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CURRENT PROBLEMS OF DRUG-RESISTANT TUBERCULOSIS AND ITS CONTROL

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Resistance to anti-tuberculosis (TB) drugs was observed soon after the anti-TB drug was introduced for treating and preventing tuberculosis. This was first observed *in vitro*, then in an animal model, and finally in human beings undergoing chemotherapy[1)2)]. However, an increase in drug resistance has been encountered in many parts of the world due to the extensive use of anti-TB drugs for treatment. There has been growing concern about the increase in drug resistance with regard to the tuberculosis control program in many parts of the world.

However, there is not much reliable drug resistance data to support such concerns. For this reason, in 1994 the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease jointly developed a global project for the surveillance of anti-tuberculosis drug resistance[3)]. Since then, 65 countries have at least completed the initial survey on drug resistance prevalence among newly registered TB patients. The data obtained between 1994 and 1999 appeared in two monographs published by the WHO in 1997[4)] and 2000[5)], and revealed that drug resistance is so ubiquitous that it is occurring throughout the world. This paper quotes excerpts of the drug resistance data that appeared in these two monographs.

1. Emergence of drug resistance

Drug resistance occurs with the selective multiplication of resistant mutants in lesions in the presence of sufficient concentrations of drugs that kill or stop multiplication of susceptible bacilli of *Mycobacterium tuberculosis* (MTB)[1)2)6)]. Drug-resistant mutants can evade the antimicrobial action of drugs in a number of ways, such as by modification of target molecules, by loss of an enzyme that converts drug molecules into active form, by reducing permeability of the cell wall or the membranes of drug molecules, by stimulating drug efflux mechanisms, or by deactivating drug molecules[7)]. Such phenotypic changes of drug susceptibility result from genotypic mutations[8)] (Table 1).

The most common mechanism by which MTB resists drug efficacy appears to be the modification of target molecules[9)10)]. An example of this is alteration of the rifampicin (RIF) binding site on β-subunit of RNA polymerase due to mutation in the *rpoB* gene, which leads to RIF resistance. Likewise, mutations in *inhA* lead to isoniazid (INH) resistance, mutations in *fas*I lead to pyrazinamide (PZA), mutations in *embCAB* lead to ethambutol (EMB), mutations in *rpsL* and *rrs* lead to streptomycin (SM) and other aminoglycosides, mutations in *gyrA* lead to fluoroquinolones (FQN), and mutations in *ulrA/dadB* lead to cycloserine (CS). Loss of enzymes encoded by *katG* (*pncA*) leads to resistance to INH (PZA). However, all the genes related to drug susceptibility and their mutation sites have yet to be found, which also leads to resistance.

Drug resistance emerges wherever and whenever the microbial environment favors the selective growth of drug-resistant mutants[1)2)6)]. The selective multiplication of drug-resistant mutants in lesions takes place mainly due to treatment with an inappropriate regimen, irregular or inadequate treatment, over-the-counter drug usage, an interruption in the drug supply, and the unavailability of free diagnosis and treatment. These factors are the major flaws of a poor TB control program.

Some patients who fail treatment for expectorate drug-resistant organisms and may infect their contacts, some of whom may develop TB displaying a primary drug resistance. Accordingly, a high prevalence of drug resistance among new cases clearly indicates the ubiquity of infectious sources for drug resistance within the community. They are the result of treatment failures created by poor case management, and also

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Table 1 Drug resistance mechanisms of *Mycobacterium tuberculosis*

Phenotypes	Genes involved	Resistant drugs
Permeability changes ?	?	?
Efflux ?	*lfrA*	Fluoroquinolones (FQN) ?
Drug inactivation	Genes encoding β-lactamase	β-lactams
	aphC ?	Isoniazid (INH) ?
Unable to activate drug molecules	*katG*	INH
	pncA	Pyrazinamide (PZA)
Modified target	*inhA*	INH
	rpoB	Rifampicin (RIF)
	*fas*I	PZA
	embCAB	Ethambutol (EMB)
	ulrA/dadB	Cycloserine (CS)
	rpsL; rrs	Streptomycine (SM); aminoglycosides
	gyrA	FQN
Increased target concentration ?	?	?

Table 2 Development and spread of anti-tuberculosis drug resistance

		Programmatic errors
	Drug susceptible cases	
CREATION	↓	Inappropriate regimens Nonadherence OTC drug sale Interrupted drug supply Unavailability of free diagnosis & treatment
	Acquired drug resistance	
SPREAD	↓	Delay or no retreatment
	Primary drug resistance	
SPREAD	↓	Delay in diagnosis and appropriate treatment
	Primary drug resistance	

transmission of drug-resistant organisms in the community. Therefore, the prevalence of drug resistance could well be used as an indicator in evaluating TB treatment programs throughout a country[11)12)]. The resistance at least to INH and RIF is called as multi-drug resistance (MDR) which presents a serious problem to tuberculosis treatment, because these two drugs have essential significance in the current TB chemotherapy (Table 2).

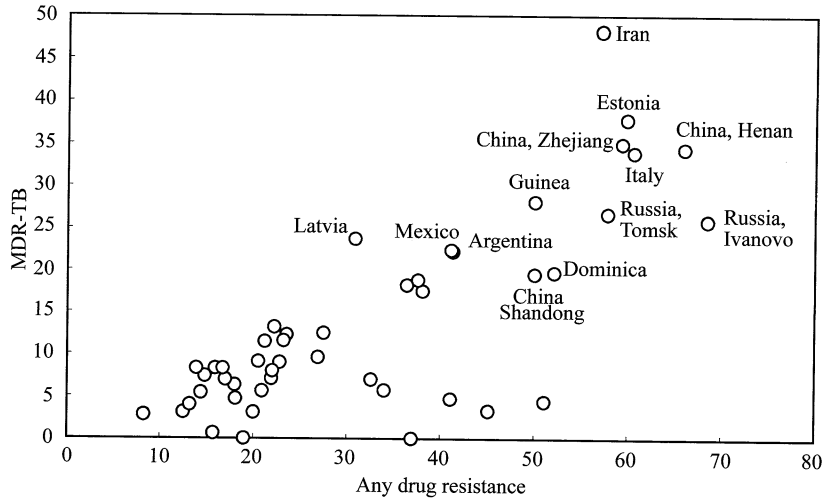
2. Acquired drug resistance[3)4)]

Anti-tuberculosis drug resistance found among previously treated cases is complicated by a combination of treatment failure cases, relapse cases, and a return after varying periods in default cases. Unless their relative proportions reflect the actual situation of those cases prevalent in the community and representative sampling is performed, the data obtained may not be reliable and may even be misleading.

However, drug resistance of previously treated cases representing the actual situation would serve as a good performance indicator for a treatment program, because a high resistance rate is derived primarily from treatment failure in cases with poor treatment programs. A low resistance rate indicates that the sample consists mainly of relapse cases, and cases returning after a short interruption in treatment. The representativeness of previously treated cases appearing in the two monographs is in question in many countries. The median of the frequency of resistance to at least one drug out of four major drugs tested (INH, RIF, SM, and EMB) which is called as "any drug resistance" was 25.2% (ranging from 8.3 to 68.5 %), with a median frequency of MDR-TB of 8.7% (ranging from 0 to 48.2%) among those previously treated patients. Any drug resistance rates in 80% of the geographic areas ranged from 20.0 to 50.0%, and MDR-TB ranged form 3.1 to 28.1%. Both any drug resistance and MDR-TB rates were found to be high in Iran, Estonia, China, Italy, Russia, and Guinea. Some countries show high rates of any drug resistance, but low MDR-TB, suggesting less use of rifampicin-containing regimens (Fig. 1).

3. Primary drug resistance[3)4)]

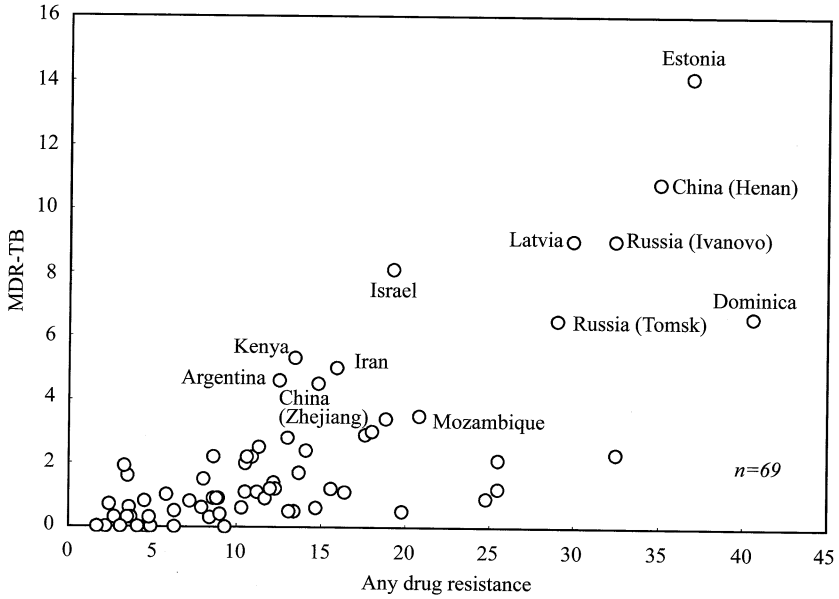
Unless prompt and effective management of acquired drug resistance cases is implemented, drug-resistant organisms can



Drug resistance among previously treated cases

	Any drug resistance	MDR-TB
Median	25.2	8.7
Range	8.3–68.5	0.0–48.2
80% of areas	20.0–50.0	3.1–28.1

Fig. 1 Correlation of any drug resistance with MDR-TB among previously treated cases in 48 countries



Drug Resistance among new cases

	Median (%)	Range (%)
Any drug resistance	11.1	1.7–40.6
MDR-TB	1.1	0–14.1
Isoniazid	6.8	0.4–28.1
Rifampicin	1.4	0–16.2
Streptomycin	6.0	0.3–32.4
Ethambutol	0.6	0–11.1

Fig. 2 Correlation of any drug resistance with MDR-TB among new cases in 69 countries

be spread in the community, and some infected individuals may develop TB with primary drug resistance. The extent of exposure, virulence of drug-resistant organisms, and immunity of infected hosts may determine the incidence of drug resistance among new cases. The median of at least one drug resistance among new cases was 10.9% (ranging from 1.7 to 40.6%), and that of MDR-TB was 1.1% (ranging from 0 to 14.1%). As isoniazid had been most extensively used since it was introduced to TB chemotherapy, INH resistance was most commonly encountered, showing a median of 6.8% (ranging from 0 to 28.1%), followed by SM resistance of 6.0 % (ranging from 0 to 26.0%), RIF resistance of 1.4% (ranging from 0 to 16.2%), and EMB resistance of 0.6% (ranging from 0 to 11.1%). Drug resistance rates in 80% of the geographic areas ranged from 3.5 to 25.5%, and MDR-TB, 0.1 to 5.3%.

Twelve geographic areas had 3% or more MDR-TB among new cases. Over 10% of MDR-TB cases were found among new cases in Estonia and the Henan province in China, and the Dominican Republic, Russia, Latvia, and Israel exhibited 6.5 to 9%. MDR-TB was not found among new cases in eight other countries (Fig. 2).

Treatment success rates of MDR-TB have been poor with either the standard regimen or with tailored regimens[13)~15)], and the majority of cases end up as incurable. They spread these deadly organisms in the community, as indicated by several outbreaks in certain areas[16)~19)]. An increase of MDR-TB will seriously threaten future TB control programs. We

Table 3 Comparative impact of directly observed treatment with the conventional therapy

Variables	Traditional treatment (Jan. 1980–Oct. 1986) n=407	Directly observed treatment (DOTS) (Nov. 1986–Dec. 1992) n=581	P-values
Failure/relapse	85 (20.9%)	32 (5.5%)	<0.001
MDR-TB	25 (6.1)	5 (0.9)	<0.001
MDR during therapy	18 (4.4)	7 (1.2)	0.003
Primary drug resistance	53 (13.0)	39 (6.7)	0.001
Acquired drug resistance	39 (9.6)	8 (1.4)	<0.001

Weis SE, et al. 1994[20], slightly changed.

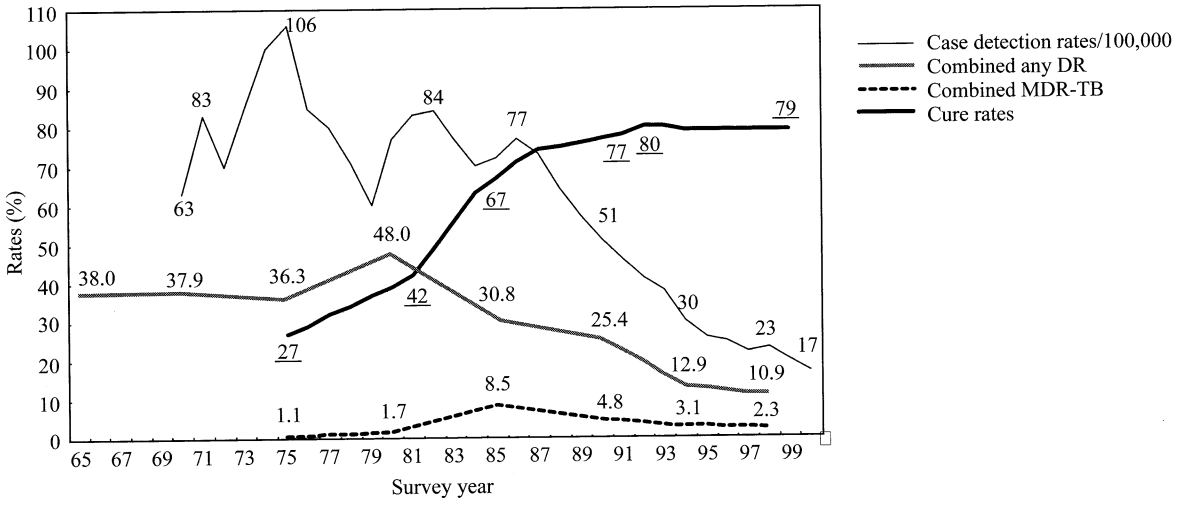


Fig. 3 Correlation of over-all cure rates of new and retreatment pulmonary tuberculosis cases with changes of drug resistance rates and case-detection rates over the time from 1966 to 2000 in Korea[11) 21)]

must therefore exert our best efforts to prevent the occurrence of such cases by improving the cure rate of newly diagnosed cases and aggressively intervening to identify and remove MDR-TB cases as soon as they become known.

4. Control of drug-resistant tuberculosis

The increase in any drug resistance results from the failure to break the chain of the creation and transmission of drug resistance cases. The ubiquity of drug-resistant organisms in air humans breath results in the build up of an infected pool of drug-resistant TB and, in turn, increases drug resistance among new cases. From the programmatic perspectives, drug-resistant organisms can be removed from the human environment only by improving the cure rates of TB cases, and thereby ultimately curbing the prevalence of drug resistance. As seen in Table 3[20], it has been clearly shown that a change in treatment policy from the traditional ineffective treatment programs to date, to an effective treatment program (i.e., directly observed treatment, short-course; DOTS) significantly reduced not only treatment failures and relapses, but also the prevalence of drug resistance.

In Korea, drug resistance substantially increased in the 1970s, owing to an expansion in case-finding activity, without improvement in the cure rate of the patients newly enrolled in treatment, as seen in Fig. 3. A cohort study done in 1975 showed a treatment success rate of a mere 27% of newly registered cases, so inevitably an increase of drug resistance cases was encountered, which showed up in a 1980 survey.

Thereafter, drug resistance prevalence steadily decreased, along with the improvement of cure rates in the 1980s, after short course chemotherapy was introduced together with the enforcement of case-management procedures. Improvement in cure rates and case-management eventually lead to a gradual decrease in new cases. A remarkable decrease in the prevalence of drug resistance in Korea, which was achieved by trial and error, clearly indicates that the only way to solve the drug resistance problem is to stop generation of treatment failure cases with drug resistance. This can be accomplished by improving the cure rate for new cases enrolled in treatment and by eliminating drug-resistant cases as soon as possible through effective and rigorous retreatment of those cases that failed initial treatment or relapsed.

5. Summary

Drug resistance emerges wherever and whenever the microbial environment favors the selective growth of drug-

resistant mutants. The programmatic errors that lead to the development of drug resistance are inappropriate regimens, non-adherence to therapy by the patients, the sale and availability of over-the-counter drugs, an interruption in the drug supply, and the unavailability of free diagnosis and treatment. As a result, drug-resistant organisms are spread in the community, generating secondary cases with primary drug resistance, which in turn can spread and generate further cases. The uninterrupted cycle of creation and spreading is responsible for increases in DR.

According to global data on anti-tuberculosis drug resistance appearing in the WHO monographs, drug resistance is so ubiquitous as to be encountered in every country. Anti-TB DR among previously treated cases was found to be very high in some countries, while it remained relatively low in others. The median of at least one drug resistance among four major drugs tested, was 25.2% (ranging from 8.3 to 68.5%), and the median MDR-TB was 8.7% (ranging from 0 to 48.2%) among those previously treated patients.

Drug resistance among new cases infected with drug-resistant organisms from patients with acquired or primary drug resistance was found to be higher in some areas than in others. The median of at least one drug resistance was 10.9% (ranging from 1.7 to 40.6%) and MDR-TB of 1.1% (ranging from 0 to 14.1%). Twelve geographic areas had levels of 3% or more of MDR-TB among new cases. The majority of MDR-TB cases end up as incurable and spread these deadly organisms in the community, as indicated by several outbreaks in certain areas. Increased MDR-TB will seriously threaten TB control programs in the future. We must therefore exert our best efforts to prevent the further generation of such cases by improving the cure rate of newly diagnosed cases, and by aggressively intervening to identify and remove MDR-TB cases as soon as possible.

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第77回総会招請講演

最近の薬剤耐性結核問題とその対策

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要旨：薬剤耐性は耐性変異株が選択されるような環境があれば容易に発生する。結核対策においては，不適切な薬剤方式，患者の不規則な受診，市中薬局での抗結核薬の販売，薬剤供給の中断，あるいは無料の診断治療が受けられない，といった問題が薬剤耐性を作り出す。薬剤耐性結核の患者は地域で菌をばらまき，初回耐性患者を作り，彼らはまた次の世代の患者を作ることになる。世界の薬剤耐性結核サーベイランスに関するWHO報告によれば，薬剤耐性はどの国にも広く行きわたっているが，国によってかなりのばらつきが見られる。既治療患者の中で主要4剤（INH，RFP，SM，EB）の少なくともいずれか1剤に耐性の割合はメジアンで25.2％（レンジ8.3％～68.5％），また多剤耐性（少なくともINHおよびRFPに耐性）の割合は8.7％（0～48.2％）であった。未治療患者では（初回耐性）についても同様にばらつくが，何らかの耐性がある者の頻度はメジアンが10.9％（レンジ1.7％～40.6％），また多剤耐性は1.1％（0～14.1％）であった。初回患者における多剤耐性の頻度が3％を超えるところも12カ国（地域）にみられた。これら多剤耐性結核患者の治療は困難で，多くが不治のうちに他人を巻き込むような状態になる。このような菌による集団発生事件すら報告されている。このような問題を予防するために，新たに発見した患者を確実に治癒し，同時に早期に多剤耐性結核を発見・治療するため最大限の努力をすべきである。

キーワーズ：結核，薬剤耐性，発病，対策，サーベイランス