

HOSPITAL TRANSMISSION OF MULTIDRUG-RESISTANT *MYCOBACTERIUM TUBERCULOSIS* IN ROSARIO, ARGENTINAJOSE AITA<sup>1</sup>, LUCIA BARRERA<sup>2</sup>, ANA RENIERO<sup>3</sup>, BEATRIZ LOPEZ<sup>2</sup>, JOSE BIGLIONE<sup>1</sup>, GUILLERMO WEISBURD<sup>1</sup>, JUAN C. RAJMIL<sup>1</sup>, CARLOS LARGACHA<sup>1</sup>, VIVIANA RITACCO<sup>4</sup>

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**Summary** Multidrug-resistant tuberculosis has emerged over the last two years at Carrasco Hospital, located in Rosario city. Nosocomial transmission among 7 AIDS patients admitted into the same ward between June and December/94 was supported by temporal clustering of cases, matching drug susceptibility, and identical IS6110 fingerprints. Among 8 non-HIV chronic cases without evidence of reciprocal contact outside the hospital, two additional clusters of 2 and 4 cases, respectively, were identified. The latter was found to be generated by a strain genetically related to the one that infected AIDS patients. It is hypothesized that an ancestor strain, common to both, might have been brought into the hospital long before the outbreak was first suspected.

**Key words:** multidrug-resistance, tuberculosis, AIDS

The transmission of multidrug-resistant tuberculosis within health care facilities has been a major challenge for the control of hospital infections since the beginning of this decade<sup>9</sup>. Association with HIV infection, accelerated spread, and an alarming high rate of fatal outcome were common features of most reported outbreaks in the USA<sup>1, 2, 3</sup>.

In Argentina, nosocomial transmission has been recently documented by molecular tools in Buenos Aires and its outskirts<sup>5, 7</sup>. Rosario city, one of the largest urban conglomerates in the country, ranks second after Buenos Aires regarding HIV-infection and AIDS-related tuberculosis<sup>4, 6</sup>. At Carrasco Hospital—a reference health centre in Rosario—25 out of the 34 AIDS-related tuberculosis cases that occurred during the last two years were due to multidrug-resistant bacilli. This

alarming frequency prompted the investigation of tuberculosis transmission within the hospital.

Multidrug-resistant isolates from 15 in-patients were typed by DNA fingerprinting using the standardized protocol for *M. tuberculosis*<sup>10</sup>. DNA was extracted from bacilli suspensions and digested with the restriction enzyme Pvu II. DNA fragments were electrophoresed in 0.8% agarose and vacuum-blotted into a positively charged nylon membrane. The IS6110 probe was a 245 basepair-DNA fragment amplified by PCR and labelled by the enhanced chemoluminescence gene detection system (Amersham International plc, Amersham, UK). *M. tuberculosis* Mtb 14323, kindly provided by Dick van Soolingen was used as reference strain.

The findings are summarized in Table 1 and illustrated in Figure 1. Three clusters of identical isolates were identified (a, b, and c), one of them involving all seven AIDS cases studied. The isolates of only two of the eight immunocompetent patients did not fit in any cluster (x and y).

Most of the eight HIV-non-related tuberculosis patients were chronic and remained infectious for

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TABLE 1.— Characteristics of strains and patients implicated in the emergence of multidrug-resistant tuberculosis at Carrasco Hospital, June/December, 1994

Strains		Patients			n
RFLP pattern	drug resistance	HIV status	outcome	ward	
a	H-R*	positive	died		7
b	H-R**	no risk	survive	II/IV	4
c	H-R	no risk	survive	II/IV	2
x	H-R-S	risk	survive	II	1
y	H-R	no risk	survive	II	

H: isoniazid, R: rifampin; S: streptomycin; E: ethambutol.

\* The isolate from one patient was also resistant to streptomycin. \*\* The isolate from one patient was also resistant to streptomycin and ethambutol.

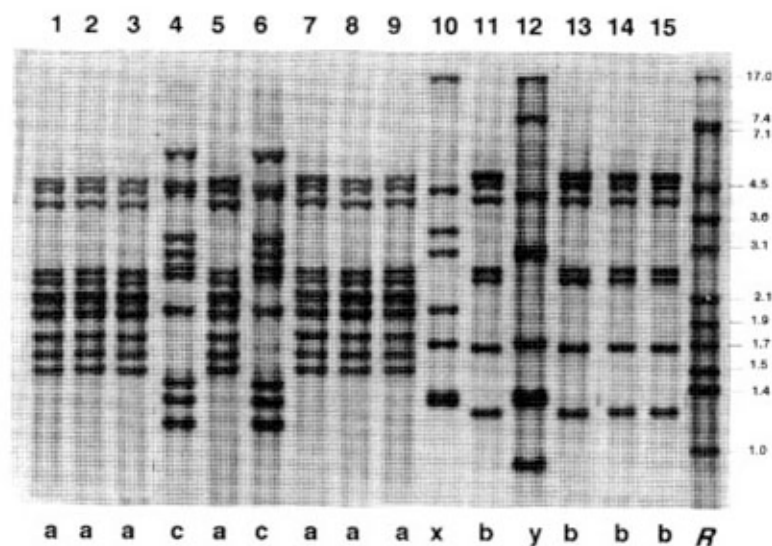


Fig. 1.— IS6110 fingerprints of *Mycobacterium tuberculosis* isolates from 15 in-patients at Carrasco Hospital, June-December, 1994. Lanes 4, 6, and 10 to 15: chronic, non-HIV-related tuberculous patients; lanes 1, 2, 3, 5, 7, 8 and 9: AIDS cases; letters at bottom indicate patterns described in Table 1; R: reference strain Mt. 14323; numbers at right indicate sizes of R DNA fragments.

prolonged periods. Contact among them outside the hospital was not proved, but most clinical records indicated repeated admissions over the previous years. The earliest case had been admitted at the hospital in 1983. Two of the clusters –b and c– corresponded to this group of patients, and occurred in wards II and IV. One patient belonging to cluster b used to visit frequently her HIV-positive relatives –who were hospitalized

in ward I– while being herself infectious, throughout 1992.

The isolates from all 7 AIDS cases that occurred in ward I between June and December/1994 had the same RFLP pattern a. Noticeably, this pattern shared a five-band motif with pattern b, suggesting that both strains originated from a common ancestor (Figure 1, fragments of 2.3, 2.5, 4.0, 4.5 and 5.0 kilobase pairs approxi-

mately). The mean age of the patients was 28 years, all but one were infectious (smear positive), and they survived 23 to 270 days to the diagnosis of multidrug-resistant tuberculosis (mean: 109 days). One of them suffered from tuberculosis since 1993, and had been repeatedly hospitalized in ward I. The remaining 6 AIDS patients had no previous history of tuberculosis, but had been admitted in the same ward before, due to other opportunistic infections.

Nosocomial transmission of tuberculosis among AIDS patients included in this study was supported by temporal clustering of cases, the matching drug susceptibility, and identical RFLP pattern. Although no definite index case could be identified for this AIDS-related outbreak, partial DNA homology was observed between the strain infecting these patients and the strain infecting four chronic non-HIV-related cases. Indeed, the very existence of a cluster such as the latter, evidences a parallel transmission among non AIDS-related patients. These preliminary findings suggest that a common ancestor might well have been brought into the hospital (or the community) years before the outbreak was first suspected.

Infection control measures for preventing the nosocomial spread of multidrug-resistant strains are still under evaluation and give rise to vigorous controversy<sup>9</sup>. It should be stressed that previously reported hospital outbreaks have accompanied a deterioration of tuberculosis control policies in the communities<sup>9</sup>. Certainly, the selective pressure that determines *in vivo* predominance of resistant mutants over antibiotic-sensitive bacilli originates in inappropriate therapy or non-compliance with treatment regimens. The emergency here reported highlights the critical importance of strengthening sound strategies aimed to ensure complete antituberculous therapy.

## Resumen

*Transmisión hospitalaria de Mycobacterium tuberculosis multirresistente en Rosario, Argentina*

La reciente emergencia de tuberculosis multirresistente en el Policlínico Carrasco de Rosario fue analizada mediante tipificación molecular

con IS6110. Se comprobó transmisión hospitalaria de una misma cepa entre 7 casos asociados al SIDA, internados en la misma sala entre junio y diciembre/94. Entre los 8 pacientes tuberculosos crónicos sin infección HIV ni evidencia de contacto recíproco extrahospitalario, 2 estaban infectados por una cepa, y otros 4 por otra. Esta última estaba genéticamente emparentada con la que infectó a los pacientes con SIDA. Se especula que un ancestro común a ambas pudo haberse instalado en el hospital años antes de que surgiera la sospecha de un brote.

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