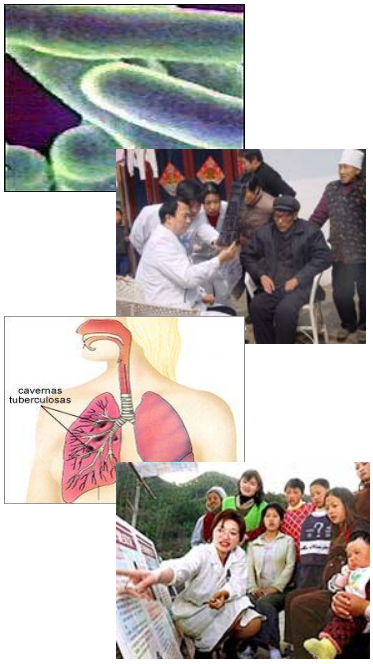

Characteristics and Treatment Management of *drug resistant tuberculosis* among registered patients in NTP-DOTS covered area of rural China

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CONTENTS

LIST OF FIGURES

LIST of TABLES

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For my parents, my mentors, all the friends and peers for the same goals …

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ABBREVIATIONS

AFB	**Acid-Fast Bacilli**
AIDS	**Acquired Immunodeficiency Syndrome**
CIDA	**Canadian International Development Agency**
CMS	**Co-operative Medical System**
CTD	**County TB Dispensary**
CXR	**Chest X-ray**
GDEP	**The Global DOTS Expansion Plan**
DOTS	**Directly observed treatment, Short Course**
EMB	**Ethambutol**
HIV	**Human Immunodeficiency Virus**
IEDC	**Infectious and Endemic Disease Control**
INH	**Isoniazid**
inhA	**Enoyl-ACP reductase**
IUATLD	**International Union Against Tuberculosis and Lung Disease**
MDR	**Multi-Drug Resistance**
MDR-TB	**Multi-Drug Resistant Tuberculosis**
MIC	**Minimum Inhibitory Concentration**
MOH	**Ministry of Health**
M. Bovis	***Mycobacterium. Bovis***
M.TB	***Mycobacterium Tuberculosis***
NTP	**National Tuberculosis Program**
ODRTB	**Other Drug Resistant Tuberculosis**
OR	**Odds Ratio**
ORR	**Overall drug Resistance Rate**
PTB	**Pulmonary Tuberculosis**
SCC	**Short-Course Chemotherapy**
STR	**Streptomycin**
TB	**Tuberculosis**
TST	**Tuberculin skin test**
VHW	**Village Health Worker**
DST	**Drug Susceptible Test**
WHO	**World Health Organization**
WPRO	**West Pacific Region Organization**

ABSTRACT

Background Despite the availability of effective anti-TB drugs and intensive effort to implement control program funded by a loan of World Bank and Ministry of Health (MOH), the control of tuberculosis in China has been further complicated and threatened by an increasing incidence of drug-resistant tuberculosis especially including multi-drug-resistant tuberculosis (MDR-TB) since 1990s.The modern TB control strategies Directly Observed treatment , Short course (DOTS) now has covered more than 90% of Chinese population, but its role on the drug resistance worth studying, since The 4th national survey on TB in 2000 simultaneously indicated 18.6% and 46.5% respectively in the initial and acquired drug resistance rate in China, both significant higher than the international baseline （10.2% and 18.4%）.

Objectives To describe the notification rate of drug resistance TB among registered cases in the setting of NTP-DOTS covered areas in rural China; to identify the socioeconomic and clinical factors related to the presence of drug resistant TB; to describe the treatment management of drug resistant TB cases in terms of accessibility of health service, treatment adherence, treatment completion and their results.

Methods This study was set up in two counties in two neighboring provinces of China: One more than 10 years' NTP-DOTS covered county - Deqing(DQ) and a less than 1 year' NTP-DOTS covered county - Guanyun (GY). Those registered in the local county TB dispensary (CTD) from April 1, 2004 to Mar 31, 2005 in addition to the availability of their drug susceptible test (DST) were the subjects of this study. Cross sectional study was performed to obtain the baseline information on their first visit to TB dispensary. The susceptibility of strain against 4 anti-TB drug including Isoniazid (INH), Rifampicin(RIF), Ethambutol(EMB) and Streptomycin(STR) was identified by the standardized proportion method. A cohort of drug resistant TB cases was established at their entrance to the treatment and their treatments were followed up for 3 times each.

Main Findings A total of 1,858 sputum specimens were collected from 784 patients (310 cases from DQ and 474 cases from GY). Growth of a Mycobacterium tuberculosis complex strain was obtained and meanwhile their questionnaires were available for 408 patients (186 cases from DQ and 222 from GY). 4 cases in DQ and 5 cased in GY were excluded due to unavailability of the drug susceptible test (DST). Among a total of 399 eligible subjects, there were 283 new cases (133 in DQ and 150 in GY) and 116 previously treated cases (49 in DQ and 67 in GY). The initial drug resistance were: DQ: overall resistance rate (ORR) (1 or more drugs), 67 (50.4%); STR 34 (25.6%); INH 39(29.3%); EMB, 19(14.3%); RIF, 7(5.3%); MDR, 5(3.8%); GY: ORR, 95 (63.3%); STR, 57(38%); INH, 46(30.7%); EMB, 16(10.7%); RIF, 27(18%); MDR, 22(14.7%); for acquired resistance, they were: in DQ: ORR, 33 (67.3%), STR, 14(28.6%); INH, 15(30.6%); EMB, 8(16.3%); RIF, 10(20.4%); MDR, 8(16.3%); in GY: ORR, 56(83.6%); STR, 32(47.8%); INH, 40(59.7%); EMB, 12(17.9%); RIF, 25(37.3%); MDR, 23(34.3%). Male(sex), Age, previous treatment history, case contact and individual income were related to the presence of multi-drug resistance TB both in two counties or either, while case contact was single a factor independent of the presence of other drug resistance TB (ODRTB) in DQ. Totally 80 (92%) ODRTB cases and 13 (100%).MDRTB cases in DQ and 101(95.3%) ODRTB and 42(93.3%) MDRTB completed the whole course of treatment. Among them, 73(83.9%) ODRTB and 7(53.8%) MDRTB cases in DQ and 86(81.1%) ODRTB cases and 17(37.8%) MDRTB cases were cured. The treatment adherence among MDRTB cases were significantly associated with the previous treatment history, education background, side effect, insurance and individual income, while education background remained relevant to the treatment adherence among ODRTB cases. The treatment success of MDRTB was associated with the previous treatment history, patient's delay, health status and individual income, while treatment success of ODRTB was related to patient's delay and treatment adherence.

Conclusions We concluded that both socioeconomics status and medical factors had the good predicative value for the presence of drug resistant TB. In an era of rapidly rising drug resistance tuberculosis incidence and declining capacity to respond, programs might wish to

consider focusing on the vulnerable population (poor population and old population) as well as to ensure adherence to a good cost-effective drug regimen that can be given to all cases and establish the well-balanced financing system to reduce the economic burden among the vulnerable population. Both socioeconomic barrier and patient's delay play a role in the treatment success of drug resistant TB and therefore should be considered in treatment management of drug resistant TB.

Key words Tuberculosis, multi-drug-resistant, National tuberculosis control program, Direct Observed short courses treatment.

1 INTRODUCTION

Followed by the resurgence of tuberculosis since the early 1990s, multi-drug-resistant tuberculosis (MDR-TB) has emerged as another threat to global tuberculosis control efforts. It is a challenge that reaches not only the area of public health as well as the context of global economy, even in the absence of treatment for MDR-TB at national-level programs in developing countries including China.

The drug resistance in *Mycobacterium Tuberculosis* is well known as the consequence resulting from the symbiotic interaction among biological, socioeconomic and health care system factors. The nonstandard therapy and the potential severe treatment outcome make it necessary to probe into risky factors influencing the development of drug resistance and its treatment result among cases. This study is focused on the characteristics and management of treatment among cases who have been diagnosed tuberculosis and registered at the TB dispensary in two national tuberculosis control programmed (NTP)- direct observed short treatment (DOTS) covered rural counties of China. It will be meaningful in the description of the present prevalence of MDRTB in rural China, the regional performance of control program and curative effect of the current standard chemotherapy, thus contributing to improving the control program, focusing on the vulnerable people and implementing the cost-efficient treatment strategy on them.

2 BACKGROUND

2.1 Distribution and prevalence of drug resistance tuberculosis

2.1.1 Global disease burden and prevalence trend of drug resistance TB

M.TB is the second killer of death in the world caused by a single infectious agent only next to Human Immunodeficiency Virus (HIV). Approximately 2 billion persons are infected with *M.TB*, and 8.8 million new cases of tuberculosis (TB) occur annually, with over 50,000 attributable deaths each week *(Kamholz, 2002)*. However, the spread of drug resistant and multi-drug resistant strains of *M. tuberculosis* (MDR-TB) has complicated this issue by increasing the treatment cost and deteriorating treatment result. MDRTB attacks 50 million people worldwide with the high risk of mortality (50%-80%) in the first 4-16 weeks of the disease and 100 times more expensive therapy for drug-resistant than that for treating drug-sensitive TB strain*(Cohn et al., 1997)*.

According to WHO report *(WHO, 2004)*, drug resistant TB has appeared in every corner of the world, although the prevalence of drug resistant TB varies in different area and countries. The overall drug resistance rate (ORR) ranged from 0% (Andorra, Iceland Malta) to 57.1% (Kazakhstan), with a median of 10.2% (95% CI: 8.8-11.6%). Among new TB cases, the median prevalence of multi-drug resistance (MDR) and over all drug resistance rate (one or more drugs) were respectively 1.1 %(ranging from 0% to 14.2%) and 7.0% (ranging from 0% to 21.7%). The median prevalence of MDR and overall drug resistance among previously treated cases was respectively 7.0 %(ranging from 0 to 58.3%) and 8.7% (27.6%). The median prevalence of resistance to Isoniazid (INH), Rifampicin (RIF), Ethambutol (EMB) and Streptomycin(STR) were respectively 5.6% (0-42.6%), 1.4% (0-15.6%), 0.8%(0-24.8%) and 6.3%(0-51.5%)*(WHO, 2002)*.

The majority of MDR-TB cases ends up as incurable and spread these deadly organisms in the community, as indicated by several outbreaks in certain areas and population. The prison

found high prevalence and seriousness of drug resistance with a mono-drug and MDR prevalence as high as respectively 20% and 18.8% *(Tansuphasiri et al., 2000; Congnin R et al., 2001)*. In Argentina, the first outbreak of MDR-TB was reported among transvestite sex workers *(Palmero et al., 2001)*. Although the HIV prevalence may increase the incidence of TB by 10%, no evidence could prove that HIV was strongly associated with the development of MDR-TB in proper treatment settings *(Espinal et al., 2001).*

From the longitude perspective, the trend of drug resistant TB has transcended the border of countries. A significant decrease in MDRTB was observed in high income countries including France *(Robert et al., 2003)*, United States and Germany as well as middle-income countries like Cuba and China Hong Kong *(WHO, 2004)*. Meanwhile, several studies reported its increasing trend in the Africa *(Abate et al., 2002),* South America (Ti*mperi et al., 2001) and* middle Europe *(Augustynowicz- Kopec et al., 2002)*. The overall MDRTB cases increased at 20% in Poland *(Augustynowicz - Kopec et al., 2002)*. In Estonia, the prevalence in all cases increased from 11.7 % in 1994 to 18.1% in 2000 *(Espinal et al., 2001).*

2.1.2 Drug resistant TB in China

Listed in one of 22 TB high burden countries, China has 16% of TB cases worldwide, among whom 27.8% were resistant to the standard anti-TB drug *(WHO, 2004)*. Despite an eventually decreasing trend in drug resistance of tuberculosis based on the former 4 national TB epidemiological surveys, the 4th national survey *(Ministry of health, China, 2002)* presented the initial overall drug resistance rate of 18.7%, among which MDRTB rate was 6.0%, much higher than the average level worldwide. In addition, this national survey found that the initial drug resistance rate was higher in rural area than urban area, while the urban area had a higher proportion of acquired drug resistant TB cases.

Although the drug resistant TB has been monitored in some areas of China, different drug susceptible tests (DST) and procedures of operation cause the poor comparability of the results. In 1996, Henan province joined the WHO global MDRTB monitoring program, followed by the participation of Shandong, Zhejiang, Guangdong, Hubei and Liaoning

province. In 2001, based on the unified method to monitor, the result of these areas showed that the initial drug resistance rates were respectively 35%, 17.6%, 14.8%, 18%, 17.5%, and 42.1% and the acquired drug resistance rates were respectively 66%, 50%, 59.3%, 33.7%, 55.8% and 60%. The overall drug resistance rates were respectively 40.5%, 7.2%, 23.4%, 21.6% , 20.2% and 43.3%*(Wang et al., 2004)*.Based on these results, the situation of initial drug resistance and primary drug resistance was still very severe in Chinese setting.

The difference in democratic and social economic characteristics partially spawns the disproportional regional distribution of tuberculosis in China. Now approximately 80% of TB cases come from rural China and the prevalence of TB manifests itself as the discrepancy of population and region *(Ministry of health, China, 2002).* The epidemic of tuberculosis mainly occurred in middle-west area with the 1.7 times probability compared to that of east coastal area *(Ministry of health, China, 2002)*. Accompanied by impacts from relatively poor economic status, insufficient health facilities and unqualified staff, the drug resistant TB was expected to occur mostly in rural China *(Ministry of Health, China, 2002).*

In China, the TB control program based on DOTS-strategy has been implemented for almost 10 years and has covered 1,164 counties by now *(WHO,2004)*. However, passive case-finding might exclude some cases from being detected or timely access to health care because of socioeconomic and cultural barriers. The situation may be even worsened since health financing system has changed from cooperative medical system to out-of-pocket payment *(Feng et al., 1995)*. The majority of rural people have no insurance schemes and financial ability to withstand the risk. In Zhejiang province of China, The average family burden in MDRTB cases (5,972 CNY) was significantly higher than that in drug sensitive cases (4,058 CNY) *(Xu et al., 2004)*. For these reasons, the MDR-TB case in rural area is more likely to delay detection or treatment because of the higher cost from second line anti-TB drug and insufficient health system. As a result, the delay in detection or treatment among MDR-TB cases not only worsens the outcome of treatment but also helps transmission of drug-resistant TB.

2.2 Causes and risky factors of drug resistant TB

The current problem in tuberculosis treatment is due to emergence of MDR-TB (resistant to at least INH and RIF). Drug resistant TB can be classified as the initial and acquired one based on the previous treatment history *(WHO, 2002)*. Its causes can be summarized in terms of pathogen related, virulence of the strain, host predisposed factor, treatment related, and TB management.

2.2.1 Pathogen related factors

Biological and molecular basis of MDRTB

Different from other pathogenic bacteria, *M.TB* is not armed with the plasmid which generally enables the transmission of drug resistance between hosts. Therefore, it is the chromosome that mediates the drug resistance in TB *(Heym et al., 1994; Martin et al., 1990).* Now, the graduate accumulation of some unrelated genetic mutation is considered as the molecular basis of MDRTB. In other words, there is no necessary association between resistances of different unrelated drugs. The probability of spontaneous mutation related to resistance to INH and RIF is respectively 1 in 10^{6} and 1 in 10^{8}, the probability of simultaneous mutation of both is $10^{-6} \times 10^{-8} = 10^{-14}$. This rare event even seldom happens among TB cases with the extensive cavitory pulmonary tuberculosis, which supposes to contain 10^{7} to 10^{9} bacilli in each tuberculosis cavity. The primary mechanism of MDRTB lies in the result of perturbation in the individual drug target genes *(Cole et al., 1994; Ramaswamy et al., 1998)*. Table 2.1 lists the mutation of drug target gene, their phenotype and the correlation rate with the drug resistance

Tab 2.1 Mutation of drug target gene, their phenotype and correlation rate with the drug resistance

Drug	Genes related to drug resistance	Correlation
Isoniazid	Enoyl acp reductase *(inhA)*	21%~34%
	Catalase-peroxidase *(katG)*	42%~58%
	Alkyl hydroperoxide reductase *(aphC)*	10%~15%
Rifampicin	RNA polymerase subnunit B *(rpoB)*	96%
Pyrazinamide	Pyrazinamidase*(pncA)*	72~97%
Streptomycin	Ribosomal protein subunit 12 *(rpsL)*	70%
	16s ribosomal RNA *(rrs)*	70%
Ethambutol	Arabinosyl transferase (*emb A, B and C*)	17%~32%

Recently, the Chinese researcher *(Cheng et al., 1996)* also found the drug resistance to RIF was related to the mutation of *rpoB* gene encoding the RNA polymerase, thus blocking its combination to the RIF；The resistance to Isoniazid was strongly associated with the mutation in *KatG*, *inhA/mabA* and *Allpc* gene. The absence of *katG* in TB genome mainly resulted in the drug resistance to Isoniazid. It was firstly reported in Chinese military hospital *(Chen et al., 2003)* that the TB multi-drug resistance resulted from the mutation of multiple targeted genes.

Virulence of strain

With spontaneously mutation at a constant frequency and selection by drug pressure, some resistant bacilli would survive and be transmitted at least occasionally in every case. Whether and how fast drug-resistant strains transmit is likely to decide the spread of the MDRTB. Based on some animal experimental results *(Palmero et al., 2002)*, MDR strain of *M.TB* presented the similar infectiousness and virulence as susceptible one. Even in some lab experiment, the drug resistant strain was less viable than the drug sensitive one in vitro and often less virulent in guinea pigs *(Dye et al.,2002; Mitchison et al., 1960; Ordway et al., 1995).* However, the results of molecular epidemiological studies also suggested that certain *M.TB strain* or called Beijing genotype had an enhanced capacity to spread within a community. This genotype was also the chief culprit of several outbreaks of MDRTB in the world *(Caminero JA et al., 2001; Pfyffer et al., 2001).*

China is where the Beijing genotype originated from. 94% TB was reportedly due to the Beijing genotype infection *(Gong, 2004)*. Considering the strong association between Beijing genotype and drug resistance, MDR-TB seems much reasonably prevalent and severe in the setting of China.

2.2.2 Host predisposed factor

In a term of genetic aspect, although the host predisposition has not been proved to play a role in the development of MDR-TB *(Sharma et al., 2003; Park et al., 2002)*, some studies

have suggested its potential impact. A study in India found that Cases with HLA-DRB1*12 and HLA–DRB1* had the double risk of getting MDRTB *(Sharma et al., 2003)*. In Korea, the susceptibility of MDRTB was strongly linked to HLA-DRB1*08032-DQB1*0601 haplotypes *(Park et al, 2002*). Some related alleles might serve as the switch to control host susceptibility to MDR-TB.

2.2.3 Clinical related factors

Generally recognized, the acquired drug resistant TB is attributed to delayed diagnosis, mistreatment and treatment default during the health care seeking of TB cases，while primary drug resistance results mostly from the wide prevalence of the uncontrolled drug resistant TB strain. The uninterrupted vicious circle of creation and spreading of drug resistant TB is responsible for the increase in drug resistance. From this perspective, the drug resistances TB played a key role in the treatment outcome *(CDC, 1999).*

Delayed diagnosis

Chronic cough for more than 2 weeks was supposed to be one of the commonest symptoms of TB case and therefore used as predictor to screen the TB case at first*(WHO,2002)*. But the chronic cough is not the typical to TB. The other common causes may be the upper respiratory infection and pneumonia. Even on chest radiographs, lung cavitation may not be present in the case of co-infection with HIV *(WHO, 2004)* and sputum may not be AFB smear-positive if the sputum is not available enough or high quality. In addition, in some area using sputum culture result as an evidence of TB diagnosis, at least 8 weeks had elapse before culture results were obtained. In China, the diagnosis of TB was based on AFB smear test in most DOTS-Covered area or radiographic exam in remote area. Much has been done in some area to shorten the time on the diagnosis, but the diagnostic delay is still common among some special population including the floating population *(Cao et al., 1994)*. In addition, Good, reliable laboratory support is rarely available in the rural area. When the facilities for culture and drug susceptible test are not accessible or capable enough of identifying the *M.TB* and MDRTB strain, the alternative clinical evidence-based method may delay or even mistaken the diagnosis.

Mistreatment

TB cases in China get the health aids from the national TB control program as well as the private medical practitioner including the Chinese medicine. Irregular, incomplete and inadequate treatments are considered the commonest causes of the acquired drug resistant tuberculosis. Mahmoudi and Iseman *(Mahmoudi et al., 1993)* found that 28 of 35 MDR-TB cases experienced an average of 3.93 errors per case in their previous treatment history. The most common errors included the addition of a single drug to a failing regimen, failure to identifying preexisting or acquired drug resistance tuberculosis, failure to supervise the completion of treatment among cases and inappropriate *Isoniazid* preventive therapy. In addition, the error did more frequently happen among drug resistant TB cases than drug sensitive TB cases. In China, Hu QF et al *(Hu et al., 2000)* found that of 105 MDRTB cases, only 20 (19%) cases accomplished the initial reasonable chemotherapy, 66(61.9%)MDRTB resulted from the inadequate provision of drug, the incorrect regimen of treatment caused 48 cases (45.7%) to develop the MDRTB and 40 cases (45.7%)intermittently combined with another new drug. In addition, unreliable regimens e.g. *Penicillin/Streptomycin* or *Thiaceptazone* plus *Isoniazid* as initial treatment are still prescribed in some remote area of China. There is also high risk in usage of some drug with poor bioavailability. Furthermore, in China, the anti-TB drug was also available in drug store or private practitioner. The unqualified persons or alternative medicine practitioners in these areas are important barriers to the successful treatment of TB in China. The free availability of anti-TB drugs may contribute to this.

Incorrect use of antibiotics may be another predisposing cause of drug resistant TB in China. There are 80 thousand people who die of the abuse of antibiotics every year in China *(Chen , 2003).* The direct role of abusing antibiotics is to disrupt normal colonies and to pose some drug pressure to induce the development of drug resistance. Although there is no reported study showing the necessary connection between this and the development of MDRTB, its impact may be suggested by exceptional high rate of drug resistance to *Streptomycin* in Chinese setting *(Ministry of Health, China, 2002)*.

Treatment default

The strictly implementation of DOTS strategy is the backbone to ensure the compliance of treatment. On the other hand, the poor compliance will increase the chance of treatment failure which is more likely due to the development of MDRTB. A study *(Wu et al., 2003)* from China showed that only 43 % of cases completed the short course treatment (n=2306) and 35% of those received standard chemotherapy (n=1051) and of them, 80% completed their treatment, which might pose a potential threat to the epidemic of drug resistant tuberculosis in China.

In the setting of western countries, demographic factors including age, sex, martial status, education level and socio-economic status were not found to be associated with the treatment compliance among TB cases. However, psychiatric illness, alcoholism, drug addiction and homelessness were the predictors of noncompliance *(Blackwell et al., 1973; Weis et al., 1994)*. This may not be entirely true in Chinese context and the relevance to these factors was also explored in this study.

In China, the issue of noncompliance with prescribed treatment is concentrated on the floating population and old population. The old people may have the poor compliance of treatment besides in TB, because of the health seeking inconvenience, the unfavorable social economic status especially in the NTP-DOTS uncovered area, where TB patients have to afford the fee for the whole treatment *(Gao et al., 2003)*. In addition, the floating population poses another challenge to treatment and control of TB. In China, the floating population takes account for the 10% of overall population and 30% of rural labor forces. Meanwhile, around 80% TB cases aggregate in rural area, while the floating population mainly from rural area is at the risk of carrying *M.TB.* The following miserable living condition and physical tension in their floating life may cause the depression of immunity system among them, which increase the danger of developing the TB at the same time. In addition, their indefinite mobility presented another difficulty in management of their treatment. After developing the disease, they may not accept the standard treatment and registry, which may in turn, makes

possible the resurgence of TB in the local setting. In Shanghai *(Hong et al., 2005)* among 125 TB cases, only 32.8% of floating population adhere to the treatment and got cured, 80 (64%) cases returned to the place of birth without treatment, 15(12%) cases completed the strengthen phase of treatment.

Side effects

The uncomfortable side effect is also the incentive to pause the anti-TB treatment. Liu et al. *(Luo et al., 2005)* found 13% of MDRTB developed as the result of pausing their treatment caused by side effect especially including the liver abnormality and the unfavorable reaction from gastrointestinal tract.

HIV and TB co-infection

Based on the biological and epidemiological evidences, the TB and HIV feed with each other. In 2001, of the 3.6 million HIV case, 1/3 suffered from the tuberculosis, 1/3 HIV case died from the TB, and 1/2 HIV cases were at the risk of developing the tuberculosis *(Coleounders et al., 2002; Hannan et al., 2000)*.

The interaction of HIV and drug resistant TB remained unclear. But the outbreak of MDRTB in U.S.A. implicated the potential connection between them. Of 8 outbreaks of MDRTB, 80% MDRTB cases were co-infected with HIV, with the fatality rate of 60% ~89%. China is estimated to have millions of HIV cases now, therefore the potential impacts from HIV still deserve concern *(Cardoso et al., 2001*).

2.3 Characteristics of drug resistant TB cases

Certain socioeconomic and clinic characteristics have been documented to be related to the presence of MDR-TB. The prior treatment is recognized as the strong predictor of MDRTB. One Population-based representative data *(Espinal et al., 2001)* found that of the 9,615 cases, 85.5% were new cases and 14.5% were previously treated cases. An approximated linear increase was observed in the likelihood of having MDR-TB according to the total time of prior TB treatment in unit of months. Other several studies presented the similar relationship

between prior treatment and drug resistance TB *(Sharma et al., 2003; Alrajhi et al., 2002; Telzak et al., 1999; Espinal et al., 1998; Mendoza et al., 1997)*. This result has already represented in the Chinese related research *(Hu, 2000)*, where most of MDRTB retreated cases were previously treated for more than 10 years (28.7%) and more than 3 years (70.1%).

In addition, U.S CDC *(Cohn, et al., 1997; Moore et al., 1997)* found that the resistance of anti TB drug varied in terms of races, age and origin of birth. The drug resistance rates in Asian, Spanish, American black and American white were respectively 17.8%, 10.8%, 6.6% and 7.4%. The people ranging from 0~19 years (10.1%) and 20~39 years (10.8%) were more likely to develop MDRTB. The foreign born was associated with MDRTB. Except for the similar findings in a systematic review of published reports in Europe (*Pablos-Mendez et al., 1997)*, previously treated history (OR: 10.23; 95%CI: 2.3-12.4), male (OR: 1.38; 95%CI: 1.16-1.65) and HIV positive (OR: 3.52; 95%CI: 2.48-5.01) were statistically associated with the MDRTB. In a study from India *(Sharma et al., 2003)*, the poor compliance to treatment, low socioeconomic status and body mass index (BMI, Kg/m^2)<18 kg/m^2 have been implicated the factors related to MDR-TB.

In China, based on some study *(Wang, 2005),* the old, male, retreated people staying in rural area were more likely to develop the MDRTB, although the result may be biased by the small number of subjects included. However, the other study made the opposite conclusion that there was no association between age and MDRTB prevalence *(Xu, 2004).*

2.4 Global strategies against drug resistant TB

The most cost effective strategy to prevent the MDRTB is through implementing the directly observed treatment short course (DOTS) strategy *(Chaulet et al, 1996)*.The DOTS does work well on the control of MDRTB by decreasing MDRTB transmission, risk of drug resistance, treatment failure, TB relapse and death. The established DOTS program in Peru has shown the reduction of MDR-TB and reducing TB mortality by 70 %*(Suárez et al, 2001)*. Its role has been also demonstrated in Benin, Cuba, the Czech Republic, and Kenya, where, now, MDR-TB has virtually disappeared. In addition, DOTS could probably reduce MDR-TB once

it has occurred; in Burkina Faso, Hong Kong *(China)*, Chile, Sierra Leone, and Uruguay, where now MDR-TB is rare or decreasing *(WHO, 2004)*. However unfortunately, this success has not been copied to the rest of the world. It has been repeatedly demonstrated that DOTS alone was ineffective against MDRTB. This has recently been acknowledged by the WHO, which published a 6-country study of the use of short-course chemotherapy (SCC) among cases with MDRTB. SCC failed in most cases, with cure rates varying between 20% and 60%*(Espinal et al., 2000*). The US Centers for Disease Control and Prevention reported cure rates as low as 5% in Russia *(CDC, 1999; Danilova et al., 1999)*. Moreover, Migliori et al *(Migliori et al, 2002)*acknowledged a 25% rate of late failures among cases with chronic MDRTB in Russia who were smear negative at the end of treatment, implicating that the true cure rate might be much lower than 47%.

Meanwhile, Failure to cure MDR-TB cases in DOTS bases program may worsen the drug resistant TB problem. Sanders M et al found *(Sanders et al., 2004)* those 2 out of 18 cases with mono-resistance to RIF relapsed later after once cured, 2 out of 8 with MDRTB failed treatment. This result might suggest MDR-TB especially resistance to RIF may have an adverse effect on treatment outcome, even with direct observed standard SCC under national program guidelines. Advocates of individualized treatment for the control of MDR-TB argued that empirical short-course chemotherapy regimens could amplify the problem of MDR-TB among cases already infected with strains resistant to one or more drugs *(Farmer et al., 1998).*

This controversiary role of DOTS on the MDRTB has also worth further exploration in Chinese setting. In Guangzhou, the southern city of China, after a period of DOTS based tuberculosis program sponsored by World Bank, the acquired drug resistance rate reduced from 20.3% in 1998 to 11.6% in 2002; the acquired multi-drug resistance rate reduced from 5.2% in 1998 to 3.4% in 2002*(Lu et al., 2001).* But since the highly-efficient detection of TB cases increased the capacity of detecting drug resistance cases, the decrease in initial drug resistance rate has not directly demonstrated the significant improvement after the implementation of DOTS strategy.

Considering a poor response in MDR-TB cases, thus, modified DOTS for the treatment of MDR-TB has been developed *(Brudney et al., 1991)* in the programmed condition. Global DOTS-Plus strategy aims to prevent the further development and spread of MDR-TB. Second line anti-TB drugs which are more toxic, expensive, and less effective than first line drugs, are used for 18-24 months under direct observation. The treatment regimen is either individualized according to drug susceptible test (DST) results or is standardized regimen to cases who fail supervised re-treatment with first line anti-TB drugs. However, pilot projects for DOTS-plus have been established in only 11 countries (Bolivia, Costa Rica, Estonia, Latvia, Haiti, Malawi, Mexico, Peru, Uzbekistan, Philippines, and the Russian Federation) *(WHO/IUATLD, 2004)* and excluded most of the TB high burden countries including China. Furthermore, its practical function deserves further discussion. Sterling et al *(Sterling et al., 2003)* emphasized that only under optimal DOTS implementation, would fewer TB death occur under DOTS-plus. If the effectiveness of DOTS decreases, even minimally the implementation of DOTS-plus would result in more deaths. *(Timothy et al., 2003)*. Therefore, the proposal on widespread implementation of DOTS-plus is still controversial. It is as stated previously, suitable for areas with an MDR-TB epidemic and where an optimal DOTS program is already in place for e.g. Peru that uses second line drug resistant TB. a national cohort study conducted in Peru on standardized treatment with second line anti-TB drugs showed that 46% of MDR-TB cases that were treated were cured, 32% failed, 11% died and 11% defaulted and resistance to five or more drugs increased the chance of an unfavorable outcome *(Suarez et al., 2001).*

2.5 Management of MDRTB in DOTS covered area

In low income countries, despite the wide coverage of DOTS strategies, the treatment of drug resistant TB has been complicated by the high cost at referral centers and other aspects. A study in Peru *(Mitnick et al., 2003)*, offered the results of community-based outpatients treatment of MDR-TB. While the results of susceptible test were not available, the cases got treated empirically under direct observation with regimens containing at least five drugs to which the strains were likely to be susceptible. The definitive regimens, determined on the

basis of the results of drug susceptibility, contained a minimum of five drugs and lasted for at least 18 months. Of the 66 cases that completed four or more months of therapy, 55 (83%) were probably cured (defined as at least 12 months of consecutive negative cultures during therapy). Five of these 66 cases (8%) died while receiving treatment. Only one case continued to have positive cultures after six months of treatment. Low haematocrit (OR: 4.09; 95% CI: 1.35-12.36) and a low BMI (kg/m^2) (OR: 3.23; 95% CI, 0.90 - 11.53) were found to be the predictors of the time to treatment failure or death. These observations suggested that community-based out-patient treatment of MDR-TB has the potential to yield high cure rates even in resource-poor settings. Other qualitative study suggested the role of nursing in the community-based management of MDR-TB.A web-based clinical and epidemiological management system facilitated sharing of the information and follow-up of treatment in MDRTB case especially in resource poor areas *(Fraser et al., 2002)*.

In addition, much should be focused on the previously treated TB cases to control the spread of MDR-TB since the failure of the prior treatment is more likely to be associated with the development of MDRTB. Saravia JC et al *(Saravia JC et al., 2001)* compared 2 retreatment strategies. One strategy A was based on national wide approach, applying a category II regimen; if their regimen failed, a standardized regimen based on 2^{nd} line drug should be followed. Strategy B was based on the result of DST. The result showed the strategy B was 3 times more likely than strategy A to cure cases (79% vs.38%, RR: 2.9; 95%CI:3.0-9.2).and meanwhile strategy B significant reduced the delay to MDR-TB diagnosis and hastened the initiation of MDR-TB therapy. From this perspective, the retreatment strategy based on DST and eliminating the category II regimen could improve clinical outcomes among category I treatment failures found to have active, infectious MDR-TB.

The response to the side effect is important component in the management of MDTB case since the failure to resistance to the side effect will cause the poor compliance of treatment, subsequently followed by the treatment failure. Torun T et al *(Torun et al., 2005)* found the only 55.5% of treatment regimen would be modified according to the side effect by the clinician and the most common side effect is ototoxicity (41.8%).

Considering the lower yield and higher cost, the DST is not the routine item in DOTS covered area. But it should be used mainly for monitoring drug resistance. Continuous monitoring of resistance in a representative sample of isolates from first-line failure and relapse cases may be more efficient and more accurate than periodic surveys among new cases, and can be used to identify MDR-TB, whose treatment should be standardized. Because of considerable risk of error in the laboratory, a specialist service offering molecular techniques may be useful for exceptional cases, but it has no place in the routine work of NTPs.

In China, the report said that the treatment of 95 initial drug resistance failed by 15% under the short course chemotherapy. The average rate of failure for 3 drugs is 42% and the relapse happened more frequently *(Yao et al., 1995)*. The factor influencing the delivery of drug mainly included the side effect (liver abnormality, the hearing injuries) and the financial deficiency *(Yan et al., 2003)*. This study also found the cure rate of chronic MDRTB was significantly lower than that of the non MDRTB, and there was no significant difference between the cure rate of primary MDRTB and acquired MDRTB.

Although the drug resistance tuberculosis has encumbered the progress of anti-TB struggle in China, there were few comprehensive studies on the management of the case with the drug resistance TB. Considering the possible adverse outcome affected by drug resistance TB, it is of great importance to describe the present situation of MDRTB, factors contributing to the development of MDRTB during the health seeking and the whole course of treatment management in order to increase the efficiency of treatment and to control the prevalence of MDRTB in China.

3 OBJECTIVES

3.1 General Objective

The general objective is to study the predicator of drug resistant TB cases and management of their treatment in counties under more than 10 year national TB control programs and new (less than 1 year) national TB control program in rural China.

3.2 Specific Objective

- To describe the prevalence of drug resistant TB among registered patients regarding to the effectiveness of TB control program respectively in NTP and new-NTP area.

- To identify the predictor in terms of social-economic characteristics and clinical feature associated with presence of drug resistant TB cases comparing to pan drug sensitive cases

- To describe the whole course of drug resistant TB treatment in terms of the treatment completion, treatment adherence and treatment success.

4 METHODS

4.1 Study setting

4.1.1 General description

Jiangsu Province and Zhejiang Province are located in eastern China and border on each other. Two counties were selected from these two interfacing provinces as the study sites. Deqing (DQ) county has been covered by NTP-DOTS program for more than 10 years (since 1994), while Guanyun (GY) had not implemented NTP-DOTS program until 1 year before start-up of this study. The selection of fields was based on the comparable characteristics of socioeconomics, demographics, and culture, the cooperation basis of local people & government, the availability of sputum specimens and study feasibility in terms of local transportation, technical and facilities condition.

Figure 4.1.the location of the field ground

As Table 4.1 showed, DQ and GY had similar socioeconomic and culture specificities, with an average annual income per capita around 3,200 CNY in 2003. Their income indices were

both a little higher than the national average of 2,895CNY. GY had a larger proportion of agriculture population compared to that of DQ. GY and DQ had respectively 14 and 11 townships. The similar three tied health system (village health stations, township hospitals and county hospitals) covered all over these two counties, with a little higher quality health faculties and facilities resource in DQ. GY had 6 county hospitals and 21 township hospitals that provided the general health service, while DQ had 2 county and 17 township hospitals that served the health related need of local people. In addition, both counties were equipped with their own county maternal & child health sector, centre for disease control and prevention (CDC) and a tuberculosis dispensary under the CDC. The other indicators of social economic aspects performed better in DQ than GY (see table 4.1).

Figure4. 2 Configuration of DQ (left) and GY (right)

Table 4.1 General Information of DQ and GY County in 2003

Items	GY county	DQ county
Demographic statistics		
Population(10,000 persons)	106	42.34
Pop. Density(person/KM^2)	564	1319
Agricultural population (%)	79	70
AAI(CNY/per agricultural capita)*	3,258	3,487
Medical information		
Mortality(/1,000 persons)	8.73	6.67
No. Of medical staff (doctor %)	1,256 (33.5%)	1,415 (49.0%)
No. of hospital bed	1110	1123

4.1.2 Drug resistant TB management in the field ground

DQ has begun the National TB control program based on DOTS Strategy since 1994, which was funded by WHO/West Pacific Region Organization (WPRO). This project was based on

the passive detection and free TB treatment. Every TB case was identified through microscopy examination, followed by 6 months' free chemotherapy for new TB cases and 8 months' free therapy for previously treated TB cases. From 2002 to now, TB control programs in both DQ and GY was financially sponsored by a Canadian International Developments of DOTS (CIDA). The principle of case detection, diagnosis and treatment was continued to the new project. After diagnosis, the TB case will obtain the free treatment and subsequent free medical service in local TB dispensary. Furthermore, in DQ, the adequate resource and referring system left by the ongoing project made it possible for the free treatment and diagnosis to cover part of acid fast bacilli (AFB) smear negative TB cases. But in DY, the newly introduction of NTP project required the change to a new referral system. The capacity in TB diagnosis, treatment and case management need further strengthening to meet the required standard.

In NTP-DOTS covered area of China, the county general hospital is qualified for diagnosing the TB and referring the identified case to county TB dispensary (CTD). In both two counties, CTD is responsible for TB care and case management. TB diagnosis followed the criteria of DOTS advocated by WHO based on AFB smear microscopy. Culture and drug susceptible test were not available in each county. Therefore, the records of TB dispensary could provide a rough picture of the notification rate of new and relapsed TB in local settings and the episode of treatment for TB cases. Based on CIDA-WHO TB work book, cases received routine treatment with standard combined regimens based on the result of AFB smear test and treatment history. New cases received an initial intensive phase of treatment with 4 or 3 drugs (AFB smear positive: *Isoniazid, Rifampicin, Pyrazinamide and Ethambutol;* AFB smear negative: *Isoniazid, Rifampicin, Pyrazinamide*) for 2 months, followed by a continuation phase with *Rifampicin* and *Isoniazid* for 4 months. Previously treated cases (relapses, failures, and defaulters [cases who did not collect drugs for at least 2 months] returning for treatment) received an initial intensive phase of treatment with 5 drugs (*Isoniazid, Rifampicin, Streptomycin, Ethambutol and Pyrazinamide*) for 2 months, followed by a continuation phase with *Rifampicin, Isoniazid, and Ethambutol* for 5 months. The strengthening phase is administered daily; however, the continuation phase is given three times a week in all

participating counties. Village health care workers in the local community administered treatment ensuring direct observation when applicable. Monitoring of treatment outcome and the change from treatment to retreatment regimens in participating counties were based on the results of sputum smear microscopy at the end of treatment and the previous treatment history.

No program was established in both two study fields to especially support the management of drug resistant TB treatment. Meanwhile without availability of drug susceptible test, multi-drug resistance TB was difficult to identify and accept the corresponding second line anti-TB regimen.

4.1.3 Prevalence and trend of TB and drug resistant TB in field grounds

Based on the routine monitoring of TB control program in these two study fields, statistics about TB registration and AFB smear positive rate were reviewed in Table 4.2. The crude reported rates of all pulmonary TB were higher in GY in terms of AFB smear positive and negative TB. Comparably, AFB smear positive cases accounted for 2 third of all pulmonary TB cases in DQ, while in GY county, the proportion rose from 5.9% in 2000 to 47% in 2002. About two third of reported TB cases in these two countries were male, which is consistent with the sex-specific TB distribution in the non-HIV epidemic countries *(Ministry of Health, China, 2002).*

No data was available both in DQ and GY in a term of the drug resistant TB. Based on the surveillance on drug resistant TB in Jiangsu Province *(Li Q et al, 2000)*and Zhejiang Province where these two counties respectively sit, the proportions of overall drug resistant TB among new cases were 34% and 38.7% respectively, and the proportions of overall drug resistance in previously treated TB cases were 58.6% and 68.7% respectively.

Figure 4.3 Notification of pulmonary TB and AFB smear-positive TB in DQ and GY

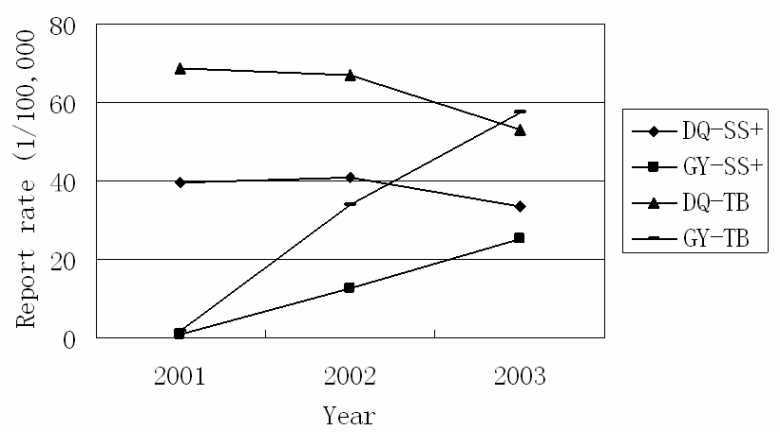

Table 4.2 Proportion of AFB smear positive TB cases diagnosed in GY and DQ

Year	GY County				DQ county			
	No. of PTB†			AFB +	No. of PTB†			AFB+
	AFB‡ smear+	AFB‡ smear-	Total	(%)	AFB‡ smear+	AFB‡ smear -	Total	(%)
2001	10	160	170	5.9	168	123	291	57.7
2002	133	221	354	37.6	173	111	284	60.9
2003	287	319	606	47.4	141	84	225	62.7

† Pulmonary TB, ‡Acid fast Bacilli

4.2 Study designs and data collection

4.2.1 Cross sectional study on drug resistance cases

Subjects were all registered TB cases diagnosed in local county TB dispensary during 2004/04/01-2005/03/31 in addition to the availability of drug susceptible test (DST) results.

Data collection: Questionnaire interview was used to investigate the TB cases when they firstly sought the health service in the local county TB dispensary. The content of interview included: A) Demographic characteristics: age, sex, gender, address, No. of family members, occupation, education and medical insurance. B) Economic status: the yearly income of family and case individual C) Medical records: AFB smear, X-ray, the main symptom, history of other chronic disease. D) Results of culture and drug susceptible test in Microbial lab of Fudan University. E) Health seeking experience: the date of initial symptom, the date of every seeking health, the date of diagnosis, the regimen of treatment, etc.

4.2.2 Cohort study on treatment result of drug resistance cases

A cohort of TB cases was established at beginning of the study to follow up the treatment management of drug resistant TB cases in the different NTP-DOTS covered areas. Some aspects were concerned as follows: 1) Case: health status, Social economic status, other disease history, side effect of treatment and self-reported treatment adherence 2) Doctor: treatment regimen, supervision and timely treatment 3) Treatment management: completion of treatment, treatment adherence and its cause and treatment result.

Subjects were all registered TB cases diagnosed in local county TB dispensary during 2004/04/01-2005/03/31 in addition to the availability of DST results.

Data collection All the eligible subjects were followed up three times during the treatment (initial treatment: 2^{nd}, 5^{th}, 6^{th} month; retreatment 2^{nd}, 5^{th}, 8^{th} month). The content of investigation surrounded the progression of treatment in terms of treatment adherence, side effect, prognosis, the response to the treatment et al.

4.3 Definition and measurement of variables

4.3.1 Poverty and socio-economic status

In this study, poverty was defined based on the self-reported household income and case's individual income. The consecutive variable of income was directly used to avoid the loss of information by using the categorical variables. According to the routines standard, the day income of less than 1USD or says 8 CNY per capita was defined as poverty. In other words, annual individual income of 3000 CNY or less or/and annual household income of 6000 CNY (supposedly 2 adult and 1 child each household) or less was considered the cut-off value of the poverty.

The education level of the subject was evaluated by the time of studying at the school in unit of year. The 0~year and 6~years of study stood for different levels of education background among subjects. Considering the largest proportion of farmers, the occupation of the subject was simply divided into farmer, minor (children and student) and non farmer. Body mass

index (BMI) is a measure of physical health based on height and weight. Here according to the routine standard, the BMI below 18.5 was defined as underweight, those BMI between 18.5 and 24.9 was normal weight and the remained was overweight.

BMI = (Weight in Kilograms / (Height in Meters) × (Height in Meters))

4.3.2 Clinical aspects

Case contact was defined as contacting the diagnosed pulmonary TB cases at home of subjects. The identification of side effect was based on the self-reported response to the anti-TB drug. Except for the minor and mild reaction, the variable "side effect" here included either the liver and gastrointestinal discomfort ness or one of them.

4.3.3 Diagnostic delay

Diagnostic delay was used to describe the accessibility of health service among TB cases. Diagnostic delay encloses the patient's delay and doctor's delay in the timeline from the onset of symptom to TB diagnosis. The patient's delay referred to that duration from onset of symptom to the first hospital visit was more than 2 weeks. Doctor's delay referred to the duration more than 2 weeks from first hospital visit to TB diagnosis.

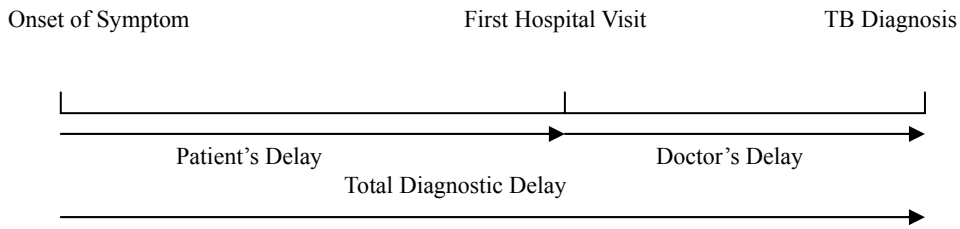

Figure 4.4 Definition of Diagnostic Delay

Definitions of independent variable were shown in Table 4.4. All the dichotomous variables were coded as 0 and 1. All the category variables with more than two categories were coded into dummy variables, which were compared with the lowest group.

Table 4.5 Variable definition in multivariate analysis

Variable	Value label
County	0: DQ or old NTP-DOTS area 1: GY or new NTP-DOTS area
Age at interview	Continuous variable
Gender	0: female 1:male
Education	0: <=6 year (primary school) 1:>6 year
Occupation	1: farmer; 2: minor (children or student); 3:non-farmer
Medical insurance	0: uninsured; 1: insured
Individual income	Continuous variable
Household income	Continuous variable
Case contact	0: no; 1: yes
Previous treatment history	0: no; 1: yes
Patient's delay	0:no or less than 2 weeks; 1: or 2 weeks or more
Doctor's delay	0:no or less than 2 weeks; 1: or 2 weeks or more

4.4 Definition of outcome

4.4.1 Treatment adherence

Considering the importance of regular and adequate regimen on the drug resistant TB treatment, here the treatment nonadherence was defined missing at least average 1 dosage of regimen within 1 week.

4.4.2 Diagnosing TB and identifying drug resistant TB

Pulmonary TB was confirmed by two consecutive smears positive for acid-fast bacilli and/or a positive culture and typical x-ray shadow (patchy, nodular shadow in the upper zone of the lung, calcification, calcified shadows or diffuse small nodular shadow). The AFB smear test was performed by the trained technician in the local CTD. All the available sputum specimens were collected and transported to the microbiological lab of Fudan University, followed by the culture and DST immediately. The bacterial strain was identified by implanting bacterial colonies separately in PNB and TCH contained bases. The *M. TB* was defined as the TCH positive and PNB negative. The *M. Bovis* was defined as the TCH negative and PNH negative simultaneously. The proportion method was used to test the susceptibility of TB strain against first-line anti-TB drugs (INH, RIF, EMB, and STR). Referred to the international standard, the final concentrations of 4 drugs in

Loewenstern-Jensen culture were respectively 0.2, 40, 2 and 10mg/L.The positive result was defined by the growth of more than 1% colonies comparing to the negative control. The definition of MDR-TB cases recommended by WHO and IUATLD is the pattern of drug resistance to at least INH and RIF. By definition, acquired resistance can only develop in cases that have prior anti-TB chemotherapy for 4 weeks or more *(Pablos-Me´ndez et al., 1997)*. In cases in which it is not known whether the case has no prior treatment or prior treatment for less than 4 weeks, the term "initial resistance" has been used by the WHO *(Crofton et al., 1997)*.

4.4.3 Treatment outcome definition

We assessed outcomes separately for those cases who reported no or less than 4 weeks' previous history of tuberculosis treatment and those who had treatment for 4 weeks or more. Cases' reports of previous treatment for tuberculosis were validated by use of registries and disease records in local TB dispensary.

Cure

Case who has completed the treatment according to country protocol and has been consistently AFB-negative for the final 6 months of treatment among the new TB cases and 8 months of treatment among the previously treated TB cases.

Treatment completed

A TB case who has completed treatment according to country protocol but does not meet the definition for cure or treatment failure due to lack of bacteriological result (i.e. fewer than 3 sputum samples each case were collected to perform the microscopy test at the end of the therapy.)

Treatment failure

Treatment failures were cases who maintained AFB smear-positive status at 5 months after the start of treatment.

Treatment default

Defaulters were cases who did not collect drugs for 2 months or more at any time after registration.

Transfer out

Transferred out was used for cases transferred to another reporting unit and for whom results were not known.

4.5 Data analysis

Epi Info 6.0 software was used to make the questionnaire, transcribe the data and check the logic error. Those subjects without drug susceptible test were excluded in statistic analysis. All the data was transcribed through the double entry. By means of SPSS 11.0, univariate and multivariate analysis were applied to quantify and qualify the treatment management and characteristics of drug resistance TB cases registered in the local TB dispensary. Categorical data were contrasted using the Mantel-Haenszel chi-square test; when expected value was less than 5, fisher's exact two tailed test was used. To compare continuous data, the student's *t*-test was used for normally distributed variables; otherwise the Wilcoxon two-sample test was chosen. Correlation coefficient was obtained with a nonparametric test of the Pearson. Binary Logistic Regression model was used in multivariate analysis to identify and quantify the relevance of individual socioeconomic and clinical factors on presence of drug resistance tuberculosis and their treatment management.

4.6 Quality assurance

Pretest

Before the study, the pretest was performed to identify the variable of interest regarding to the characteristics and management of drug resistant TB cases.

Training and motivation

The group of interviewers comprised non-clinical anti-TB health workers in Local County, village and town. The interviewer was trained and examined as regards to the objective and

method of investigation and the significance of the investigated item. Within initial 3 months of investigation, we connected the interviewer twice per month to seek and solve the possible problem. To ensure the quality of investigation and enthusiasm of interviewers, the interviewers were motivated by the rewards corresponding to quality of their job and their workload.

Rechecking the questionnaire

Every questionnaire was checked carefully to avoid missing items. The incompetent questionnaire was reinvestigated to ensure the quality of investigation. The 10% of subjects was reinvestigated to confirm that the accordance rate of main items between 2 interviews was more than 90%.

Quality control in lab practice

All the specimens available were stored at the temperature of 0 degree. Internal quality control was performed by the technician himself in the local CTD both in two counties. Based on the workbook "quality control of microscopy examination", every technician was trained before their laboratory practice. All the slides were read by two different staffs. The slide having discordant result was remained and finally identified by the chief in laboratory. Each week, 10% of specimens were reexamined to assure the accordant result more than 95% both in two county CTD. As for the external quality assurance, specimens in CTD were sampled and examined, twice by provincially reference lab, once by national reference lab every year.

The specimens of sputum were collected airproof in the sputum bottle. All the specimens were stored in cold boxes and transported in Bus within 1 day to the microbial lab in Fudan University each month.

In microbial lab in Fudan University, internal quality control was performed by the special staff in terms of the storage of specimen, the procedure of operation and the reading of result. 10% of specimens were re-checked by the external lung hospital in Shanghai. The accordant

rates of drug resistance were: STR (91.2%), INH (92.7%), EMB (89.6%) and RIF (94.8%).

4.7 Ethic consideration

Before the formal interview, the subject was informed of the objective of the study and its importance in TB control of China, while the written consent should be signed. In addition, the privacy of subject was protected by code instead of the respondent's name. The data was accessible only to the interviewer and researcher. The questionnaire would be locked in a safe cabinet and destroyed by the main investigator at the end of the 2 years' study. Some experts were assigned to solve any question related to the study even after investigation. The identified MDRTB case was suggested referring to up level TB hospitals for treatment with 2^{nd} line medicine. This study gained the permission from the institutional review board of school of public health in Fudan University.

This study is by-product of the Program: "the Molecular epidemiology of tuberculosis transmission in rural China" sponsored by the Chinese national nature funds, which began on April 1st, 2004 and ended in May, 2006. The writer is one of main researchers participated in data collection, data analysis and lab practice including culture, drug susceptible test and MIRU-based genotyping.

5 RESULTS

5.1 General characteristics of subjects

From April 1st 2004, to March 31st,2005, totally 784 subjects were registered in the county TB dispensary of two study fields, respectively 310 in DQ and 474 in GY. From them, 1,858 sputum specimens were collected in all. 90 cases in DQ and 227 cases in GY were diagnosed non-pulmonary TB (NPTB) patients by manifestation of AFB smear negative and culture negative simultaneously. Meanwhile, 17 cases in DQ and 9 cases in GY didn't response to the questionnaire interview. Totally 203 subjects in DQ and 230 in GY were smear positive and/or bacterial culture positive. After bacterial culture, growth of *M.TB* complex strain was obtained respectively 186 isolates in DQ and 222 isolates in GY. 4 isolates in DQ and 5 isolates in GY failed the drug susceptible test (DST) and were ruled out of the study. Finally, 399 culture positive pulmonary TB (PTB) cases were eligible for this study, 182 in DQ and 217 cases in GY. Among eligible subjects, 120（65.9%） in DQ and 133（61.3%） in GY were AFB smear positive. The demographics of subjects (sex and age), as well as education level were well comparable (p>0.05) between 2 counties. However, DQ county had more underweight (55.5%) subjects with higher annual individual income (mean: 6,617CNY) and household income (mean: 11,167 CNY), while more subjects in GY were normal weight (47.9%), with lower annual individual income (mean: 2,408CNY) and household income (mean: 6,016CNY) (Table 5.1). The important difference in some main socioeconomic aspects required the following study specific to the county.

5.2 Prevalence of drug resistance in local setting

5.2.1 Case classification

Based on the case definition recommended by WHO, the GY(26.9%) had as many previously treated TB cases as DQ (30.9%) and the ratio between previously treated and new cases was comparable in the two counties (p>0.05) (see table 5.2).

5.2.2 Lab exam

Among 399 eligible PTB subjects, the AFB smear positive rate (65.9%) in DQ was a little higher than that (61.3%) in GY, but there was no statistical difference between 2 counties ($p>0.05$) (Table5.2). Simultaneously AFB smear positive and culture negative were 7 (3.8%) in DQ and 3 (1.38%) in GY; simultaneously AFB smear negative and culture positive were 62 (34.1%) and 84 (38.7%); simultaneously AFB smear positive and culture positive were 113(62.1%) in DQ and 130 (59.9%) in GY (see table 5.2).

5.2.3 Microbial strain

After cultured in respectively on PNB and TCH contained culture bases, 5 (2.7%) isolates in DQ and 7 (3.2%) isolates in GY were identified to be the *M. Bovis* strain, while the remained 177 (97.3%) isolates in DQ and 210 (96.8%) isolates in GY were confirmed the *M.TB* strain. No other microbial strain was identified in this study. (Table 5.2)

5.2.4 Drug resistance

5.2.4.1 Drug resistance rate

Among the 399 TB isolates, overall resistance rate (ORR) (1 or more drugs) were respectively 100(54.9%) isolate in DQ and 151(69.6%) in GY. Simultaneous resistance to at least RIF and INH (MDR) were identified among 13(7.1%) cases in DQ and 45(20%) cases in GY. 87(47.8%) case in DQ and 106(48.8%) cases in GY suffered from other combined drug resistance (Table 5.3). In terms of the more than 2 drug resistance pattern, multi-drug resistance (at least for RIF and INH) took account for the largest proportion. In addition, the pattern of "RIF+EMB only" drug resistance was not observed in this study (table 5.3).

5.2.4.2 Rank of drug resistance

For the initial drug resistance, the rank of 4 first-line anti TB drugs resistance were: INH, 39(29.3%); STR, 34(25.6%); EMB, 19(14.3%); RIF, 7(5.3%) in DQ; STR, 57(38%); INH, 46(30.7%); RIF, 27(18%); EMB, 16(10.7%) in GY. For the acquired resistance, the rank of 4 first line anti TB drug resistance were: INH, 15(30.6%); STR, 14(28.6%); RIF, 10(20.4%); EMB, 8(16.3%) in DQ; INH, 40(59.7%); STR, 32(47.8%); RIF, 25(37.3%); EMB, 12(17.9%) in GY (table 5.4).

5.2.4.3. Drug resistance specific to previous treatment history

In DQ, the initial drug resistance rate of MDRTB and ODRTB, were respectively 3.8% and 46.6%, while the acquired drug resistance of those were respectively 16.3% and 51%.In addition, the chi2 test confirmed the previously treated TB cases in DQ was more likely to develop the single RIF drug resistance and multi-drug resistance ($p<0.05$). In GY, The rate of initial drug resistance rate of multi-drug and other drug were 14.7% and 48.7%, while the acquired drug resistance rate was respectively 34.3% and 49.3%. The Chi2 test suggested that the previously treated TB cases in GY was more likely to develop the single INH, single RIF and multi-drug resistance ($p<0.05$).Meanwhile the table showed the drug resistance especially including the multi-drug resistance was more prevalent in GY than DQ ($p<0.05$) (Table 5.4) .

5.2.4.4. The correlation between RIF and Multi-Drug Resistance

Among 69 RIF resistant isolates, 3 (4.3%) were only resistant to the RIF. 58 (84.1%) isolates were simultaneously resistant to INH, among which 38 isolates (65.5%) were resistance to EMB or/and STR. In addition, the presence of resistance to RIF was significantly associated with other 3 drugs resistance ($p<0.05$), the coefficients of Person's correlation with STR, INH and EMB were respectively 0.1999, 0.791 and 0.193 (Table 5.5).

5.3 Predictors of drug resistance

Demographic and clinical characteristics of drug resistant TB (index group) and drug pan-sensitive TB (controls), with index group stratified according to the county were presented respectively in Table 5.6 and Table 5.7. Logistics Regression model was used to estimate the relationship between these factors and the presence of drug resistant TB cases. This model included male (sex), age (mean) at interview, health status (BMI), occupation, individual income(mean) , household income (mean), previous treatment history, and case contact.

5.3.1 The characteristics of drug resistant TB cases in DQ

In DQ, univariate analysis shows that age, previous treatment history, case contact, individual

and household income were related to the presence of MDRTB ($p<0.05$), while male (sex) occupation and case contact were also linked to the presence of other drug resistance ($p<0.05$). In multivariate analysis, age, previous treatment history, case contact and individual income remained to be predictors of the presence of drug resistant TB. The elder (OR: 1.22; 95%CI:1.12-6.63) subjects with the previous treatment history (OR: 4.98; 95%CI:1.56-8.03) , lower Individual income (OR:0.79; 95%CI: 0.03-0.92) and contacting case (OR:7.84; 95%CI:1.71-25) at home, were more likely to have the drug resistant TB, while the variable associated with the presence of other drug resistance was contacting case at home (OR:2.9; 95%CI:1.13-7.52).(table 5. 6)

5.3.2 The characteristics of drug resistant TB cases in GY

Based on the Chi2 test (table 5.7), previous treatment history, Health Status (BMI), case contact and individual income were related to the MDRTB ($p<0.05$), while no variable was linked to other drug resistance. Logistic Regression analysis (table 5.6) concluded that male(sex)(OR:2.1; 95%CI: 1.06-15.6), the previous treatment history (OR: 3.94; 95%CI: 2.04-12.48), health status (BMI) (Normal weight/underweight: OR: 0.082; 95%CI: 0.018-0.38; Overweight/ underweight: OR:0.076; 95%CI:0.008-0.72), case contact (OR: 4.8; 95%CI: 1.32-7.24) and individual income (OR: 0.15; 95%CI: 0.04-0.89) were associated with the presence of the MDRTB (Table 5. 7).

5.4 Management of drug resistant TB cases

Among all the identified cases, 6 (46.2%) in DQ and 18 (40%) in GY MDRTB cases had not initiated the first visit to the health provider within 2 weeks after onset of symptom, while 15 (17.2%) ODRTB cases in DQ and 23 (21.7%) ODRTB cases in GY delayed seeking health care. In addition, 5 MDRTB cases (38.5%) in DQ and 4 (8.9%) cases in GY had not got the diagnosis within 2 weeks after their firstly seeking health care, while among 3 ODRTB cases both in two field grounds, diagnosis were delayed. During the initial two months of treatment, in DQ, 2 cases transferred out for traveling to other place and 1 case defaulted the treatment due to the side effect. In GY, 3 cases (including 1MDRTB cases) transferred out due to work outside the place of birth and another 1 cases defaulted due to side effect. Within the

following 4 months of treatment, 3 cases in DQ paused treatment due to the side effect (2 in liver, one in gastrointestinal tract) , while 1 case in DQ and 4 (including 2 MDRTB cases) cases in GY transferred out due to working outside the place of birth and another one defaulted due to untold reason. As a result, 13 (100%) in DQ and 42(93.3%) MDRTB cases in GY completed the whole treatment, while 80 (92%) in DQ and 101(95.3%) in GY ODRTB completed the treatment **(**figure 5.2)

5.5 Treatment adherence of drug resistant TB treatment

In this study, the treatment adherence was identified as those without missing or less than one regimen every week. Similar proportions of other drug resistance case adhered to the treatment regimen between DQ (75.9%) and GY (72.6%) (p>0.05). There was also no statistical difference of treatment adherence between DQ (46.2%) and GY (55.6%) in a term of MDRTB treatment (table5.8). The Logistic Regression analysis was used to analyze factors influencing the treatment adherence specific to the county; the included variables were age, male sex, previous treatment history, education, occupation, side effect, medical insurance, individual income and household income.

5.5.1 Treatment adherence of treatment in DQ

The Chi2 test analysis showed that education and side effect were important factors related to treatment adherence among MDRTB cases (p<0.05), while age was perceived to influence the treatment adherence among other drug resistant TB cases (table 5.10). The Logistic Regression analysis concluded that side effect (OR: 0.84; 95%CI: 0.37-0.96) was associated with the treatment adherence of MDRTB treatment (Table 5.10).

5.5.2 Treatment adherence of treatment in GY

The Chi2 test analysis showed that the previous treatment history, education, side effect , insurance and individual income influenced the treatment adherence among the MDRTB cases, while education remained relevant to the treatment adherence among ODRTB cases (p<0.05). The Logistic Regression based model concluded that previous treatment history(OR: 0.37; 95%CI:0.29-0.84),education (OR: 3.6; 95% CI: 1.07-5.53), side effect (OR: 0.32;

95%CI: 0.041-0.92), medical insurance (OR:1.12; 95%CI: 1.032- 4.89) and individual income (OR: 1.11; 95%CI: 1.02-4.08) were associated with the treatment adherence of MDRTB treatment, while the variable associated with treatment adherence of ODRTB treatment was education (OR: 1.98; 95% CI: 1.27- 3.63) (Table 5. 11*)*.

5.5.3 Causes for treatment nonadherence

The commonest causes of treatment nonadherence both in DQ and GY were difficult toleration of the side effect and geographic barrier. Other cause included temporary constraint, forgetfulness to take the drug and feeling better. (Table 5. 9)

5.6 Treatment success of drug resistant TB cases

The success of treatment here was identified as the consecutive AFB smear negative at the end of treatment. Compared to the treatment success rate (84.1%) in drug sensitive cases in DQ, 73(83.9%) ODRTB cases and 7 (53.8%) MDRTB cases got the treatment successful. In addition, compared to the drug sensitive cases (81.8%) in GY, 86(81.1%) ODRTB and 17(37.8%) MDRTB cases were cured (see table 5.12). Logistic Regression analysis was used to explore factors influencing the treatment success specific to the county. The variables included age, male sex, previous treatment history, health status (BMI), Occupation, treatment adherence, patient's delay, doctor's delay, individual and household income.

5.6.1 Treatment success of drug resistant TB cases in DQ

Among the drug resistant TB cases, the patient's delay was considered factor influencing the treatment success (p<0.05), while the previous treatment history and patient's delay were related to the treatment success of other drug resistance in DQ (p<0.05). In the multivariate logistic model, the variables significantly associated with treatment success of MDRTB were patient's delay (OR: 0.07; 95%CI: 0.006-0.83), while patient's delay (OR: 0.08; 95%CI: 0.005-0.72) and previously treatment history (OR: 0.84; 95%CI: 0.24-0.95) played a role in the treatment success of ODRTB (Table 5.13).

5.6.2 Treatment success of drug resistant TB cases in GY

The univariate analysis using chi2 test showed that health status (BMI), previous treatment history, treatment adherence and individual income influenced the treatment success of MDRTB while health status and treatment adherence were related to the treatment success of ODRTB. On multiple Logistic Regression, previous treatment history (OR: 0.21; 95%CI: 0.15- 0.87), health status (BMI) (Normal/underweight: OR: 1.19; 95%CI: 1.06-5.09), treatment adherence (OR:3.1; 95%CI: 1.05- 5.38), individual income (OR: 1.11; 95%CI: 1.02-6.08) and patient's delay (OR:0.19; 95%CI:0.023-0.92) were significant independent predictors of MDRTB treatment success , while variables associated with the treatment success of ODRTB were treatment adherence (OR: 3.38; 95%CI: 1.23-8.85) and health status (Overweight/underweight: OR: 4.38; 95%CI: 1.98-9.46; normal weight/underweight: OR: 3.87; 95%CI: 1.09-8.73) (table 5.14).

6 DISCUSSIONS

6.1 Methodological considerations

6.1.1 Precision of quantities studies

Precision is defined as the quality of being reproducible in amount of performance. The sample size of the study and statistics efficiency could be considered as two components to improve the precision of the study. The sample size should be enough to seek for the potential association between exposure and disease, while the cost should be minimized corresponding to acquire the similar statistical information. From this perspective, the sampling strategy plays a great role in it.

Based on the feasibility of the study, 2 NTP-DOTS covered counties in 2 neighboring provinces were selected as study fields, where all the TB cases registered in local TB dispensaries within 1 year were taken as the subjects. Although this sampling strategy increased the cost, it effectively reduced the error which always occurs in random sampling. In addition, in NTP-DOTS covered area almost all the registered TB cases are referred to the TB dispensaries and accept the treatment there, so the information from them would reflect almost all the situation of registered TB case in local settings. Certainly, there existed few cases that might self-treat or accept the health service from the private practitioner due to geographic and socioeconomic barrier, but the very small proportion of these people would make the estimation much near to the reality. In addition, considering the fact that 1/3 people has carried the TB bacteria, almost half of cases were not detected and registered in China *(Ministry of health, China, 2004)*. Based on these facts, the finding and result in this study might underestimate the real situation. In addition, a small number of subjects were obtained in terms of MDRTB in different socioeconomic aspects especially in DQ. This might cause some result to attribute to the chance rather than the real association.

The post study power was calculated to examine the adequacy of the sample size we used in this study. When comparing the MDRTB rate between DQ (7%) and GY (20%) counties. At

α=0.05 level, the study power could reach 92.7% when both standard deviation for both population was 2.5; the study power could reach 96.4% when both standard deviation for both population was 5. It suggested that the sample size was adequate to find the difference between two populations of different settings. Compared to the initial drug resistance rate in another NTP-DOTS covered area (42.8%) *(Yang et al., 2004)*, when the overall drug resistance rate in DQ was 50.4%, at α=0.05 level, the study power could reach 85.7% supposedly standard deviation was 2.5. Similarly, Compared to the initial drug resistance rate in another new NTP-DOTS covered area (58.1%) *(Yang et al., 2004),* when the overall drug resistance rate in DQ was 63.4%, at α=0.05 level, the study power could reach 93.5% supposedly standard deviation was 2.5. It suggested the finding and result from this study could much reasonable reflect the truth.

In addition, Multivariate analyses based on Logistic Regression model, was used to improve the statistical efficiency through the procedure of model fitting and effect estimation.

6.1.2 Internal & external validity

Internal validity means the reduction of systematic error or bias. The bias happens in the selection of subject and the way to collect the information. In this study, the subject should be those registered in the local TB dispensary and those whose results of DST were available. From this perspective, we constrained the results only to those registered cases, so this selection bias has been controlled to some degree. Another selection bias could be caused by lacking isolates for some cases. Constrained by the limited sensitivity in AFB smear test and culture, those TB cases might be not included in this study by the manifestation of culture negative or/and AFB smear test negative. In our study, 10 (5.5%) cases in DQ and 4 (1.8%) cases in GY were AFB smear positive but culture negative, whose DST result were unavailable and therefore were excluded from this study. The very small proportion of this issue would not influence the conclusion significantly. In addition, Table 6.1 listed the distribution of main studied factors between eligible group and those who diagnosis based on clinical or radiographic evidence in this study. It is found that it didn't make difference between 2 groups in terms of main socioeconomic variables except the health status and

occupation ($p<0.05$). In additions, in the cross sectional study of predicators influencing the development of drug resistant TB, all the subjects including drug sensitive TB cases were elicited from the same population registered in the local TB dispensary. In this point, the result and finding from this study would reasonably reflect the setting, where the subjects arose. All above indicated that the selection bias could be controlled effectively in this study.

Information bias might happen in this study. The economic status here was evaluated by using the individual and household income, which might misclassify the subjects by neglecting the other economic- related indices including house structure size, expense on building, floor and wall material. But considering the very contribution of individual income and household income to the individual economic status, these two variables were used to provide a rough snapshot of the individual economic status. In addition, the pulmonary TB was confirmed by 2 consecutive AFB smear positive or/and at least one culture positive. The false positive might happen due to the cross contamination in the experimental practice. In addition, the AFB smear is only sensitive for more than 5000~10,000 strains per ml. *（Kent et al., 1985）* The false negative would happen when no enough sputum was collected to reach this baseline. In our study, to ensure the quality of detection, each specimen was implanted into 2 culture bases. Every batch of specimens was cultured together with the experimental standard strain H37Rv as the positive control and culture without *M.TB* strain as the negative control. The error in reading results could reduce by double reading and rechecking each week. Furthermore, since the characteristics related to TB might cause the social stigma and economic barrier, e.g. unemployment. The respondent might hide or distort some facts intentionally. The details of study were informed to the respondent before every interview and confidentiality was strictly followed throughout the study in order to get the reliable information from the respondent. In addition, considering the difference in the main variable of study between 2 fields, all the data analysis was based specific to the county, in order to avoid the potential bias due to the different characterisitics of the subjects respectively in two fields.

External validity is the generalization of the result or finding beyond the source population.

This study was established in two counties from two relatively a little higher income provinces in southern China. The finding and result of the study may not effectively copy to rest area of China especially including relatively poor northwestern area. In addition, since this study was based on the result of DST, two counties had to be selected where the DOTS based TB control program had already been in place. In those counties without the NTP-DOTS covered, the TB cases are mainly diagnosed using X-ray in the township hospital instead of county hospital or TB dispensary. Although AFB smear microscopy is used in diagnosis, it doesn't be regulated, and it could be done in township and county hospitals, which makes the collection of sputum specimen unfeasible. Fortunately by now, NTP-DOTS program has been expanded up to 19 provinces in China. Based on these considerations, we selected one county with more than 10 years NTP and the other with less than 1 year NTP. Since the distribution of TB in new NTP covered county was supposed to resemble that of the general population, the population prevalence of TB could be reflected in the new NTP County to such a degree that the external validity could be established.

6.2 The current drug resistant TB prevalence and trend in China

The high rate of anti-TB drug resistance is considered an important feature of tuberculosis prevalence in China *(Ministry of Health, China, 2002)*. But since DST has not been formally introduced to tuberculosis control program, the drug resistance status of most infectious *M.TB* strain remained unclear in China, which necessarily impedes the effective treatment and monitoring of drug resistant TB. So far, the method of DST has not been unified, which subsequently cause the poor comparability of result from different settings. Therefore this situation makes it necessary to introduce and unify the DST method. This study was based on the result through the standardized proportion method of DST, which enabled the comparison with result from WHO/IUATLD and thus reflected the general distribution of drug resistant TB in local setting.

Based on the proportion method of DST, it was found that 100 (54.9%) cases in DQ and 151(69.6%) cases in GY were resistant to at least one first line anti TB drug. On the whole, the INH resistance happened more frequently than RIF resistance whatever in two counties.

The initial drug resistance rate in this study was 50.4% in DQ and 63.4% in GY, both higher than national average level (18.6%) *(Ministry of Health, China, 2002)*, while the acquired drug resistance rates in both fields (67.3% in DQ Vs.83.6% in GY) were still much higher than the national level (46%). Meanwhile, WHO/IUATLD reported the initial drug resistance rate in Chinese Henan Province were 35% in new cases and 66% in previously treated cases *(WHO, 2000).* Compared to these results around 2000, in our study, a significant increase in drug resistant TB was observed especially among the new cases. Both in two counties, the high increase in drug resistance to INH and STR might contribute to this result.

Some study demonstrated *(Espinal et al., 2001)* that the initial drug resistance was the good estimation of the prevalence of drug resistance in the community, thus reflecting the performance of controlling the drug resistance in local setting. In this study, the initial drug resistance rate was higher between old NTP county and new NTP county, which suggested the likelihood that the epidemics of drug resistant TB was established in local setting. Considering the similar situation of initial drug resistance rate between 2 fields, the long term implementation of DOTS in DQ might not play a role in controlling the drug resistance.

In addition, the high drug resistance to STR was significant in GY especially for new cases, which might be associated with the improper use of antibiotics before standard anti TB treatment. The 4th national epidemiological survey *(Ministry of Health, China, 2002)* showed that 61% MDRTB cases were simultaneously resistant to STR, while the rate of drug resistance to STR was 65.2% among previously treated TB cases. In addition, Some Chinese studies have already reported the extensive STR drug resistance happened to the treatment against Staphylococcus *(Ye et al., 2003)* and Enterococcus *(Xu et al., 2004)*. In contrast, the drug resistance in DQ was more likely to happen in INH both for new and previously treated cases, which might attribute to the long term use of INH in anti-TB treatment *(Kong et al., 2003).* This high rate of INH resistance was also observed in other areas with a long history of using INH *(WHO, 1997).*This both suggested the drug resistance exhibit different properties in different local setting and the corresponding control should be focused on different aspects.

The previously treated TB cases both in two counties were more likely to develop the single RIF drug resistance and multi-drug resistance, which may be consistent with the potential role of prior treatment on the development of MDRTB. RIF has a very low rate of natural mutation in related targeted gene (10^{-8}), but the retreatment increased this chance significantly *(Sharma et al., 2004)*. This finding was also observed in the similar setting of other NTP-DOTS covered Chinese area *(Yang et al., 2004).*

Among the 4 first line drug recommended by WHO, the drug resistance to STR, INH and RIF were put into the first 3 places, consistent with the surveillance data performed by WHO/IUATLD on 72 countries *(WHO, 2000).* In addition, the single drug resistance was more likely to happen in STR and INH or both, since these two drugs have been used for a long time and have a relative high rate of natural mutation in related targeted gene. By contrast, the low EMB drug resistance might be related to the short term use of it. Philippines has begun to replace the PAS with EMB since 1960s. The long term use of it made the EMB drug resistance up to 39% *(Mendoza et al., 1997).*

According to WHO/IUATLD Global Project on Anti-TB drug resistance Surveillance (1999-2000), some MDR-TB Hotspots were identified in the area with multi-drug resistance rate more than 3% (*WHO 2000; Espinal, 2001*).Our study revealed the likelihood that the tendency of drug resistance was towards more than 2 drug resistances. The rate of more than 2 drug resistance was 18.7% in DQ and 30.4% in GY. The high poly drug resistance (drug resistance to at least 2 anti-TB drugs) posed a potential threat to TB control based on 4 first line drugs chemotherapy. The commonest pattern of mono-drug resistance was only STR drug resistance, which might caused the confusion about the practical contribution of STR to the anti-TB treatment under the Chinese setting especially for the previously treated cases.

In addition, among 69 RIF resistant isolates, 58 isolates (84%) were simultaneously resistant to the INH. Among these 58 isolates, 38 isolates (65.5%) were simultaneously resistant to another one or both of STR and EMB. Similarly, Heep et al found *(Heep et al, 2003)* 73 of 80

isolates were resistant to INH and 60 of 73 isolates were simultaneously resistant to other one or two drug .Watternson et al reported *(Watternson et al, 2002)* that in U.K, 92.9% RIF resistance concurred simultaneously with the INH resistance. Therefore, the drug resistance to RIF is a valuable predictor for the multi-drug resistance and implicates its importance in drug resistant TB surveillance.

The situation of drug resistance may reflect the performance of TB control program and related to the efficacy of MDRTB treatment and prevalence of HIV in local setting *(Ministry of Health, China 2002).* In this study, the abnormal higher initial and acquired drug resistance both in old and new DOTS covered area might suggest the inefficient management of TB cases, irregular chemotherapy, the abuse of antibiotics and difficulties in referring system.

6.3 The factor facilitating and inhibiting the drug resistance

The concept of drug resistance contains clinical drug resistance and microbial drug resistance. Due to the natural and artificial reason, 1% drug resistance strain would become predominant within several months. Therefore, the clinical drug resistance is defined as more than 1% drug resistance strains. Microbial drug resistance refers to the phenomena that the drug-sensitive microbe grows resistant to the drug due to the spontaneous mutation. Because of the inadequate selection of drug, the ratio of susceptible strain to drug resistant strain reverses. Considering the rare opportunity of drug resistance caused by the natural mutation, the development of drug resistant TB prove to be the artificial results *(Katalinic- Jankovic et al., 2004)*

Our study looked at factors influencing the development of drug resistant TB in different NTP covered area of rural China. It was found that male TB cases had relative higher level of drug resistance in GY (OR: 2.1; 95%CI: 1.06-15.6). And the ratio of MDRTB between male and female was significantly large. The reason might be the poor adherence to drug treatment among male cases during the previous treatment, which probably resulted from excessive lassitude after work, smoking and drink *(Gao et al., 2002).* In addition, this sex discrepancy was similarly observed in the general TB distribution. The ratio of TB prevalence between

male and female was 1.5-2.3:1. *(WHO, 1998).*The age (OR: 1.22; 95%CI: 1.12-1.63) was in direct proportion to the development of drug resistance tuberculosis in DQ. The poor adherence to the treatment and physical condition may contribute to the high risk of drug resistance among the elders *(Sevim et al., 2002).*

In addition, the case in the poor economic status was more likely to develop the MDRTB both in two areas in terms of individual income. It suggested the potential association between the poverty and MDRTB even in different settings. Many studies *(Christy et al., 1994; Ahlburg, 2000; Barr et al., 2001)* have confirmed the necessary connection and interaction between poverty and TB, while the association between MDRTB and poverty need further confirmation based on the epidemiological and experimental evidence. The subjects of this study were from the rural China and most of them were farmers (51.6% in DQ and 59.1% in GY). Despite of the substantial growth of economics in China, most of farmers are still living in comparable poverty. In addition, the poor population tended to be malnourished and staying in the crowed condition, which might increase the chance of being infected with TB and treatment failure *(Karyad et al., 2002).* The population census *(VanRie et al., 1999)* in Southern Africa reported the TB prevalence in Children was related to the education level of their parents (r=-0.64), household income(r=-0.6) and the crowded environment (r=-0.32) and the impoverished children was more likely to get the TB. This statement was consistent with the conclusion that the most of TB cases were the poor in the Balandish setting *(Khan et al., 2000).* This feature of TB distribution was also observed in China. The 4th TB national survey revealed *(ministry of health, China, 2002)* that the poor western area (451/10,000) had more pulmonary TB prevalence than relatively richer eastern area (254/10,000), while the TB mortality in rural area was much higher than that in urban area. The association between health and development of MDRTB was also validated in this study. This situation may be even worsened since health financing system has changed from cooperative medical system to out-of-pocket payment *(Feng et al., 1995).* As a result, the majority of rural people have no insurance schemes and financial ability to withstand the risk, which may worsen their health status and meanwhile prompt the prevalence of TB in local setting.

In this study, the previous treatment history was strongest predictor independent of the presence of drug resistant TB especially including the multi-drug resistant TB both in two counties. Whatever in DQ and GY, the previously treated TB cases were around three times as much likely as to develop the MDRTB.Many studies *(WHO, 2004)* showed the prevalence of MDRTB was low where the treatment of TB was successful. The association between previous treatment history and presence of MDRTB was also observed in the similar setting, especially for those with previous treatment more than 1 month. Retreatment elongated the period of treatment and meanwhile increased the possibility of genetic mutation related to drug resistance *(Kam et al., 2003; Timperi et al., 2001).* In addition, the treatment failure might result from the partially drug resistance *(Vasquez-Campos et al., 2003)* and the defect in the management of treatment. The subsequent repeated use of first line drug might pose the pressure on the drug selection and subsequently worsen this issue.

Although NTP-DOTS have been implemented in DQ for almost 10 years, the poor, old and previously treated population who contacted the TB case at home was in risk of MDRTB. This may reveal the weakness of NTP indirectly. The NTP was based on the passive case detection, which may exclude some vulnerable population including old population and poor population. In addition, the NTP-DOTS project only sustains the fee of treatment rather than other financial loss followed by the disease. The poor and the elder population might be more concerned about the economic loss and therefore refuse to seek the health aids *(Gwatkin et al., 2000).* The 4th national TB epidemiological survey in China found: almost half of TB cases have not been detected and registered, for which the economic aspect was the commonest cause. Meanwhile, the default rate of seeking health care was reduced by 10% in 2000 comparable to that in 1990 due to the economic reason. As a result, the inadequate and mistreatment among the poor and old cases might cause and complicate the epidemics of drug resistant TB in China.

6.4 Treatment adherence

Treatment Adherence is a term used to describe how well a case or client is sticking to the chemotherapy. Nonadherence to TB treatment is a major problem in TB control. Of cases

reported in the United States for 1994 *(Bradford et al, 1996)*, 14% of cases who were started on treatment had not completed a full course. The inadequate treatment may cause the failure to maintain the Minimal inhibition concentration (MIC), which ensure the minimal concentration to inhibit the growth of the pathogen. Inadequate treatment among drug resistant TB case can lead to relapse, continued transmission, and the development of more other drug resistance. In this point, increases in missed dosage correlated with increases in possibility of the treatment failure.

The treatment adherence includes the intermittent treatment and pause of treatment. In this study, the nonadherence was defined as self-reported missing at least one regimen within one week. Totally 25.8% cases in DQ and 30.4% of case in GY admitted missing at least one dosage of medication. These issues became worsen especially among MDRTB cases and proportions of their treatment adherence were respectively 46.2% in DQ and 55.6% in GY.

A component of case management that helps ensure that cases adhere to therapy is directly observed therapy (DOT). DOT means that a health care worker or another designated person watches the case swallow each dosage of TB medication. DOT ensures an accurate account of how much medication the case really took. But the efficacy of DOTS on treatment adherence among the drug resistant TB cases was not confirmed in this study. In the long-term DOTS covered DQ, the adherence among the multi-drug resistance cases was still at the low level, although this conclusion might be biased by the small sample size. The problem might lie in the matter of the case management. The good case management should be in concert with DOTS to really make DOTS programs effective. MDR-TB should always be treated with a daily regimen and under direct observation. There are no intermittent regimens for treatment of MDR-TB.

Both in GY and DQ, cases who were intolerant to side effect were significantly less likely to adhere to therapy. Only in GY, were the education, medical insurance and individual income related to the treatment adherence among subjects. The most common reasons related to treatment nonadherence were the difficulty in tolerating the side effect and geographic

barrier.

In this study, the side effect including the liver dysfunction and gastrointestinal discomfort ness might play a role in pausing taking drug, which was consistent with other study performed in the similar setting*(Huang et al., 2002).* The psychological and physical adverse effect tends to make the patient give up the treatment much easily.

Spite of a large number of chest clinics distributed throughout the area of fields, there is only one TB dispensary in local setting which provides the DOTS based treatment. It might bring a big problem for those living in the remote area to collect the drug regularly every week. Although the laboratory practice seemed to perform better in DQ than GY, the related test appliance and faculty were both scarce. 3 in DQ and 4 in GY medical staffs were reported to be responsible for the diagnosis and treatment of TB cases in the local TB dispensary. The disproportional health resource poses a potential threat to the effective implementation of TB control program.

Among other reasons, forgetfulness to deliver the drug seemed a ridiculous reason under the setting of DOTS strategy since the community health worker is responsible for the direct observed treatment. There is a need to strengthen this area and the sense of the responsibility among them should be encouraged by financial motivation and training.

In our study, the association between treatment adherence and socioeconomic characteristics could be established in new DOTS covered area. Those staying in the poverty were more likely to disobey the treatment regimen. The role of poverty on treatment adherence of TB was observed in other area of China. Due to the economic burden, 44.5% of TB cases stopped the treatment in Anhui province of *China (Wu et al., 2003)*. In Wu Han, the efficacy of DOTS program was assessed *(Huang et al., 2002)*. It was reported that most of cases could not afford the medical fee and thus discontinued their treatment and most of them defaulted the treatment due to feeling better, suggesting the importance of individual self-consciousness. Meanwhile, the case's awareness is in accordance with their education background. Our study

also found the good education background might contribute to the treatment adherence especially in the new NTP area. The poorly educated population has no knowledge enough to comprehend the information from the health provider. This was already confirmed by several qualitative and quantity studies in Chinese setting *(Pan et al., 2005; Huang et al., 2002).* The following low awareness to TB enabled them to be treated irregularly. In this point, the demographic, acculturation, and economics status were considered to determine the adherence of treatment among drug resistant TB cases. Thus, the fundamental improvement of TB epidemics might require the effort not only from the medical area but also from the politic and cultural support.

In addition, the previously treated TB case more likely did not follow the regimen. The longer the treatment lasted, the more poorly the drug regimen was followed. This conclusion was also made from one study performed in Blandish *(Chowdhury et al., 2002)* This study showed that among 3,886 TB cases under the 1 year treatment, 10% of them did not follow it but among 1,741 under 8 months treatment, all of them complete the treatment. Although the different size of sample was used, the shorter duration of treatment seemed to make the patient follow the regimen more easily.

Thus treatments among drug resistant TB cases were more likely to be distorted by the socioeconomic burden, side effect and geographic barrier.

6.5 Management of drug resistant TB cases

Although the DOTS strategy were supposed to cover all the TB cases in NTP area, totally 96.6% of ODRTB case in DQ and 94.9% of ODRTB case in GY completed the standard treatment in the first 2 months. In addition, the proportion of completing the treatment among MDRTB was 97.8% in GY and however all the 13 MDRTB cases in DY completed the treatment. This finding might compare favorable with a recent study done in China Hon Kong, where 86% MDRTB cases completed DOT in the first two months of treatment *(Huang et al., 2002)*. In the present study, Cases continued to follow the DOTS after the intensive phase, 93.3% of MDRTB cases in GY completed the secondary phase of treatment. Such result

might be satisfactory for the TB case, but for the drug resistant TB, even a little incompletion of treatment might pose a much serious threat to fail treatment *(Cardoso et al., 2001).* There were relatively few data from a similar rural setting for comparison, since this strategy has not been applied absolutely uniformly for all cases or has not been applied throughout treatment. However it was confirmed that the inadequate and interrupted treatments lead to the treatment failure and the development of MDRTB *(Cardoso et al., 2001; Coninx et al., 1998).*

In China, low-income areas have less resource needed for effective management of MDRTB: less-equipped laboratory facilities that can provide accurate DST results, expert medical faculties experienced in drug resistant TB management, and the funds to pay for the expensive second-line drugs and the system of detecting and monitoring the drug resistance *(Ministry of Health ,China, 2002)*. These all make it difficult to manage the drug resistant TB case even in the setting covered by NTP-DOTS. The default in treatment between two fields implicated that the problem of management of drug resistance, the less-equipment and unqualified staff were considered main barriers in this setting *(Ministry of Health, China, 2002).*

In addition, management of side effect is important component to manage the treatment of drug resistant TB. The failure to resist the side effect was the main cause to make the case default treatment. Furthermore, the floating population was still blind zone of TB control even in the NTP-DOTS covered area. 3 drug resistant case in DQ and 7 cases in GY default the treatment due to work outside the place of birth. The difficulty in managing the floating population in NTP covered area worsens the epidemics and control of Drug resistance in China. The following concern should be focused on the floating population by strengthening their awareness and monitoring their treatment. The effectiveness of the emphasis on the management of floating cases was suggested in one study performed in Shanghai. *(Shen et al., 2005)*. After making the treatment of floating case free of charge, the rate of completion treatment rose from 78.7% before that to 97.6%.

Therefore, Localized areas with high prevalence of MDRTB are therefore more likely due to poor treatment programs rather than local transmission of MDRTB *(Failover et al., 1999).* This study confirmed that TB control programs should continue to concentrate on effective management of all the TB cases using the DOTS strategy. Meanwhile, some study also suggested that MDRTB incidence in the "hot spots" would be reduced more rapidly by effective treatment of drug-resistant cases in the area where the DOTS-plus is well in place *(Tupasi et al., 2003).* WHO and other authorities have advocated that DOTS-plus treatment would be validated in various circumstances *(Kim et al., 2002; Reide et al., 2002).* The Green Light commit (GLC) has developed the guidelines for establishing MDRTB treatment centers and developed the cheaper second-line drug, which might make DOTS-plus programs increasingly possible in resource-poor settings. The success of a pilot project providing standardized MDRTB treatment regimen in Peru justified that such DOTS-plus programs were feasible at least in middle-income countries *(Talbot et al., 1993).* Increase in coverage of DOTS in different population and combination with new drug resistant TB control program may be the avenue to improve the management of drug resistant TB in the setting of high epidemic area in China.

6.6 Treatment outcome of drug resistant TB

Drug resistant TB plays a direct role in the efficacy of chemotherapy against tuberculosis. This study reported that drug resistant TB cases took account for 54.9% in DQ and 69.6% of the detected cases registered in the local TB dispensary at the same time. It presented a big challenge and threat to the tuberculosis control program. The initial drug resistance significantly influenced the efficacy of short course treatment *(WHO, 2004).* Without the drug susceptible test in most of NTP-DOTS covered area of China, the regimen would not be modified according to the susceptibility of infected strain and thus increase the possibility of treatment failure and induce the development of drug resistance simultaneously.

In our study, a cohort of drug resistant TB cases was followed up during their treatment. The treatment success was defined consecutive AFB smear negative at the end of 6^{th} month treatment. 83.9% other drug resistant TB cases in DQ and 81.1% in GY were cured, while 7

(53.8%) in DQ and 17(37.8%) MDRTB cases in GY were cured by presenting AFB smear negative at the end of treatment. this result was well comparable to the study in the similar setting *(Wang SM et al, 2006)*, where the cure rate for the MDRTB cases was 43.2% and the cure rate for the ODRTB was more than 80%.This suggest the SCC play a positive role in the treatment of other drug resistance but performed worse in treating the MDRTB cases.

The multivariate analysis based on Logistic Regression model showed that previous treatment history and patient's delay were factors influencing the outcome of drug resistant TB both in two fields. Health status, treatment adherence, diagnostic delay and individual income was another effective factors related to treatment outcome singly in GY.

The passive case-finding approach require the cases' recognition of TB suggestive symptoms on their own, case's health seeking and appropriate diagnostic performance of the health provider make the control of TB function well. In this study, the patient's delay and doctor' s delay were measured to describe the accessibility to health service among TB cases especially including the drug resistant TB cases. The interaction between these and treatment outcome was the concern of this study. As the study went, the patient's delay was the important component to decide the treatment outcome of drug resistant TB case. Especially in the NTP-DOTS covered area, the diagnosis should come out within 24 hours of AFB smear test and treatment should follow immediately, which might effectively avoid doctor's delay. In this point, the delay of individual health seeking practice shapes the destiny of drug resistant TB cases. Furthermore, in NTP-Covered area, the county hospital was only recognised to be responsible for diagnosis of the TB and local TB dispensary would strictly put DOTS strategy on the TB cases. Some study showed that most cases in the rural area did not know about the knowledge of TB *(Liu et al., 2005)*. And indeed 38 (20.9%) in DQ and 66 (30.4%) in GY didn't visit the formal medical facilities until 2 weeks after the first symptom in our study. In addition, the traffic inconvenience and economic burden might barricade their timely seeking treatment. The poor self-consciousness and social-economic status of drug resistance cases cause them to select the self-treatment or seek the health aid from the private practitioner or informal medical facilities. Even though some anti-TB drug could be provided by the

informal medical facilities, the DOTS strategy would not be followed. This suggests that attention should be paid to increase the awareness of TB among the general population and optimize the allocation of resources to suit the general needs.

In our study, the social economic status also posed the influence on the treatment outcome especially in the new NTP-DOTS covered GY. Some study *(Lawn et al., 1998)* found that poor people were reluctant to initiate their health seeking and more frequently visit village health stations rather than hospital due to lack of money. National TB control program provides the free health service to the AFB smear positive TB cases, but the premise is that the case should seek health service in the local county hospital covered by the DOT strategy. Before they reach the local TB dispensary, all the medical service is charged. With the collapse in the system of cooperative health service, 90% rural population has to sustain the medical fee. Coupled by the increasing price of health service, the proportion of medical fee to the Disposable income rose from 2.77% to 3.15%, which significantly increase the burden of medical service. In addition, one study performed in the similar setting found that no significant difference of medical fee was found between the poor and rich cases *(Xu et al., 2004).* People in different socioeconomic status paid the similar medical service, which caused inequity of medical financing. In turn, this barrier to access the health facilities caused the failure of treatment among drug resistant TB cases. We also found that the individual income might influence the treatment success among MDRTB cases in GY. They all suggested that the purchase power was the factor influencing the treatment outcome. As a result, the need of health service could not be satisfied, the mild disease become serious, and then difficult to cure, which turn to a vicious circle from poverty to TB and vice versa.

Despite being treated with different regimen corresponding to previous treatment history, treatment outcome in this study was poorer in the previously treated TB cases compared to that in new cases. Among the multi-drug resistant TB cases, these seem to be valuable in the guidance of treatment among drug resistant TB cases. In addition, high initial multi-drug resistance in GY made the standardized regimen less effective than expected. This all suggested the treatment of drug resistance should be modified according to the susceptibility

of infected strain rather than the previous treatment history.

Developing countries face a huge and increasing burden of tuberculosis *(WHO, 2002).*Innovative and cost-effective ways of implementing the directly observed, short-course (DOTS) strategy of the WHO are now needed. Our findings suggested that when four drugs were given throughout treatment, drug regimen based on the previous treatment history didn't work well on the MDRTB case in the setting with high prevalence of drug resistance. Both most new and previously treated MDRTB cases remained AFB smear positive until the end of 5 months of treatment. These findings did not imply that current international practice was wrong; rather that it might y be possible to be modifying according to the susceptibility of TB strain combined. The high cost followed by test and treatment was likely to complicate the confusion and impede its implementation. In addition, a study from Hong Kong (China) showed that 16% MDRTB cases simultaneously were resistant to the second line drug *(Kam et al., 2003).* Considering these facts, Simplifying protocol of identifying drug resistant strain and introduction of another cost effective treatment regimens are more likely to ease this issue and aid the control of drug resistant TB in China. Advocating for one cost-effective alternative anti TB drug for all drug resistant TB especially for multi-drug resistant TB is equitable and might attract the considerable support from the formal and informal donator.

7 CONCLUSIONS AND RECOMMENDATIONS

A high rate of drug resistant TB was noted among the TB patients registered in the local TB dispensary of field ground. Both socioeconomic (age, sex and individual income) and clinical (case contact and previous treatment history) characteristics were good predictors related to presence of drug resistance TB. In addition, the treatment adherence among them was also easily distorted by the socioeconomic barrier and side effect. The current used NTP-DOTS project might neglect the vulnerable population by finding the patient based on passive detection. The patient's delay and socioeconomic factors might influence the treatment outcome of drug resistance TB cases. The regimen based on the previous treatment history might perform worse in treating MDRTB case in the area with a high prevalence of drug resistance TB cases.

The recommendation goes as follows:

1. The NTP-DOTS project should be implemented and expanded to most area of China especially including the remote area. The vulnerable population (the poor and the elder) should become the concern of the TB control program since they are in a risk of developing the drug resistant TB. The TB control activities should be intensified including reinforcement of directly observed treatment, measures to improve patient treatment adherence and defaulter tracing.

2. The health education should be offered to increase the treatment adherence and shorten the diagnostic delay due to the artificial reason. The multi-media should be motivated to arouse general awareness to prevent and treat TB. In addition, the treatment adherence should be strengthened through counseling, education and support by trained healthcare worker.

3. The treatment management of drug resistant TB patient should be focused on the local people as well as the floating population. From this perspective, the network of sharing information worked well to follow up the patients when the patient leaves. The timely

updating of information about the treatment of patient enables the doctor to modify the regimen and patient to adhere to their treatment.

4. Well-balanced financing system should be established to reduce the disease burden, thus increasing the treatment adherence and treatment success as well. Drug resistant TB is a still poverty related disease. In addition, the economic barrier poses an important threat to the treatment success. A well-balance financing system enables to share the economic burden among the participants and thus motivate them to seek treatment more actively.

5. The regiment based on the previous treatment history does not perform well especially in a setting of high prevalence in drug resistant TB in China. Considering the high cost and unfavorable prognostics of the current used second line anti-TB drug, the simplified method of drug susceptible test and more cost-effective anti-TB drug should be advocated.

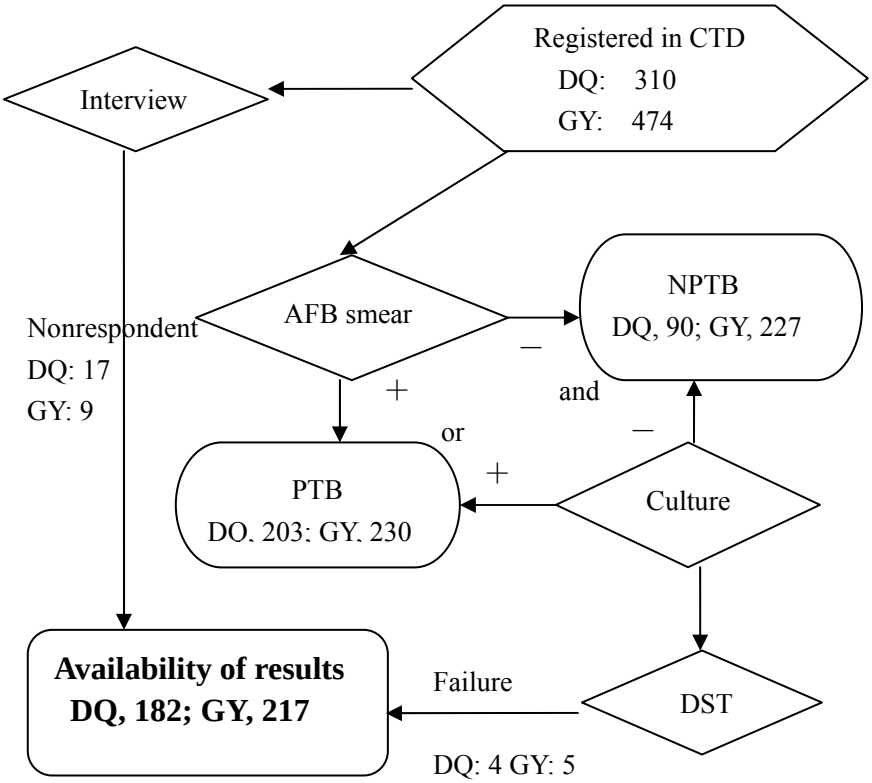

Fig 5.1 Inclusion of the eligible subjects

Note: NPTB, non pulmonary TB; PTB, pulmonary TB; AFB, Acid fast Bacilli; DST, Drug susceptible test. CTD, county TB dispensary

Table 5.1 General characteristics of subjects in fields

VARIABLES	DQ (n=182)		GY (n=217)		*Chi2*
	No.	**%**	**No.**	**%**	***p*†**
Sex					
male	134	73.6	161	74.2	0.02
female	48	26.4	56	25.8	0.90
Health(BMI)					
underweight	101	55.5	82	37.8	25.87
normal	78	42.9	104	47.9	0.0001*
overweight	3	1.6	31	14.3	
Education					
0~year	74	40.7	93	42.9	0.2
6~years	108	59.3	124	57.1	0.66
Occupation					
farmer	94	51.6	137	63.1	8.87
minor	7	3.9	14	6.5	0.012*
non-farmer	81	44.5	66	30.4	
Age(mean) at interview ‡	47±12		49±15		0.32
Household income (mean, CNY) ‡	11,167±2,124		6,016±1,947		0.0001*
Individual income (mean, CNY) ‡	6,617±1.995		2,408±916		0.0001*

†*p*-value from chi2 test. ‡ Student *t-test* * $p<0.05$

Table 5.2 Clinical characteristics of PTB cases with bacterial isolates in the study

All cases	DQ (n=182) No	DQ (n=182) %	GY (n=217) No	GY (n=217) %	Chi2	*p*†
Case classification						
new	133	73.1	150	69.1	0.75	0.39
previously treated	49	26.9	67	30.9		
Lab exam						
AFB smear +	120	65.9	133	61.3	0.92	0.34
AFB smear + and Culture -	7	3.8	3	1.4		
AFB smear - and Culture +	62	34.1	84	38.7		
AFB smear + and Culture +	113	62.1	130	59.9		
Microbial strain						
M.TB	177	97.3	210	96.8	0.08	0.78
M.Bovis	5	2.7	7	3.2		

†: *p*-value from chi2 test. *: $p<0.05$

Table 5. 3 Drug resistance patterns according to number of drugs

All cases	DQ(n=182) No	DQ(n=182) %	GY(n=217) No	GY(n=217) %	Chi2	*p*†
Overall drug resistance	100	54.9	151	69.6	9.09	0.0026*
Multi-drug resistance	13	7.1	45	20.7	14.73	0.0001*
Other drug resistance	87	47.8	106	48.8	0.04	0.84
RIF only	2	1.1	1	0.5		
RIF+STR only	1	0.6	2	0.9		
RIF+EMB only	0	0	0	0		
RIF+EMB+STR	1	0.6	4	1.8		
INH only	29	15.9	28	12.9		
INH+STR only	7	3.9	8	3.7		
INH+EMB only	0	0	2	0.9		
INH+STR+EMB	5	2.7	3	1.4		
STR only	21	11.5	48	22.1		
STR + EMB only	7	3.8	2	0.9		
EMB only	14	7.7	8	3.7		
At least 1 Drug Resistance	100	54.9	151	69.6		
At least 2 drugs resistance	34	18.7	66	30.4		
At least 3 drugs resistance	10	5.5	27	12.4		
At least 4 drugs resistance	1	0.5	5	2.3		

†: *p*-value from chi2 test. *: $p<0.05$

Table 5.4 Comparison of drug resistance between previously treated and new TB cases

	New		Previously treated		*p*†
	No.	**%**	**No.**	**%**	
DQ	n =133		n =49		
STR	34	25.6	14	28.6	0.68
INH	39	29.3	15	30.6	0.87
EMB	19	14.3	8	16.3	0.73
RIF	7	5.3	10	20.4	0.0018*
ORDTB	62	46.6	25	51	0.60
MDRTB	5	3.8	8	16.3	0.002*
GY	n=150		n=67		
STR	57	38	32	47.8	0.17
INH	46	30.7	40	59.7	0.001*
EMB	16	10.7	12	17.9	0.14
RIF	27	18	25	37.3	0.0021*
ODRTB	73	48.7	33	49.3	0.94
MDRTB	22	14.7	23	34.3	0.001*

†: *p*-value from chi2 test. *: $p<0.05$

Table 5.5 The contribution of RIF resistance (n =69) to combined drugs resistance

Drug combination	**No.**	**%**
Single RIF	3	4.3
RIF+INH	20	29
RIF+STR	3	4.3
RIF+EMB	0	0
RIF+INH+X	32	46.4
RIF+X+Y	5	7.2
RIF+INH+X+Y	6	8.7

X: Y: EMB/STR

Table 5. 6 Characteristics of drug resistant TB cases in DQ

VARIABLES	MDRTB (n=13)	ODRTB (n=87)	Pan-sensitive (n=82)	MDR vs Pan-sensitive		ODR vs Pan-sensitive	
	n (%)	n (%)	n (%)	*p*†	OR(95%CI)‡	*p*†	OR(95%CI)‡
Average age at interview	62 ± 9	57 ± 13	44 ± 21	0.018*	1.22 (1.12-6.63)*	0.15	1.02 (0.99-3.05)
Male (sex)	11 (84.6)	57 (65.5)	66 (80.5)	0.2	2.08 (0.05-5.88)	0.0067*	0.93 (0.75-4.98)
Previous treatment history	8 (61.5)	25 (28.7)	16 (19.5)	0.002*	4.98 (1.56-8.03)*	0.6	0.98 (0.67-3.81)
Health status (BMI)							
underweight	10 (76.9)	49 (56.3)	42 (51.2)	0.2	1	0.63	1
normal	3 (23.1)	36 (41.4)	39 (47.6)		0.7(0.07~6.9)		0.43 (0.29-4.16)
overweight	0 (0)	1 (1.1)	2 (2.4)		-		0.68 (0.19-5.45)
Occupation							
farmer	11 (84.6)	35 (40.2)	48 (58.5)	0.18	1	0.029*	1
minor	-	6 (6.9)	1 (1.2)		-		8.13 (0.82-20.8)
non-farmer	2 (15.4)	45 (51.7)	34 (41.5)		0.24 (0.02-5.68)		1.67 (0.29-5.95)
Case contact	8 (61.5)	29 (33.3)	11 (13.4)	0.0001*	7.84 (1.71-25)*	0.0023*	2.9 (1.13-7.52)*
Individual income(CNY)	4,173 ± 362	6,864 ± 611	6,950 ± 1,561	0.0001*	0.79 (0.03-0.92)*	0.62	1.01 (0.7-4.14)
Household income(CNY)	9,996 ± 427	15,241 ± 876	16,380 ± 2,773	0.027*	0.62 (0.01-5.93)	0.6	1.02 (0.8-5.03)

† *p*-value from chi2 test. ‡ Odd Ratio adjusted on the Logistic Regression model

* *p<0.05*

Table 5.7 Characteristics of drug resistant TB cases in GY

VARIABLES	MDRTB (n=45)	ODRTB (n=106)	Pan-sensitive (n=66)	MDR vs Pan-sensitive		ODR vs pan-sensitive	
	n (%)	n (%)	n (%)	*p*†	OR(95%CI)‡	*p*†	OR(95%CI)‡
Average age at interview	58 ± 11	48 ± 18	46 ± 24	0.055	1.03 (0.99-5.07)	0.17	1.023 (0.9-5.1)
Male (sex)	38 (84.4)	75 (70.8)	48 (72.7)	0.11	2.1 (1.06-15.6)*	0.9	1.75 (0.7-6.98)
Previous treatment history	23 (51.1)	33 (31.1)	11 (16.7)	0.001*	3.94 (2.04-12.48)*	0.94	1.6 (0.6-5.8)
Health status(BMI)							
underweight	38 (84.4)	29 (27.4)	15 (22.7)	0.0001*	1	0.78	1
normal	5 (11.1)	60 (56.6)	39 (59.1)		0.082 (0.018-0.38)*		0.92 (0.39-3.16)
overweight	2 (4.4)	17 (16)	12 (18.2)		0.076 (0.008-0.72)*		0.68 (0.19-4.45)
Occupation							
farmer	34 (75.6)	60 (56.6)	43 (65.2)	0.14	1	0.53	1
minor	0 (0)	9 (8.5)	5 (7.5)		-		2.13 (0.81-5.86)
nonfarmer	11 (24.4)	37 (34.9)	18 (27.3)		0.79 (0.32-6.86)		1.072 (0.39-4.95)
Case contact	25 (55.5)	41 (38.7)	19 (28.8)	0.0039*	4.8 (1.32-7.24)*	0.16	1.91 (0.73-7.5)
Individual income (CNY)	1,002 ± 487	2,596 ± 731	2,981 ± 883	0.02*	0.15 (0.04-0.89)*	0.22	1.01 (0.97-5.12)
Household income (CNY)	3,574 ± 581	7,396 ± 864	7,165 ± 1,266	0.083	0.39 (0.18-5.93)	0.95	1.07 (0.96-5.27)

† *p*-value from chi2 test. ‡ Odd Ratio adjusted on the Logistic Regression model

* *p<0.05*

Fig 5.2 Management of treatment among drug resistant TB cases

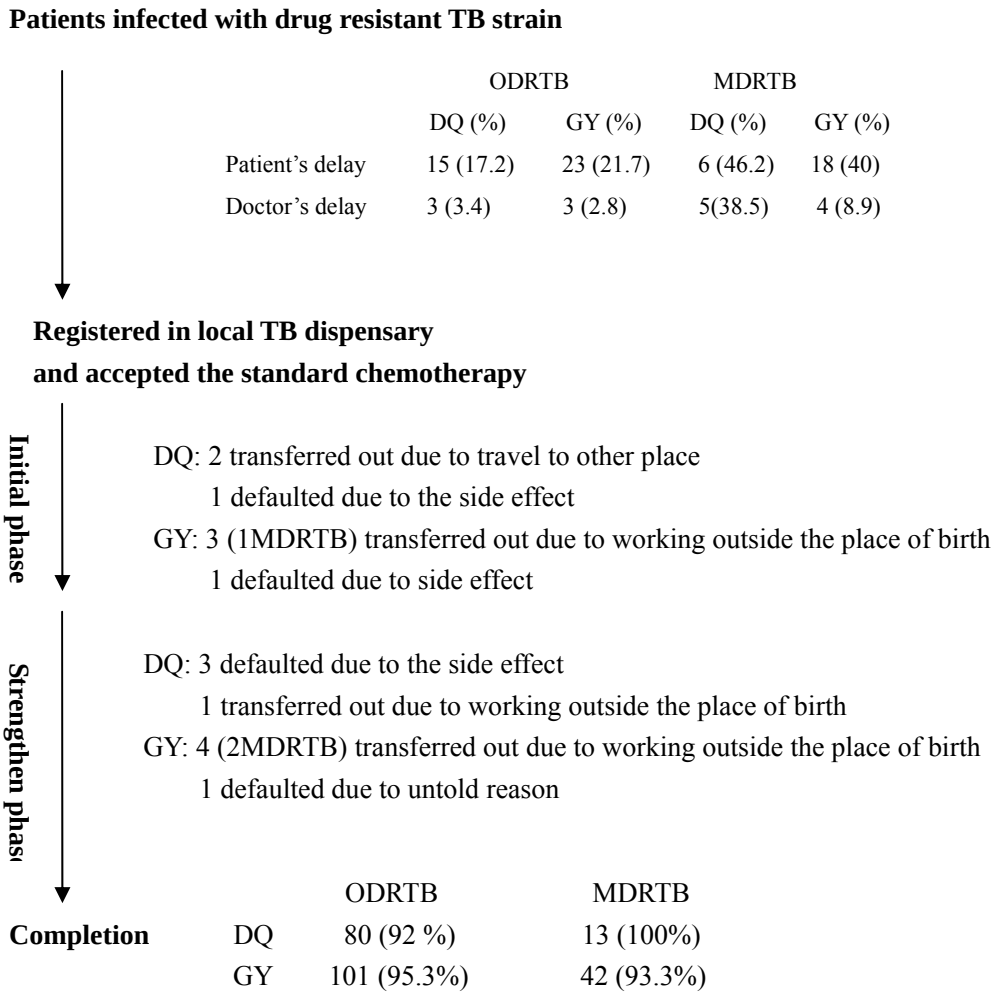

Table 5.8 Treatment adherence of drug resistant TB cases between DQ and GY

	DQ		**GY**		**Chi2**
	No	**%**	**No**	**%**	***p*†**
Drug sensitive TB	n=82		n=66		
Treatment adherence					
yes	63	76.8	49	74.2	0.13
no	19	23.2	17	25.8	0.72
ODRTB	n = 87		n = 106		
Treatment adherence					
yes	66	75.9	77	72.6	0.26
no	21	24.1	29	27.4	0.61
MDRTB	n = 13		n = 45		
Treatment adherence					
yes	6	46.2	25	55.6	0.36
no	7	53.8	20	44.4	0.55

† *p*-value from chi2 test. * $p<0.05$

Table 5.9 Causes for treatment nonadherence among drug resistant TB cases in DQ and GY

Items	DQ (n=28)		GY (n=49)	
	No	%	No	%
difficultly tolerate the side effect	10	35.7	17	34.7
geographic barrier	7	25	15	30.6
forget to deliver the treatment	5	17.9	5	10.2
busy	3	10.7	6	12.2
feel better	2	7.1	4	8.2
others	1	3.6	2	4.1

Table 5.10 The factors influencing the treatment adherence in DQ

VARIABLES	MDRTB (n=6)	ODRTB (n=66)	Adherence vs Not in MDRTB		Adherence vs Not in ODRTB	
	n (%)	n (%)	*p* †	OR (95%CI)‡	*p* †	OR (95%CI)‡
Average age at interview	55 ± 12	43 ± 18	0.055	0.94 (0.48 − 5.21)	0.047*	0.93 (0.21 − 6.25)
Male (Sex)	5 (83.3)	45 (68.2)	0.91	0.87 (0.01 − 15.5)	0.089	2.78 (0.78 − 8.46)
Previous treatment history	2 (33.3)	16 (24.2)	0.053	0.67 (0.51 − 5.95)	0.7	0.74 (0.16 − 6.38)
Education						
0~year	1 (16.7)	26 (39.4)	0.013*	1	0.78	1
6~year	5 (83.3)	40 (60.6)		2.16 (0.39 − 4.38)		2.35 (0.47 − 7.49)
Occupation						
farmer	5 (83.7)	27 (40.9)	0.91	1	0.7	1
minor	-	5 (7.6)		-		1.21 (0.31 − 10.61)
non-farmer	1 (16.7)	34 (51.5)		1.67 (0.16 − 4.33)		1.13 (0.79 − 3.93)
Side effect	2 (33.3)	8 (12.1)	0.026*	0.84 (0.37 − 0.96)*	0.48	0.43 (0.24 − 7.91)
Medical insurance	4 (66.7)	48 (72.7)	0.72	1.32 (0.73 − 7.52)	0.17	2.01 (0.63 − 4.56)
Individual income(CNY)	5,958 ± 998	7,593 ± 763	0.069	1.37 (0.68 − 8.92)	0.55	1.21 (0.68 − 6.81)
Household income(CNY)	10,291 ± 1,791	15,785 ± 1,610	0.34	1.82 (0.75 − 9.94)	0.51	1.34 (0.14 − 7.35)

† *p*-value from chi2 test. ‡ Odd Ratio adjusted on the Logistic Regression Model

* *p<0.05*

Table 5.11 The factors influencing the treatment adherence In GY

VARIABLES	MDRTB (n=25)	ODRTB (n=77)	Adherence vs Not in MDRTB		Adherence vs Not in ODRTB	
	n(%)	n(%)	*p* †	OR(95%CI)‡	*p* †	OR(95%CI)‡
Average age at interview	57 ± 13	56 ± 18	0.796	0.98 (0.92－5.06)	0.171	1.09 (0.67－6.03)
Male (sex)	20 (80)	57 (74)	0.053	0.83 (0.47－5.61)	0.22	1.69 (0.8－8.9)
Previous treatment history	6 (24)	22 (28.6)	0.001*	0.37 (0.29－0.8)*	0.35	0.70 (0.31－3.56)
Education						
0~year	5 (20)	31 (40.3)	0.005*	1	0.004*	1
6~year	20 (80)	46 (59.7)		3.6 (1.07－5.53)*		1.98 (1.27－3.63)*
Occupation						
farmer	17 (68)	43 (55.8)	0.18	1	0.48	1
minor	-	8 (10.4)		-		1.17 (0.13－10.9)
non-farmer	8 (32)	26 (33.8)		1.04 (0.52－4.37)		1.10 (0.31－5.9)
Side effect	10 (40)	25 (32.5)	0.023*	0.32 (0.041－0.92)*	0.132	0.33 (0.11－3.84)
Insurance	20 (80)	42 (54.5)	0.04*	1.12 (1.03－4.89)*	0.38	0.96 (0.26-5.68)
Individual income (mean)	2,736 ± 653	3,164 ± 990	0.043*	1.11 (1.02－4.08)*	0.304	1.19 (0.76－5.83)
Household income (mean)	4,496 ± 787	8,497 ± 1,781	0.45	1.04 (0.88－5.93)	0.283	1.27 (0.83－5.96)

† *p*-value from chi2 test. ‡ Odd Ratio adjusted on the Logistic Regression Model

** p<0.05*

Table 5.12 Treatment results of drug resistant TB cases

	DQ		**GY**	
	No.	**%**	**No.**	**%**
Drug sensitive TB	n=82		n=66	
I phase completion	79	96.3	63	95.5
II phase completion	74	90.2	59	89.4
success	69	84.1	54	81.8
failure	5	6.1	5	7.6
defaulted	8	9.8	7	10.6
ODRTB	n=87		n=106	
I phase completion	84	96.6	104	98.1
II phase completion	80	92	101	95.3
success	73	83.9	86	81.1
failure	7	8	15	14.2
defaulted	7	8	5	4.7
MDRTB	n=13		n=45	
I phase completion	13	100	44	97.8
II phase completion	13	100	42	93.3
success	7	53.8	17	37.8
failure	6	46.2	24	54.5
defaulted	0	0	3	6.7

Table 5. 13 Treatment success of registered drug resistant TB in DQ

VARIABLES	■DRTB (n=7)	ODRTB (n=73)	Treatment Success vs failure in ■DRTB		treatment success vs failure in ODRTB	
	n(%)	n(%)	*p*†	OR(95%CI)‡	*p*†	OR(95%CI)‡
Average age at interview	56 ± 14	55 ± 18	0.21	0.87(0.26-6.32)	0.76	0.98(0.4-5.99)
Male (sex)	6 (85.7)	43 (58.9)	0.91	1.36(0.68-8.76)	0.57	0.24(0.023-1.21)
Previous treatment history	3 (42.9)	17 (23.3)	0.72	0.78(0.25-7.91)	0.01*	0.84(0.24-0.95)*
Health status						
underweight	5 (71.4)	41 (56.2)	0.61	1	0.4	1
normal	2 (28.6)	30 (41.1)		1.93 (0.07-8.76)		1.38(0.07-4.73)
overweight	-	1 (1.4)		-		1.33(0.27-6.35)
Occupation						
farmer	6 (85.7)	30 (41.1)	0.91	1	0.27	1
minor	-	4 (5.5)		-		1.61 (0.075-5.02)
non-farmer	1 (14.3)	40 (54.8)	0.24	0.17(0.03-9.87)		1.39 (0.19-5.46)
Treatment adherence	5 (71.4)	55 (75.3)	0.48	5.65(0.21-9.26)	0.79	1.06 (0.01-9.25)
Patient's delay	1 (14.3)	4 (5.5)	0.012*	0.07(0.006-0.83)*	0.004*	0.08 (0.005-0.72)*
Doctor's delay	2 (28.6)	2 (2.7)	0.84	1.06(0.05-16.19)	0.36	0.4 (0.03-4.83)
Individual income(CNY)	5,146 ± 561	7,066 ± 859	0.59	1.08(0.16-6.68)	0.059	1.08 (0.72-4.92)
Household income(CNY)	10,500 ± 727	16,173 ± 1,232	0.78	1.03(0.29-7.99)	0.28	1.07 (0.73-6.42)

† *p*-value from chi2 test. ‡ Odd Ratio adjusted on the Logistic Regression Model

* *p<0.05*

Table 5.14 Treatment success of registered drug resistant TB in GY

VARIABLES	MDRTB (n=17)	ODRTB (n=86)	treatment sucess vs failure in MDRTB		treatment success vs Failure in ODRTB	
	n (%)	n (%)	*p*†	OR(95%CI)‡	*p*†	OR(95%CI)‡
Average age at interview	57 ± 16	46 ± 21	0.8	0.91 (0.27-5.10)	0.42	0.87 (0.72-6.69)
Male (Sex)	16 (94.1)	56 (65.1)	0.16	4.03 (0.03-7.54)	0.29	1.68 (0.23-4.93)
Previous treatment history	5 (29.4)	24 (27.9)	0.023*	0.21 (0.15-0.87)*	0.85	0.90 (0.14-5.21)
Health status (BMI)						
underweight	11 (64.7)	19 (22.1)	0.021*	1	0.013*	1
normal	4 (23.5)	52 (60.4)		1.19 (1.06-5.09)*		3.87 (1.09-8.73)
overweight	2(11.8)	15 (17.4)		-		4.38 (1.98-9.46)
Occupation						
farmer	12 (70.6)	48 (55.8)	0.56	1	0.62	1
minor	-	6 (7)		-		1.03 (0.29-4.48)
non-farmer	5 (29.4)	30 (34.9)		0.22 (0.08-8.19)		1.04 (0.91-5.24)
Treatment adherence	14 (82.4)	68 (79.7)	0.0048*	3.1 (1.05-5.38)*	0.0021*	3.38 (1.23-8.85)*
Patient's delay	3 (17.6)	14 (16.3)	0.17	0.19 (0.023-0.92)*	0.54	0.93 (0.21-5.83)
Doctor's delay	1 (5.9)	2 (2.3)	0.43	0.59 (0.23-15.43)	0.51	0.86 (0.26-12.99)
Individual income(CNY)	3,097 ± 786	3,164 ± 856	0.044*	1.11 (1.02-6.08)*	0.3	1.08 (0.54-8.39)
Household income(CNY)	4,141 ± 1,561	8,297 ± 1,837	0.056	1.04 (0.88-7.93)	0.28	1.45 (0.24-7.42)

† *p*-value from chi2 test. ‡ Odd Ratio adjusted on the Logistic Regression Model

* *p<0.05*

Table 6.1 The comparison of general characteristics between eligible and ineligible subjects

VARIABLES	**Eligible (n=399)**	**Ineligible (n=359)**	***p*†**
	No (%)	No (%)	
Average age at interview	51±21	58 ±25	0.14
Male sex	295 (73.9)	270 (75.2)	0.69
Previous treatment history	116 (29.1)	105 (29.2)	0.99
Health(BMI)			
underweight	183 (45.9)	101 (28.1)	0.0001*
normal	182 (45.6)	215 (59.8)	
overweight	34 (85.2)	43 (12)	
Education			
0～year	167 (41.8)	172 (47.9)	0.12
6～year	232 (58.2)	187 (52.1)	
Occupation			
farmer	231 (57.9)	248 (69.1)	0.006*
minor	21 (5.3)	14 (3.9)	
non-farmer	147 (36.8)	101 (26.9)	
Treatment adherence	286 (71.1)	237 (66.7)	0.09
Patient's delay	101 (25.3)	92 (25.6)	0.92
Doctor's delay	26 (6.5)	28(7.8)	0.49
Household income	8,390 ± 3,610	9,434 ± 2,481	0.13
Individual income	4,573 ± 2,075	4620 ± 2,522	0.25

† *p*-value from chi2 test. * $p<0.05$

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ANNEX

Questionnaire on TB diagnosis and treatments in patients from rural China

code：□□□□

Dispensary：_____ ； Investigator：_____； Date：_____/_____ /_____

.General information

1．Name:_____; Gender：□male □ female; Birth date (yy/mm/dd) ____/ __/____;
Residence: county_____town_____village_____； Tel:_____

2．Education: □ illiteracy □ under primary school □ primary school □ junior high school □ senior high school and occupational education □ college and above

3．Marriage：□ unmarried □ married □ widow/widower □ divorced

4．Occupation：□preschool children □student □cadre, teacher and health work of village □farmer □family sideline production □craft making □worker in small villages and towns factory □hard labor outside the town □employee of government □others:

5．Do you have a job outside your town within one year?
□Yes（to question no.6） □No（to question no.7）

6．How long for this job? from / / to / / ,
What kind job is it? .

7． What kind of medical care insurance do you have: □ Government insurance □labor insurance □rural collective insurance □ commercial medical insurance □out of pocket □others:

1． Has BCG been vaccinated? (1) Yes. Age at first BCG injection _____ Year old (2) No

8． Weight ____ Kg , Height ____ cm

.Social economic information

1．Family size: (persons); No. able to work: .

2．The patient is a: □ able to work □supported member □ minor

3．□No. of rooms of the house: , size of the house m2, construction year: / / ,
cost of the house (yuan)
□Housing type: □storied building □one-storied house made of bricks and tiles
□one-storied house made of mud □others

4．The floor of your house is made of:
□porcelain tile □bricks □cement □without processing □others

5．The farmland contracted with your family (acres); Number of breeding poultry: ;

Number of domestic animal : pigs: ,sheep: , cattle .

6. The source of income of the patient: □full time work □short-term jobs □farming
□family alternate income □individual business □supported by offspring
□national alms □others

7. Family pure income per year (yuan);
In the local area, your family is: □rich □average □poor

8. Pure income of the patient per year: (yuan); proportion of the family income:
□≤25% □≤50% □≤75% □≤100%

9. Is your family ranked as the poor family in the village: □Yes □No
□ If yes，the year of the rank to be made: ;
what do you think about the main reason to be poor:
□fewer labor force □poor natural condition □natural disaster □manmade factor □disease or injury □others
□If yes, how much subsidy do you get from the village government:_____(yuan)/year

10. What kind of the valuable items do you have in your family as follow?
□black-and-white television □color television □washing machine □refrigeratory
□motorcycle □tricycles □truck □cattle or horse □valuable furniture
□none of above

.Information on treatment after recognized by TB dispensary：

1. The result of first 3 AFB smear test: _____; _____; _____.
2. Present treatment scheme is _____.
3. Besides TB, do you have any other chronic disease (lasting over 1 year)；
□Yes（next question）；□No
4. The most serious disease influencing your living is: _____
5. Date of TB diagnosis ____/_____/_____.
6. Healthcare facility for TB diagnosis:
□county hospital □above county hospital □county TB dispensary □others_____
7. How long did it take from first health seeking and final diagnosis
□under 2weeks □2-3weeks □3-4weeks □4-5weeks □5-6weeks □6-7weeks
□7-8weeks □more than 8 weeks（ _____w）
8. If over 2 weeks, why? □don't care □no free time □long distance to hospital □worry about money
□light symptom □others_____
9. Date of initial treatment for TB_____/_____/_____
10. How long did it take from final diagnosis to regular TB treatment □under 1 week□1-2 weeks
□2-3weeks □3-4weeks □4-5weeks □5-6weeks □6-7weeks □7-8weeks
more than 8 weeks（ _____w）
11. If over 1 week, why? □don't care □no free time □long distance to hospital □worry about money
□light symptom □others_____

. Information of diagnosis and treatment before TB diagnosed

ITEM	Health Seeking				
	1st	2nd	3rd	4th	5th
Health seeking for □cough □hemoptysis □fever □chest pain □inertia □night sweat □routine physical examination □other symptom _____					
Date of occurrence of symptoms_____					
Date of health seeking					
Date of occurrence of symptoms_____					
Date of health seeking					
Healthcare provider： □county hospital □county TB dispensary □town hospital □village health station □pharmacy and self-medication □others_____					
Reason for facility selecting： □near to home □familiar with some provider □serious symptom □light symptom □high quality of medical treatment □others _____					
Examination □fluoroscopy □X-ray picture□blood RTO □AFB smear test □CT □others_____					
Diagnosis					
Date of diagnosis					
If health seeking happened longer than 2 weeks after symptom, the reason is: □care little □no time □far away to hospital □afraid of spending□light symptom □others_____					
Treatment provided					
Treatment lasting (days)					
Expense of examination					
Expense of treatment					
Expense of transportation and accommodation					
Other expenses: _____					
Medical expense covered by collective medical insurance					
If had been referred, the reasons is： ① self-requested □Dr's suggestion □others' suggestion □others					
Have you asked self- referred but refused by the doctor? □yes □no					
Time consumed to the health facility (hr)					
Time consumed for seeing a doctor (hr)					

Follow-up questionnaire on treatment of TB

Unit：_____ ； Investigator：_____； Date：_____/____ /___

.General information：

Name ：_____ ； Gender：□male □female； Birth date：_____/_____ /_____/；

Residence：_____county_____town _____village telephone:_____

.The follow-up information

	2nd month	5th month	$6^{th}/8^{th}$ month
Treatment scheme			
Result of AFB smear test			
Current symptom ：□ cough □expectoration □fever □chest pain □hypodynamia □night sweat □hemoptysis □not any symptom □others_____			
Comply of treatment scheme □Yes □No			
Incompliance reason：□It doesn't matter to treat TB □drug too expensive□serious side-effect of the drug □no free time□long distance to the hospital, □Forget to take pills□ stop taking drugs because of the improvement of the symptoms □others_____			
No of Days in stopping treatment			
Loss-to-follow up (1)Yes (2) No			
Reason for loss-to-follow up: (1) death (2) transfer out (3) migration (4)others _____			
Main side effect: (1)liver (2)tinnitus (3) gastrointestinal tract （4）others			
Treatment outcome: (1)no change (2) recover (3) worsen (4) others			