

Outcome of first-line tuberculosis treatment in migrants from Vietnam

International Organization for Migration Tuberculosis Working Group*

SUMMARY

SETTING: Screening and treatment of tuberculosis in prospective migrants from Vietnam, in the framework of the Orderly Departure Programme.

OBJECTIVE: 1) To describe the outcome of first-line tuberculosis treatment, and 2) to investigate the role of prognostic factors on treatment outcome.

DESIGN: Cohort of consecutive smear-positive patients identified by screening before departure, and followed up until cure or failure, for a maximum of two years.

RESULTS: Seven hundred and twenty-nine patients were consecutively diagnosed with infectious tuberculosis. Patients received directly observed treatment with rifampicin, isoniazid, ethambutol and pyrazinamide for a minimum of 6 months, or until sputum conversion was maintained for 6 consecutive months. The cumulative

percentage of cure with first-line treatment was 50.2% (SE = 2%) at 7 months, and 92.8% (SE = 2%) at 24 months. Young patients without cavities achieved the highest percentage of cure. Stratified testing confirmed the negative effect on the chance of cure of age >45 years ($P < 0.001$), and cavities ($P < 0.001$), while the effect of previous treatment was not significant ($P = 0.105$).

CONCLUSIONS: While the overall cure rate was satisfactory, older patients and those with cavities required prolonged treatment and reached a less satisfactory level of cure.

KEY WORDS: tuberculosis; immigrants and emigrants; Vietnam

TUBERCULOSIS IS A MAJOR public health problem in South-East Asia. The World Health Organization (WHO) estimated that out of 3.8 million cases reported in the world in 1990, 49% were in South-East Asia.¹ The situation is particularly severe in Vietnam, due to the disruption of communicable disease control during the war, and the difficulty of rebuilding a public health infrastructure once the war ended. In 1973-1974, a mass survey of individuals with cough, conducted by the Tuberculosis Control Institute, revealed 2.5 smear-positive persons per 1 000 population.² In South Vietnam, from 1986 to 1992, the National Tuberculosis Control Programme reported a rate of 100 new smear-positive cases per 100 000 population. Currently, the probability that an uninfected individual will become infected with *Mycobacterium tuberculosis* within one year is 3.2% in the age group 15-19, and is declining very slowly over time.³

In the aftermath of the Vietnam war, about 1.5 million people fled Vietnam and found refuge in the United States, Canada, Australia, and other Western countries, often after months or years spent in refugee

camp. In 1979, the Vietnamese Government and the United Nations High Commissioner for Refugees established the Orderly Departure Programme in order to stop hazardous departures by sea, and to provide those who qualified for migration (mainly cases who could be reunited with their families) with an opportunity to do so in a regular and organized fashion. As part of the prerequisites for migration, eligible persons underwent medical screening in Ho-Chi-Minh City. Those with active tuberculosis were treated with directly observed chemotherapy, short-course (DOTS).⁴

We report the outcome of first-line chemotherapy in 729 smear-positive prospective migrants treated consecutively from 1 November 1992 to 31 October 1994. Successful treatment or failure to be cured are the two possible outcomes of first-line tuberculosis treatment. As opposed to other studies reporting only the total percentage of cure, we used a methodology that permitted an analysis of the occurrence of these two competing events over time, and of the role of potential prognostic factors. The implications of

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these results for tuberculosis control in migrants are also discussed.

PATIENTS AND METHODS

The International Organization for Migration (IOM) has been responsible for the screening and treatment of tuberculosis in refugees and prospective migrants from Vietnam since 1979, first in refugee camps and later in Vietnam.⁵ The programme has been described in detail elsewhere.⁶ Briefly, prospective migrants from Vietnam underwent medical screening before departure, according to the requirements of receiving countries, in two hospitals in Ho-Chi-Minh City. Receiving countries (mainly the United States, Australia and Canada) applied stringent criteria for the diagnosis of tuberculosis in prospective migrants, and in particular required a prolonged period of consistent smear negativity before considering a patient cured and authorizing migration.⁴ The main aspects of the screening and treatment programme are presented below.

As part of pre-departure medical screening a chest X-ray was taken; if it was compatible with active tuberculosis, sputum was collected on three consecutive days, and smear-positive cases were treated. Treatment was administered daily, under direct supervision by medical staff, in the premises of the two main hospitals in Ho-Chi-Minh City—30th April and Cho-Ray. The initial treatment of smear-positive patients consisted of isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z) for two months (2HREZ). If sputum conversion occurred at the second month, pyrazinamide could be discontinued, while isoniazid, rifampicin and ethambutol were continued for an additional four months (4HRE). If smear results were consistently negative, the case was considered cured after 6 months of treatment. Cases who did not have a negative sputum smear at the second month, or whose sputum smears were intermittently positive, continued treatment with RHEZ until either bacteriological conversion was maintained for at least 6 consecutive months or treatment with second-line drugs was started (adding capreomycin, cycloserine, ethionamide, ofloxacin, and stopping rifampicin). In summary, cure with first-line drugs was achieved after 6 months of DOTS in early converters, and after at least 8 months in those who converted after the second month.

Sputum smear examination was repeated every second week for the first 2 months, then monthly to monitor treatment effect; X-rays were repeated every 2 months. As in most developing countries, sputum culture for diagnostic purposes and for sensitivity testing was not readily available in Vietnam. Sputum specimens of the most difficult cases were sent for analysis to the laboratory of the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

All patients with infectious tuberculosis who were started on antituberculosis treatment were entered in a database that was regularly updated. The following information was routinely recorded: sex, age, previous antituberculosis treatment at any time in the past and its duration, initial X-ray results, monthly smear results, type and dosage of antituberculosis drugs, severe side-effects requiring treatment interruption, and final outcome.

Statistical analysis

For the purpose of this study, the following mutually exclusive outcomes were considered: 1) cure with first-line drugs (defined as smear results consistently negative for 4 months if sputum conversion occurred within the first 8 weeks of treatment, or for 6 months if it occurred subsequently); and 2) failure to be cured with first-line treatment, including the need to switch to second-line treatment, patient non-adherence, severe side-effects requiring treatment interruption, and death. The availability of the exact date of the first of all possible treatment-related events permitted the occurrence of cure or failure over time to be described in terms of cumulative incidence (CI) curves,⁷ i.e., the accumulating percentage of either event over time, assessing cure and failure as competing treatment outcomes. The estimated standard error (SE) of the CIs at specified time-points was also reported.

The time to cure or failure extended from the beginning of first-line treatment to either cure or failure, whichever occurred first. If neither outcome occurred (patient still on treatment with first-line drugs), the observation was recorded at the time of the last update of the database (31 October 1994 for all patients); thus all patients in the programme contributed to the analysis, irrespective of duration of follow-up.

To assess the effect of selected factors, such as presence of cavities, on the chances of cure, appropriate statistical testing was conducted comparing cumulative incidences of cure among sub-groups of interest.⁸ The methodology extends to stratified tests, which allow the same comparison but within strata of patients who share the same characteristics (e.g., a test of the effect of the presence of cavities versus no cavities among younger men, older men, younger women and older women would correspond to a test of the effect of cavities stratified by age and sex). In this way the effect of potential confounders (such as age and sex) can be removed from the comparison of interest (such as patients with versus those without cavities). A similar testing procedure was not performed on cumulative incidence of failure because the number of events was too small.

Comparison of distribution of characteristics of interest among sub-groups of patients was performed by χ^2 test. All reported *P*-values are two-sided.

Table 1 Main demographic and clinical characteristics of the study sample

	<i>n</i>	%
Age (years)		
≤30	245	33.6
31–45	133	18.2
46–60	183	25.1
≥61	168	23.1
Sex		
Male	487	66.8
Female	242	33.2
Previous tuberculosis treatment		
No	504	69.1
Yes	225	30.9
Presence of cavities on X-ray		
No	620	85.1
Yes	109	14.9

RESULTS

From 1 November 1992 to 31 October 1994, 131 241 prospective migrants were screened for tuberculosis before their departure from Vietnam. During this period, a total of 729 consecutive persons were diagnosed as having infectious tuberculosis—a prevalence of 556 per 100 000 screened—and started directly observed, short-course chemotherapy; 82% of cases were bound for the United States, 16% for Canada, and 2% for Australia.

Table 1 details patients' characteristics. The median age was 44 years (range 8–86 years) for all patients, and 47 and 38 years, respectively, for males and females. The duration of previous tuberculosis treatment was available for 212 out of 225 patients, with a median of 7 months (range 1–25 months). Finally, in our cohort only one patient, who later switched to second-line treatment, was positive for the human immunodeficiency virus (HIV).

Table 2 suggests a strong association between the age of the patients, previous tuberculosis treatment

and the presence of cavities on X-ray. Patients aged over 45 had more often received previous treatment than patients aged 15 or less (39.3% vs. 23.0%, $P < 0.0001$) and more frequently presented with cavities (18.2% vs. 11.9%, $P = 0.017$). Patients with previous tuberculosis treatment also presented more frequently with cavities than those without previous treatment (25.6% vs. 11.1%, $P < 0.0001$).

At the end of two years, and ignoring the timing of the events, 207 patients were still on treatment while 522 had reached an outcome: cure with first-line treatment (481), switch to second-line treatment (19), patient non-adherence (14), treatment interruption due to severe side-effects (2), and death (6). In subsequent analyses, the distinction between various types of first-line treatment failure has been ignored.

Table 3 details the overall cumulative percentages of cure and failure for the entire sample, represented graphically in Figure 1 for the whole follow-up period. The cumulative percentage of cure at 7 months was 50.2% (SE = 2%); it was 88.5% (SE = 2%) at 18 months. The overall programme yield with first-line treatment was 92.8% (SE = 2%) at 24 months. After the sixth month of treatment 2.9% (SE = 1%) of patients had failed; this percentage reached 7.2% (SE = 1%) by the fourteenth month.

Table 4 details the percentage of cure according to age and presence of cavities. As can be observed very clearly from Figure 2, younger patients without cavities achieved the highest percentage of cure, as opposed to older patients with cavities who fared the worst, reaching the lowest cure rates at the slowest pace. Being old only, or presenting cavities only, yielded CIs of cure somewhere between these two extremes. The interpretation of the estimated CIs is less reliable beyond the first year, due to the relatively small number of events. Figure 3 similarly displays the complementary CI curves for failure.

With the purpose of identifying those factors that

Table 2 Cross-tabulations of age, presence of cavities and previous tuberculosis treatment

	Number with characteristic	Total in group	%	<i>P</i>
Previous tuberculosis treatment according to age				
Age (years)				
≤45	87	378	23.0	<0.0001
>45	138	351	39.3	
Presence of cavities on X-ray according to age				
Age (years)				
≤45	45	378	11.9	0.017
>45	64	351	18.2	
Presence of cavities on X-ray according to previous tuberculosis treatment				
Previous tuberculosis treatment				
No	56	504	11.1	<0.0001
Yes	53	225	25.6	

Table 3 First-line treatment: cumulative percentages of cure and failure

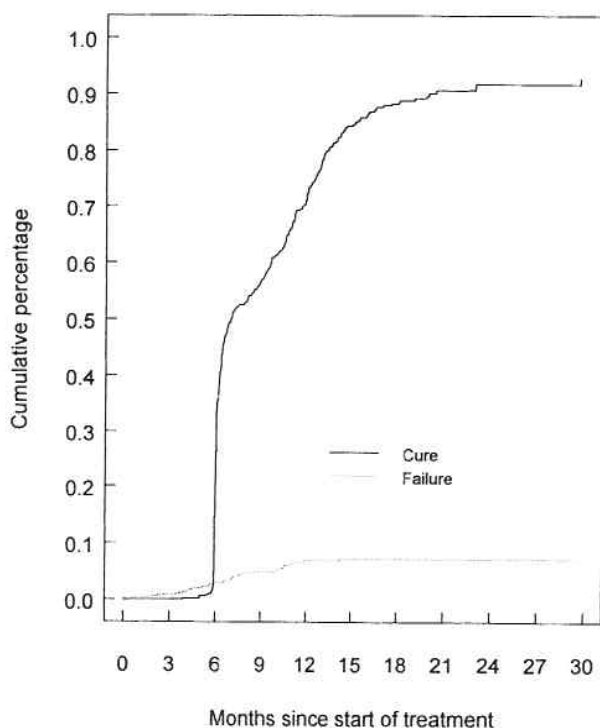
	Months								
	3	6	7	8	9	12	14	18	24
Cure*	—	26.3	50.2	53.0	58.2	70.4	82.1	88.5	92.8
Failure†	0.8	2.9	3.3	4.4	5.0	6.9	7.2	—	—

* SE \leq 2% at all time points.† SE \geq 1% at all time points.

affected the chance of cure, we tested the effect of sex ($P = 0.972$), age below or above 45 years ($P \leq 0.001$), cavities ($P \leq 0.001$), and previous treatment ($P \leq 0.001$). The latter three necessary factors were retained for a further analysis in order to assess whether the role of each was maintained after allowance for the other two. Stratified testing confirmed the effect on the cumulative percentage of cure over time of age ($P \leq 0.001$) and of cavities ($P \leq 0.001$), but not of previous treatment ($P = 0.105$).

DISCUSSION

As stated in the Introduction, tuberculosis remains a serious problem in Vietnam, due to the legacy of the war and to the difficult economic situation experienced after the war.⁹ Our survey of prospective migrants found a prevalence of 556 smear-positive cases per 100 000, higher than that of 100 per 100 000 reported by the Tuberculosis and Lung Disease Centre, probably because of the active case-finding performed in our programme and the relatively

**Figure 1** Cumulative percentages of cure and failure.

high representation of elderly persons among the prospective migrants.

The results of this study further confirmed the effectiveness of directly observed short-course chemotherapy for tuberculosis. Two essential factors of successful treatment, compliance and supervision, were present in our programme: patients were highly motivated to adhere to treatment in order to be allowed to migrate, and destination countries made sufficient resources available to run a highly supervised programme, with unusually frequent controls of clinical and bacteriological parameters. It has to be stressed that the programme applied particularly strict requirements in terms of diagnosis, treatment, monitoring, and evaluation of treatment outcome, because receiving countries feared to admit migrants with active tuberculosis, creating a potential risk for themselves and the local population. As the programme employed far more resources than are normally available to national tuberculosis programmes in developing countries, it should not be considered an appropriate option at the community level, although in the present case it permitted DOTs to be evaluated in a rigorously controlled situation.

The overall cure rate with first-line treatment reached 92.8%, in line with the results of model programmes in developing countries.¹⁰⁻¹² However, it should not be overlooked that a cure rate of 70.4% was reached at one year, and that the additional 20% of cure was accumulated only after a further 12 months of treatment. The analytical approach used in this paper has allowed the dynamics of the response to first-line tuberculosis treatment and the identification of sub-groups presenting special behaviour to be described over time. The curve describing the overall cumulative percentage of cure showed that a good proportion of patients (50%) reached cure by the seventh month of treatment; after this time the percentage of cure increased at a slower rate. A sub-group analysis provided one element that may explain this behaviour: older age and the presence of cavities considerably delayed the response to treatment. On the other hand, the fact that when stratifying for age and presence of cavities the prognostic value of previous

Table 4 First-line treatment: cumulative percentages of cure according to age and presence of cavities on X-ray

	6 months % \pm SE	12 months % \pm SE	18 months % \pm SE
Age \leq 45 years			
Cavities			
No	29.3 \pm 0.5	81.2 \pm 1.0	93.7 \pm 1.5
Yes	7.7 \pm 2.5	59.8 \pm 8.0	89.7 \pm 10.0
Age > 45 years			
Cavities			
No	30.7 \pm 3.0	69.6 \pm 3.0	86.6 \pm 3.0
Yes	5.6 \pm 3.0	48.8 \pm 8.0	69.9 \pm 8.0

SE = standard error.

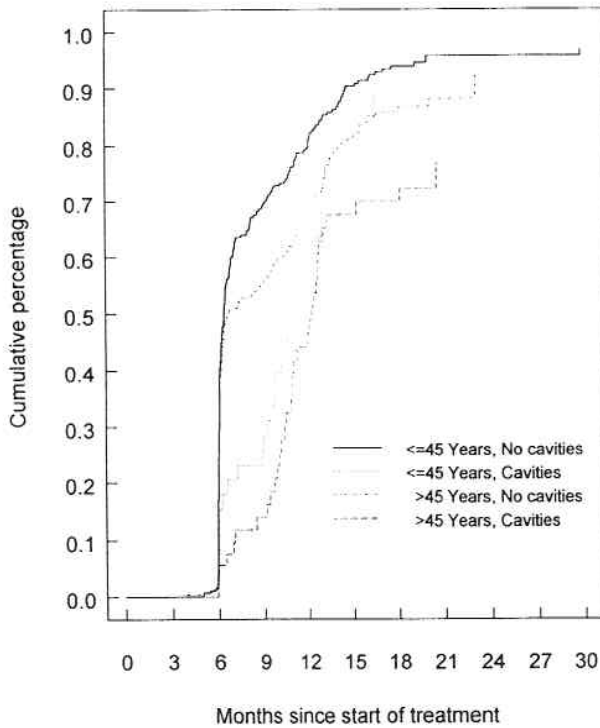


Figure 2 Cumulative percentages of cure according to age and presence of cavities.

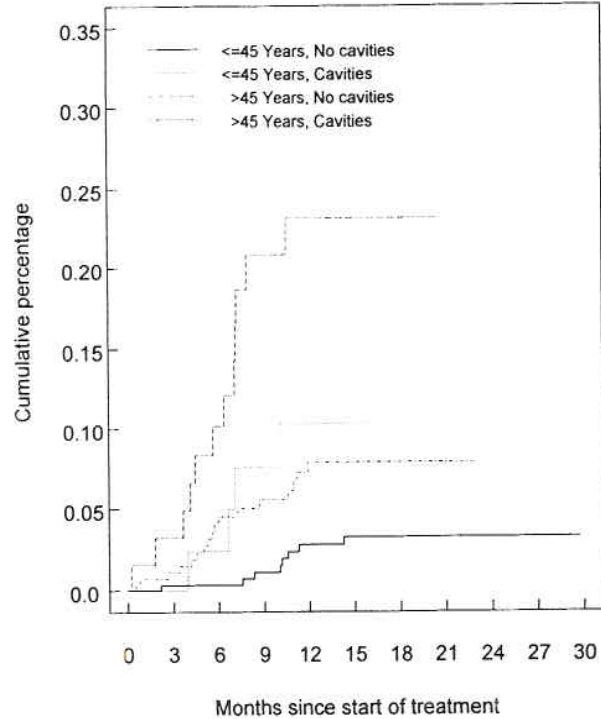


Figure 3 Cumulative percentages of failure according to age and presence of cavities.

tuberculosis treatment disappeared suggests the following considerations. The first obvious epidemiological explanation is that age and cavities act as confounders of what turns out to be a spurious association between outcome and previous treatment. The second, more clinical, implication is that exposure to previous treatment should not automatically be seen as synonymous with multidrug-resistant tuberculosis, as suggested by many authors,¹²⁻¹⁴ since given enough time 92.8% of patients are eventually cured. Further investigation is needed to clarify this issue.

International migration is increasingly a global phenomenon. During the 1980s, approximately 25-30 million people left their home country every year, including four million refugees, and there is no sign that this rate of flow will decrease.¹⁵ Tuberculosis control among immigrant groups has been the object of increasing attention in receiving countries, because a disproportionate number of new tuberculosis cases occurs in foreign-born persons.^{16,17} The adequacy of medical screening has been criticized, and a tightening of screening procedures overseas has been proposed. However, in spite of a very careful screening and treatment programme such as the one described in this paper, many cases will manifest only after migration because of the unique characteristics of the disease, such as reactivation of a dormant infection and transmission shortly before or after migration.¹⁸ We still know too little about the mechanisms at work and the groups exposed to the highest risk. A follow-up study of Vietnamese migrants to Australia is cur-

rently underway to clarify the specific risk factors for tuberculosis before and after migration. The results will be invaluable for tailoring follow-up programmes to the needs of immigrant communities in the first few years after arrival, when the highest incidence of tuberculosis is recorded.

Finally, tuberculosis control cannot be achieved in isolation. The WHO has convincingly demonstrated that tuberculosis is a world-wide emergency, with 90 million new cases and 30 million deaths expected in this decade.¹ In order to improve tuberculosis control in low prevalence countries, it is also imperative to assist high prevalence countries in their efforts to control tuberculosis. As Frieden put it: "... if we were as concerned today about tuberculosis in the developing world as we are about tuberculosis in the United States, we could prevent cases here and abroad for decades to come."¹⁹

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R É S U M É

CADRE : Dépistage et traitement de la tuberculose chez les candidats migrants du Vietnam, dans le cadre du Programme Régulier de Départ.

OBJECTIFS : 1) Description des résultats du traitement de première ligne de la tuberculose, et 2) investigation de l'influence des facteurs pronostiques sur les résultats du traitement.

SCHÉMA : Cohorte de patients consécutifs à bacilloscopie positive identifiée lors du dépistage avant leur départ, et suivis jusqu'à guérison ou échec pendant un maximum de deux ans.

RÉSULTATS : Le diagnostic de tuberculose contagieuse a été porté chez 729 patients consécutifs. Un traitement directement supervisé a été appliqué (rifampicine, isoniazide, éthambutol, pyrazinamide) pendant au moins

six mois ou jusqu'à ce que la négativation se soit maintenue pendant au moins six mois consécutifs. Le taux cumulatif de guérison après traitement de première ligne est de 50,2% (ES = 2%) à 7 mois et de 92,8% (ES = 2%) à 24 mois. Le pourcentage le plus élevé de guérison s'observe chez les jeunes patients non cavitaires. Un test par stratification confirme un effet négatif sur les chances de guérison pour l'âge >45 ans ($P < 0,001$) et pour la présence d'excavations ($P < 0,001$), alors que l'effet d'un traitement antérieur n'est pas significatif ($P = 0,105$).

CONCLUSIONS : Le taux général de guérison est satisfaisant. Toutefois les patients âgés et les porteurs de cavités nécessitent une prolongation du traitement et atteignent des taux moins satisfaisants de guérison.

R E S U M E N

MARCO DE REFERENCIA : Detección y tratamiento de los tuberculosos en los futuros inmigrantes de Vietnam, en el marco del Programa de Patida Regular.

OBJETIVO : 1) Describir el resultado del tratamiento de primera línea de la tuberculosis, y 2) investigar el papel de los factores de pronóstico en el resultado del tratamiento.

MÉTODO : Cohorte de pacientes consecutivos con esputo positivo diagnosticados por detección antes de la partida y seguidos hasta la curación o el fracaso, por un máximo de 2 años.

RESULTADOS : Se diagnosticaron 729 pacientes consecutivos como portadores de tuberculosis activa. Los pacientes recibieron un tratamiento directamente observado con rifampicina, isoniacida, etambutol y pirazinamida por un mínimo de 6 meses o hasta la conversión del

esputo mantenida por 6 meses consecutivos. El porcentaje acumulativo de curación con el tratamiento de primera línea fue del 50,2% (SE = 2%) a los 7 meses y de 92,8% (SE = 2%) a los 24 meses. Los enfermos jóvenes sin cavidades alcanzaron el mayor porcentaje de curación. Los tests estratificados confirmaron el efecto negativo de la probabilidad de curación de la edad mayor de 45 años ($P < 0,001$) y de la presencia de cavidades ($P < 0,001$), mientras que le efecto del tratamiento previo no fue significativo ($P = 0,105$).

CONCLUSIONES : Mientras la tasa general de curación fue satisfactoria, los enfermos adultos y aquellos con cavidades requirieron tratamientos más prolongados y alcanzaron un nivel menos satisfactorio de curación.