ERJ Express. Published on May 30, 2007 as doi: 10.1183/09031936.00131406

New recommendations for the duration of respiratory isolation based on the time to detect *M. tuberculosis* in liquid culture.

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Short Title:
TB isolation and the TTD-TB test

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Word Count

Body of article: 2677 words

Abstract: 270 words

ABSTRACT

We hypothesised that time to detect *Mycobacterium tuberculosis* in liquid culture of sputum from patients with pulmonary tuberculosis may be a better indicator for the duration of respiratory isolation than sputum smear status.

We reviewed pre-treatment and during-treatment sputum acid-fast bacilli smear and culture results in 284 patients with pulmonary tuberculosis. The time to detect *M. tuberculosis* in liquid culture (TTD-TB) was the number of days from inoculation of the Mycobacterial Growth Indicator Tube to culture detection and visualisation of acid-fast bacilli.

The median TTD-TB for smear group 0 (no bacilli seen) was 14 days (interquartile range 12-20). This value was used as the standard at which release from isolation could be permitted. In smear group 4 (>9 AFB/hpf in sputum specimens before treatment) patients the TTD-TB exceeded 14 days after a median of 25 days of treatment.

We recommend that patients in smear groups 1 and 2 (1-9 AFB/100 hpf and 1-9 AFB/10 hpf in sputum specimens before treatment) receive treatment in respiratory isolation for 7 days, provided the risk of drug resistance is low. Smear group 3 (1-9 AFB/hpf) patients should receive treatment in respiratory isolation for 14 days; and smear group 4 patients for 25 days. These criteria would have reduced the duration of respiratory isolation by 1516 days in our 146 study participants with sputum smear positive pulmonary tuberculosis.

Provided clinical and radiographic criteria are satisfactory, use of TTD-TB could enable the duration of respiratory isolation to be predicted from the pre-treatment sputum smear grade. Our recommendations enable isolation to end well before sputum becomes smear negative, with considerable benefits to patients and health-care providers.

KEY WORDS

infectivity

pulmonary tuberculosis

respiratory isolation

time to detect tuberculosis in liquid culture (TTD-TB)

transmission

treatment

INTRODUCTION

Drug treatment of active tuberculosis (TB) is a key factor in interrupting transmission of this disease. The duration of treatment required to render patients non-infectious varies between individuals and remains largely unknown.[1] It is recommended that patients with sputum smear positive pulmonary TB (PTB) receive initial treatment in respiratory isolation.[2-4] Infectivity is closely related to sputum smear status.[5-10] Patients with negative sputum smears are not routinely placed in respiratory isolation even though they may transmit tuberculosis.[11] This is because smear negative cases are less infectious than those who are smear positive,[5-8] reflecting the number of viable bacilli expectorated.[9,10] Treatment rapidly reduces colony counts of *M. tuberculosis* in the sputum of patients with pulmonary TB.[12,13]

Contemporary liquid culture methods allow for the rapid detection of *M. tuberculosis,* particularly in highly smear positive samples. We hypothesised that time to detect *Mycobacterium tuberculosis* in liquid culture may be a better indicator for the duration of respiratory isolation required than sputum smear status: after weeks of treatment, smear status alone does not show whether organisms are viable. In the present study the initial objective was to examine whether time to detect tuberculosis in liquid culture (TTD-TB) correlated with smear status; if so, it would provide an indirect indication of the number of viable bacilli in sputum samples. The second objective was to determine the duration of treatment required to reduce the TTD-TB of a patient with positive sputum smears to that of a sputum smear negative

patient, and by implication, the time at which they could be released from respiratory isolation. The final objective was to estimate of the number of days of respiratory isolation that might have been saved if the study population was subject to new recommendations we devised, based on TTD-TB.

METHODS

This study was a retrospective, laboratory based audit. A study proposal was submitted to the local ethics committee, who advised that formal ethical approval was not required. The Auckland District Health Board mycobacterial laboratory was our regional reference laboratory. Patients with pulmonary TB were identified from its database.

Inclusion and exclusion criteria

To be eligible for inclusion in the study, patients were required to have had a positive sputum or induced-sputum TB culture between January 1st 2000 and December 31st 2003. To increase uniformity within the principal group analysed (patients with fully susceptible isolates), only patients receiving isoniazid, rifampicin, and pyrazinamide, with or without ethambutol, were included. Patients in respiratory isolation were treated with daily therapy and each dose was observed by a nurse. Patients whose isolates were resistant to isoniazid, rifampicin or pyrazinamide were excluded, as were patients who did not receive treatment at our hospital, or who were receiving treatment when their first positive specimen was received in our laboratory.

Laboratory methods

Sputum specimens were processed following standard smear and culture methods[14] in a fully accredited mycobacterial reference laboratory. Microscopy was performed on all specimens which were also cultured using both Lowenstein-Jensen solid medium (Fort Richard, Auckland, NZ) and the BACTEC 960 (Becton Dickinson, Sparks, USA) Mycobacterial Growth Indicator Tube (MGIT) broth, used in a BACTEC MGIT 960 incubator. The BACTEC MGIT 960 system is a continuously monitored device. There is neither reader bias, nor reading interval bias in identifying a positive culture. Specimens taken before treatment were incubated until culture positive, or for up to 28 days, when they were deemed to be culture negative. Specimens from patients already known to have TB (those receiving treatment) were incubated for 42 days.

Susceptibility testing to first line drugs was performed with the BACTEC MGIT 960 system. Susceptibility to pyrazinamide was further confirmed by the Wayne method.[14] *M. tuberculosis* complex was identified by nucleic acid probe testing (GenProbe, California). We defined TTD-TB as the number of days from inoculation of the MGIT to the detection of positive growth and visualization of acid-fast bacilli (AFB) in the smear from the positive MGIT broth.

Data Collection and Sputum Sampling

Initial data collected on patients included patient characteristics, start date of culture, date of positive MGIT culture, smear grade,[14] TTD-TB of each specimen, isolate drug susceptibility and the number of days patients spent in

respiratory isolation. Patients were grouped by their highest pre-treatment smear grade (Table 1). All patients had at least two sputum specimens examined before assignment to their group.[15] The policy for patients in respiratory isolation was for sputum samples to be collected weekly. Once a sample was smear negative then two further samples were collected on the next two days to test whether the patient still required respiratory isolation.[2]

Data Analysis

Once patients had been allocated to the appropriate smear group, pre-treatment median TTD-TB and interquartile range values were calculated for each group. Culture negative specimens taken before treatment were assigned a TTD-TB of 29 days – one day longer than the incubation period for these specimens. Due to the retrospective study design and performance in a clinical, non-research setting, sputum specimens were not obtained at strictly uniform intervals. Thus, specimens taken after starting therapy had to be grouped into 7-day periods. To avoid over-estimating treatment effect on TTD-TB, only culture positive specimens were analysed after treatment had started. For example, in group 2 the median TTD-TB would become 24 days rather than 19 days in the second week of treatment if the culture negative samples were included in the analysis.

Spearman's correlation coefficient was used to examine the strength of relationships between TTD-TB vs. smear grade in pre-treatment specimens, smear grade vs. duration of treatment, and TTD-TB vs. duration of treatment. All calculations were made using SPSS 14.0 for Windows.

RESULTS

Before treatment, 589 sputum or induced-sputum samples from 284 patients were culture positive for *M. tuberculosis*. Twenty-three patients were excluded, and in 20 this was because of drug resistance. Table 1 shows patient characteristics in each smear group and the duration of inpatient respiratory isolation. After exclusion criteria were applied, 648 specimens from 261 patients were analysed to determine pre-treatment TTD-TB values (Table 2). Specimens that were smear-negative (patient smear group 0) had a median TTD-TB of 14 days (interquartile range 12-20). In specimens from smear group 4 patients the median TTD-TB was 5 days (interquartile range 4-6). An inverse correlation was observed between the TTD-TB and smear grade on specimens collected before treatment had begun (Spearman's correlation coefficient -0.87, $p<0.01$). As expected, duration of isolation closely followed the time to smear conversion to negative: for the smear group 3 patients the median time spent in inpatient isolation was 27 days (interquartile range 18-37 days); and for the smear group 4 patients it was 38 days (interquartile range 27-53 days). Sputum became smear negative after a median of 25 days of treatment (interquartile range 17-34 days) in group 3, and after 34 days (interquartile range 24-51 days) in group 4.

Table 2 shows the median TTD-TB and interquartile range for each smear group by day-ranges that correspond to weeks of anti-tuberculous treatment. For specimens from smear group 1 and 2 patients, median TTD-TB values exceeded 14 days (i.e. that of smear negative patients before treatment) in

the second week of treatment. Analysis of smear groups one and two were limited by the small proportion of patients who had a positive sputum culture after seven days of treatment. In these two groups only 10/36 patients had a culture positive specimen after 7 days of treatment. The median TTD-TB for these specimens was 17 days (interquartile range 14-22). In contrast 25/26 (96%) smear group 3 patients and all smear group 4 patients had a culture-positive specimen after treatment had started.

Figures 1 and 2 each show the percentage of patients in groups 3 and 4 in whom TTD-TB was 14 days or more, by duration of therapy. A patient was only deemed to have a TTD-TB >14 days once the TTD-TB of all subsequent specimens had exceeded 14 days. Before treatment, none of the patients in smear groups 3 or 4 had a TTD-TB $\geq$14 days. A median of 15 days of treatment (interquartile range 13-23 days) was required before the TTD-TB in specimens from group 3 patients had increased to 14 days. Twenty-five days of treatment (interquartile range 16-33 days) was required to achieve this TTD-TB in group 4. There was a stronger correlation between duration of treatment and TTD-TB than sputum smear grade, as shown for smear group 4 patients in figures 3 and 4. Spearman's correlation coefficient for duration of treatment and TTD-TB in specimens from smear group 4 patients was 0.801 ($p<0.01$), while that for duration of treatment and smear grade was -0.552 ($p<0.01$).

DISCUSSION

In 2003 New Zealand adopted guidelines similar to those published by the USA Centers for Disease Control and Prevention. The guidelines advocate

respiratory isolation for patients with pulmonary tuberculosis until appropriate therapy has been established, clinical improvement has occurred and three sputum samples on separate days have become smear negative.[2-4] Other authorities recommend isolation for 14 days after starting effective treatment.[16] It often takes many weeks for patients with severe PTB to become sputum smear negative. Smears can remain positive long after sputum cultures have become negative, and some patients remain smear positive for many weeks despite a dramatic reduction in viable organisms.[9,17] Thus, there are strong grounds for suspecting that the AFB smear is a poor measure of infectivity after effective treatment has started. Despite this, there has been no recent information to help resolve dissatisfaction with the present guidelines.[1,18]

Although TTD-TB is useful in predicting TB treatment outcome and detecting non-responders,[19] to our knowledge, it has not previously been used to estimate the time required in respiratory isolation. In the present study we have demonstrated that TTB-TB correlates well with pre-treatment sputum smear grade, and with duration of treatment. We believe it is logical to end respiratory isolation once the TTD-TB of sputum from smear positive patients has increased to that of smear negative patients. Unfortunately, an individual patient's TTD-TB cannot be used to determine the duration of respiratory isolation because of delay in obtaining TTD-TB results: these are only known once the cultures become positive. We have therefore used group TTD-TB results (with allocation to a particular group based on the highest pre-treatment sputum smear grade) in making the recommendations that follow.

New recommendations for the duration of respiratory isolation

Our recommendations, for patients at low risk of drug resistance or with proven drug susceptible isolates, are shown in table 3. Patients were grouped according to clinical indicators and the pre-treatment sputum smear grade. For patients with non-extensive, non-cavitatory disease, we used each group's treatment period required to increase the *median* TTD-TB to ≥14 days to decide when isolation should end. With TB treatment, TTD-TB rapidly increased in smear group 1 and 2 patients to that of smear negative patients who had received no treatment. We interpret this as showing that it is safe for patients with smear grades 1 and 2 to receive treatment with only a week in respiratory isolation, provided the clinical situation is appropriate, and the risk of drug resistance is low. Similarly, group 3 patients could be released from isolation after 14 days' treatment (figure 1). The results of drug susceptibility testing should be available about this time. A median of 25 days of treatment was required in smear group 4 patients to achieve a TTD-TB ≥ 14 days. We believe it is reasonable, in a group 4 patient with a susceptible isolate and disease which is not severe radiologically, who has improved clinically and is no longer coughing, to be discharged after 25 days of respiratory isolation.

Patients with extensive PTB or cavitatory PTB have a greater bacterial load and are more infectious than cases with lesser radiological disease.[20] Therefore we recommend that in this group a more conservative approach be used. For such cases, it may be appropriate to base the duration of isolation on the duration of treatment required for *90% of the group* to achieve a TTD-

TB of 14 days. This was 28 days in group 3 and 42 days in group 4 patients (figures 1 and 2). There were 8/26 (31%) smear group 3 patients and 17/81 (21%) smear group 4 patients who were considered to have severe disease on radiological or clinical grounds.

The impact of new recommendations for the duration of respiratory isolation: number of days of isolation saved.

To measure the reduction in respiratory isolation that would have occurred in our study population, we compared the duration of hospital stay to the duration of isolation based on our new recommendations. Duration of hospital stay was used as a surrogate for total duration of respiratory isolation. However, some patients were isolated at home because they met criteria that made this appropriate[2] Thus, duration of hospital stay under-estimates the actual duration of respiratory isolation.

Most patients in this study would have had significant reductions in respiratory isolation had our recommendations been in use, although 26/143 (18%) patients would have required a median of five extra days (interquartile range 3-7) of isolation. We estimate that 1516 days of respiratory isolation could have been saved in 143 patients (table 4); even when the patients who would have required a longer duration of isolation are taken into account. The most significant potential for reduction in duration of isolation was found in the patients with severe or extensive disease. In smear group 3, 201 days would have been saved in 8 such patients compared to a reduction of only 124 days in the remaining 18 patients. In smear group 4, 424 days would have been

saved in 17 patients with severe or extensive disease, compared to 545 days in the remaining 64 patients.

The main weakness of this study is that it does not directly address infectivity. We have made the assumption that smear positive patients (on treatment) who have a TTD-TB of > 14 days are no more infectious than smear negative patients who have the same TTD-TB. We note that the present guidelines make a similar assumption based on sputum smear status.[2-4] The validity of our recommendations for respiratory isolation could be tested by a prospective study that utilises our recommendations and measures the incidence of tuberculosis in close contacts of infectious cases.

Of possible concern is the fact that, in our model, sputum specimens from many patients would remain culture positive when released from isolation. However, further isolation until sputum smears become negative does not ensure culture conversion.[21] Thus, we suspect that culture conversion, like smear conversion, is a relatively blunt instrument in many cases, for determining infectious potential. We suspect that infectious potential ends before smear and culture conversion. Indeed, previous studies have suggested that most transmission of infection occurs before the diagnosis of TB has been made.[22,23]

Prolonged isolation comes at considerable cost to individuals as well as to health-care providers, and the rationale for this has been seriously questioned.[1,18] While the need for three smear negative sputum specimens

before removal from isolation is an appropriate measure for the control of outbreaks of multi-drug resistant TB, its use is questionable in other settings. In this study we have shown how TTD-TB could be used to estimate when sputum smear positive patients will have the same infectious risk as smear negative, culture positive patients, provided the isolate is susceptible to standard first-line agents and patients are cough-free. TTD-TB can be used to guide the decision about when it is safe to stop respiratory isolation. We recommend that this includes raising the TTD-TB criterion for ending isolation for subjects with initially severe pulmonary disease to the duration of treatment required for 90% of the particular smear group to achieve a TTD-TB of $\geq$14 days (rather than *median* TTD-TB of that group).

The new recommendations are based on clinical indicators and the pre-treatment sputum smear grade. They enable the duration of respiratory isolation to be predicted early in the treatment course (albeit with the caveat that satisfactory clinical and/or radiological improvement occurs). We believe that this approach would considerably reduce the number of days of respiratory isolation. Using TTD-TB, isolation may end before sputum becomes smear negative, with considerable benefits to patients and health-care providers.

STATEMENT OF INTEREST

No grants or gifts were received. None of the authors has a financial or other potential conflict of interest relating to matters in this study.

REFERENCES

1. Iseman M. An unholy trinity - three negative sputum smears and release from tuberculosis isolation. Clin Infect Dis 1997;25:671-2

2. Paterson A, McEnnis V, Martin P, et al. Infection control in tuberculosis [monograph on the Internet]. New Zealand Ministry of Health; 2003. Available from: http://www.moh.govt.nz/moh.nsf/0/4760DF3580A6F5B5CC256C86006ED394/$File/9.InfectioncontrolinTB.pdf

3. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. MMWR Morbid Mortal Weekly Rep 2005;54(RR-17):1-141

4. Centers for Disease Control and Prevention. Controlling tuberculosis in the United States. MMWR Morbid Mortal Weekly Rep 2005;54(RR-12):1-81

5. Sepkowitz K. How contagious is tuberculosis? Clin Infect Dis 1996;23:954-62

6. Liippo K, Kulmala K, Tala E. Focusing tuberculosis contact tracing by smear grading of index cases. Am Rev Respir Dis 1993;148:235-6

7. Shaw J, Wynn-Williams N. Infectivity of pulmonary tuberculosis in relation to sputum status. Am Rev Tuberc 1954;69:724-33

8. Davies B. Infectivity of tuberculosis. Thorax 1980;35:481-2

9. Hobby G, Holman A, Iseman M, Jones J. Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. Antimicrob Agents Chemother 1973;4:94-104

10. Yeager H, Lacy J, Smith L, LeMaistre C. Quantitative studies mycobacterial populations in sputum and saliva. Am Rev Respir Dis 1967;95:998-1004

11. Behr M, Warren S, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear negative for acid-fast bacilli. Lancet 1999;353:444-9

12. Jindani A, Aber V, Edwards E, Mitchison D. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 1980; 121:939-49

13. Jindani A, Dore C, Mitchison D. Bactericidal and sterilizing activities of antituberculosis drugs during the first 14 days. Am Rev Respir Dis 2003;167:1348-54

14. Pfyffer GE, Brown-Elliott B, Wallace R. *Mycobacterium:* General characteristics, isolation and staining procedures. In Murray P, Barron E,

Jorgensen J, Pfaller M and Yolken R, editors. Manual of clinical microbiology 8th edition. Washington, D.C: ASM press; 2003. p. 532-59

15. Mixides G, Shende V, Teeter LD, Awe R, Musser JM and Graviss EA. Number of negative acid-fast smears needed to adequately assess infectivity of patients with pulmonary tuberculosis. Chest 2005;128:108-15

16. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Thorax 1998;53:536-8

17. Al-Moamary M, Black W, Bessuille E, et al. The significance of the persistent presence of acid-fast bacilli in sputum smears in pulmonary tuberculosis. Chest 1999;116:726-31

18. Winters R. Guidelines for preventing the transmission of tuberculosis: A better solution? Clin Infect Dis 1994;19:309-10

19. Epstein M, Schluger N, Davidow A, et al. Time to detection of *Mycobacterium tuberculosis* in sputum culture correlates with outcome in patients receiving treatment for pulmonary tuberculosis. Chest 1998;113:379-86

20. Marks SM, Taylor Z, Qualls NL, et al. Outcomes of contact investigations of infectious tuberculosis patients. Am J Respir Crit Care Med. 2000;162:2033-8

21. Long R, Bochar K, Chomyc S, et al. Relative versus absolute noncontagiousness of respiratory tuberculosis on treatment. Infect Control Hosp Epidemiol 2003;24:831-8

22. Gunnels J, Bates J, Swindoll H. Infectivity of sputum-positive tuberculous patients on chemotherapy. Am Rev Respir Dis 1974;109:323-30

23. Kamat S, Dawson J, Devadatta S, et al. A controlled study on the influence of the segregation of tuberculosis patients for one year in a five-year period in close family contacts in South India. Bull WHO 1966;34:517-32

TABLES

Table 1. Characteristics of study patients with pulmonary tuberculosis.

Smear Group	0	1	2	3	4
Sputum smear*	0 AFB/ 300 hpf	1-9 AFB/ 100 hpf	1-9 AFB/ 10 hpf	1-9 AFB/ hpf	>9 AFB/ hpf
Number of patients	118	21	15	26	81
Female (%)	56 (47)	8 (38)	5 (33)	15 (58)	47 (58)
Mean age +/- standard deviation (range)	41 +/-18 (15-90)	32 +/- 14 (15-59)	45 +/- 23 (19-93)	46 +/- 21 (17-81)	43 +/- 18 (18-86)
Median duration of inpatient isolation: days (interquartile range)		9 (3-15)	17 (11-21)	27 (18-37)	38 (27-53)

*Smear grade was determined from the highest pre-treatment sputum smear AFB count, using Ziehl-Neelsen stain. AFB= acid fast bacilli. hpf=high power field.

Table 2. The effect of TB treatment on time to detect drug susceptible *M tuberculosis* in liquid culture (TTD-TB).

		Days of treatment						
		Day 0	Day 8-14	Day 15-21	Day 22-28	Day 29-35	Day 36-42	Day ≥43
Smear group 0	Number of patients	118						
	Number of specimens	317						
	Median TTD-TB (interquartile range) (days)	14 (12-20)						
Smear group 1	Number of patients	21	6					
	Number of specimens	53	14					
	Median TTD-TB (interquartile range) (days)	11 (9-14)	15 (13-18)					
Smear group 2	Number of patients	15	4					

	Number of specimens	40	14					
	Median TTD-TB (interquartile range) (days)	9 (8-12)	19 (15-22)					
Smear group 3	Number of patients	26	16	13	12	7		
	Number of specimens	52	26	31	22	20		
	Median TTD-TB (interquartile range) (days)	7 (6-8)	14 (12-16)	15 (14-18)	16 (14-18)	19 (16-20)		
Smear group 4	Number of patients	81	63	54	50	40	32	26
	Number of specimens	186	84	90	92	83	52	94
	Median TTD-TB (interquartile range) (days)	5 (4-6)	11 (9-13)	14 (12-17)	14 (12-16)	15 (14-18)	17 (13-19)	19 (16-22)

Table 3. Recommended duration of isolation* for patients with pulmonary tuberculosis at low risk for drug resistance or with known susceptible isolates†, based on pre-treatment sputum smear grade

Initial Smear Grade	Duration of isolation for non-severe disease‡ (provided satisfactory clinical improvement occurs)	Duration of isolation for severe disease§ (extensive cavitation /frequent or severe cough/minimal clinical improvement)
0	0 days	Until clinical improvement
1	7 days	Until clinical improvement after 7 days
2	7 days	Until clinical improvement after 7 days
3	14 days	28 days
4	25 days	42 days

*duration of isolation is based on number of days of treatment required to increase TTD-TB to ≥ 14days.

†if drug resistance is suspected, respiratory isolation should continue until isolate known to be susceptible.

‡ based on the time taken for 50% of patients to achieve TTD-TB ≥ 14 days (figures 1 and 2)

§ based on the time taken for 90% of patients to achieve TTD-TB≥ 14 days (figures 1 and 2)

Table 4. The reduction in the duration of respiratory isolation in patients with sputum smear positive pulmonary tuberculosis using a newly proposed system based on TTD-TB data.

Smear Group	1	2	3	4	Total
Number of patients	21	15	26	81	143
Days of respiratory isolation using proposed system*	7	7	14 (28)	25 (42)	
Median duration of hospital stay (days)	9	17	27	38	
Number of days of respiratory isolation saved	56	166	325	969	1516

* In smear groups 3 and 4 patients with severe disease, a longer duration of isolation is recommended as shown in brackets.

FIGURE LEGENDS

Figure 1. The duration of treatment and development of (1) TTD-TB $\geq$14 days and (2) sputum smear negativity, in sputum group 3 patients; p=0.03 (Wilcoxon Signed-Rank test).

Figure 2. The duration of treatment and development of (1) TTD-TB $\geq$14 days and (2) sputum smear negativity, in sputum group 4 patients; p=0.003 (Wilcoxon Signed-Rank test).

Figure 3. Sputum smear results versus duration of treatment in smear group 4 patients.
Line of best fit (solid line) and 95% confidence intervals (hatched lines) are shown; Spearman's correlation coefficient for sputum smear and duration of treatment = - 0.552 ($p<0.01$).

Figure 4. The time to detect tuberculosis in liquid culture (TTD-TB) versus treatment duration in smear group 4 patients.

Line of best fit (solid line) and 95% confidence intervals (hatched lines) are shown; Spearman's correlation coefficient for TTD-TB and treatment duration = 0.801 ($p<0.01$).

FIGURES

Figure 1.

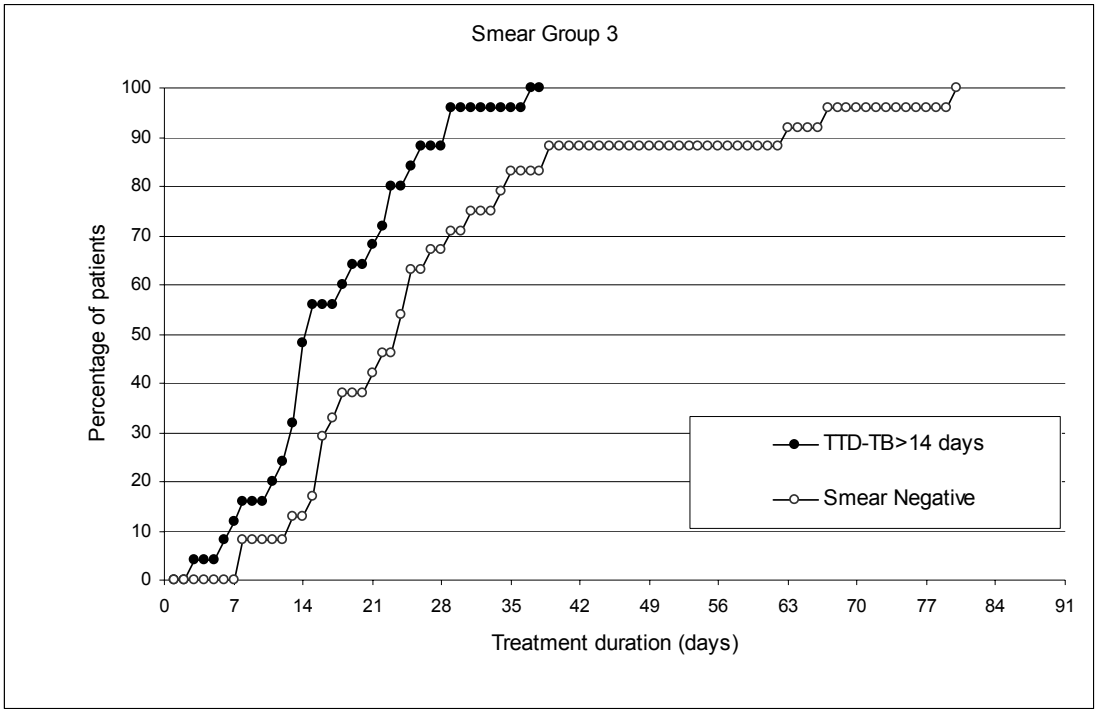


Figure 2.

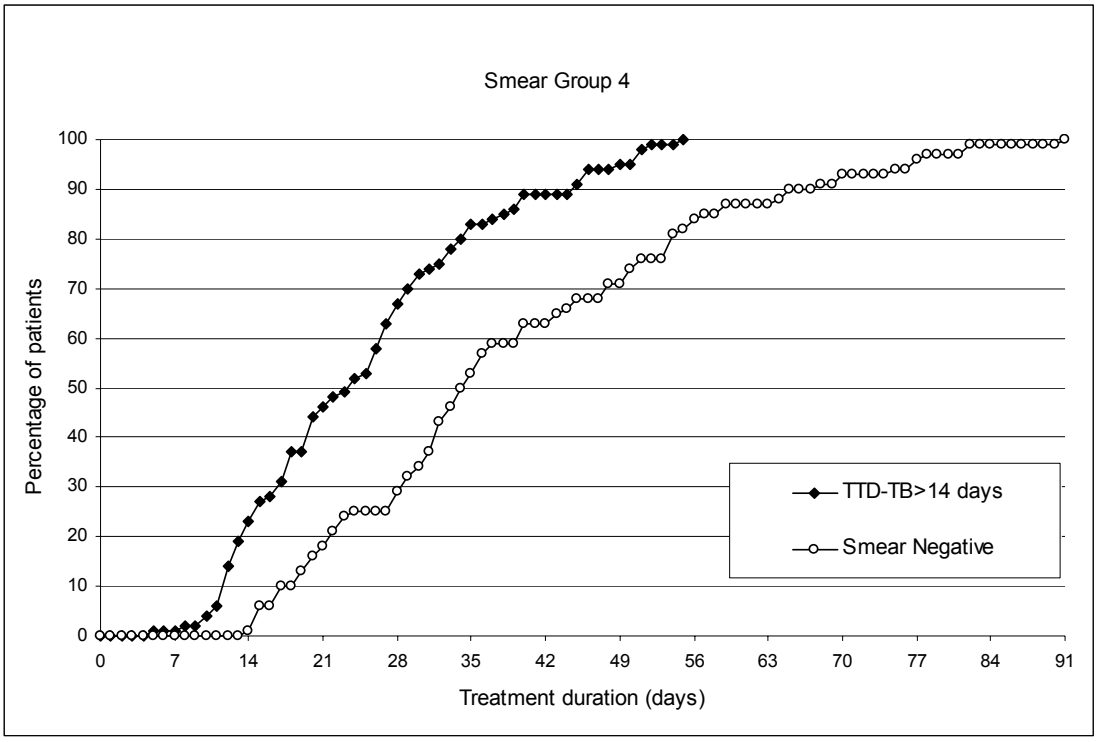


Figure 3.

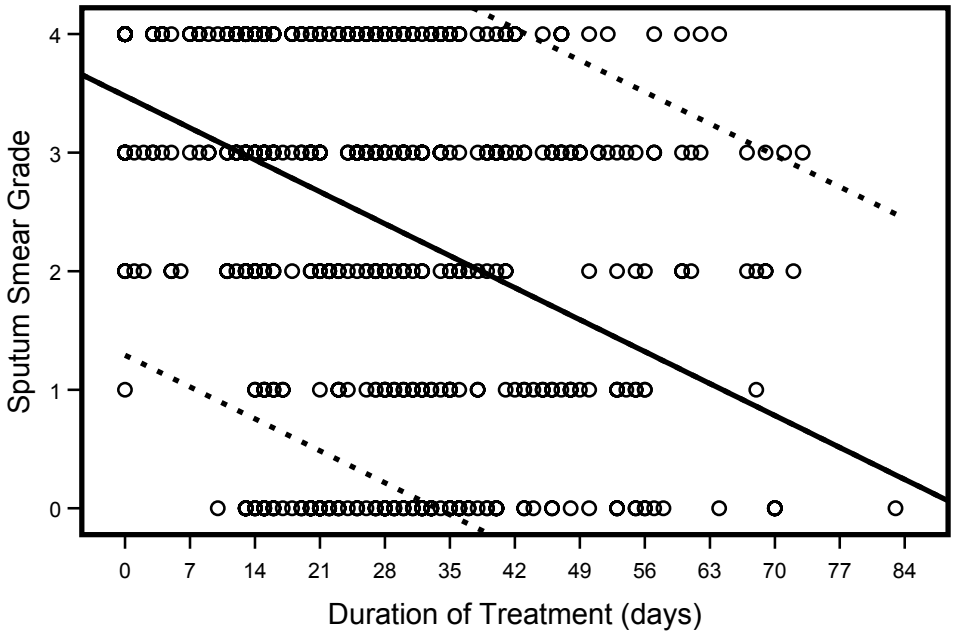
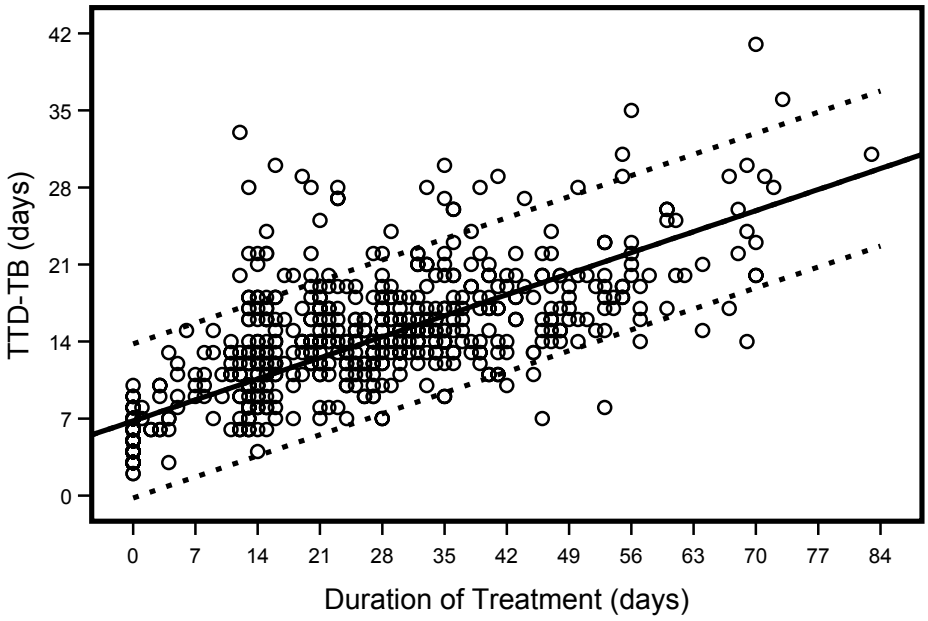


Figure 4.


TTD-TB (days)
42
35
28
21
14
7
0
0
7
14
21
28
35
42
49
56
63
70
77
84
Duration of Treatment (days)