Drug Susceptibility Test and Treatment Outcome of Recurrent Pulmonary Tuberculosis in Thailand

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Background: *Recurrent pulmonary tuberculosis has more drug resistance than in new case.*
Objective: *To study drug susceptibility test and outcomes of recurrent pulmonary tuberculosis in the Central Chest Institute of Thailand.*
Material and Method: *Patients registered as recurrent pulmonary tuberculosis between 2011 and 2013 were retrospective reviewed.*
Results: *There were 102 cases, 76 males and 26 females. Mean age was 47.7 years old (range 18 to 79). Anti-HIV was done in 77 from 102 cases (75.5%) and one was HIV positive. All had pulmonary tuberculosis and five cases also had pleural involvement. CXR showed cavity in 58.1%. The number of cases that had drug resistance to streptomycin, INH, rifampicin, ethambutol, ofloxacin, kanamycin was 16, 11, 11, 5, 3, 1 (16.7, 11.5, 11.5, 5.2, 3.1, 1%) respectively. There were 74 pansusceptible (75.5%), six streptomycin monoresistance (6.1%), six multi-drug resistance (6.1%), three INH monoresistance (3.1%), three INH polyresistance (3.1%), three rifampicin monoresistance (3.1%), two rifampicin polyresistance (2 %), one ethambutol monoresistance (1%), and four cases that drug susceptibility test result was not available from both culture and Line probe assay. Average time after complete treatment from previous tuberculosis infection to recurrence was 10.9 years (range 1 month to 41 years). There were 67 cures (65.7%), one complete of treatment (1%), three failures (2.9%), one death (1%), 16 defaults (15.7%), and 14 transfers (13.7%).*
Conclusion: *Most recurrent pulmonary tuberculosis in the present study was pansusceptible. Streptomycin monoresistance, INH resistance (mono and poly drug resistance) and MDR-TB was the most common drug resistance. The number of MDR-TB was more than in new case. INH polyresistance and rifampicin polyresistance had poor outcomes.*

Keywords: *Relapse, Reinfection, TB, DST, Drug resistance*

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Recurrent pulmonary tuberculosis is the diagnosis of pulmonary tuberculosis (positive sputum smear or culture) after successful treatment (cure or completed treatment)[1,2]. This recurrent pulmonary tuberculosis can be divided into three subgroups, first, relapse pulmonary tuberculosis from the same strain organism as the first infection, then it can have the same drug susceptibility test (DST) or has more acquired drug resistance; second, reinfection pulmonary tuberculosis with another different strain, which it can have the same or different DST from the first infection; third, there are mixed infections (more than one strain of tuberculosis) at the first diagnosis but the second strain was not detected. After the first strain (that is usually susceptible to first line drug (FLD)) was eradicated then the second strain (that may have some drug resistance to FLD) could grow and became the dominant organism[3-6]. Basic microbiological laboratory tests such as AFB stain and culture cannot detect different strain organism. DNA fingerprinting determined by spoligotyping, RFLP (Restriction fragment length polymorphism), MIRU (mycobacterial interspersed repetitive unit) can differentiate these recurrent pulmonary tuberculosis cases whether they were the same or different strains with limited sensitivity. Whole genome sequencing can even detect these different strains more accurately[7]. With these advanced laboratory tests, we can differentiate these heterogeneous groups of recurrent pulmonary tuberculosis. DST of the second infection is the most important data that will help physician to choose proper drug regimens. The three categories of recurrent pulmonary tuberculosis mentioned above would have some impact to DST. The local epidemiological data such as high or low incidence of tuberculosis infection, high burden of drug resistance

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tuberculosis can also have greater impact to DST result of recurrent tuberculosis infection[8-11]. We reported the result of DST of recurrent pulmonary tuberculosis in Thailand, a high burden country for tuberculosis.

Material and Method

Patients registered as recurrent pulmonary tuberculosis between 2011 and 2013 from Central Chest Institute of Thailand were retrospective reviewed. Recurrent pulmonary tuberculosis was defined as rediagnosis of tuberculosis (positive sputum culture or positive smear) after successful treatment (cure or complete of treatment). Sputum was sent to the laboratory for AFB smear by fluorescent microscopy, culture with Lowenstein Jensen medium (LJ medium), drug susceptibility test (DST) by proportional method to isoniazid, rifampicin, ethambutol, streptomycin, kanamycin, and ofloxacin. Line probe assay (HAIN Lifescience) was done in 10 cases. Degree of pulmonary involvement from CXR was classified into mild (involve a total area of lung less than that occupied by the right upper lobe as visualized on a postero-anterior radiograph), moderate (total extent did not exceed an area equivalent to the whole of one lung), severe (more than the whole of one lung)[12]. Cavity size was measured by the largest diameter and its perpendicular line. Individualized treatment regimen was chosen by physician. Cases were followed-up after complete treatment except default and transfer out. Outcomes are defined as cure, complete treatment, default, death, failure, or transfer out by WHO criteria[13].

Results

There were 102 recurrent pulmonary tuberculosis patients (76 male and 26 female) from 4,255 tuberculosis cases (2.4%). Mean age was 47.7 years old (range 18 to 79). Mean BMI was 18.7 (range 11.8 to 26.5). Anti-HIV was done in 77 from 102 cases (75.5%) and one was HIV positive. Nineteen from 102 cases had co-morbid (DM, hypertension, COPD, asthma, gout, chronic renal failure, heart disease, bronchiectasis, old cerebrovascular disease, and neurofibromatosis). All had pulmonary tuberculosis and five cases also had pleural involvement. CXR had cavity in 58.1%. Degree of pulmonary involvement from CXR was classified into mild (12%), moderate (48.9%), and severe (39.1%). There were average 1.8 cavities in CXR (range 1 to 5). Cavity size was average 3.2 cm (range 1.2 to 9 cm). Degree of positive AFB smear was 1+ (34.3%), 2+ (23.5%), 3+ (41.2%) and negative smear but positive culture in 1%. Degree of positive culture was 1+ (8.8%), 2+ (22.5%), 3+ (41.2%), 4+ (21.6%), and 5.9% had negative culture but positive smear. DST from culture was available in 96 from 102 cases. The number of cases that had drug resistance to streptomycin, INH, rifampicin, ethambutol, ofloxacin, kanamycin was 16, 11, 11, 5, 3, 1 (16.7, 11.5, 11.5, 5.2, 3.1, 1%) respectively (Fig. 1). There were 74 pansusceptible (75.5%), six streptomycin monoresistance (6.1%), six multi-drug resistance (6.1%), three INH monoresistance (3.1%), three INH and streptomycin polyresistance (3.1%), three rifampicin monoresistance (3.1%), two rifampicin polyresistance (2%), one ethambutol monoresistance (1%), and four cases that DST result was not available from both culture and LPA (Fig. 2), (two culture medias were contaminated with bacteria and the other two were

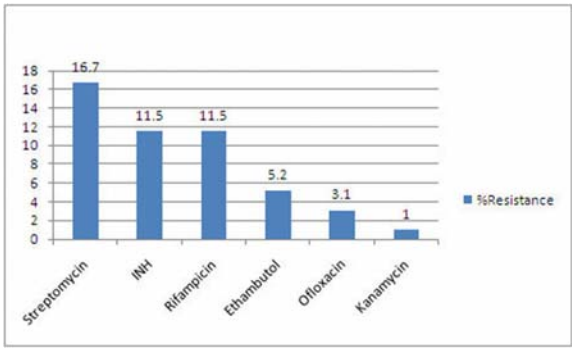

Fig. 1 Drug resistance rate of individualized drug (n = 96).

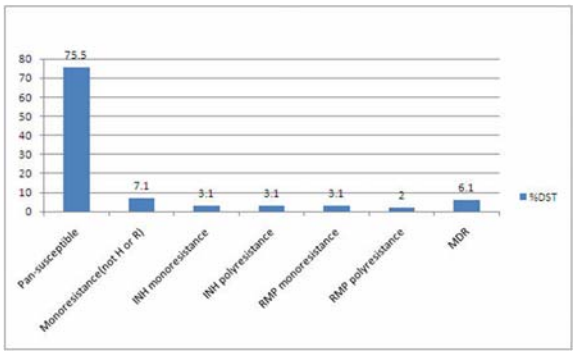

Fig. 2 Drug resistance rate from drug susceptibility test (n = 98).
H = INH; R or RMP = rifampicin; MDR = multidrug resistance; DST = drug susceptibility test.
Additional 2 cases which LPA showed HR susceptible, and H resistance R susceptible (both were culture negative) were included in pansusceptible and INH monoresistance respectively.

truly negative). Line probe assay (LPA) from HAIN Lifescience was done in 10 cases. Five cases of LPA showed INH and rifampicin susceptible (same as culture result). One case showed INH and rifampicin resistance or MDR (same as culture result). One case showed INH and rifampicin susceptible but culture was negative. Three cases showed INH resistance rifampicin susceptible with different culture results. First case culture was INH and streptomycin polyresistance, second case culture was MDR, which was discordant from LPA result, third case culture grew with Mycobacterium avium complex (MAC), which was defined as colonization (it was not detected in the following samples collected later).

After excluding 16 default and 14 transfer out cases, 48 from 72 cases (66.7%) were followed-up after completion of treatment, which averaged 57.4 weeks (range 4 to 210 weeks). Smear and culture conversion time was 66.1 days (1 to 259 days) and 63.8 days (range 1 to 182 days), respectively. Time after complete of treatment from previous tuberculosis infection to recurrence was 10.9 years (range 1 month to 41 years, SD 10.7). Drug regimens categorized with outcomes were shown in Table 1. There were 67 cures (65.7%), one complete of treatment (1%), three failures (2.9%), one death (1%), 16 defaults (15.7%), and 14 transfers (13.7%).

Outcomes were categorized with DST (Table 2). Average duration of treatment in 68 cases that had cure or complete of treatment was 36.7 weeks (range 20 to 102 weeks). Pansusceptible, monoresistance (not INH or rifampicin), and INH monoresistance had good outcome. Two cases in INH monoresistance group had been cured (RZE regimen was used and both had non-cavitary pulmonary tuberculosis). However, INH and streptomycin polyresistance was the largest group that failed to treatment (two from three cases). Regimens used in both failure cases were 3HRZE/7RE, 3HRZE/5HREO. PZA was not used throughout in the regimens, and injecting agent was not used in initial phase of both cases. Both also had cavitary pulmonary tuberculosis and moderate to severe pulmonary involvement. Rifampicin monoresistance had failed in one case. The regimen was 2HRZE/10HRE/6HE. All rifampicin polyresistance cases had worse outcomes, died in one case (from hepatitis and acute renal failure, which were side effect of antituberculosis drugs) and default in the other one. MDR-TB had better outcomes

Table 1. Drug regimens categorized with outcomes in patient who result of treatment could be defined (default and transfer out cases were excluded)

Regimens	Outcomes				Total
	Cure	COT	Failure	Death	
2HRZE/4HR	15 (93.8%)	1 (6.3%)	0 (0%)	0 (0%)	16 (100%)
2HRZE/7HR	25 (100%)	0 (0%)	0 (0%)	0 (0%)	25 (100%)
2HRE/7HR	3 (100%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
6RZE	3 (100%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
MDR[1]	3 (100%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
4 drugs (noIA)/2-3 drugs[2]	5 (62.5%)	0 (0%)	3 (37.5%)	0 (0%)	8 (100%)
5 drugs (IA)/2-4 drugs[3]	13 (92.9%)	0 (0%)	0 (0%)	1 (7.1%)	14 (100%)
Total	67 (93.1%)	1 (1.4%)	3 (4.2%)	1 (1.4%)	72 (100%)

H = INH; R = rifampicin; Z = PZA; E = ethambutol; IA = Injection agent; MDR = multidrug resistance; COT = complete of treatment.

Regimen compose of initial phase/continuation phase. Number represent duration in months.

[1] = MDR regimens were as follows: Kanamycin+levofloxacin+ethionamide+cycloserine+PAS in 2 cases, Kanamycin+ofloxacin+ethionamide+cycloserine+PZA in 1 case.

[2] = 4 drugs (no IA)/2-3 drugs = 4 drugs selected from INH, rifampicin, ethambutol, pza, ofloxacin or levofloxacin (no injecting agent) were used in initial phase. After smear and culture conversion, 2-3 drugs were selected in continuation phase (9-12 months).

[3] = 5 drugs (and IA)/2-4 drugs = 4 drugs selected from INH, rifampicin, ethambutol, pza, ofloxacin or levofloxacin plus 1 injecting agent (streptomycin or kanamycin) were used in initial phase. After smear and culture conversion, 2-4 drugs were selected in continuation phase (9-12 months).

Table 2. Outcomes categorized with drug susceptibility test (n = 102)

Drug susceptibility	Cure and COT	Fail	Death	Default	Transfer out	Total
Pansusceptible	50 (67.6%)	0 (0%)	0 (0%)	13 (17.6%)	11 (14.9%)	74 (100%)
Monoresistance (S, E)	6 (85.7%)	0 (0%)	0 (0%)	1 (14.3%)	0 (0%)	7 (100%)
INH monoresistance	2 (66.7%)	0 (0%)	0 (0%)	0 (0%)	1 (33.3%)	3 (100%)
INH polyresistance	1 (33.3%)	2 (66.7%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
R monoresistance	2 (66.7%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
R polyresistance	0 (0%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	2 (100%)
MDR	4 (66.7%)	0 (0%)	0 (0%)	1 (16.7%)	1 (16.7%)	6 (100%)
No DST result	3 (75%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	4 (100%)
Total	68 (66.7%)	3 (2.9%)	1 (1%)	16 (15.7%)	14 (13.7%)	102 (100%)

S = streptomycin; E = ethambutol; H = INH; R = rifampicin; MDR = multidrug resistance; DST = drug susceptibility test
COT = complete of treatment

than INH or rifampicin polyresistance. Three from six MDR-TB cases had recurrent in early three months after complete treatment from first infection.

Discussion

From WHO report 2015[1], estimated incidence of tuberculosis burden in 2014 in Thailand was 120,000 (171:100,000). There were 65,753 new notification cases (91.81%), 1,969 relapses (2.74%), 3,896 previously treated, excluding relapse (5.44%) from 71,618 TB notification cases. Estimated of MDR-TB burden in new and retreatment cases were 3.3, 20% respectively. The number of recurrent tuberculosis in the present study was 2.4%. Success rate of treatment of recurrent tuberculosis in the present study was 65.7%.

Most cases in the present study were male, HIV negative, and had no co-morbid disease. Pansusceptible and monoresistance (not INH or rifampicin) were the largest groups 79.4% (81/102) and had good outcome. From the Fourth Surveillance of Drug resistance in Tuberculosis in Thailand 2012, there were 12.21%, and 29.59% of INH resistance in new and previously treated cases, 2.22%, and 23.98% of rifampicin resistance in new and previously treated cases, 2.03%, and 18.88% of MDR-TB in new and previously treated cases respectively[14]. The number of INH resistance in the present study and in drug resistance surveillance report was not much different (11.5 versus 12.2%). The number of rifampicin resistance (11.5%), MDR-TB (6.1%) in the present study was more than in new cases but less than in previously treated cases in drug resistance surveillance report. The recurrent tuberculosis was not an included treatment after default and treatment after failure cases, which were the groups that had more drug resistance. Whether these recurrent tuberculosis patients in the present study were relapse or reinfection (because DNA fingerprinting was not available), they had more drug resistance and MDR-TB than in new cases. In the study of Cox[15] in Uzbekistan, end of treatment outcomes may not reflect long-term status of patients. There was high disease recurrence after successful treatment, even drug susceptible. Recurrent tuberculosis increased significantly with increased drug resistance. Recurrent tuberculosis of new cases in pansusceptible, monoresistance, polydrug resistance, and MDR-TB was 23, 33, 58, and 67% respectively. Recurrent tuberculosis may result from inadequate treatment regimen, initial drug resistance, poor adherence, and poor drug quality.

Reinfection can also contribute to recurrent tuberculosis from 12 to 77%[4,9]. Those who had successfully treated tuberculosis were more likely to have recurrent tuberculosis than new case because their protective immunity could not protect another infection. From report of Verver[8] in Cape Town, South Africa, the incident rate of tuberculosis attributable to reinfection after successful treatment was four times than that of new tuberculosis. The frequency of exogenous reinfection in a high-burden countries would be greater than that in a low-burden countries because of increased risk of exposure[8-10,16,17].

Shen[18] reported that the frequency of exogenous infection increased with the amount of time that elapsed between the end of tuberculosis treatment for the first episode of tuberculosis and the date that the second episode was diagnosed. Bang[11] reported that in Denmark, a country with a low-incidence of

tuberculosis, between 1992 and 2005, the cumulative hazard ratio for relapse increased up to four years after treatment completion, whereas reinfection continued to increase throughout 14 years in their study. In our study, time after complete of treatment of first infection to recurrence was 10.9 years on average, while the case that had the longest time was 41 years. This implied that some of our cases may come from reinfection. Thailand is a high burden country for tuberculosis. This will increase risk of exposure and reinfection. Recurrence of these tuberculosis cases could occur at anytime during the 41 years.

Beijing phenotype strains had a higher capacity to have acquired drug resistance because they had more virulence. Most of tuberculosis strains in Thailand were Beijing phenotype from nationwide study in 1997 and 1998[19]. Yoshiyama[20] reported in 2004 about the study of acquired drug resistance in recurrent tuberculosis in Northern Thailand. Only one from 22 cases had reinfection from RFLP study. Most cases were relapse and had more acquired drug resistance. Acquired drug resistance among full susceptible were 12.9% (4/31), and 87.5% (7/8) among INH-resistance. In our study INH resistance (both mono and poly drug resistance) was the second largest group (6.2%). Two INH monoresistant patients had successful outcome while two from three streptomycin and INH polyresistant patients had failed to treatment. PZA was early stopped and injecting agent was not used in both failure cases. LPA in first case was INH resistance, rifampicin susceptible and sputum smear for AFB converted to negative, physician decided to use rifampicin and ethambutol (previously HRZE in initial phase) in the third month (which it was not really fit to the definition of sputum conversion that need two consecutive negative smear) and AFB smear was positive again in the fourth month. The patient in this case had also poor compliance. The second case sputum smear for AFB was negative after three months of HRZE (which was also not a true sputum conversion) and regimen was changed to HREO, smear was positive in the fourth month. This case had good compliance.

Risk of acquiring further drug resistance in the presence of initial drug resistance is higher than the risk of acquiring resistance in susceptible strain[21]. In systematic review of Lew[22] acquired drug resistance in initial pansusceptible, monoresistance, and polyresistance was 0.8, 6, and 14% respectively. Failure and relapse were most strongly associated with initial drug resistance. From report of Cox and Quy[23,24] INH and streptomycin polydrug resistance posed a significant amplification risk, 12% of them turned to be MDR-TB strains during treatment. In contrast to INH monoresistance, no case developed or acquired drug resistance. All three failure cases in the present study were the result of improper regimens or poor compliance. INH polyresistance, rifampicin mono, or poly resistance groups had very high risk to fail and worse outcomes.

The present study had limitation from its retrospective observation study, selection bias. To study natural course of tuberculosis in cohort study would take a lot of time. Information from the present study can help the understanding of the natural history of tuberculosis.

In conclusion, most recurrent pulmonary tuberculosis in the present study was pansusceptible. Streptomycin monoresistance, INH resistance (mono and poly drug resistance), and MDR-TB was the most common drug resistance. There was more MDR-TB than new cases. INH polyresistance and rifampicin polyresistance had poor outcomes.

What is already known on this topic?

Recurrent pulmonary tuberculosis is composed of relapse, reinfection, and mixed infection. Relapse occurs from the same strain organism as the first infection. It usually occurs soon after the first infection treatment (0.5 to 2 years) is completed. Initial drug resistance (especially INH resistance), inadequate treatment regimens, and poor adherence are the main causes of the relapse. Reinfection with another strain makes it difficult to predict its DST. Reinfection could occur many years after first infection (14 years in one report from Denmark, which is low-incidence country). Recurrent pulmonary tuberculosis is the heterogeneous groups of relapse, reinfection, and mixed infection. DST and outcomes of these recurrent pulmonary tuberculosis in Thailand are not known and difficult to predict.

What this study adds?

Most recurrent pulmonary tuberculosis in Thailand was pansusceptible (75.5%). Streptomycin monoresistance, INH resistance (mono and poly drug resistance), and MDR-TB was the most common drug resistance. The number of rifampicin resistance, MDR-TB in the present study was more than in new case in the Fourth surveillance drug resistance in tuberculosis in Thailand in 2012. However, it was less than in previously treated case. Recurrent tuberculosis had more drug resistance and MDR-TB than in new cases. INH polyresistance and rifampicin polyresistance had

poor outcomes (failure and death). They should be aggressively treated with proper regimens.

Potential conflicts of interest

None.

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การศึกษาผลการทดสอบความไวต่อยาต้านวัณโรคและผลการรักษาในผู้ป่วยวัณโรคที่กลับเป็นซ้ำในคนไทย

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ภูมิหลัง: *ผู้ป่วยวัณโรคที่กลับเป็นซ้ำมีการดื้อยาต้านวัณโรคมากกว่าผู้ป่วยรายใหม่*

วัตถุประสงค์: *ศึกษาผลการทดสอบความไวต่อยาต้านวัณโรค และผลของการรักษาในผู้ป่วยวัณโรคที่กลับเป็นซ้ำในสถาบันโรคทรวงอก*

วัสดุและวิธีการ: *เวชระเบียนที่ถูกบันทึกว่าเป็นผู้ป่วยวัณโรคที่กลับเป็นซ้ำในปี พ.ศ. 2554-2556 ได้รับการทบทวน*

ผลการศึกษา: *ผู้ป่วย 102 ราย (ชาย 76 ราย, หญิง 26 ราย) อายุเฉลี่ย 47.7 ปี (18 ถึง 79 ปี) มีการตรวจ Anti-HIV 77 ราย, 1 รายผลเป็นบวก ทุกรายเป็นวัณโรคปอด 5 รายมีวัณโรคเยื่อหุ้มปอดร่วมด้วย ภาพเอกซเรย์ปอดมีโพรงแผล 58.1% จำนวนผู้ป่วยที่ดื้อต่อยา streptomycin, INH, rifampicin, ethambutol, ofloxacin, kanamycin เท่ากับ 16, 11, 11, 5, 3, 1 (16.7, 11.5, 11.5, 5.2, 3.1, 1%) ตามลำดับ มีผู้ป่วยที่มีผลทดสอบความไวต่อยาต้านวัณโรคเป็น pansusceptible 74 ราย (75.5%), streptomycin monoresistance 6 ราย (6.1%), MDR 6 ราย (6.1%), INH monoresistance 3 ราย (3.1%), INH polyresistance 3 ราย (3.1%), rifampicin monoresistance 3 ราย (3.1%), rifampicin polyresistance 2 ราย (2%), ethambutol monoresistance 1 ราย (1%) และมี 4 ราย ที่ไม่ทราบผลทดสอบความไวต่อยาต้านวัณโรค เวลาเฉลี่ยที่กลับเป็นวัณโรคซ้ำหลังหยุดการรักษาครั้งแรก 10.9 ปี (1 เดือน ถึง 41 ปี) ผลของการรักษา มี 67 ราย รักษาหาย (65.7%), 1 ราย กินยาครบ (1%), 3 รายรักษาล้มเหลว (2.9%), 1 รายเสียชีวิต (1%), 16 รายขาดการรักษา (15.7%) และ 14 รายย้ายไปรักษาที่อื่น (13.7%)*

สรุป: *วัณโรคที่กลับเป็นซ้ำในการศึกษานี้ส่วนใหญ่ยังตอบสนองต่อยาต้านวัณโรค มีการดื้อยาต้านวัณโรคมากในกลุ่ม streptomycin monoresistance และ INH resistance (mono and poly drug resistance) และ MDR-TB มีผู้ป่วย MDR-TB สูงกว่าในผู้ป่วยรายใหม่ INH polyresistance และ rifampicin polyresistance มีผลการรักษาที่ไม่ดี*