



Transmission of multidrug-resistant and extensively drug-resistant tuberculosis in a metropolitan city

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ABSTRACT: Multidrug-resistant (MDR)- tuberculosis (TB) and extensively drug resistant (XDR)-TB reportedly lead to increased household transmission.

This is a retrospective cohort study of active TB occurring among household contacts exposed to MDR-TB.

Of 704 contacts in 246 households, initial screening identified 12 (1.7%) TB cases (prevalent cases) and 17 (2.4%) contacts that subsequently developed active TB (secondary cases) after a median (range) duration of 17 (5–62.5) months. Eight prevalent cases and three secondary cases had MDR-TB. TB incidence rates per 100 000 person-years were 254.9 overall and 45.0 for MDR-TB. XDR-TB in the index MDR-TB patient significantly increased the odds of identifying a prevalent TB case to 4.8 (95% CI 1.02–22.5), and the hazard of finding a secondary TB case to 4.7 (95% CI 1.7–13.5). Molecular fingerprinting confirmed household transmission of MDR-TB. Of 20 retrievable isolates from 27 XDR-TB index cases, restriction fragment length polymorphism analysis showed clustering among 13 (65%), with 11 (55%) due to recent transmission by n-1 method and an identifiable household source in only three (27.2%) of the 11 cases.

XDR-TB relative to MDR-TB significantly increases household transmission of TB, probably reflecting prolonged/higher infectivity, and indicating a need for prolonged household surveillance. XDR-TB may largely transmit outside of the household settings.

KEYWORDS: Case finding, contact investigations, extensively drug-resistant tuberculosis, multidrug-resistant tuberculosis

Tuberculosis (TB) is still an infectious disease of public health importance today.

Of particular concern is the occurrence of multidrug-resistant (MDR)-TB defined by bacillary resistance to at least isoniazid and rifampicin, and extensively drug-resistant (XDR)-TB, which is MDR-TB with additional resistance to any fluoroquinolone, and at least one of the three second-line injectable drugs (kanamycin, amikacin and capreomycin). MDR-TB and XDR-TB reportedly require prolonged treatment, with a high risk of treatment failure [1, 2]. Slow bacteriological conversion and treatment failure may increase the risk of transmission within the community, as suggested by reports of secondary TB transmission within the household [3, 4]. However, few studies have systematically evaluated the magnitude of such transmission risks within a defined geographical area, such as a metropolitan city.

Designated as a Special Administrative Region in the People's Republic of China, with autonomy

regarding its own infrastructure including housing, transport and healthcare, Hong Kong is a metropolis with a population of 7 million. It is classified by the World Health Organization (WHO) as an intermediate TB burden area. The annual incidence and notification rate of TB cases in Hong Kong has steadily declined from 7072 cases (109 per 100 000 population) in 1997 to 5193 cases (74 per 100 000 population) in 2009 [5]. Around 1% of the culture-confirmed TB cases are MDR-TB (30–40 cases each year), of which approximately 10% are XDR-TB [5]. Around 40–50% of the MDR-TB (15–20 cases) cases are new cases without history of previous TB treatment [6, 7]. It has been a regular practice in Hong Kong to screen for active TB among household TB contacts regardless of sputum smear status [8]. Chest radiography (CXR) is the main screening tool. All contacts with initially negative screens are advised to seek immediate medical attention for any subsequent symptoms and signs suggestive of TB. Further workup is carried out in the presence of CXR abnormalities or suspicious symptoms.

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Because of universal neonatal bacille Calmette–Guérin vaccination coverage (and extensive revaccination in primary schools before 2000) [9], the tuberculin skin test was not used routinely in the investigation of contacts except among young child contacts (aged below 5 years) of smear-positive index cases prior to 2005. As there is no universally agreed prophylactic treatment for MDR-TB, close contacts of MDR-TB cases are followed up half-yearly for active disease without any preventive treatment. The current study is a retrospective cohort analysis of household contacts exposed to MDR-TB in this locality.

METHODS

All MDR-TB patients notified from 1997 to 2006 were identified from the territory-wide TB registry and laboratory surveillance data as reported previously [10].

The contact investigation records of all MDR-TB patients (index cases) were reviewed to identify all household contacts, defined as persons living and sleeping in the same household as the index case for at least 1 month. Their initial screening and subsequent follow-up results were also ascertained from the contact investigation records. At the end of the study, the names and identification card numbers of all identified contacts were cross-matched with the territory-wide TB registry and death registry to detect any cases of TB or date of death after the active surveillance period. An observation was censored when the contact died from any causes other than TB or no TB developed by the end of the study period (31 May 2011). The rate of TB development was calculated as the number of active TB cases per person-years. Diagnostic and clinical information of all identified TB cases was verified by checking the relevant medical records. An active case of TB was defined as disease proven by isolation of *Mycobacterium tuberculosis*, or in the absence of bacteriological confirmation, disease diagnosed on clinical, radiological and/or histological grounds together with an appropriate response to TB treatment.

The respective relationships between the occurrence of prevalent and secondary TB cases among household contacts exposed to MDR-TB and the index case's characteristics were examined. A prevalent case was defined as a case of TB disease detected in the initial screening, whereas a secondary case referred to a case detected in the subsequent surveillance period. Univariate analysis of categorical data was performed by the Pearson's Chi-squared test or the Fisher's exact test, as appropriate. Significant predictors of prevalent and secondary TB cases were identified in logistic risk models and Cox models, respectively. A two-tailed p-value <0.05 was taken as statistically significant. Statistical analyses were performed using SPSS version 16.

As part of the local surveillance, DNA fingerprinting with restriction fragment length polymorphism (RFLP) analysis was carried out in: 1) MDR-TB with a prevalent and secondary case identified in the contact screening to ascertain whether the same *Mycobacterium tuberculosis* strain was transmitted within the household; 2) All XDR-TB cases in this cohort to assess the degree of molecular clustering; using standardised methods with a 245-bp right-sided probe and internal molecular weight standards [11]. Clusters were defined as groups of two or more isolates having an identical IS6110 RFLP pattern, allowing for the presence, absence or shifting of no more than one band.

This study was approved by the ethics committee of the Department of Health (Hong Kong SAR, China). All patients were informed at the time of care delivery that the clinical data collected would be used for statistical analysis and research purposes.

RESULTS

Table 1 summarises the characteristics of the 270 MDR-TB cases with case categories and clinical outcomes classified according to the criteria proposed by LASERSON *et al.* [12]. Over 45% were new cases with no prior history of TB treatment (Laserson's MDR case category 1). Approximately 13% were new immigrants. A total of 142 (51.8%) were ever smokers. Comorbidities were present in 141 (52.2%). Voluntary HIV testing was offered to all TB patients and the overall incidence of HIV positivity was low (1.1%). Eight (2.9%) cases showed potential epidemiological linkage by household (four families), including two pairs (1.5%) of XDR-TB cases and two pairs (1.5%) of other MDR-TB cases.

Figure 1 shows the flowchart of household contact tracing. Excluding 14 MDR-TB patients with no household contacts and 10 with missing contact records, 246 index MDR-TB patients were recruited for household contact analysis. Among 736 household contacts, 32 were excluded as they did not attend for screening. Among the 704 household contacts included in the final analysis, 12 (1.7%) prevalent cases were found: three XDR-TB cases associated with three XDR-TB index cases; one XDR-TB, four MDR-TB, three drug-susceptible TB and one culture negative TB case associated with seven MDR-TB index cases. The median number of contacts per index case was three (range 1–8). RFLP analysis among 11 index-prevalent contact pairs showed 100% concordance in three pairs with XDR-TB, 100% concordance in one MDR-TB index case pairing with one contact with XDR-TB, 50% concordance in four non-XDR MDR-TB pairs, and no concordance in three MDR-TB index cases pairing with three contacts with drug-susceptible TB.

Among the 692 household contacts with no TB found during the initial screening, 17 (2.5%) secondary cases were found in 15 households, including six (two XDR-TB, two drug-susceptible TB and two culture-negative TB) cases among 94 contacts exposed to XDR-TB, and 11 (one MDR-TB, two streptomycin and isoniazid-resistant TB, two drug-susceptible TB and six culture-negative TB) among 598 contacts exposed to non-XDR MDR-TB. RFLP among eight index-secondary contact pairs showed 100% concordance in one pair of XDR-TB patients, 100% concordance in one pair of non-XDR MDR-TB patients, 100% concordance in two MDR-TB index cases pairing with two contacts with non-MDR-TB (streptomycin and isoniazid-resistant), and no concordance in four MDR-TB index cases pairing with four contacts with drug-susceptible TB. Both index cases of the two pairs of MDR-TB matching with non-MDR-TB were retreatment cases. The follow-up time was 6669 (mean \pm SD 8.77 \pm 3.98) person-years overall, 1005 (10.58 \pm 4.23) person-years among contacts exposed to XDR-TB and 5664 (8.51 \pm 3.88) person-years among contacts exposed to non-XDR MDR-TB, giving TB incidence rates of 254.9, 597.0, and 194.2 cases per 100 000 person-years, respectively.

Tables 2 and 3 show the respective relationships between index case's characteristics and the occurrence of prevalent TB

TABLE 1 Baseline characteristics of a cohort of 270 multidrug-resistant (MDR) tuberculosis (TB) patients in Hong Kong (1997–2006)

Parameters	XDR-TB	Other MDR-TB	Total	p-value
Subjects n	27	243	270	
Demographics				
Age years	41 (32–54)	46 (35–62)	46 (34–60)	0.480
Males	15 (55.6)	173 (71.2)	188 (69.6)	0.094
Nonpermanent immigrants (<7 years)	5 (18.5)	31 (12.8)	36 (13.3)	0.400
Ever smoker	14 (51.8)	128 (52.6)	142 (51.8)	0.670
Adverse social factors (incarceration, drug addict, financial assistance)	7 (25.9)	64 (26.3)	71 (26.3)	0.963
Comorbidities				
Diabetes mellitus	2 (7.4)	45 (18.5)	47 (17.4)	0.149
Renal impairment	0 (0)	6 (2.5)	6 (2.2)	0.409
Lung cancer	2 (7.4)	8 (3.3)	10 (3.7)	0.283
Other malignancy	2 (7.4)	23 (9.5)	25 (9.3)	0.726
Obstructive lung disease	4 (14.8)	31 (12.8)	35 (13.0)	0.763
Elderly care home or institutional	0 (0)	8 (3.3)	8 (3.0)	0.339
CVS disease (HT, IHD)	1 (3.7)	16 (6.6)	17 (6.3)	0.401
Liver cirrhosis	0 (0)	7 (2.9)	7 (2.6)	0.372
Any comorbidity	9 (33.3)	132 (54.3)	141 (52.2)	0.044
WHO case category				
1 (no history of TB treatment)	11 (40.7)	113 (46.5)	124 (45.9)	0.001
2 (treatment with first line for >1 month)	10 (37.0)	124 (51.0)	134 (49.6)	
3 (treatment of second line for >1 month)	5 (18.5)	3 (1.2)	6 (2.2)	
4 (transferred in cases)	1 (3.7)	3 (11.1)	6 (2.2)	
Pulmonary TB only	26 (96.3)	219 (90.1)	245 (90.7)	0.537
Pulmonary and extrapulmonary TB	1 (3.7)	18 (7.4)	19 (7.0)	
Extrapulmonary TB	0 (0.0)	6 (2.5)	6 (2.2)	
HIV positive	0 (0.0)	3 (1.2)	3 (1.1)	0.844
Pulmonary disease				
Positive AFB smear	17 (63.0)	152 (64.4)	169 (64.3)	0.82
Minimal extent on chest radiograph	17 (63.0)	145 (61.2)	162 (61.4)	0.544
Moderate extent on chest radiograph	6 (22.2)	70 (29.5)	76 (28.8)	
Severe extent on chest radiograph	4 (14.8)	22 (9.3)	26 (9.8)	
Cavitary disease	6 (23.1)	104 (43.9)	110 (41.8)	0.041

Data are presented as median (range) or n (%), unless otherwise stated. XDR: extensively drug resistant; CVS: cardiovascular disease; HT: hypertension; IHD: ischaemic heart disease; WHO: World Health Organization; AFB: acid-fast bacilli.

cases and secondary TB cases among household contacts exposed to MDR-TB. Among 607 household contacts exposed to 220 non-XDR MDR-TB index patients, nine prevalent TB cases (including one XDR-TB and four MDR-TB cases) and 11 secondary cases (including one MDR-TB case) were found; whereas among 97 household contacts exposed to 26 XDR-TB index patients, three prevalent TB cases (all XDR-TB cases) and six secondary cases (including two XDR-TB cases) were identified. Logistic regression analyses showed that sputum smear negativity and XDR-TB in the index case significantly increased the odds of identifying prevalent TB cases among household contacts exposed to MDR-TB to 4.3 and 4.8, respectively. Cox regression analyses showed that cavitary lung disease and XDR-TB in the index case significantly increased the hazards of having secondary cases among household contacts exposed to MDR-TB to 3.7 and 4.7 respectively.

The above regression analyses on prevalent and secondary cases were based on all the positive cases identified by contact tracing and not on the molecularly concordant cases, as some of the contact cases were culture-negative and not all of the positive cultures were retrievable for RFLP analysis. RFLP analysis performed in 11 retrievable isolates (eight drug-resistant and three fully susceptible) among 12 prevalent cases and eight retrievable isolates (four drug-resistant and four fully susceptible) among 17 secondary cases in household contact tracing showed concordant cases in three XDR-TB clusters A, B and C; one XDR-TB to MDR-TB cluster D; two MDR-TB clusters E and G; and two MDR-TB pairing with streptomycin and isoniazid-resistant TB clusters F and H (table 4). In sensitivity analyses using prevalent and secondary cases identified to be “truly positive” by RFLP, XDR-TB was still shown to be a significant predictor for prevalent cases

TABLE 2 Index case characteristics and the occurrence of prevalent tuberculosis (TB) cases among household contacts exposed to multidrug-resistant (MDR)-TB: logistic regression analyses

Index case characteristics	Proportion of households with a prevalent TB case %	Unadjusted OR (95% CI)	p-value by univariate analysis	Adjusted OR (95% CI) [#]
Permanent resident				
Yes	3.4	0.60 (0.12–2.95)	0.62	
No	5.6			
Adverse social factors				
Present	4.2	1.21 (0.31–4.81)	0.73	
Absent	3.5			
Sputum smear⁺				
Negative	3.6	5.55 (1.45–20)	0.04 [†]	4.3 (1.02–18.51)
Positive	0.7			
Cavitary disease⁺				
Yes	0.9	0.15 (0.02–1.18)	0.05 [†]	
No	5.8			
Extent on chest radiograph >equivalent of right lung				
Yes	3.8	1.02 (0.12–8.37)	1.0	
No	3.8			
Bacterial susceptibility⁺				
XDR-TB	11.1	4.21 (1.02–17.37)	0.05 [†]	4.8 (1.02–22.5)
Non-XDR MDR-TB	2.9			
Smoking status				
Ever smoker	2.1	1.92 (0.71–5.20)	0.2 [†]	
Nonsmoker	5.5			

XDR: extensively drug resistant. [#]: variables were selected by backward stepwise selection with p-values for entry and removal being 0.05 and 0.10, respectively; [†]: values by Fisher exact test; ⁺: covariates included in multiple logistic regression analysis.

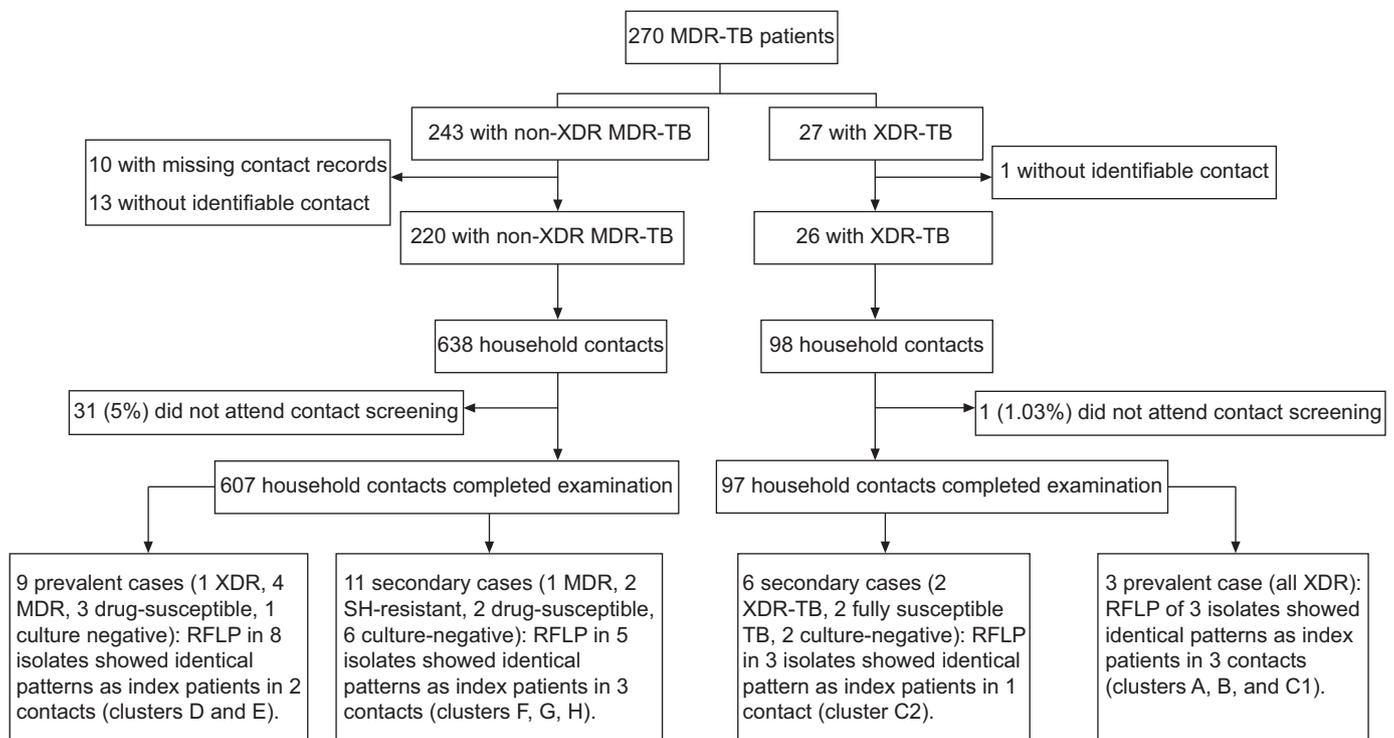


FIGURE 1. Contacts exposed to 270 multidrug-resistant (MDR) tuberculosis (TB) patients (1997–2006). XDR: extensively drug resistant; RFLP: restriction fragment length polymorphism; SH-resistant: streptomycin and isoniazid resistant.

TABLE 3 Index case characteristics and the occurrence of secondary tuberculosis (TB) cases among household contacts exposed to multidrug-resistant TB: Cox regression analyses

Index case characteristic	Unadjusted hazard ratio (95% CI)	p-value by univariate analysis	Adjusted hazard ratio (95% CI) [#]
Permanent resident	2.70 (0.36–20.40)	0.33	
Adverse social factors [†]	2.07 (0.80–5.38)	0.13	
XDR-TB [†]	3.30 (1.24–8.92)	0.02	4.7 (1.7–13.5)
Cavitary disease [†]	2.68 (1.02–7.05)	0.05	3.7 (1.4–10.3)
Sputum smear positive [†]	2.61 (0.75–9.09)	0.13	
CXR extent of disease	0.61 (0.08–4.61)	0.63	
Ever smoker	1.92 (0.71–5.20)	0.20	
WHO treatment outcome at 2 years: cured or completed treatment [†]	0.48 (0.18–1.26)	0.14	

XDR: extensively drug resistant; CXR: chest radiograph; WHO: World Health Organization. [#]: variables were selected by backward stepwise selection with p-values for entry and removal being 0.05 and 0.10, respectively; [†]: covariates included in multi-variable Cox regression analysis.

($p=0.013$) and a suggestive trend of association was also found for secondary cases ($p=0.068$).

RFLP analysis in 20 non-duplicate retrievable isolates from 27 XDR-TB cases included in this retrospective cohort showed nine additional cases outside the household in cluster A (eight cases) and cluster C (one case). Overall, molecular clustering was found in 13 (65%) of 20 retrievable XDR-TB specimens (nine cases in cluster A and four cases in cluster C; 75% for new cases, 58.3% for retreatment cases). Disregarding the effect of incomplete sampling [13] and using the n-1 method [14] (cases other than the first case in each cluster are counted as resulting from recent transmission), 11 out of 20 (55%) of XDR-TB cases were considered to have resulted from recent transmission, but only three (one case in cluster A and two cases in cluster C) or 27.2% of the above 11 cases had an identifiable source within the household. Figure 2 shows the temporal development of four XDR-TB molecular clusters (including one non-XDR MDR-TB case in cluster D).

DISCUSSION

In this study, 124 (45.9%) of the MDR-TB cases notified in Hong Kong from 1997 to 2006 did not have prior history of anti-TB treatment. RFLP analysis confirmed household transmission of MDR-TB. A high degree (65%) of molecular clustering was found among XDR-TB isolates, highlighting the importance of recent transmission (55% by n-1 method) with approximately a quarter of such transmission occurring within the household. 12 (1.7%) prevalent TB cases were found among household contacts, with approximately two-thirds being MDR-TB cases. 18 (2.5%) secondary TB cases were found in the remaining household contacts cases occurring at a secondary TB rate of 255 per 100 000 person-years with a mixture of drug resistance patterns. The occurrence of prevalent and secondary TB cases within a household can be independently predicted by the index case's characteristics: sputum smear negativity and XDR-TB for a prevalent TB case, and cavitary lung disease and XDR-TB for secondary TB cases.

Drug-resistant TB is either primary or acquired. Primary drug resistance occurs as a result of transmission of drug-resistant

TB strains whereas acquired drug resistance develops because of inadequate treatment. Traditionally, acquired drug resistance has been emphasised as the principal mechanism by which drug-resistant TB develops. However, in recent MDR-TB reports, the prevalence of new cases with no previous TB treatment has been rising in both high-prevalence HIV settings (South Africa: 55% [15]) and low-prevalence HIV settings (Shanghai, China: 60% [16]; Latvia: 37% [17]; Japan: 45% [18]). In the present study, we found a similarly high proportion (>45%) of new cases among MDR-TB patients (*i.e.* Laserson's MDR case category 1), and observed a much higher molecular clustering rate among the XDR-TB cases in this study (65%) than the clustering rate reported among general TB patients (29.2%) in Hong Kong [19]. Similarly high clustering rates were also reported among XDR-TB patients in Japan (71%) [18] and Europe (82%) [20], again highlighting the importance of recent transmission for these extensively drug-resistant cases. A substantial proportion of MDR-TB with primary drug resistance in Hong Kong may be anticipated from the significant decline in acquired drug resistance among MDR-TB cases [21].

Our study showed prevalent TB and incident TB in 1.7% and 2.5% of household contacts respectively. Overall, TB, either incident or prevalent, is found in 4.1% of the MDR-TB contacts, which is higher than the corresponding prevalence rates of 1.9% and 1.7% reported among household contacts of drug-susceptible TB in the same locality [8, 22], but lower than the reported rates of 5% in another MDR-TB contact study in 2011 [23] and 4.5% in one meta-analysis [24]. While smear positivity and cavitary disease were shown to be significant predictors of TB among contacts exposed to predominantly drug-susceptible TB in our previous study [22], this study found a significant association between an XDR-TB index patient and the occurrence of both prevalent and secondary cases among contacts exposed to MDR-TB. This likely reflects the prolonged duration of infectivity of index cases with XDR-TB. Heightened awareness of TB symptoms (*e.g.* chronic cough) in the presence of a known prevalent TB case in the household might have led to early medical consultation, and this may underline the association between the negative smear status of the index case with a prevalent case in the same household.

TABLE 4 Multidrug-resistant (MDR) tuberculosis (TB) cases among households with restriction fragment length polymorphisms (RFLP) showing a similar pattern

Index case characteristics (cluster label)	Contact details	Contact's treatment compliance	Contact's sputum conversion at second or third month	Contact's treatment outcome
Index A: M/26 diagnosed TB in May 1997; XDR-TB with additional resistance to S, M, Z, Ethio, Oflo, Amik, Kana, Capreo (cluster A)	Index A's mother: F/54, diagnosed TB in Oct 1996; XDR-TB with additional resistance to S, M, Z, Ethio, Oflo, Amik, Kana, Capreo RFLP showed identical strain to that of index A	Defaulted treatment	Persistently positive culture	Committed suicide in 1998
Index B: F/34 diagnosed TB in Sept 2003; XDR-TB with additional resistance to S, M, Ethio, Oflo, Amik, Kana, Capreo (cluster B)	Index B's father: M/65 diagnosed TB in December 1996; XDR-TB with additional resistance to S, M, Ethio, Oflo, Amik, Kana, Capreo RFLP showed identical strain to that of index B	Defaulted treatment after 1 week; claimed to go back to China	Not converted; culture positive in 1996 and 2002	Died from respiratory failure in February 2002
Index C1: F/24 diagnosed TB in July 2000; XDR-TB with additional resistance to S, M, Z, Ethio, Oflo, Amik, Kana, Capreo (cluster C)	Index C1's grandfather: diagnosed TB in November 1986; XDR-TB with additional resistance to S, M, Z, Oflo, Amik, Kana, Capreo, with acquired resistance to Ethio since 1993 RFLP showed identical strain to that of index C1	Fair compliance Failure case with repeated treatment in 1986 to 1998; 1991 to 1994	Persistently positive culture from 1986 to 2004	Retreated from 2004 to 2005 with long-term hospital care; died in 2005
Index C2: M/30 diagnosed TB in July 1997; XDR-TB with additional resistance to S, M, Z, Oflo, Amik, Kana, Capreo; defaulted treatment and follow up, additional resistance to Ethio found in 2010 specimen (cluster C)	Index C2's father: M/45 diagnosed TB in March 1997; XDR-TB with additional resistance to S, M, Z, Oflo, Amik, Kana, Capreo with acquired resistance to Ethio since 1998 RFLP showed identical strain to that of index C2	Poor compliance with multiple defaults	Declared failure case in January 1999	Died of TB in September 1999
Index D: M/37 diagnosed TB in May 2003; MDR-TB with additional resistance to S, M, Z, Amik, Kana, Capreo (cluster D)	Index D's father: diagnosed TB in November 1989; MDR-TB with initial resistance to S, M, Z, Amik, Kana, Capreo; then XDR-TB with acquired resistance to Oflo, Cycloserine RFLP showed identical strain to that of index D	Failure case since 1992, Poor with multiple default and retreatment	Not converted	Died from respiratory failure in May 2004
Index E: M/20, diagnosed TB in July 2000; MDR-TB with additional resistance to S and Oflo (cluster E)	Index E's friend: M/20 diagnosed TB in April 1992 MDR-TB with additional resistance to S and Oflo RFLP showed one band difference from index E Father of index E's friend: diagnosed TB in May 1990 MDR-TB with additional resistance to S, then acquired resistance to Oflo RFLP showed one band difference from index E	Defaulted treatment in 1994 and 1996, discharge against medical advice Defaulted treatment in 1991; poor compliance from 1992 to 1996	Not converted; persistently positive culture in 1994 and 1996 Not converted; culture positive in 1992, 1995 and 1996	Died of massive haemoptysis in November 1998 Died from massive haemoptysis in September 1996
Index F: M/30 diagnosed in Dec 2002; TB with resistant to S and H (cluster F)	Index F's father: diagnosed TB in Aug 1997; initially TB with resistance to S and H; poor compliance; subsequently MDR-TB; relapse in Nov 2007 with TB resistance to S and H but not MDR RFLP showed identical strain to that of index F	Poor compliance with intermittent default	Yes	Cured in 1999
Index G: F/18 diagnosed TB in March 2002; MDR-TB (resistant to H and R only) (cluster G)	Index G's brother: M/17 diagnosed TB in Jan 1997; MDR-TB (resistant to H and R only) RFLP showed identical strain to that of index G	Good compliance	Yes	Cured
Index H: M/50 diagnosed TB in Jan 2004; initially S, H-resistant; poor compliance; subsequently MDR-TB (cluster H)	Index H's son: M/27 diagnosed TB in Sept 2005; TB with resistance to S and H RFLP showed identical strain to that of index H	Poor compliance	Yes	Defaulted treatment since August 2006

XDR: extensively drug resistant; S: streptomycin; H: isoniazid; R: rifampicin; M: ethambutol; Z: pyrazinamide; Ethio: ethionamide; Oflo: ofloxacin; Amik: Amikacin; Kana: Kanamycin; Capreo: capreomycin.

Among eight retrievable isolates from 17 secondary cases identified by the contact tracing, only four cases had concordant strains as proven by RFLP (XDR-TB cluster C2, MDR-TB cluster G and two MDR-TB pairing with streptomycin and isoniazid-resistant TB clusters F and H). The occurrence of different resistance patterns within individual molecular clusters could have resulted from progressive acquisition of resistance by the source strain during the prolonged infectious period while under treatment or the presence of multiple clones (of the same strain) showing varying degrees of drug resistance in the infected host.

RFLP analysis confirmed the transmission of MDR-TB among household contacts while regression analysis showed XDR-TB

had a higher risk of household transmission among all MDR-TB cases. On further examination of the clinical details in these households (table 4), most of them involved XDR-TB patients with persistent sputum culture positivity because of either default or treatment failure. Although the overall prognosis of XDR-TB patients is poor, with slow sputum culture conversion, high percentage of treatment failure and early mortality within 1 year [1, 2, 15], some XDR-TB patients can survive for years (as in the case of Index C1's grandfather), thus posing a substantial risk to their families.

In this study, approximately a quarter of the presumably recently transmitted XDR-TB cases had traceable sources within

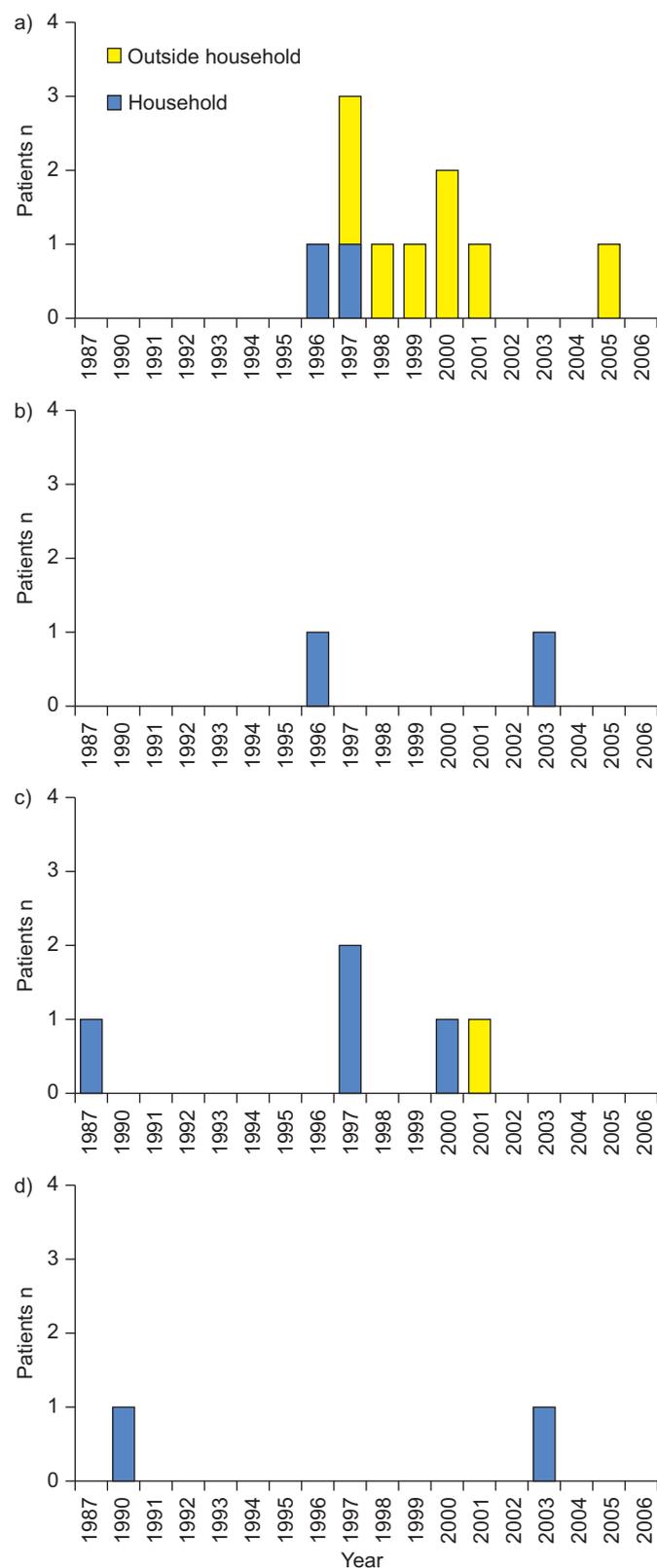


FIGURE 2. Temporal developments of four clusters (with the prevalent case in contact tracing included). a) Cluster A: 10 extensively drug-resistant (XDR) tuberculosis (TB) cases; b) cluster B: two XDR-TB cases; c) cluster C: five XDR-TB cases; and d) cluster D: one multidrug-resistant TB and one XDR-TB case.

the household. A major proportion of the ongoing transmission therefore appears to take place outside the household. Hong Kong, with a population of 7 million living in an area of 1104 km², is one of the most densely populated regions in the world. It is conceivable that the congregated effect of the small transmission risks during very frequent person-to-person contact may have accounted for the high proportion of the molecular clustered cases without apparent epidemiological links. In Norway, an XDR-TB patient lost to follow-up led to an outbreak of 15 XDR-TB cases with the same strain with identical RFLP and spoligotyping DNA patterns, and this accounted for 40% of the country's MDR-TB cases from 1994 to 2005, highlighting the transmission risk of such cases in the community [25, 26]. It has been suggested that evolution of drug resistance bears a fitness cost, thereby attenuating the overall transmissibility and virulence of the pathogen [27]. This premise might not hold true for some drug-resistant *M. tuberculosis* strains, e.g. those with a Ser315Thr mutation in the *katG* gene, which has been recently reported with clustering of MDR-TB [28] and XDR-TB patients [18]. Recent studies have also shown that compensatory mutations in the isoniazid [29] and rifampicin [30] resistance gene conferred high competitive fitness both *in vitro* and *in vivo*, favouring the spread of these resistant strains.

In recent years, experts in high-prevalence drug-resistant TB settings have advocated long-term treatment of failure MDR-TB patients in sanatoria to minimise infectious risk [31]. However, in the absence of effective treatment, strict isolation may be difficult to enforce, as it could imply life-long solitary confinement. Caution may also be required to minimise untoward publicity, which could adversely affect passive case finding, and unidentified drug-resistant cases could pose a greater risk of transmission within the community. In this regard, the WHO has expressed the view that forced isolation of drug-resistant TB should be used only as a last resort when other means have failed [32]. These pros and cons of setting up a sanatorium for drug-resistant TB should be shared with the general public and the final consensus should be based on the value judgment made by society.

In conclusion, the high proportion of new cases and molecular clusters among MDR-TB patients notified in Hong Kong highlighted the contribution of primary drug resistance within the densely populated community, which paralleled a falling trend in acquired drug resistance among MDR-TB patients. The occurrence of XDR-TB relative to non-XDR MDR-TB in the index patient significantly increases the risk of household transmission of TB. Nonetheless, this study suggests that XDR-TB in Hong Kong is largely transmitted among lower-risk social contacts outside the household setting.

STATEMENT OF INTEREST

None declared.

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