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Risk factors for delay in the diagnosis and treatment of tuberculosis at a referral hospital in Rwanda

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SUMMARY

SETTING: Kigali University Hospital, the main referral centre for TB in Rwanda.

OBJECTIVE: To evaluate delays in the diagnosis and treatment of tuberculosis (TB) and associated risk factors.

DESIGN: Prospective data collection of patients treated for pulmonary TB (PTB) or extra-pulmonary TB (EPTB) between June and September 2006.

RESULTS: Of 104 patients with a mean age of 35 years (range 17–84) recruited into the study, 62% were HIV-positive. EPTB was diagnosed in 60 cases. The median total, health care and patient delays were respectively 57, 28 and 25 days. The health system delay before referral was significantly longer than the delay at our institution (18 vs. 6 days, $P < 0.0001$). Risk factors for a longer health system delay at our institution were smear-negative PTB or EPTB (OR 5.12) and a trial of antibiotics (OR 2.96). The latter was also found to significantly prolong total delay (OR 2.85), as did rural residence (OR 4.86). No significant association was found between patient delay and age, sex, profession or health insurance status.

CONCLUSION: Smear-negative PTB and EPTB were associated with longer health system delays. A trial of antibiotics significantly increased the health system delay. Its use, recommended by the World Health Organization in case of smear-negative TB and EPTB in developing countries, needs validation at the tertiary health care level.

KEY WORDS: tuberculosis; antibiotic trial; diagnostic delay; reference level; Rwanda

DELAYS in tuberculosis (TB) treatment can result in a higher risk of morbidity and mortality as well as a higher risk of transmission of the disease in the community. Early diagnosis and effective treatment are the two key factors in effective TB control. Delays in diagnosis and treatment of TB have been described in both high and low prevalence countries with considerable variations in time, from 8.1 weeks in New York,[1] to 12 weeks in Botswana[2] to 16 weeks in Ghana.[3] Most of these studies report on smear-positive pulmonary TB (PTB) only. We found only two reports, both from high-income countries, that also included smear-negative TB and EPTB cases.[1,4]

The incidence of smear-negative TB and EPTB in sub-Saharan Africa is steadily rising, mainly due to the spread of the human immunodeficiency virus (HIV) pandemic.[5] The lack of rapid, simple and accurate diagnostic tools for smear-negative TB and EPTB may play a key factor in delaying timely diagnosis and treatment.[5]

The present study was designed to investigate risk factors for delays in diagnosis and treatment of all TB cases, including smear-negative TB and EPTB, in the main referral hospital of Rwanda, a small East African country with a TB incidence of 89 per 100 000 population[6] and an HIV prevalence of 3% in 2005.[7]

PATIENTS AND METHODS

The protocol was approved in writing by the Research Committee of the Kigali University Hospital (Centre Hospitalier Universitaire de Kigali, CHUK) and the Faculty of Medicine of the National University of Rwanda.

Study setting

The present study was conducted at the CHUK, one of the three tertiary hospitals in Rwanda. Situated in the centre of the capital, the CHUK is Rwanda's main referral hospital, receiving patients from the various health centres in the district as well as patients from all over the country. At the time of our study, the CHUK, although a tertiary hospital, was also delivering secondary health care service, as this level of care was inexistent in the district.

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Study design and subjects

After verbal consent was obtained a questionnaire survey was conducted by interviewing newly diagnosed patients with PTB or EPTB at the Department of Internal Medicine, CHUK, between 1 July and 1 September 2006. Inclusion criteria were age >15 years, diagnosis of TB and/or start of TB treatment at CHUK. Patients who were unable to give information about their delay were excluded. Eligible patients were interviewed in the local language by the same medical officer shortly after diagnosis (up to 2 weeks).

A total of 82 consecutive in-patients and 22 out-patients were studied. The questionnaire included socio-economic characteristics, health insurance status, clinical information on current illness and health service utilisation for suspected TB symptoms. Case files and referral letters were also reviewed to confirm details given by patients.

Definitions

Adapted from previous studies,[1] patient delay was defined as the time from the appearance of the first symptoms to the first contact with a health care provider. Health care system delay was the time from the first contact with a health care provider to the time of diagnosis. We distinguished health care system delay at the referring centre as the time from the first contact with a health care provider to time of arrival at the CHUK, and health care system delay at CHUK as the time from the first visit at our institution to the time of diagnosis. Treatment delay was defined as the time from diagnosis to the start of treatment. The total delay is the sum of the various delays mentioned, i.e., the time from the first symptoms reported by the patient to the start of anti-tuberculosis treatment.

TB was diagnosed according to the recommendations of the national TB guidelines.[6] As mycobacterial culture is not performed routinely in Rwanda, the majority of the diagnoses of smear-negative PTB and EPTB were based on clinical and radiological criteria.

Urban dwellers were those living in and around Kigali (⩽20 km), and rural dwellers were those who lived >20 km from Kigali.

Data analysis

Dichotomised health care system and total delay were compared for different subgroups using odds ratios (ORs) and 95% confidence intervals (CI). To identify factors independently associated with patient, health care system and total delay, a multivariate logistic regression analysis with delay time dichotomised according to the medians was performed. When appropriate, a non-parametric test (χ^2) was used where assumptions of normality were not met. Statistical significance was taken as $P < 0.05$.

RESULTS

A total of 104 patients successfully completed the questionnaire. Nine other patients were excluded: six were unable to provide information about the length of their delay prior to transfer, and three died before the interview took place. Among the 104 patients included, 57% were men, and the mean age was 35 years (range 17–84). The majority (87%) lived in Kigali city. Forty-five per cent were employed and had a regular income. Health insurance was available for 65%. More than three quarters of the patients were referrals: 64% from public health centres, 13% from district hospitals, 7% from private centres and 4% from prison. Most patients (79%) required hospitalisation.

At the time of the study, voluntary HIV counselling and testing for TB patients was part of the national policy and 95% had benefited from this service. Sixty-two per cent were found to be HIV-positive (Table 1).

Cough and fever were the most frequently reported symptoms and signs on admission (respectively 87% and 86%), followed by weight loss (61%), night sweats (54%), chest pain (39%) and haemoptysis (11%). The symptoms experienced at the earliest stages of the disease were similar, although all had become more frequent on referral to the hospital.

Of the 104 patients, 44 had PTB, of whom 16 were smear-negative. Among the 60 EPTB cases, TB pleurisy ($n = 19$), miliary TB ($n = 11$) and disseminated TB ($n = 11$) were the most common diagnoses. Empiric antibiotic treatment was given to 72/104 patients on admission at CHUK for a mean duration of 7 days. Forty-nine of 72 patients (68%) were smear-negative PTB or EPTB cases.

The median total delay was 57 days (range 8–240 days) and was equally affected by patient and health

Table 1 Patient characteristics

Characteristics	Patients *n* (%)
Age, years, mean	35
Sex	
Male	45 (43)
Female	59 (57)
Residence	
Urban	91 (88)
Rural	13 (12)
Profession	
Salaried	47 (45)
No salary	57 (55)
Health insurance	
Affiliated	68 (65)
Non-affiliated	36 (35)
HIV status	
Positive	65 (62)
Negative	34 (33)
Unknown	5 (5)
Hospital admission status	
In-patient	82 (79)
Out-patient	22 (21)

HIV = human immunodeficiency virus.

Table 2 Distribution of time delays

	Median delay	
	Days	Range
Patient delay	25	0–216
Health service delay	28	1–194
At primary and/or secondary level	18	0–191
At referral hospital (CHUK)	6	0–45
Treatment delay	1	0–6
Total delay	57	8–240

CHUK = Centre Hospitalier Universitaire de Kigali.

care system delays (Table 2). The total delay was <2 months in 56% of the patients and <1 month in 18%.

The median patient delay was 25 days (mean 31, range 0–216). Fifty-nine per cent of the patients consulted a health official within 1 month after the onset of symptoms. A longer median patient delay was noted for rural patients compared to urban dwellers (31 vs. 24 days) and for HIV-positive compared to HIV-negative patients (30 vs. 22 days), however without reaching statistical significance. Age, sex, profession and health insurance status did not influence the patient delay.

The median overall health care system delay was 28 days (mean 39, range 1–194), mainly due to delay at the referring centre. The median health care delay prior to referral was 18 days (range 0–191), compared to 6 days (range 0–45) at the referral hospital (Table 2). No significant difference in delay was found between the private and public referring centres.

Risk factors for a longer health system delay at the CHUK were smear-negative PTB or EPTB (adjusted OR 5.12, $P = 0.002$) and antibiotic trial (adjusted OR 2.96, $P = 0.022$) (Table 3). The latter was also found to significantly prolong the total delay in an unadjusted analysis (unadjusted OR 2.85, $P = 0.020$), as was rural residence (unadjusted OR 4.86, $P = 0.014$). An adjusted analysis for total delay could not be performed given the small number of rural residents.

The median treatment delay was 1 day (range 0–6). Ninety per cent of the patients were started on treatment within 24 h of diagnosis.

DISCUSSION

This study highlights the delay from the onset of symptoms until diagnosis and treatment of PTB or EPTB as observed at the main referral hospital of Rwanda.

Delay in the diagnosis of pulmonary, and particularly smear-positive, TB has been reported by many authors.[2,3,8–11] However, we found only two reports evaluating delays in TB diagnosis that included smear-negative and extra-pulmonary forms of the disease. Both reports were from industrialised countries.[1,4]

EPTB was more frequently seen (58%) in our study than in previous studies by Farah et al. (31%)[4] and by Sherman et al. (34%).[1] The rate of HIV-TB co-infection (62%) and the selection of severely ill and atypical cases inherent to a referral hospital may partially explain this.[5,12]

The median total delay of 57 days (8 weeks) compared favourably with a total delay of ⩾12 weeks reported in several studies in resource-constrained countries such as Uganda,[9] Tanzania,[13] Botswana,[2] Ghana,[3] Malaysia[14] and Vietnam.[15] However, long total delays have also been found in industrialised countries such as the UK (78 days)[16] and the United States (89 days).[17]

There is no universally accepted delay from the onset of symptoms to the diagnosis of TB. Some authors suggest 1 month,[18] while others accept 2.[19] In our study, 56% of the patients were started on TB treatment within 2 months, and only 18% within 1 month.

Rural residence is a common risk factor for longer total delays[8] as well as health care system[2] and patient delays.[3,13,20] In our study, rural residents experienced longer total delays, however without statistical significance. The small number of rural residents in this study population could be one of the reasons.

We found no association of social factors such as age, sex, profession, health insurance status and residence with patient delays. In several series, older people tended to wait longer to visit a health professional.[20,21] In Norway, on the other hand, it was the younger age group that tended to present later.[4] Female sex was found to be a predisposing factor in some studies,[22] and male sex in others.[23] In Uganda, subsistence farmers experienced longer delays.[9] Not

Table 3 Patient characteristics as risk factors for delay at referral hospital, showing unadjusted and adjusted ORs ($n = 104$)

		Delay >6 days				
	n	*n* (%)	Unadjusted OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
Age >35, years	53	23 (49)	1.03 (0.47–2.24)	>0.1	—	—
Male sex	59	29 (50)	1.14 (0.52–2.50)	>0.1	—	—
Rural residence	13	8 (62)	1.82 (0.55–6.09)	>0.1	—	—
No salary	57	28 (49)	0.95 (0.43–2.07)	>0.1	—	—
Health insurance	68	36 (54)	1.82 (0.79–4.21)	>0.1	—	—
Negative HIV serology	34	17 (50)	0.94 (0.41–2.17)	>0.1	—	—
Out-patient	22	13 (59)	0.58 (0.22–1.53)	>0.1	—	—
Antibiotic trial	72	39 (54)	2.15 (0.88–5.21)	0.083	2.96 (1.16–7.52)	0.022
EPTB/SNPTB	76	43 (57)	4.03 (1.46–11.16)	0.004	5.12 (1.85–14.14)	0.002

OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus; EPTB = extra-pulmonary tuberculosis; SNPTB = smear-negative pulmonary tuberculosis.

having health insurance was associated with long patient delay in Thailand.[24]

The health care system delay of 28 days is comparable with the delay reported in the Norwegian study,[4] and is much longer than the 15-day delay in the US study;[1] both of these address a similar study population.

When dividing the health care system delay into delay prior to transfer to the referral hospital and delay at the referral hospital, the latter was found to be significantly shorter in this study. A final diagnosis was established in 81% of patients within 2 weeks of the first visit/admission. Both the evolving symptom pattern in advancing disease as well as the availability of diagnostic tools and medical expertise may have contributed to the short in-hospital delay.

Similar to previous reports, smear-negative TB and EPTB were associated with a longer health care system delay.[1,4] This delay has most often been attributed to the unusual presentations and difficulty of diagnosis. However, an unreasonably high threshold for the initiation of anti-tuberculosis treatment, particularly in smear-negative disease, has been suggested to cause delay in the management of patients with TB.[25,26] Clinicians prefer diagnostic proof before committing a patient to treatment.

More than two thirds of the patients (72/104) received a 1-week antibiotic trial at our institution. Patients who have received an antibiotic trial have significantly longer health care system and total delays. This strategy is recommended by the WHO to improve the diagnosis of smear-negative TB and EPTB in resource-constrained settings. The latest WHO recommendations emphasise the fact that antibiotic treatment in the HIV-positive population is aimed at treating a possible bacterial co-infection, and not at excluding TB. It should therefore not further delay TB treatment when clinical suspicion is high.[27] Although useful at the primary health care level, the use of this policy is debatable at the secondary and tertiary levels.[28]

This study has several limitations. First, patients were recruited from a single referral hospital in Rwanda, and the results may thus not apply to other settings. Second, the information about the main events in health-seeking behaviour and diagnosis is mainly self-reported, implying a certain recall bias. Data on antibiotic use prior to referral are often imprecise and preclude detailed validation of this strategy. Third, the diagnosis of smear-negative TB and EPTB remains largely presumptive. We were unable to confirm it by culture, and the recent policy of national decentralisation in health care prevented the clinical follow-up of our patients.

We may conclude that the delay in the diagnosis and treatment of TB for patients presenting at the main referral hospital in Rwanda is relatively long, and that this was equally affected by patient and health care system delay. Reducing these delays may require a comprehensive approach that focuses on increasing the awareness of TB among patients, improving access to health care, training of primary health care workers in the early recognition of less common TB presentations and complications and streamlining the referral process. The Ministry of Health's National Tuberculosis Programme has recently launched an intensive national educational campaign designed to improve clinical and diagnostic knowledge of health care staff.

The appropriate use of antibiotics in the diagnosis and treatment of TB according to the latest WHO recommendations should be incorporated into the National TB Programme guidelines, thereby enforcing its use at the primary health care level. The use of antibiotics in TB management at the tertiary level, however, needs to be validated.

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RÉSUMÉ

CONTEXTE : Centre Hospitalier Universitaire de Kigali, un des principaux centres de référence.
OBJECTIFS : Evaluer le délai du diagnostic et du traitement de la tuberculose (TB), ainsi que ses facteurs de risque.
SCHÉMA : Collecte de données prospectives des patients traités pour une TB pulmonaire (TBP) ou extrapulmonaire (TBEP) entre juin et septembre 2006.
RÉSULTATS : Nous avons recruté 104 patients. L'âge moyen était 35 ans (17–84 ans). Soixante-deux pour cent étaient positifs pour le virus de l'immunodéficience humaine. TBEP a été diagnostiquée dans 60 cas. Le délai médian total, le délai du système de santé et du patient ont été respectivement de 57, 28 et 25 jours. Le délai du système de santé avant transfert était significativement plus long que le délai au niveau de notre institution (18 vs. 6 jours ; $P < 0{,}0001$). Les facteurs de risque pour le délai du système de santé dans notre institution sont la TBP à microscopie négative ou la TBEP (OR 5,12) et une antibiothérapie d'essai (OR 2,96). Cette dernière est également associée à un délai total plus long (OR 2,85). Il en est de même pour la résidence rurale (OR 4,86). Il n'y a pas d'association entre le délai-patient et l'âge, le sexe, la profession ou l'assurance-santé.
CONCLUSION : La TBP à microscopie négative et la TBEP ont été associées à un délai plus long du système de santé. Une antibiothérapie d'essai, elle aussi, a prolongé le délai du système de santé. Son utilisation, recommandée par l'Organisation Mondiale de la Santé dans les cas de TB à microscopie négative et dans les TBEP dans les pays en voie de développement, demande une validation au niveau des soins de santé tertiaires.

RESUMEN

MARCO DE REFERENCIA : Hospital universitario de Kigali, un centro importante de referencia.
OBJETIVO : Evaluar el retraso en el diagnóstico y el tratamiento de la tuberculosis (TB) y sus factores de riesgo.
MÉTODO : Recopilación prospectiva de datos de los pacientes tratados por TB pulmonar (TBP) y extrapulmonar (TBEP) entre junio y septiembre de 2006.
RESULTADOS : Se incluyeron 104 pacientes, con promedio de edad de 35 años (de 17 a 84 años), de los cuales 62% tuvieron serología positiva para el virus de la inmunodeficiencia humana. Se diagnosticó TBEP en 60 casos. La mediana global del retraso fue 57 días, aquella dependiente del sistema de salud 28 días y la del paciente 25 días. El retraso del sistema de salud previo a la remisión fue significativamente mayor que el retraso en el hospital (18 contra 6 días ; $P < 0{,}0001$). Los factores de riesgo de un mayor retraso del sistema de atención en el hospital fueron la TBP con baciloscopia negativa o TBEP (OR 5,12) y un tratamiento antibiótico de prueba (OR 2,96) ; este último prolongó también en forma significativa el retraso global (OR 2,85), como la residencia rural (OR 4,86). No se encontró asociación significativa entre el retraso del paciente y su edad, sexo, profesión o estado de cobertura de salud.
CONCLUSIÓN : La TBP con baciloscopia negativa o TBEP se asoció con un mayor retraso dependiente del sistema de salud. Un tratamiento antibiótico de prueba prolongó en forma significativa el retraso del sistema. La administración de este tratamiento de prueba, recomendado por la Organización Mundial de la Salud en casos con baciloscopia negativa y en casos de TBEP en países en vías de desarrollo, precisa validación.