

Drug-resistant Tuberculosis in Singapore, 1995 to 1996

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Abstract

Singapore's tuberculosis incidence of 49 to 57 per 100 000 population for 1987 to 1996 presents a picture that is intermediate between developed and developing countries. The proportion of drug-resistant isolates has remained stable at 4.3% to 5.5% from 1992 to 1996 despite rising HIV rates.

From 1995 to 1996, of the 199 consecutive drug-resistant isolates at the Central Tuberculosis Laboratory, 66% were mono-resistant, 22% dual-resistant and 12% resistant to more than two drugs. Isoniazid resistance was most prevalent, being found in 72% of isolates, followed by streptomycin resistance in 45%. Resistance to isoniazid and streptomycin (21%) was more common than to isoniazid and rifampicin, i.e. multidrug resistance (MDR) (14%).

The small numbers indicated by the low overall prevalence of resistance and the predominance of single-drug resistance support the current initial choice of the standard short course with its three-drug initial phase.

Of the 170 cases with matching National Tuberculosis Registry data, 72% of drug-resistant cases represented initial and 28% acquired resistance; testifying to the effectiveness of present day treatment regimens in suppressing resistance when compliance is assured.

Case-control analysis using 244 drug-sensitive controls randomly selected from notifications in 1995 to 1996 showed an odds ratio for drug-resistance between subjects with a previous history and no previous history of tuberculosis of 2.47 (95% CI 1.40 to 4.37; $P = 0.0007$). With each increment in the number of episodes of tuberculosis experienced, there was a trend of resistance to progressively more drugs ($P = 0.00004$). This association remained even when a logistic regression model including all predictor variables was fitted.

No associations were found with age, history of contact with tuberculosis, cavitory disease and, most notably, with human immunodeficiency virus infection.

This study reaffirms that a history of previous tuberculosis should increase clinicians' index of suspicion for drug resistance, the urgency with which culture and sensitivity results are sought and the vigour with which patients are followed-up and compliance monitored.

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Introduction

The increasing worldwide occurrence of drug-resistant strains of tuberculosis (TB), including multidrug-resistant tuberculosis (MDR TB),^{1,2} is arousing concern internationally over the limited range of available anti-TB drugs, and conjuring fears of an enforced return to radical surgery as the only curative option for some cases.

In analysing the nosocomial and institutional outbreaks of resistant strains of *Mycobacterium tuberculosis* that occurred in some US cities, often in association with human immunodeficiency virus (HIV) infection,³ it has

been difficult to distinguish the key risk factors. Factors such as HIV, disintegration of TB treatment and control programmes, poverty, incarceration, homelessness and substance abuse lead to inadequate chemotherapy and poor compliance,³ promoting the selection of resistant strains.

Molecular tools such as restriction fragment length polymorphism (RFLP) fingerprint analysis have contributed significantly to knowledge of the epidemiology of tuberculosis. Use of this methodology has identified a significant proportion of the MDR TB occurring amongst the HIV-infected population in New York City as attrib-

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utable to transmission from the HIV seronegative population, implicating suboptimal treatment of TB in that population as an important factor in these outbreaks.⁴

Singapore's annual incidence rate of tuberculosis, which has been stable at between 49 to 57 per 100 000 over the last 10 years,⁵ is higher than the rates of most developed countries but lower than those in most developing countries (Table I). In the Australasian region for example, Australia has had tuberculosis rates of 5.5 to 5.9 per 100 000 between 1986 and 1992.¹ In contrast, the overall incidence for the Southeast Asian region in 1990 was estimated by WHO to be 237 per 100 000.⁶ It is noteworthy that Singapore's rates of tuberculosis have not risen despite the marked increase in HIV infection; nor has the incidence of drug resistance increased.⁵ Because of this intermediate picture between developed and developing countries, we decided to investigate the epidemiology of drug-resistant tuberculosis in Singapore, with a view to identifying specific risk factors and elucidating underlying mechanisms. In addition, we sought to distinguish the profile of individuals with drug-resistant strains of tuberculosis.

Subjects and Methods

The study sample comprised 199 consecutive patients from whom specimens were submitted to the Central Tuberculosis Laboratory during the calendar years 1995 and 1996 which demonstrated positive growth of *Mycobacterium tuberculosis* resistant to one or more first-line anti-tuberculous drugs: isoniazid (INH), rifampicin, ethambutol and streptomycin. Detection of mycobacterial growth, identification of *Mycobacterium tuberculosis* complex and drug susceptibility testing were carried out using the BACTEC® 460TB System (Becton Dickinson Diagnostic Isolation Systems, Maryland, USA). The critical drug concentrations in use for defining resistance at the time of the study are shown in Table II.

For comparison, a group of controls with drug-sensitive tuberculosis was selected by taking a 10% random sample of all patients with tuberculosis notified to the National Tuberculosis Notification Registry during the period from 1995 to 1996 using the sampling programme

"rsample" in Epi-Info version 6, excluding those with resistant cultures. In this manner, 244 individuals with strains of *M. tuberculosis* sensitive to all drugs tested were admitted as a control group.

Epidemiologic and clinical data were then appended to the microbiologic data for individual cases and controls by using dBASE IV® software (Ashton-Tate, California, USA) to cross-link subjects with their notification records maintained in the National Tuberculosis Registry database at the Department of Clinical Epidemiology, Tan Tock Seng Hospital.⁷ This was done using unique personal identification numbers: National Registration Identity Card (NRIC) numbers for Singapore residents; and passport, hospital registration, work permit or other numbers for non-residents. The source of this registry data is the notifications submitted by medical practitioners when they diagnosed episodes of tuberculosis, whether new or relapse. Complete data are available from 1981 to the present, and partial data from 1958 to 1980.

Subjects who were co-infected with HIV were identified by cross-linking with the National HIV Registry, which is also maintained by the Department.

Descriptive and case-control analysis was carried out with Epi-Info version 6 software. Multivariate analysis was conducted with STATA® release 5 (Stata Corporation, Texas, USA)

Results

Exclusions

Additional susceptibility testing, to kanamycin and ethionamide, was carried out in 17 (9%) of the 199 cases with drug-resistant tuberculosis, where it had been requested by the attending physicians. Each of these cases had demonstrated resistance to at least one of the four first-line drugs. Eight (47%) of the 17 were found resistant to ethionamide, but none to kanamycin. Because susceptibility to these two drugs had not been tested for the remaining 182 (91%) of the 199 cases, these data were excluded from further analysis.

Of the 199 cases with drug-resistant tuberculosis, no matching registry data could be found for 27 (14%). This

TABLE I: TUBERCULOSIS INCIDENCE RATES IN 1990 FOR SELECTED WORLD REGIONS

WHO region	Incidence (per 100 000)
Southeast Asia	237
Western Pacific*	136
Africa	191
Industrialised countries**	23

* Includes all countries of the Western Pacific Region of WHO, except Japan, Australia and New Zealand.

** Western European countries, USA, Canada, Japan, Australia and New Zealand.

TABLE II: CRITICAL DRUG CONCENTRATIONS FOR SUSCEPTIBILITY TESTING OF *M. TUBERCULOSIS* USING THE BACTEC® 460TB SYSTEM

Drug	CDC* (mcg/ml)
Streptomycin	6.0
Isoniazid	0.1
Rifampicin	2.0
Ethambutol	7.5

* Critical drug concentrations

is either because they had not been notified or perhaps had been notified under different personal identification numbers than the ones used in their laboratory culture request forms. Attempts to cross-link this group manually by using their names were unsuccessful.

Types Of Drug Resistance

One hundred and thirty-two (66%) of the 199 cases were resistant to only one drug, 43 (22%) were resistant to two drugs and 24 (12%) to more than two drugs. When individual drugs were considered, resistance was most prevalent to INH, being found in 144 (72%) of the 199 cases. Next most common was streptomycin resistance, found in 90 (45%) of the cases, followed by rifampicin resistance in 40 (20%) and ethambutol resistance in 14 (7%). Twenty-eight (14%) of the cases fulfilled the criteria for MDR TB, while 41 (21%) exhibited resistance to streptomycin and INH with or without other drugs.

When only 172 (86%) of the 199 individuals who had matching registry data were considered, 114 (66%) were mono-resistant, 41 (24%) were dual-resistant and 17 (9.9%) were resistant to more than two drugs, a profile not much altered from the overall group. It was again found that resistance to INH was most common, being found in 124 (72%) individuals, followed by resistance to streptomycin in 78 (45%), rifampicin in 32 (19%), and ethambutol in 9 (5%). Twenty-eight (16%) cases were MDR TB, while 35 (20%) were resistant to streptomycin and INH with or without other drugs.

Clinico-epidemiologic Profile of Subjects with Drug-resistant Tuberculosis

The following clinico-epidemiologic profile of a cohort of individuals with drug-resistant tuberculosis refers to the 172 cases for whom matching registry records could be found. Notified data were sometimes incomplete, as reflected in the varying denominators of the reported proportions.

In 130 (76%) of 170 cases, the current episode involving a drug-resistant strain of *M. tuberculosis* was reportedly the first episode of tuberculosis. Eight of these 130 individuals however had earlier culture results showing sensitivity to all four first-line drugs; the intervals between the earlier culture and the culture showing resistance ranged from 63 to 390 days. Forty (24%) of the 170 cases had a history of previous tuberculosis. The highest number of recorded episodes of tuberculosis was 5 for 2 subjects, while another 4 subjects had each experienced 4 episodes (Table III).

Among the 130 with no previous tuberculosis, 93 (72%) were resistant to one drug and 37 (28%) to two or more drugs. Resistance to INH was most common, being found in 88 (68%) persons, followed by resistance to streptomycin in 64 (49%), rifampicin in 19 (15%) and ethambutol in 6 (5%). Seventeen (13%) had MDRTB, and

TABLE III: DISTRIBUTION OF STUDY SUBJECTS BY RECORDED FREQUENCY OF TUBERCULOSIS EPISODES

No. of episodes	No. of subjects (%*)
1	130 (76)
2	22 (13)
3	2 (7)
4	4 (2)
5	2 (1)
Total	170 (99)

* Total does not add up to 100% because of rounding error

TABLE IV: DISTRIBUTION OF STUDY SUBJECTS BY ETHNIC GROUP

Ethnic group	No. (%)	
	Cases	Controls
Chinese	123 (72)	179 (73)
Malay	23 (13)	33 (14)
Indian	10 (6)	14 (6)
Others	16 (9)	18 (7)
Total	172 (100)	244 (100)

26 (20%) were resistant to streptomycin and INH with or without other drugs. In comparison, of the 40 with previous tuberculosis, 20 (50%) were resistant to one drug, and 20 (50%) to two or more drugs ($P = 0.01$). Resistance was most common to INH in 35 (88%) persons, followed by rifampicin in 13 (33%), streptomycin in 12 (30%) and ethambutol in 3 (8%). Eleven (28%) had MDR TB ($P = 0.08$) and 8 (20%) were resistant to streptomycin and INH, with or without other drugs ($P = 1.00$).

The mean age was 50 years, with an age range of 14 to 85 years. One hundred and thirty-four (78%) of the 172 were male and 38 (22%) were female. The majority, 123 (72%) of 172 were Chinese (Table IV).

One hundred and thirty-six (81%) of 167 subjects from whom residency data were available were either Singapore Citizens or Permanent Residents. The remaining 31 (19%) were foreigners but temporarily in Singapore for social visits, business, employment, as family members of those employed here, or for other reasons. None of the 31 had registry information indicating their country of origin.

A history of prior contact with a known case of tuberculosis was elicited from only 10 (7%) of the 134 case subjects, of whom 9 cited household exposure and 1 workplace exposure. In the remaining 162 (93%), contact either could not be recalled or was unknown.

Sixty-two (36%) of the 172 cases had no *Bacillus Calmette-Guerin* (BCG) scars detectable on examination by their attending physicians, 55 (32%) had one or more scars and in the remaining 55 (32%) the reporting physician either was in doubt or was unable to ascertain whether

there was a scar.

Distribution of cases by disease extent, according to the "Diagnostic Standards and Classification of Tuberculosis" of the National Tuberculosis and Respiratory Disease Association of the USA,⁸ is shown in Table V. Thirty-nine (24%) of 161 cases from whom relevant information were available presented with minimal disease, 86 (53%) with moderate, and 28 (17%) with far advanced disease. Cavitory disease was present in 58 (37%) of 159 cases who had this information available.

Case-Control Analysis

A case-control analysis was carried out using the 172 study subjects with drug-resistant disease as cases, and the 244 patients with drug-sensitive tuberculosis selected as described earlier as controls.

Although cases (mean age 50 years, age range 14 to 85 years) were slightly younger than controls (mean age 52 years, age range 12 to 96 years), this was not statistically significant ($P = 0.2$). Sex distribution was also not significantly different between the two groups ($P = 0.3$).

Subjects were subsequently categorised into age groups of 15 to 49 and ≥ 50 , there being no individual below 15 years of age. Carrying out a priori stratification by age group and sex, no statistically significant differences were demonstrable between cases and controls for ethnic group, residency status, history of contact with a known case of tuberculosis and past vaccination with BCG (Tables IV, VI, VII and VIII).

TABLE V: DISTRIBUTION OF STUDY SUBJECTS BY EXTENT OF PULMONARY DISEASE*

Extent	No. of subjects (%)
Minimal	39 (24)
Moderate	86 (53)
Far advanced	28 (17)
Miliary	3 (2)
Primary	5 (3)
Total	161 (99)

* According to the "Diagnostic Standards and Classification of Tuberculosis", National Tuberculosis and Respiratory Disease Association.*

TABLE VI: DISTRIBUTION OF CASES AND CONTROLS BY RESIDENCY STATUS

Residency status	No. (%)	
	Cases	Controls
Residents*	136 (81)	211 (88)
Non-residents	31 (19)	30 (12)
Total	167 (100)	241 (100)

* Includes Singapore Citizens and Permanent Residents

Among drug-resistant cases, 130 (76%) of 170 for whom this information was available had first episodes of tuberculosis and 40 (24%) had relapses. Among controls, 217 (89%) of 244 were first episodes and 27 (11%) relapses. The odds ratio for having drug-resistant tuberculosis between subjects with a previous history (i.e. relapse) and no previous history (i.e. first episode) of tuberculosis was 2.47 (95% CI 1.40 to 4.37; $P = 0.0007$). A very highly significant observed trend ($P = 0.000004$) was that with each increment in the number of recorded episodes of tuberculosis there was an accompanying shift in the distribution of subjects towards being resistant to progressively more drugs (Fig. 1).

In this study, the distribution of extent of disease, as previously defined, and the prevalence of cavitation did

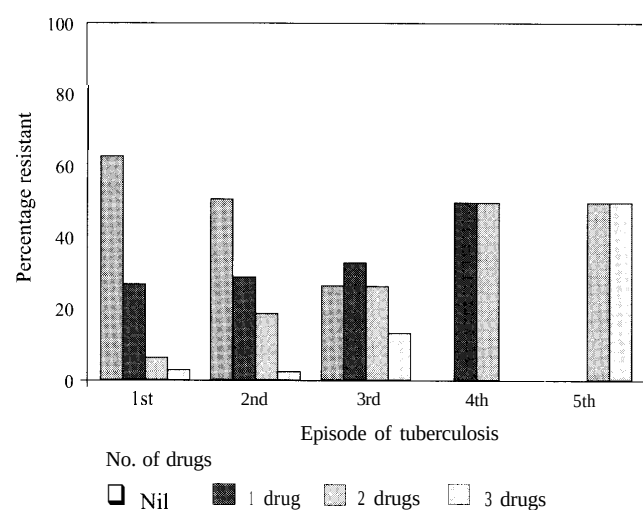


Fig. 1. Distribution of level of drug resistance by number of past episodes of tuberculosis.

TABLE VII: DISTRIBUTION OF CASES AND CONTROLS BY CONTACT HISTORY

History of contact	No. (%)	
	Cases	Controls
Yes	10 (7)	17 (8)
No	124 (93)	190 (92)
Total	134 (100)	207 (100)

TABLE VIII: DISTRIBUTION OF CASES AND CONTROLS BY PAST *BACILLUS CALMETTE-GUERIN* (BCG) VACCINATION*

BCG vaccination	No. (%)	
	Cases	Controls
Yes	55 (32)	69 (28)
No	62 (36)	99 (41)
Indeterminate	55 (32)	76 (31)
Total	172 (100)	244 (100)

* As determined by examination of BCG scar

not differ between cases and controls.

One case (0.5%) and 3 (1%) controls had concurrent HIV infection. In comparison, the prevalence of HIV among all tuberculosis notifications in the two years 1995 and 1996, obtained by cross-linking the tuberculosis and HIV registries was 1%.

Multivariate analysis with a logistic regression model including all predictor variables confirmed that the only significant association was between increasing frequency of past episodes and resistance to progressively more drugs.

Discussion

Types Of Drug Resistance

The observed predominance of resistance to INH, streptomycin and the combination of these two drugs in Singapore is consistent with the experience of most countries in the "pre-rifampicin" era.^{2,9-12} Streptomycin, a broad-spectrum antibiotic, was the earliest chemotherapeutic agent used in the treatment of tuberculosis, and was in addition used for other infections. The inevitable failure of streptomycin monotherapy led to adoption of the 3-drug combination comprising streptomycin, INH and p-amino-salicylic acid (PAS). Unfortunately, inadequate application of this effective regimen allowed emergence of drug resistance, often to both INH and streptomycin.² Development of rifampicin resistance and the emergence of MDR TB followed later, with the widespread use of rifampicin in short-course chemotherapeutic regimens from about the mid-1980s.² In Singapore, resistance to INH and streptomycin (with or without other drugs) constitutes 21% of all resistant tuberculosis, and is more common than resistance to INH and rifampicin, or MDR, which makes up 14%.

Age and Drug Resistance

No association was found between age and drug-resistant tuberculosis in our study. A few investigators have found an association between increasing age and drug resistance.^{13,14} In contrast, other investigators have found younger age to be a risk factor for resistance.^{15,16} These conflicting findings may simply reflect differences in the dominant mechanism producing the resistance. It may be that most resistance is initial, due to the circulation of a few endemic drug-resistant strains. Young age might then be a risk factor, since younger persons are more physically and socially mobile. Alternatively, most resistance may be acquired by repeated inadequate therapy or refractory non compliance; older age might then correlate with more long-standing selection pressure promoting the development of drug-resistance. These contrasting epidemiologic situations would be reflected in Restriction Fragment Length Polymorphism (RFLP) fingerprint surveys by more clustering of strains in the former instance, and more

heterogeneity in the latter. Thus, for example, the finding of more clustering of RFLP strains among patients below 50 years of age with MDR TB in New York City was attributed to the greater exposure of younger individuals to recent infection with the extant MDR strains.¹⁷

In Singapore, we have also found from RFLP fingerprinting of a sample of both sensitive and resistant tuberculosis isolates that age below 50 is associated with more clustering.¹⁸ We are presently unable to accurately distinguish initial from acquired resistance using routinely collected data. If, however, more clustering among drug-resistant strains indicates predominant initial resistance and conversely less clustering indicates predominant acquired resistance, an RFLP fingerprint survey of drug-resistant tuberculosis in Singapore may perhaps enable us to document the differential incidence of initial and acquired resistance in different age groups.

HIV and Drug Resistance

This study did not find any association between HIV infection and drug-resistant tuberculosis or MDR TB. In contrast, numerous US studies have found such an association in metropolitan areas.¹⁹⁻²² It is not clear whether these observed associations reflect a causal relationship or an ecologic fallacy. It is possible that factors such as intravenous drug use, poverty, homelessness, incarceration, overcrowding and deterioration of tuberculosis treatment and control programmes constitute a milieu which predisposes to both HIV and drug-resistant tuberculosis.^{16,23,24} However, epidemiologic evidence from San Francisco-which has an effective tuberculosis control programme in which over 95% of patients complete therapy-did implicate AIDS as an independent risk factor for acquired drug resistance (ADR).²¹

In contrast to the finding in San Francisco, studies of transmission patterns using RFLP fingerprinting in other cities indicate that MDR TB occurring in association with HIV arises largely from infection with initially resistant strains.^{17,19,20} In New York City, 75% of MDR TB among HIV-infected patients were transmitted from inadequately treated seronegative individuals.⁴ Thus, there is epidemiologic evidence that HIV can account for both initial and acquired resistance.

In Singapore, the percentage of tuberculosis that is drug-resistant has been stable at 4.3% to 5.5% over the past 5 years (Table IX),⁵ despite the uptrend of HIV and AIDS.⁵ This supports the contention that the association between HIV and drug-resistant tuberculosis observed in other countries is more ecologic than aetiologic. Thus, an increase in drug-resistant tuberculosis may not be inevitable with the rise of HIV, but may be contained by an effective tuberculosis treatment programme.²⁵

TABLE IX: INCIDENCE OF DRUG-RESISTANT TUBERCULOSIS IN SINGAPORE, 1992 TO 1 996⁵

	1992	1993	1994	1995	1996*
Single-drug	3.4	4	3.5	3.5	3.9
Multiple-drug	0.9	1.5	0.8	1.1	0.8
Total	4.3	5.5	4.3	4.6	4.7

* Preliminary data

History Of Contact and Drug Resistance

Nine of the 10 who provided a contact history reported that exposure occurred in the domestic rather than occupational context. Although we did not find any difference in contact history between cases and controls (Table VII), it should be noted that the vast majority (93%) of patients, whether with drug-resistant or drug-sensitive tuberculosis, reported no recent contact with any person known to have tuberculosis. This may represent a failure of the attending physicians to ascertain and patients to volunteer exposure history. It may be that the long incubation period of tuberculosis makes recall by patients difficult or renders the epidemiologic link obscure to physicians. It is also possible that transmission occurring in unusual environmental contexts^{26,27} goes unrecognised.

Relapse and Drug Resistance

We had expected to find a larger proportion of relapses among drug-resistant (24%) than drug-sensitive (11%) tuberculosis patients. However, it was surprising to note that for 130 of the 170 (76%) drug-resistant cases, this was their first episode of tuberculosis.

But does initial resistance really comprise three-quarters of all drug resistance? In 8 cases, an earlier culture result demonstrating sensitivity to all drugs was traceable from the culture records; the time intervals between this earlier result and the result demonstrating resistance ranged from 63 to 390 days. These few cases, therefore, are an artefact of the working definition of what constitutes a notifiable episode of disease. Cases are notified as either new or relapse, the latter term implying treatment and cure of previous episodes of tuberculosis. However, no requirement exists for separate notification of the emergence of a drug-resistant strain midway through treatment of an episode of tuberculosis originally documented to be drug-sensitive, since this situation is considered neither a new case nor a relapse. Instead, the new culture result is linked to the originally-notified case. Retrospective studies such as this may then inadvertently misclassify initially-sensitive strains as resistant, thus spuriously inflating the latter category.

Errors due to misclassification of an episode by the

primary notifying source are minimised by our access to all TB drug sensitivity results done in Singapore since 1990, and a registry system that actively and continually seeks out notification errors.

Excluding the 8 cases, our estimate of the proportion of resistance that is initial is 122 of 170, or 72%. The corollary of this is that only 48, or 28% of the 170 cases in the study had acquired resistance, testifying to the effectiveness of present day treatment regimens in suppressing resistance when compliance is assured.

Documenting the prevalence of clustering of RFLP fingerprint patterns among cases of drug-resistant tuberculosis may answer the question of whether transmission of initially-resistant strains indeed plays a more important role than ADR due to poor compliance.

Past History Of Tuberculosis and Drug Resistance

This study has confirmed that as the number of episodes of tuberculosis experienced increases, there is a trend of increasing proportions of subjects resistant to greater numbers of drugs (Fig. 1). It is commonly considered that the emergence of drug-resistant *M. tuberculosis* is ultimately induced by the selection pressure inherent in poor compliance or inadequate treatment.²⁸⁻³¹ In contrast, relapses after compliance with short course chemotherapy are usually with sensitive organisms.³² It may well be that in many of the individuals who reported multiple episodes of tuberculosis, unsatisfactory compliance was not detected by the attending physician during follow-up, and that there was in effect chronic infection from which repeated inadequate therapy eventually selected a resistant mutant.

The observed trend may also have arisen partly because the greater the number of past episodes, the higher the likelihood of having been treated with regimens in common use during the decades 1950 to 1970, which will not have included the sterilising drugs rifampicin and pyrazinamide. If so, this effect will recede in the decades ahead and diminish the trend towards increasing resistance associated with multiple relapses.

Cavitary Disease and Drug Resistance

Cavitary pulmonary disease has been reported to be a risk factor for acquisition of drug resistance.³³ Selection of resistant strains is facilitated by rapid multiplication to perhaps 10⁸ to 10⁹ bacilli within pulmonary cavities¹⁰ because of their higher oxygenation. In this study no correlation was found between drug resistance and either advanced or cavitary disease.

Conclusion

The overall prevalence of drug-resistant *M. tuberculosis* in Singapore is low. Two-thirds of culture-positive resistant strains show resistance to only a single drug. INH resistance is commonest, being present in 3/4

of cases. Fourteen per cent of all cases of resistant tuberculosis are MDR. Twenty-one per cent of cases are resistant to INH and streptomycin, with or without other drugs.

Seventy-two per cent of resistant cases are primary, whereas 28% have acquired resistance, testifying to the effectiveness of present day treatment regimens in suppressing resistance when compliance is assured.

The small numbers indicated by the low overall prevalence of resistance of 4.3% to 5.5% among residents, of whom the majority moreover have single drug resistance, does not constitute a convincing indication for altering the current initial choice of the standard short course with its three-drug initial phase.

In contrast to reports from other countries,^{19,22} co-infection with HIV and tuberculosis in Singapore is not associated with drug-resistant tuberculosis. There is also no association with age, contact with another person with tuberculosis, or cavitory disease.

A past history of tuberculosis increases the odds by 2½ times of having resistant tuberculosis. Additionally there is a trend of progressive resistance to more drugs with greater numbers of past episodes of tuberculosis. However, the possible utilisation of earlier regimens without rifampicin or pyrazinamide represents a potential confounder in this association. If so, this effect will recede in the decades ahead and diminish the trend towards increasing resistance associated with multiple relapses. Nonetheless, multiple past episodes should increase clinicians' index of suspicion for drug resistance, and influence the urgency with which culture and sensitivity results are sought, the choice of initial drug regime, and the vigour with which patients are followed-up and compliance monitored.

It may be desirable to seek separate notifications for tuberculosis cases that have been notified once, but acquire drug resistance midway through treatment. This would facilitate more accurate distinction of initial from acquired resistance. RFLP-based fingerprint analysis is a useful tool in supporting epidemiologic inferences about the origins of drug-resistant strains.

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