The challenge of re-treatment pulmonary tuberculosis at two teaching and referral hospitals in Uganda

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Abstract

Background With an annual tuberculosis (TB) incidence of about 350 cases per 100,000 of the population, Uganda is a high burden country. Moreover, it is evident that some TB patients have been treated for a previous episode of the disease.

Objective To highlight the burden of re-treatment pulmonary TB and examine patient factors associated with re-treatment among adults at two teaching and referral hospitals, Mbarara and Mulago

Methods A descriptive cross sectional study with data collection between September 2004 and March 2005; we calculated the prevalence and used logistic regression to explore factors associated with re-treatment.

Results The prevalence of re-treatment pulmonary TB at Mbarara based on medical records was 30.0% (95%CI: 21.2 to 40.0), and 21.3% (95%CI: 12.9 to 31.8) from exit interviews. The corresponding estimates at Mulago hospital were 12.0% (95% CI: 6.4 to 20.0) and 43.9% (33.0 to 55.3). Compared to the 18-26 year age category, the prevalence odds ratio (POR) for a seven-year increase in age was 1.54 (95%CI: 1.04-2.28; p = 0.027), while female patients were 0.39 (95%CI: 0.17-0.90; p = 0.025) times less likely to report re-treatment disease than males, in this facility-based study.

Conclusions Re-treatment pulmonary TB is frequent at the two teaching and referral hospitals. A contribution to re-treatment prevention should entail more rigorous management of new TB cases, particularly at lower levels of care.

Keywords Tuberculosis, pulmonary, re-treatment, prevalence

Introduction

Tuberculosis (TB) remains one of the leading causes of ill health and death in developing countries, where co-morbidity with human immunodeficiency virus (HIV) has increased the disease burden. With an estimated annual incidence of 350 new cases per 100,000 of the population, Uganda is one of the high-burden Sub Saharan countries in the world.[1] The TB treatment strategy in the country is predominantly community-based directly observed treatment with short course chemotherapy (CB-DOTS) and is free of charge.

Early detection of TB and expeditious anti-tuberculosis chemotherapy are critical for effective TB control[2]. The target is to achieve at least 70 percent detection of sputum smear positive cases and to successfully treat 85 percent of patients[1,3]. In Uganda, the case detection rate is reported to have dropped below 50 percent and treatment success, approximately 68% of sputum smear positive cases[1,4,5]. Moreover, it is evident that some TB patients at Mbarara and Mulago teaching

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and referral hospitals have been treated for a previous disease episode. The problem of re-treatment TB has also been highlighted elsewhere[6-8].

Re-treatment tuberculosis

Re-treatment is inevitable for patients with recurrent TB, those who defaulted on previous therapy and in cases were initial treatment has failed. In 2004, approximately 891 (2.0%)[5] case notifications in Uganda were reported as re-treatment cases with the exclusion of relapse. However, the case classification and pathogenesis of recurrence are still obscure[9-11]. In general terms, recurrence of TB may be a result of relapse in patients otherwise previously treated successfully, or re-infection. Many studies[12-15] indicate that a significant proportion of recurrent TB may be attributable to relapse with the same *Mycobacterium tuberculosis* strain, particularly following recent completion of treatment. Lambert et al[9] in a systematic review suggest that re-infection per se may have few implications for TB control except in settings with considerably high incidence, while immunocompromised patients are reported to be at greater risk of re-infection TB[16]

Poor patient compliance, increasing age, emergence of multi drug resistant mycobacteria, co-morbidity and chronic alcoholism[6,17-19] have been associated with re-treatment. Additionally, HIV

seropositive patients have generally been shown to have more frequent episodes of recurrence[12,14,20,21] compared to seronegative patients.

We carried out a study to highlight the burden of re-treatment pulmonary TB and to examine patient factors associated with re-treatment at two teaching and referral hospitals, Mulago and Mbarara. Mulago hospital is a 1,500 bed national referral hospital located in Kampala, in Central Uganda, while Mbarara hospital has about one-fifth the capacity of Mulago and is a regional referral hospital in the South Western part of the country. These hospitals are active TB treatment centres and about 50 percent of TB patients attending clinics have HIV co-infection.

Methods
Study design and participants
This was a cross sectional design involving review of selected records and hospital exit interviews of a simple random sample of adult patients. Participants were new or re-treatment ambulatory patients attending TB clinics at Mulago and Mbarara hospitals, irrespective of the level of compliance to previous anti-tuberculosis treatment. We included patients who had been on treatment for four months or less and were aged 18-50 years. Patients with extra pulmonary tuberculosis and those who did not consent to the exit interview were excluded from the study.

Data collection
At Mulago and Mbarara hospitals, diagnosis of pulmonary TB is made on the basis of clinical examination, chest radiography and sputum smear microscopy. Following diagnosis, DOTS is initiated and supervised by health workers for institutionalised patients during the initial intensive phase, while CB-DOTS is undertaken in collaboration with family, community and health volunteers. Such CB-DOTS treatment supporters perform the duties of directly observing anti-tuberculosis medicine administration and of reminding patients to obtain refills.

We systematically selected medical records from those archived between January 2001 and December 2003 for review of pulmonary TB cases. Socio-demographic, clinical, microbiological, and re-treatment data were extracted from 101 records at Mbarara hospital and 100 at Mulago hospital using structured forms.

Eighty-two pulmonary TB patients were interviewed from Mbarara and 83 from Mulago hospital. Patient data, which was collected between September 2004 and March 2005, included socio-demographic characteristics, self-reported co-morbidity, drug treatment, and attitudes toward TB treatment.

We considered a patient with re-treatment pulmonary TB as one who had been previously treated for TB but subsequently determined by a clinician as having active pulmonary TB and commenced on antituberculosis therapy. This non-specific definition included cases of relapse, re-infection, re-treatment TB after failure and re-treatment TB after default. A new TB patient was defined as one who had never received treatment for TB; relapse as a patient previously treated for TB and declared cured or who completed treatment, and was diagnosed with sputum smear positive TB; re-treatment TB after failure as a patient previously treated for TB but who remained sputum smear positive at five months or later during treatment; and, re-treatment TB after default as a patient previously treated for TB but who had interrupted treatment for two or more consecutive months[22]. Previous episodes of TB were ascertained from physicians' cases notes or by reports of study participants.

Data analysis
We calculated the prevalence of re-treatment pulmonary TB based on records and patient interviews and computed binomial confidence intervals for these estimates. The frequencies of characteristics of interviewed patients were compared between the two hospitals. Furthermore, new TB patients and those on re-treatment were compared for socio-demographic and clinical characteristics, attitudes towards treatment and co-morbidity, including self-reported HIV serostatus.

Factors associated with re-treatment were analysed using logistic regression. Initially, we accounted for centre effect and then examined confounding and effect modification through the inclusion of variables with a p-value of 0.2 or less during univariate analysis. The final model included only those variables found to be independent factors. A p value of 0.05 or less was considered statistically significant. Analyses were performed using STATA 8.

Ethical considerations
This study was approved by the Research and Ethics Committee of the Faculty of Medicine, the Institutional Review Boards of Mbarara and Mulago hospitals and registered with the Uganda National Council for Science and Technology (UNCST).

Results
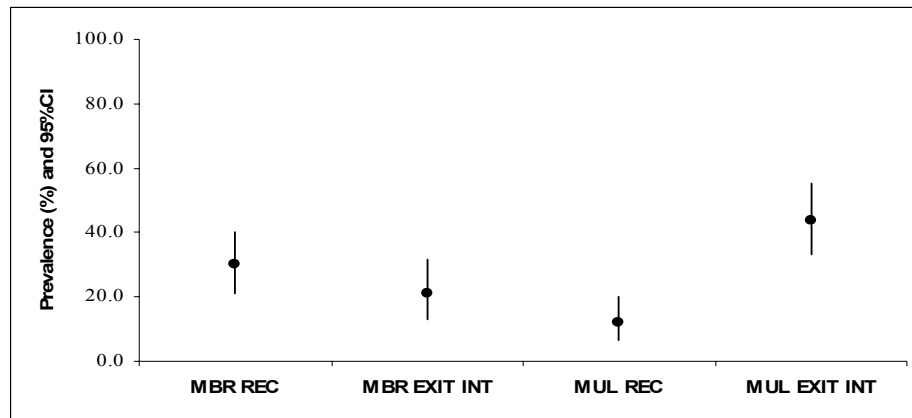### Prevalence of re-treatment pulmonary tuberculosis
Figure 1 shows the prevalence estimates of re-treatment pulmonary TB. Prevalence from exit interviews was

lower at Mbarara hospital and higher at Mulago hospital.

Although few records reported the time interval between previous and current pulmonary TB episodes, recurrent illness most often occurred within eight months of the previous disease episode; 15 (83.3%) at Mbarara and 12 (80.0%) at Mulago hospital.

Figure 1 Prevalence of re-treatment tuberculosis among adults with pulmonary TB at Mbarara and Mulago hospitals between 2001 and 2005

MBR=Mbarara, MUL=Mulago, EXIT INT=Exit Interview 2004-5, REC=records review 2001-3

Factors associated with re-treatment pulmonary tuberculosis

Table 1 shows the association between socio-demographic, clinical and treatment-related factors and re-treatment pulmonary TB in adult patients.

Re-treatment pulmonary disease was more frequent amongst older patients at Mbarara hospital. Males at Mulago hospital were also more likely to have had a previous episode. Additionally, new pulmonary TB patients at Mulago hospital's TB unit were significantly more likely to point out a greater pill burden compared to previously treated patients.

Amongst the re-treatment pulmonary cases, 5 (29.4%) at Mbarara and 14 (38.9%) at Mulago pointed out that they did not complete their previous antituberculosis treatment.

Univariate and multivariate prevalence odds ratios (PORs) for socio-demographic characteristics and co-morbidity are presented in Table 2. Univariate analysis indicated a significant association between age (POR = 1.68; 95%CI: 1.20-2.35; p = 0.002) and re-treatment pulmonary TB. After partial adjustment for centre effect, increasing age remained significant (POR = 1.73; 95%CI: 1.22-2.45; p = 0.002) while female gender was protective (POR = 0.51; 95%CI: 0.21-0.90; p = 0.025) against re-treatment. Furthermore, subsistence farmers were 4.63 fold (95%CI: 1.26-17.0; p = 0.021) more likely to have re-treatment TB compared to unemployed patients.

Multivariate analysis with adjustment for occupation and centre effect showed that increasing age and male gender were independently associated with re-treatment pulmonary TB amongst adult patients. Compared to the 18-26 year age category, the prevalence odds ratio for a seven-year increase in age was 1.54 (95%CI: 1.04-2.28; p = 0.027), while female patients were 0.39 (95%CI: 0.17-0.90; p = 0.025) times less likely to have re-treatment disease than males.

Discussion

Re-treatment pulmonary TB accounted for 12 to 44 percent of cases, with different estimates of prevalence derived from records and patient interviews at Mulago and Mbarara referral hospitals. Prevalence based on exit interviews might have been influenced by the frequency of hospital visits of re-treatment cases compared to new patients. The record of patients attending the TB clinic is enumerated once, while at any one time, a patient who was previously registered could have visited the facility during the time of the study. If patients with re-treatment TB visit the facility more often because of the need for more frequent clinical and microbiological assessment, then there is a possibility that the prevalence estimate could be slightly higher. Conversely, if treatment seeking habits of re-treatment cases are poor, then the prevalence, based on interviews would correspondingly appear low compared to that derived from medical records. Nevertheless, re-treatment TB appears to be of major concern, making an important contribution to the burden of pulmonary disease at the two hospitals. This particularly raises questions regarding the effectiveness of TB treatment and patient follow up at lower levels of care.

Table 1 Factors associated with re-treatment pulmonary TB among adult patients at Mbarara and Mulago hospitals between September 2004 and March 2005

Patient characteristic	Hospital Mbarara n (%)			Mulago n (%)		
	New	Re-treatment	p value	New	Re-treatment	p value
Socio-demographic						
Age (years); n = 160						
18-26	25 (96.2)	1 (3.8)	0.002[a]	13 (61.9)	8 (38.1)	0.162[a]
27-34	19 (82.6)	4 (17.4)		17 (60.7)	11 (39.3)	
35-42	12 (63.2)	7 (36.8)		10 (58.8)	7 (41.2)	
43-50	7 (58.3)	5 (41.7)		4 (33.3)	8 (66.7)	
Gender; n = 153						
Male	31 (75.6)	10 (24.4)	0.519	12 (40.0)	18 (60.0)	0.014
Female	31 (81.6)	7 (19.4)		29 (69.0)	13 (31.0)	
Marital status; n = 138						
Single	23 (85.2)	4 (14.8)	0.745[b]	17 (51.5)	16 (48.5)	0.766
Married	29 (80.6)	7 (19.4)		22 (55.0)	18 (45.0)	
Household size; n = 156						
Mean (SD)	5.3 (3.1)	5.3 (2.8)	0.938[c]	5.2 (2.1)	5.1 (2.9)	0.888[c]
Household case of TB; n = 149						
Yes	14 (73.7)	5 (26.3)	0.260	14 (48.3)	15 (51.7)	0.285
No	46 (85.2)	8 (14.8)		28 (60.9)	18 (39.1)	
Occupation; n = 159						
Unemployed	5 (83.3)	1 (16.7)	0.158[b]	14 (60.9)	9 (39.1)	0.353[b]
Student	3 (100.0)	0 (0.0)		4 (80.0)	1 (20.0)	
Subsistence farmer	13 (59.1)	9 (40.9)		1 (25.0)	3 (75.0)	
Non-professional	31 (86.1)	5 (13.9)		17 (60.7)	11 (39.3)	
Professional	9 (81.8)	2 (18.2)		8 (42.1)	11 (57.4)	
Self reported co-morbidity (n = 165)						
None reported	39 (84.8)	7 (15.2)	0.159[b†]	29 (56.9)	22 (43.1)	0.956[b]
HIV/AIDS	23 (71.9)	9 (28.1)		11 (57.9)	8 (42.1)	
Diabetes mellitus	0 (0.0)	0 (0.0)		2 (40.0)	3 (60.0)	
Other	1 (50.0)	1 (50.0)		4 (57.1)	3 (42.9)	
Adherence						
Ever missed doses; n = 159						
Yes	11 (68.8)	5 (31.2)	0.289	16 (66.7)	8 (33.3)	0.278
No	51 (81.0)	12 (19.0)		30 (53.6)	26 (46.4)	
Subjective improvement (n = 148)						
Yes	61 (79.2)	16 (20.8)	0.218[b]	32 (54.2)	27 (45.8)	1.000[b]
No	0 (0.0)	1 (100.0)		6 (60.0)	4 (40.0)	
Attitudes toward treatment (n = 161)						
Disease is serious	61 (79.2)	16 (20.8)	1.000[b]	44 (55.7)	35 (44.3)	1.000[b]
Treatment too long; n = 163	10 (76.9)	3 (23.1)	1.000	24 (61.5)	15 (38.5)	0.380
Drugs too many	8 (88.9)	1 (11.1)	0.675[b]	25 (75.8)	8 (24.2)	0.003

[a]Chi square test for trend
[b]Fisher's exact test
[c]Independent ttest
[†]Six degrees of freedom

Table 2 Univariate and multivariate prevalence odds ratio (POR) for re-treatment pulmonary tuberculosis among adult patients at Mbarara and Mulago hospitals between September 2004 and March 2005

Patient characteristic (n = 165)	Univariate association		Multivariate association			
			Adjusted for centre effect[a]		Adjusted for centre effect and confounding[b]	
	Crude POR	95%CI	Adjusted POR	95%CI	Adjusted POR	95%CI
Socio-demographic						
Age (years)[c]	1.68	1.20-2.35	1.73	1.22-2.45	1.54	1.04-2.28
Female gender	0.51	0.26-1.03	0.43	0.21-0.90	0.39	0.17-0.90
Occupation						
Unemployed	1.00		1.00		1.00	
Student	0.27	0.03-2.53	0.31	0.03-3.04	0.32	0.03-3.46
Subsistent farmer	1.63	0.55-4.83	4.63	1.26-17.00	3.45	0.85-14.0
Non-professional	0.63	0.24-1.64	1.01	0.37-2.78	0.57	0.18-1.78
Professional	1.45	0.51-4.16	1.88	0.62-5.70	0.62	0.17-2.29
Self reported comorbidity						
None reported	1.00		1.00			
HIV/AIDS	1.17	0.57-2.42	1.40	0.66-3.00	-	
Diabetes mellitus	3.52	0.56-22.20	2.26	0.35-14.55	-	
Other unknown disease	1.88	0.47-7.49	2.87	0.36-6.19	-	

[a]Accounted for centre effect; p values are derived from the Wald test

[b]Multiplicative model of best fit adjusted for centre effect, age, gender and occupation of the patient; p values for gender and age in this model are likelihood-based estimates

[c]Seven-year age bands relative to the 18-26 year age group

We broadly defined re-treatment pulmonary TB to include treatment failure, default and recurrence, as it was not possible to distinguish between these categories in the design. Appropriately applied, TB treatment is often efficacious and failure rates, low. However, some patients default on their therapy. In 2003, 0.4 percent of TB patients in Uganda were reported to have failed treatment, 19 percent were reported to have defaulted on treatment[5], while the contribution of recurrence is not well quantified. One study based in Uganda by Johnson et al[23] found a relatively low recurrence rate of 3.1 per 100,000 person years, which rate was influenced by HIV co-infection. However, this recurrence rate was for a nine-month rifampicin containing regimen while the current standard treatment for a new case of pulmonary TB is an eight-month ethambutol-containing regimen. In addition, close monitoring for adherence and exclusion of patients who did not complete treatment make this estimate less pragmatic.

Recurrences of pulmonary TB have been reported to be especially more frequent among HIV-infected patients with low CD4 lymphocyte count[8,24] and in carriers of homozygous haptoglobin with residual lung changes following initial disease episodes[25]. However the latter findings have not been adequately corroborated. One could argue that the short interval between TB episodes suggests that a majority of patients previously defaulted or had a recurrent TB episode arising from relapse of the previous infection. This is further supported by the relatively high proportion of patients with re-treatment pulmonary TB who reported not having completed their previously prescribed therapeutic regimen. In this study, older adult males were more likely to report re-treatment pulmonary TB. Male patients however, were less likely to report HIV co-infection. Older adult male patients might have therefore been more likely to default on previous TB treatment, and also at greater risk of recurrence. However these findings may also suggest poorer help seeking behaviour among female patients with re-treatment TB.

Relapse per se, is said to occur if there is insufficient bacteriological cure of previous disease. It can be considered a measure of the efficacy of the anti-tuberculosis drug regimen having accounted for other patient and health system factors[6] Connolly et al[26] found a 5 percent frequency of relapse at 18 months following DOT regardless of HIV co-infection and previous treatment history, while the rate of sputum smear conversion was not predictive of relapse. Various influences have been reported to increase the risk of recurrence due to relapse; poor treatment regimens, for example those formerly involving thiacetazone[23], too short a duration of treatment, primary or acquired drug resistance[9,27,].

The high frequency of re-treatment amongst older patients in this study is expected, but also suggests that re-infection may have a role to play. There is an increase in the risk of new infection with age in this high incidence setting. Moreover, HIV infection together with

progressive immuno-suppression with age, which is common among TB patients, increase the rate of breakdown to active disease following re-infection with mycobacteria[16]. Of particular concern are settings where the background risk of infection or re-infection is high or among very close contacts of infectious index cases[28]. This underscores the significance of spatial clusters in re-infection TB. A systematic review of studies on recurrent TB by Lambert et al[9] indicated that the proportion of recurrences due to re-infection could be at both extremes (0 to 100 percent), with its importance varying by setting. Notable from our findings was that the presence of a known household case of TB was not associated with re-treatment. However, it is possible that patients were not aware of a case of TB in the household since case detection is on the basis of passive reporting other than active surveillance to identify contacts with the disease.

More robust evidence on re-treatment and recurrent TB can be obtained by a prospective analysis with repeat clinical and microbiological assessments and adjustments for various patient, treatment-related and health system factors. Molecular identification of mycobacterial strains would be necessary to examine the significance of relapse, re-infection and mixed infections[29]. In addition, the contribution of primary, acquired and extensive antimycobacterial drug resistance is of considerable interest.

Limitations

No data were readily available on repeat sputum smears. Therefore, the proportion of re-treatment TB attributable to treatment failure could not be quantified. However, pulmonary TB patients were reported to normally "dry up" quickly, implying that production of sputum ceases soon after initiation of treatment. Treatment failure therefore appears to contribute little to the problem of re-treatment TB. Another drawback was that we could not ascertain recurrence using molecular techniques because of the cross sectional design and the lack of historical data on mycobacterial strains.

Conclusion

Re-treatment pulmonary TB is frequent at the two teaching and referral hospitals. It is therefore of public health concern and efforts should be geared towards its prevention. The need for rigorous management of new TB cases should be re-emphasised, particularly at lower levels of care. Furthermore, potential benefits of long-term follow up of previously treated patients at risk of requiring TB re-treatment should be explored.

References

1. World Health Organisation. Global tuberculosis control: surveillance, planning, financing. WHO report 2005. WHO/HTM/TB/2005.349. 2005. Geneva.

2. Reider HL. Epidemiologic basis of tuberculosis control. International Union Against Tuberculosis and Lung Disease, 1999.

3. Dermot, Pierre, Sergio, and Anthony. Treatment of tuberculosis, guidelines for national programmes. 1997. WHO.

4. WHO. Global tuberculosis control, country profile, Uganda. WHO report. 2002. WHO.

5. World Health Organisation. Global tuberculosis control: surveillance, planning, financing. WHO report 2006. WHO/HTM/TB/2006.362. 2006. Geneva.

6. de Oliveira HB, .Moreira Filho DC. Tuberculosis recurrence and its risk factors. *Rev Panam. Salud Publica* 2000; 7:232-41.

7. Didilescu C, Ibraim E, Plopeanu D. A study of the risk factors for relapse in pulmonary tuberculosis patients and the results of the re-treatment. *Pneumologia.* 2000;49:247-52.

8. Garcia Ordonez MA, Martinez GJ, Orihuela CF, Jimenez OF, Colmenero Castillo JD. Recurrent tuberculosis in patients with coinfection by HI. *Rev Clin.Esp.* 2003; 203:279-83.

9. Lambert ML, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Van der SP. Recurrence in tuberculosis: relapse or reinfection? *Lancet Infect.Dis.* 2003;3:282-7.

10. Gavrilenko VS, .Khruleva TS. The current aspects of the recurrence of tuberculosis of the respiratory organs in adults. *Probl. Tuberk.* 1996; 2-4.

11. Solacolu V, .Teodoru M. False recurrences in pulmonary tuberculosis. *Rev Ig Bacteriol. Virusol. Parazitol. Epidemiol. Pneumoftiziol. Pneumoftiziol.* 1980; 29:57-60.

12. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001;358:1687-93.

13. Bandera A, Gori A, Catozzi L, Degli EA, Marchetti G, Molteni C *et al*. Molecular epidemiology study of exogenous reinfection in an area with a low incidence of tuberculosis. *J.Clin.Microbiol.* 2001;39:2213-8.

14. Hawken M, Nunn P, Gathua S, Brindle R, Godfrey-Faussett P, Githui W *et al*. Increased recurrence of tuberculosis in HIV-1-infected patients in Kenya. *Lancet* 1993;342:332-7.

15. Sterling TR, Alwood K, Gachuhi R, Coggin W, Blazes D, Bishai WR *et al*. Relapse rates after short-course (6-month) treatment of tuberculosis in HIV-infected and uninfected persons. *AIDS* 1999;13:1899-904.

16. Fitzpatrick LK, Okwera A, Mugerwa R, Ridzon R, Ehiner J, Onorato I. An investigation of suspected exogenous reinfection in tuberculosis patients in Kampala, Uganda. *Int.J.Tuberc.Lung Dis.* 2002;6:550-2.

17. Burukhina LV, Zolotovskaia EA, Prudnikova ZA, Vershinin AV, Kolmakova PL. Causes of recurrence of pulmonary tuberculosis: short and long term results of treatment. *Probl.Tuberk.* 1995;29-31.

18. Liu XR. A study on the relapse and its potential causes in pulmonary tuberculosis. *Zhonghua Jie.He.He.Hu Xi.Za Zhi.* 1993;16:69-72, 122.

19. Ormerod LP, .Prescott RJ. Inter-relations between relapses, drug regimens and compliance with treatment in tuberculosis. *Respir.Med.* 1991;85:239-42.

20. Mallory KF, Churchyard GJ, Kleinschmidt I, De Cock KM, Corbett EL. The impact of HIV infection on recurrence of tuberculosis in South African gold miners. *Int.J.Tuberc.Lung Dis.* 2000;4:455-62.

21. Daley CL. Tuberculosis recurrence in Africa: true relapse or re-infection? *Lancet* 1993;342:756-7.

22. Instructions for completion of the WHO/EuroTB data collection form for TB cases notified in 2005, treatment outcomes for cases registered in 2004, and financial information for fiscal years 2005-2007. www.eurotb.org/data_collection/english/tb_data_form_2006_instructionseng.doc . 2007. 5-4-2007.

23. Johnson JL, Okwera A, Vjecha MJ, Byekwaso F, Nakibali J, Nyole S *et al*. Risk factors for relapse in human immunodeficiency virus type 1 infected adults with pulmonary tuberculosis. *Int.J.Tuberc.Lung Dis.* 1997;1:446-53.

24. Pulido F, Pena JM, Rubio R, Moreno S, Gonzalez J, Guijarro C *et al*. Relapse of tuberculosis after treatment in human immunodeficiency virus-infected patients. *Arch.Intern.Med.* 1997;157:227-32.

25. Eisaev BA, .Kaminskaia GO. Assessment of tuberculosis recurrence risk in phenotyping haptoglobin in patients with post-tuberculous residual changes in the lungs. *Probl.Tuberk.* 1992;8-11.

26. Connolly C, Reid A, Davies G, Sturm W, McAdam KP, Wilkinson D. Relapse and mortality among HIV-infected and uninfected patients with tuberculosis successfully treated with twice weekly directly observed therapy in rural South Africa. *AIDS* 1999;13:1543-7.

27. Kritski AL, Rodrigues de Jesus LS, Andrade MK, Werneck-Barroso E, Vieira MA, Haffner A *et al*. Retreatment tuberculosis cases. Factors associated with drug resistance and adverse outcomes. *Chest* 1997;111:1162-7.

28. Kondo A, Oketani N, Kuwabara K, Maruyama Y, Miyao H, Saito Y *et al*. An outbreak of pulmonary tuberculosis probably due to exogenous reinfection at a nursing home for the elderly. *Kekkaku* 2002; 77:401-8.

29. van Rie A, Victor TC, Richardson M, Johnson R, van der Spuy GD, Murray EJ *et al*. Reinfection and mixed infection cause changing Mycobacterium tuberculosis drug-resistance patterns. *Am J Respir Crit Care Med* 2005;172:636-42.