At that time, the isolated strain was sensitive to HERS. She completed 8 months

of treatment with HERZ and was cured in June 2003. However, in November 2006, a follow-up chest radiograph (Fig. 1B) and sputum cultures confirmed recurrent disease. DST showed resistance to HR, so she was treated with E, Z, S, Pto, and Mfx. Streptomycin was used for 6 months, and she completed an 18-month treatment course and was cured in September 2008.

### 2.3. Case 3

Case 3 is the index patient's older son. He was diagnosed with pulmonary TB in May 2005, at the age of 14 years, during a regular health checkup. A chest radiograph revealed infiltrations in the left upper lobe (Fig. 1C). He was treated with HERZS, but 2 months later DST showed HER resistance. The regimen was switched to Z, S, Pto, Rfb, and Mfx. Streptomycin was used for 7 months. He completed 18 months of treatment and was cured in January 2007.

### 2.4. Case 4

Case 4 is the index patient's younger son. He was first diagnosed in November 2006, at the age of 13 years. A chest radiograph revealed infiltrations and cavitations over the left upper lobe (Fig. 1D). The first *M. tuberculosis* isolate was fully drug susceptible, and he was treated with HERZ. However, due to persistent positive

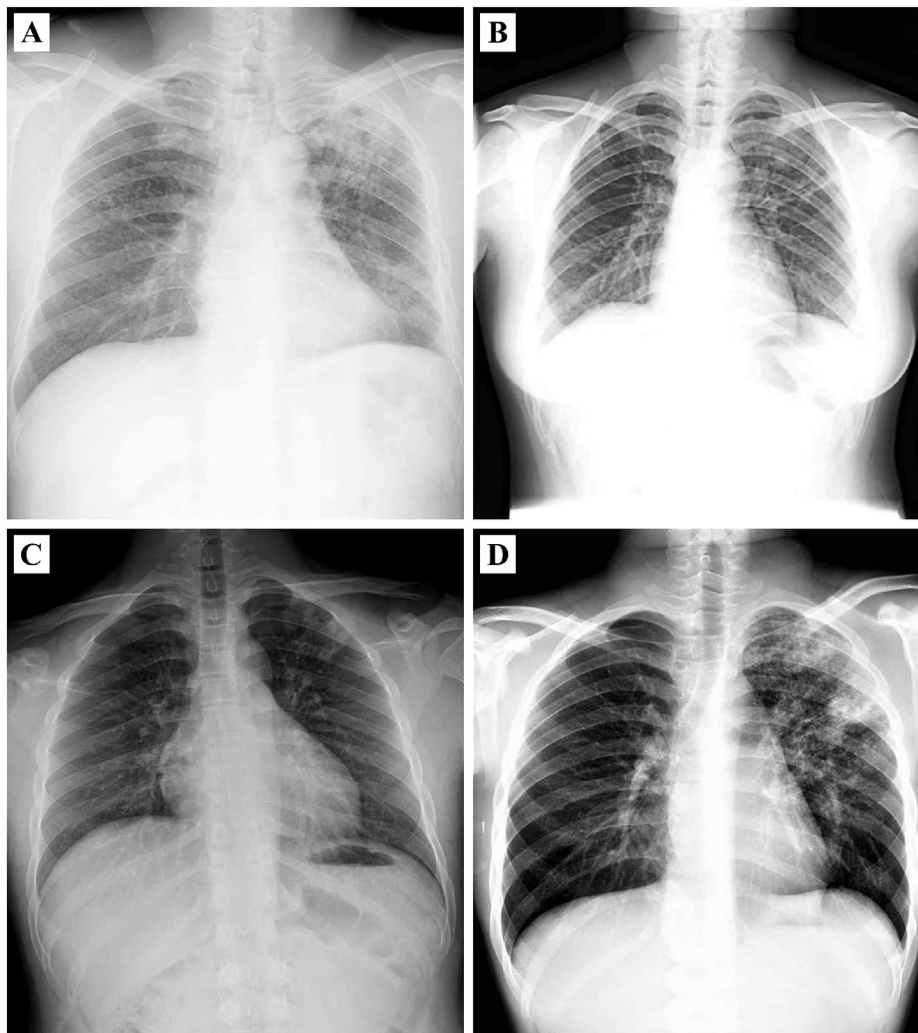


Fig. 1. Chest radiographs of four patients with multidrug-resistant tuberculosis: (A) Case 1, (B) Case 2, (C) Case 3, and (D) Case 4.

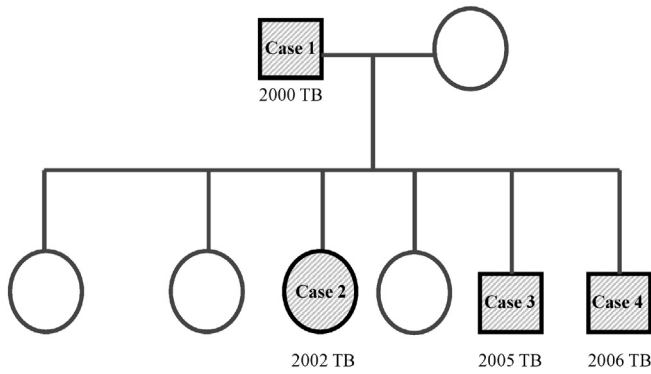


Fig. 2. Pedigree of MDR-TB family. MDR-TB = multidrug-resistant tuberculosis.

sputum cultures 3 months after starting treatment, DST was repeated and revealed resistance to HERS. The regimen was switched to Z, kanamycin, para-aminosalicylic acid, Pto, Rfb, and Mfx. He was cured in March 2009 after sputum conversion for 18 months. All four patients were tested for antibodies to HIV by enzyme immunoassay, and all were found to be negative (Fig. 2).

Drug susceptibility testing was performed by the indirect proportion method. *M. tuberculosis* isolated from all four patients revealed similar multiple drug resistance to first-line HER and second-line ofloxacin. Fortunately, the strains were sensitive to kanamycin (Table 1). Isolates of MDR-TB stains from the four patients showed identical genotypes indistinguishable from each other by spoligotyping and *Mycobacterium* interspersed repetitive units—variable-number tandem-repeat (MIRU-VNTR) typing (Table 2).

3. Discussion

The household transmission in this family was proved by identical spoligotyping and MIRU-VNTR typing. The MDR-TB outbreak outlined in this study shows the potential of molecular epidemiology and field epidemiology in illustrating the sequence of transmission in clusters of MDR-TB. In the early 1950s, investigators reported that isoniazid-resistant strains of *M. tuberculosis* lacked catalase activity and were less virulent in guinea pigs and mice [6–10] than susceptible strains. It was hypothesized that drug-resistant strains of *M. tuberculosis* might be less capable of being transmitted and less likely to produce secondary cases compared with drug-susceptible strains [9]. However, observations by Snider et al [10] suggested that the population in contact with MDR-TB bacilli developed the disease at the same rate as those in contact with drug-susceptible bacilli. More recently in Brazil, Teixeira et al [11] found that transmission and development of TB were comparable between household contacts with MDR-TB and those with drug-susceptible TB. In South Africa, Schaaf et al [12]

Table 1  
DST of strains of four patients.

Case	Date	H	Rif	E	Sm	Km	Pto	PAS	Ofx	Cm	Rifabutin
1	Nov 25, 2006	R	R	R	R	S	S	S	R	S	R
2	Nov 17, 2006	R	R	R	S	S	R	S	R	S	R
3	Nov 17, 2006	R	R	R	S	S	S	S	R	S	R
4	May 17, 2006	R	R	R	R	S	S	S	R	S	R

Cm = capreomycin; DST = drug-susceptibility test; E = ethambutol; H = isoniazid; Km = kanamycin; Ofx = ofloxacin; Pto = prothionamide; R = resistant; R = Rif; S = susceptible; Sm = streptomycin.

Table 2  
Genotyping results of strains of four patients.

Case	Spoligotype	MIRU-VNTR																							
		MT01	MT02	MT03	MT04	MT05	MT06	MT07	MT08	MT09	MT10	MT11	MT12	MT13	MT14	MT15	MT16	MT17	MT18	MT19	MT20	MT21	MT22	MT23	MT24
1	Beijing	2	7	2	3	3	2	3	4	4	4	4	4	6	3	11	2	5	3	2	1	3	4	2	3
2	Beijing	2	7	2	3	3	2	3	4	4	4	4	4	6	3	11	2	5	3	2	1	3	4	2	3
3	Beijing	2	7	2	3	3	2	3	4	4	4	4	4	6	3	11	2	5	3	2	1	3	4	2	3
4	Beijing	2	7	2	3	3	2	3	4	4	4	4	4	6	3	11	2	5	3	2	1	3	4	2	3

MIRU-VNTR = *Mycobacterium* interspersed repetitive units—variable-number tandem repeat.

examined the prevalence of PPD reactivity and active TB in children, and concluded that the incidence of infection and disease in children in contact with MDR-TB adult index cases was comparable with that occurring in children in contact with drug-susceptible adult index cases. Our report confirmed the household transmission of MDR-TB infection from an adult index case to his three children.

The MDR-TB genotypes from all four patients belonged to the Beijing family. Beijing family genotypes of *M. tuberculosis* were first recognized in 1995. This family of strains accounted for 86% of tuberculosis isolates collected from Beijing, China [13], and it has spread worldwide. In 2005, Jou et al [14] reported that 187 of 421 *M. tuberculosis* isolates (44.4%) collected randomly in four geographic regions of Taiwan belonged to Beijing family genotypes. Antituberculosis drug resistance has been found more often in Beijing family genotype strains (46.4%) than in non-Beijing family genotype strains (34.4%). A countrywide study in Estonia also showed a strong correlation between the Beijing family and drug resistance. The Beijing family accounted for 87.5% of all MDR-TB isolates and 67.2% of all isolates with any drug resistance [15].

Some strains of the Beijing family have been demonstrated to have high virulence and were associated with active transmission young people who had BCG immunizations in Vietnam [16]. The adult index case in our study developed MDR-TB due to poor compliance with the drug regimen (acquired resistance), followed by transmission of MDR-TB to his children in close household contact (primary transmission). This emphasizes the importance of an effective drug delivery program such as DOT to improve drug compliance and prevent the emergence of drug-resistant cases. In addition, the prolonged infectious period of the index case increased the risk of household transmission. Timely diagnosis of MDR-TB and effective patient-centered treatment would help prevent transmission of MDR-TB in families and communities.

In recent years, several fingerprinting methods for typing mycobacteria isolates have become available. The most widely used molecular methods for *M. tuberculosis* isolates are IS6110 restriction fragment length polymorphism (RFLP) typing, spoligotyping, and MIRU-VNTR typing. IS6110 RFLP typing of *M. tuberculosis* has been the gold standard for genotyping. However, it is laborious, time consuming, and expensive.

The optimized MIRU-VNTR set combined with spoligotyping showed a slightly higher predictive value for the study of TB transmission than the current gold standard IS6110 RFLP [17]. Spoligotyping combined with MIRU-VNTR is less labor intensive than IS6110 RFLP. Because of its rapidity and ease of data exchange and comparison, this method has the potential to replace RFLP as the gold standard, and can help facilitate research and international comparisons in the molecular epidemiology of TB.

Early detection and appropriate treatment of MDR-TB can result in a favorable response. Although the three children of the index case were infected with the same MDR-TB strain, their cases were

detected early and they were compliant with treatment with second-line medications. Noncompliance of the index case resulted in the occurrence of MDR-TB, and he failed to show conversion even after years of treatment with second-line drugs. He is now under forced isolation for the rest of his life in a negative pressure setting. This serves as a solemn reminder of the importance of early detection and medical compliance.

In summary, to our knowledge, this is the first documentation of a familial MDR-TB outbreak affecting HIV-seronegative patients in eastern Taiwan.

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