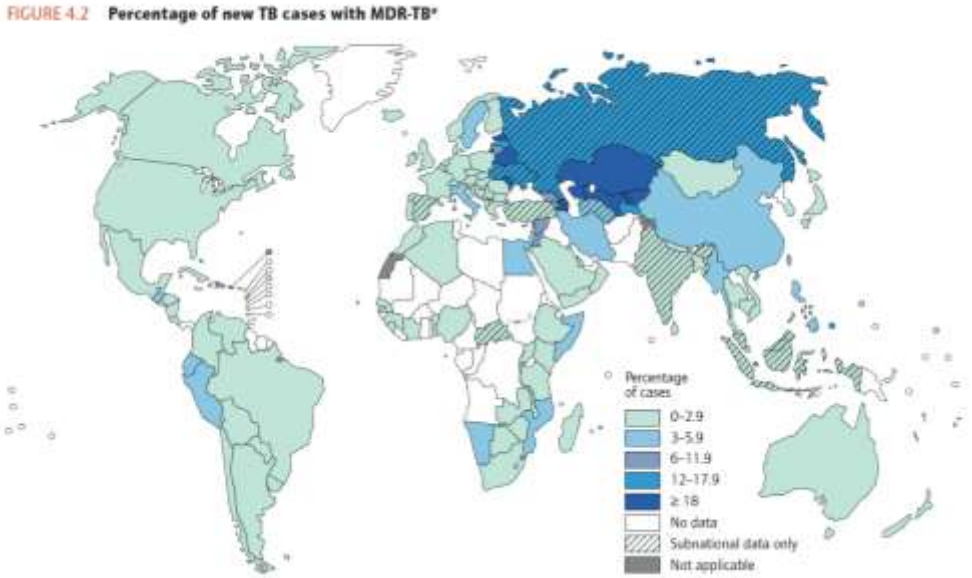
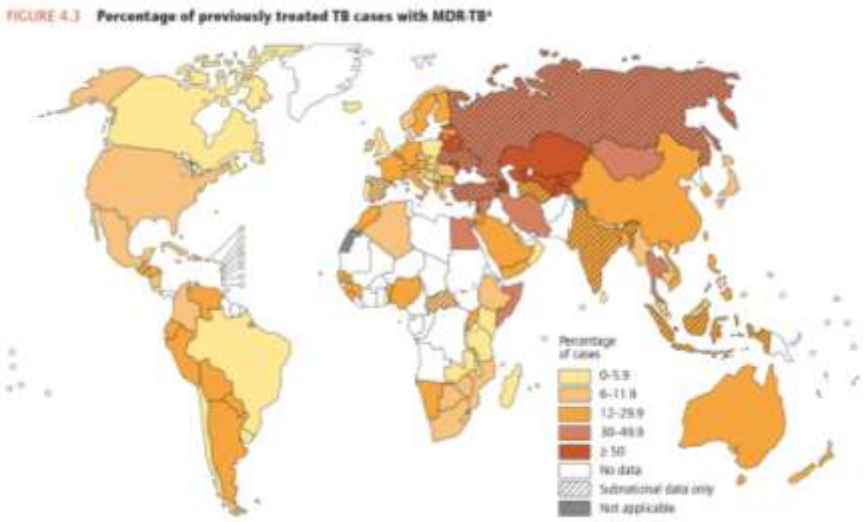
Molecular Epidemiology and the Genesis of Drug Resistant TB in South Africa





PROCEDURES IN THE CONTROL OF TUBERCULOSIS

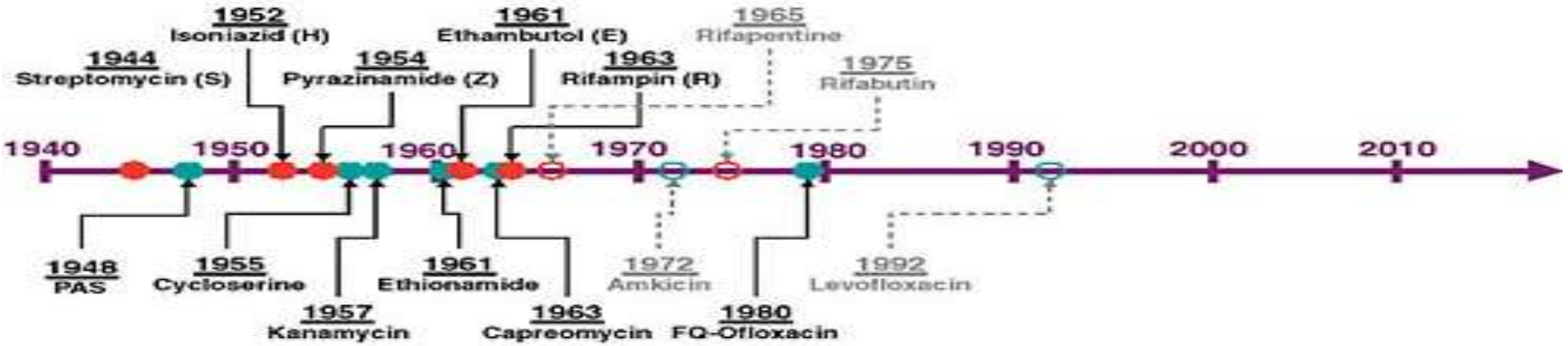
THE PRACTICAL APPROACH: 4. DIAGNOSIS AND TREATMENT

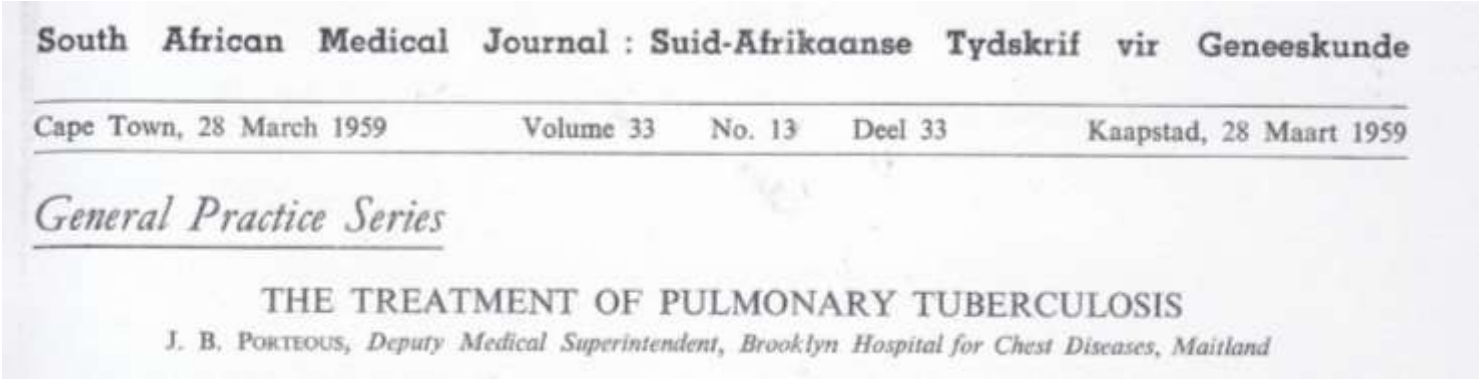
B. A. DORMER, M.D., D.P.H.

Council for Scientific and Industrial Research Unit in Tuberculosis, King George V Hospital, Durban

"The indiscriminate giving of streptomycin in South Africa has resulted in a large number of cases with completely resistant organisms-mostly chronic cases who will be a permanent source of danger to others."

"The sensitivity of the patient's organisms to the drugs should be tested after each course."





South African Medical Journal : Suid-Afrikaanse Tydskrif vir Geneeskunde

Cape Town, 28 March 1959 Volume 33 No. 13 Deel 33 Kaapstad, 28 Maart 1959

General Practice Series

THE TREATMENT OF PULMONARY TUBERCULOSIS

J. B. Porteous, *Deputy Medical Superintendent, Brooklyn Hospital for Chest Diseases, Maitland*

"It is generally accepted that streptomycin, isonicotinic acid hydrazide (INAH) and para-aminosalicylic acid (PAS) should be used in the treatment of pulmonary tuberculosis"

"When using combinations of these 3 drugs, it is essential to request regular laboratory tests for the emergence of drug resistance in the organisms."

South African Medical Journal December 1967

RESISTANT TUBERCULOSIS IN AN INPATIENT HOSPITAL POPULATION IN CAPE TOWN

A. D. GINSBURG, M.D., F.C.P. (S.A.), A. CAVVADAS, M.B., CH.B., F. JUDELSOHN, M.B., CH.B. AND H. R. ACKERMANN, M.B., CH.B., T.D.D. (WALES), *From the City Hospital for Infectious Diseases, Cape Town, and the Department of Medicine, Groote Schuur Hospital, Cape Town*

Study Period 1962 to 1964

Primary resistance
streptomycin 5.29%
isoniazid 14.9%

Acquired resistance
streptomycin 21%
isoniazid 39%

NATIONAL SURVEILLANCE OF RESISTANCE TO ANTI-TUBERCULOSIS DRUGS, SOUTH AFRICA 1965 - 1988

Dr K Weyer
TBRI

Epidemiological Comments

Table 1: OVERALL RESISTANCE TO THE FIVE MAJOR TUBERCULOSIS DRUGS
TBRI DRUG RESISTANCE SURVEILLANCE PROGRAMME 1965-1988

SURVEILLANCE PERIOD	DRUG	NUMBER OF PATIENTS	RESISTANCE (%)	95% CI
1965-1970	INH	15 960	28,8	28,1-29,5
	SM	15 963	33,8	33,1-34,5
	RMP	377	6,4	3,9- 8,9
	ETH	7 729	20,8	20,0-21,7
	EMB	2 210	1,5	1,0- 2,0
1971-1979	INH	16 322	23,2	22,6-23,9
	SM	16 344	10,6	10,6-11,0
	RMP	2 376	2	0,7- 1,6
	ETH	16 275	6,1	5,8- 6,5
	EMB	4 866	1,5	1,1- 1,8
1980-1989	INH	16 430	14,2	13,7-14,7
	SM	16 420	12,1	11,6-12,6
	RMP	16 429	1,8	1,6- 2,1
	ETH	16 422	2,5	2,2- 2,7
	EMB	16 430	1,2	1,1- 1,4

Editorial Comment: “ There is no doubt about the seriousness of these findings and drug resistance will not be overcome in the short term.”

S Afr Med J. 1995 Jun;85(6):499-504.

Tuberculosis drug resistance in the Western Cape.

Weyer K, Groenewald P, Zwarenstein M, Lombard CJ.

MRC National Tuberculosis Research Programme, MRC Centre for Epidemiological Research, Parowvallei, W. Cape.

Table III. Initial and acquired drug resistance, Western Cape tuberculosis drug resistance survey

	Resistance (%)*			
Drug	Initial (*N* = 3 928)	Acquired (*N* = 1 920)	Unknown (*N* = 1 418)	Overall (*N* = 7 266)
Isoniazid	3,9 (3,3 - 4,6)	10,8 (9,4 - 12,3)	9,0 (7,5 - 10,5)	6,8
Rifampicin	1,1 (0,7 - 1,4)	4,2 (3,3 - 5,1)	2,2 (2,7 - 4,7)	2,4
Ethambutol	0,2 (0,04 - 0,3)	0,3 (0,05 - 0,5)	0,2 (0,0 - 0,4)	0,2
MDR†	1,1 (0,7 - 1,4)	4,0 (3,1 - 4,9)	3,4 (2,4 - 4,4)	2,3

* 95% confidence intervals in parenthesis.
† Resistance to isoniazid and rifampicin.

J Infect Dis. 1999 Nov;180(5):1608-15.

Transmission of a multidrug-resistant Mycobacterium tuberculosis strain resembling "strain W" among noninstitutionalized, human immunodeficiency virus-seronegative patients.

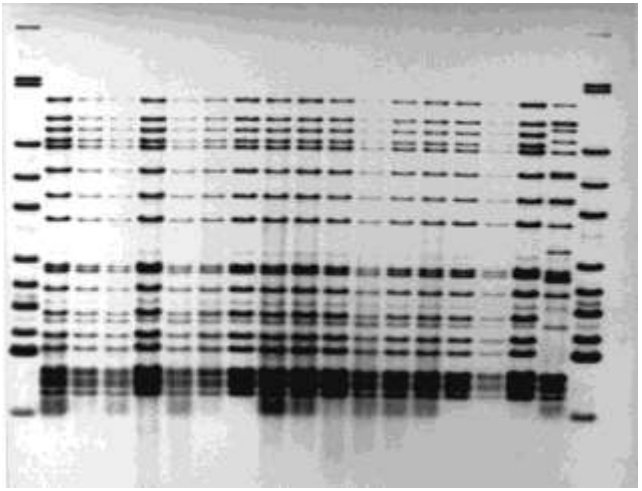
van Rie A, Warren RM, Beyers N, Gie RP, Classen CN, Richardson M, Sampson SL, Victor TC, van Helden PD.

Department of Paediatrics and Child Health, University of Stellenbosch, Tygerberg, Leuven, Belgium.

Abstract

Since 1990, several outbreaks of multidrug-resistant tuberculosis (MDR-TB) have been described among institutionalized patients infected with human immunodeficiency virus (HIV). We describe a community MDR-TB outbreak among HIV-seronegative patients in Cape Town, South Africa. Isolates were characterized by restriction fragment length polymorphism (RFLP) analysis and dot-blot hybridization analysis of mutations conferring resistance for isoniazid, rifampin, streptomycin, and ethambutol. All isolates were identical on RFLP analysis. In 2 patients, RFLP analysis showed exogenous reinfection during or after treatment for drug-susceptible TB. Mutation analysis confirmed the genotypic identity of the isolates. The infecting strain was genotypically related to strain W, which is responsible for the majority of MDR-TB outbreaks in New York City. Transmission of MDR-TB is thus not limited to HIV-seropositive patients in an institutional setting but occurs within a community.

N = 16 (1993 to 1997)



katG 315 (AGC to ACC)
rpoB 531 (TCG to TTG)
embB 306 (ATG to ATA)
rrs 513 (CAG to CCG)

Patient	Sex	Age	Diagnosis DR-TB	Epidemiological link	Resistance pattern INH	RIF	SM	EMB	THIA	ETH
1*	m	23	Jan-93	housemate of "index case"						
2	m	21	Mar-93	brother of patient 1						
3	m	42	Aug-93	friend of sister of patient 1						
4*	f	15	Aug-93	sister of patient 5 and 6						
5*	m	28	Sep-93	brother of patient 4 and 6						
6	f	18	Sep-93	sister of patient 4 and 5						
7	m	29	Oct-93	no interview (died)						
8*	f	29	Nov-93	sister of patient 1						
9	f	11	Mar-94	daughter of patient 8						
10*	m	24	Apr-94	friend of patient 1, 2 and 8						
11*	f	28	Sep-94	cousin of patient 4, 5 and 6						
12*	f	32	Nov-94	no interview (moved)						
13	f	39	Jun-95	no epidemiological link						
14*	m	50	Feb-96	no epidemiological link						
15*	f	37	Mar-97	cousin of "index case"						
16	f	23	Mar-97	friend of patient 8						

* initial isolate available for mutation analysis
resistance detected by conventional susceptibility testing on initial isolate
additional resistance detected by mutation analysis only on initial isolate
additional resistance detected by conventional susceptibility testing on follow-up isolate
additional resistance only detected by mutation analysis only on follow-up isolate

Lancet. 2000 Jul 1;356(9223):22-5.

Classification of drug-resistant tuberculosis in an epidemic area.

Van Rie A, Warren R, Richardson M, Gie RP, Enarson DA, Beyers N, Van Helden PD.

Department of Paediatrics and Child Health, University of Stellenbosch, South Africa.

Abstract

BACKGROUND: Traditionally, patients with drug-resistant tuberculosis are classified as having acquired drug-resistant or primary drug-resistant disease on the basis of a history of previous tuberculosis treatment. Only cases of primary drug resistance are assumed to be due to transmission of drug-resistant strains.

METHODS: This descriptive study of 63 patients with drug-resistant tuberculosis assessed the relative contribution of transmission of drug-resistant strains in a high-incidence community of Cape Town, South Africa, by restriction-fragment length polymorphism (RFLP). The RFLP results were compared with the results obtained by traditional classification methods.

FINDINGS: According to RFLP definitions, 52% (33 cases) of drug-resistant tuberculosis was caused by transmission of a drug-resistant strain. The proportion of cases due to transmission was higher for multidrug-resistant (64%; 29 cases) than for single-drug-resistant (no cases) tuberculosis. By the clinical classification, only 18 (29%) patients were classified as having primary drug-resistant tuberculosis (implying transmission). The clinical classification was thus misleading in 25 patients.

INTERPRETATION: The term acquired drug resistance includes patients infected with strains that truly acquired drug resistance during treatment and patients who were initially infected with or reinfected with a drug-resistant strain. This definition could lead to misinterpretation of surveillance studies, incorrect evaluation of tuberculosis programmes, and delayed diagnosis and treatment of patients with multidrug-resistant disease. The clinical term acquired drug resistance should be replaced with the term "drug resistance in previously treated cases", which includes cases with drug resistance due to true acquisition as well as that due to transmitted drug-resistant strains.

	All patients (n=63)	Multidrug resistant* (n=45)	Single-drug resistant (n=12)	Multiple-drug resistant (n=6)
Clinical classification				
Acquired	45 (71%)	32 (71%)	8 (67%)	5 (83%)
Primary	18 (29%)	13 (29%)	4 (33%)	1 (17%)
RFLP classification				
Unique	24 (38%)	11 (24%)	11 (92%)	2 (33%)
Cluster	39 (62%)	34 (76%)	1 (8%)	4 (67%)
Transmission†	33 (52%)	29 (64%)	0	4 (67%)

*Resistance against at least isoniazid and rifampicin. †n–1.[7]

Table 1: **Classification of 63 patients with drug-resistant tuberculosis by clinical method and by RFLP analysis**

PLoS One. 2010 Nov 15;5(11):e13901.

Epidemic levels of drug resistant tuberculosis (MDR and XDR-TB) in a high HIV prevalence setting in Khayelitsha, South Africa.

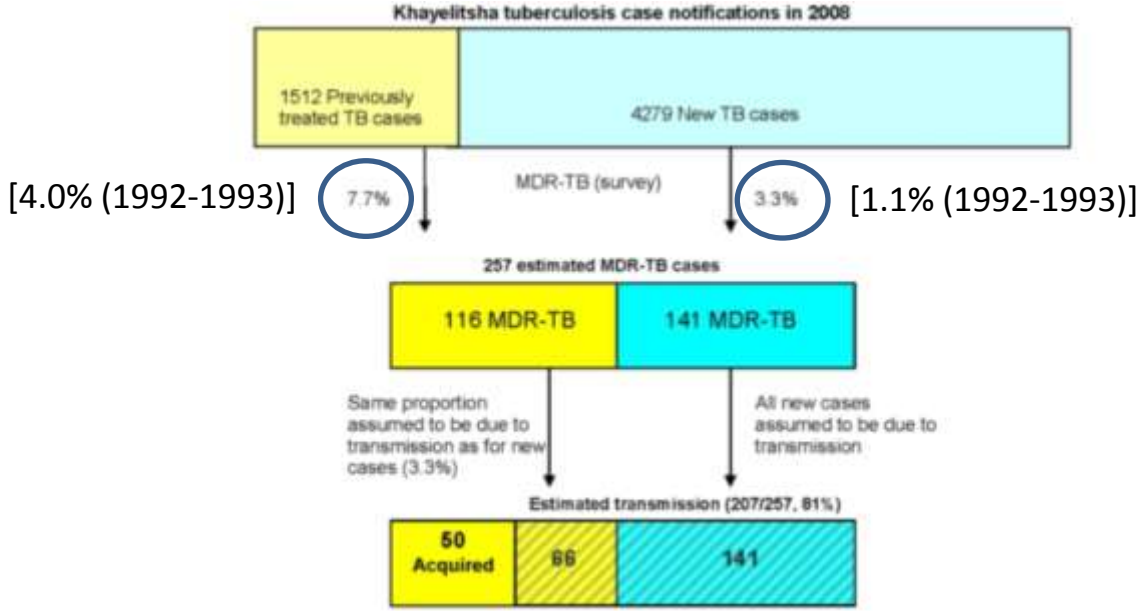
Cox HS, McDermid C, Azevedo V, Muller O, Coetzee D, Simpson J, Barnard M, Coetzee G, van Cutsem G, Goemaere E.
Burnet Institute, Melbourne, Australia. hcox@burnet.edu.au

Abstract

BACKGROUND: Although multidrug-resistant tuberculosis (MDR-TB) is emerging as a significant threat to tuberculosis control in high HIV prevalence countries such as South Africa, limited data is available on the burden of drug resistant tuberculosis and any association with HIV in such settings. We conducted a community-based representative survey to assess the MDR-TB burden in Khayelitsha, an urban township in South Africa with high HIV and TB prevalence.

METHODOLOGY/PRINCIPAL FINDINGS: A cross-sectional survey was conducted among adult clinic attendees suspected for pulmonary tuberculosis in two large primary care clinics, together constituting 50% of the tuberculosis burden in Khayelitsha. Drug susceptibility testing (DST) for isoniazid and rifampicin was conducted using a line probe assay on positive sputum cultures, and with culture-based DST for first and second-line drugs. Between May and November 2008, culture positive pulmonary tuberculosis was diagnosed in 271 new and 264 previously treated tuberculosis suspects (sample enriched with previously treated cases). Among those with known HIV status, 55% and 71% were HIV infected respectively. MDR-TB was diagnosed in 3.3% and 7.7% of new and previously treated cases. These figures equate to an estimated case notification rate for MDR-TB of 51/100,000/year, with new cases constituting 55% of the estimated MDR-TB burden. HIV infection was not significantly associated with rifampicin resistance in multivariate analyses.

CONCLUSIONS/SIGNIFICANCE: There is an extremely high burden of MDR-TB in this setting, most likely representing ongoing transmission. These data highlight the need to diagnose drug resistance among all TB cases, and for innovative models of case detection and treatment for MDR-TB, in order to interrupt transmission and control this emerging epidemic.



Estimating the burden of rifampicin resistant tuberculosis in Khayelitsha.

J Clin Microbiol. 2012 Mar;50(3):995-1002. Epub 2011 Dec 14.

Population structure of multi- and extensively drug-resistant Mycobacterium tuberculosis strains in South Africa.

Chihota VN, Müller B, Mlambo CK, Pillay M, Tait M, Streicher EM, Marais E, van der Spuy GD, Hanekom M, Coetzee G, Trollip A, Hayes C, Bosman ME, Gey van Pittius NC, Victor TC, van Helden PD, Warren RM.

DST/NRF Centre of Excellence for Biomedical Tuberculosis Research/MRC Centre for Molecular and Cellular Biology, Division of Molecular Biology and Human Genetics,Faculty of Health Sciences, Stellenbosch University, Stellenbosch, South Africa. vchihota@auruminstitute.org

Abstract

Genotyping of multidrug-resistant (MDR) Mycobacterium tuberculosis strains isolated from tuberculosis (TB) patients in four South African provinces (Western Cape, Eastern Cape, KwaZulu-Natal, and Gauteng) revealed a distinct population structure of the MDR strains in all four regions, despite the evidence of substantial human migration between these settings. In all analyzed provinces, a negative correlation between strain diversity and an increasing level of drug resistance (from MDR-TB to extensively drug-resistant TB [XDR-TB]) was observed. Strains predominating in XDR-TB in the Western and Eastern Cape and KwaZulu-Natal Provinces were strongly associated with harboring an inhA promoter mutation, potentially suggesting a role of these mutations in XDR-TB development in South Africa. Approximately 50% of XDR-TB cases detected in the Western Cape were due to strains probably originating from the Eastern Cape. This situation may illustrate how failure of efficient health care delivery in one setting can burden health clinics in other areas.

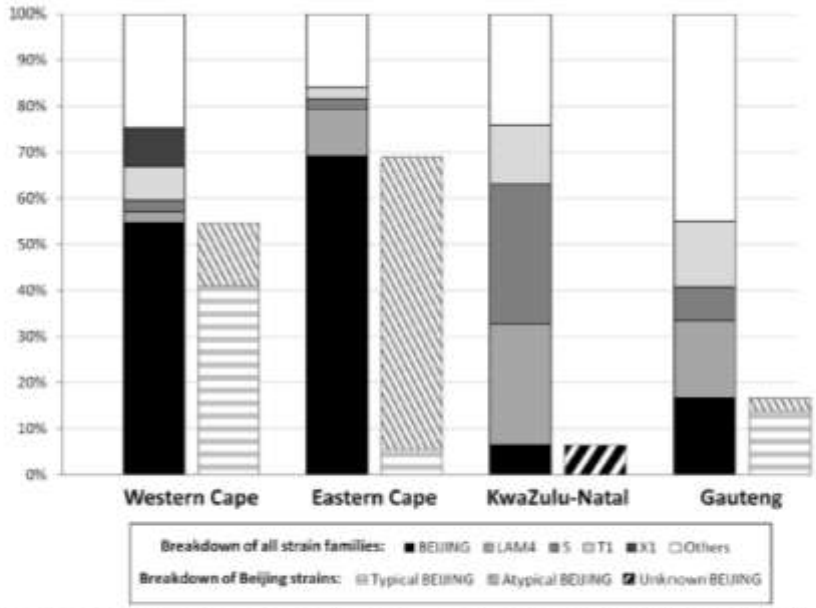


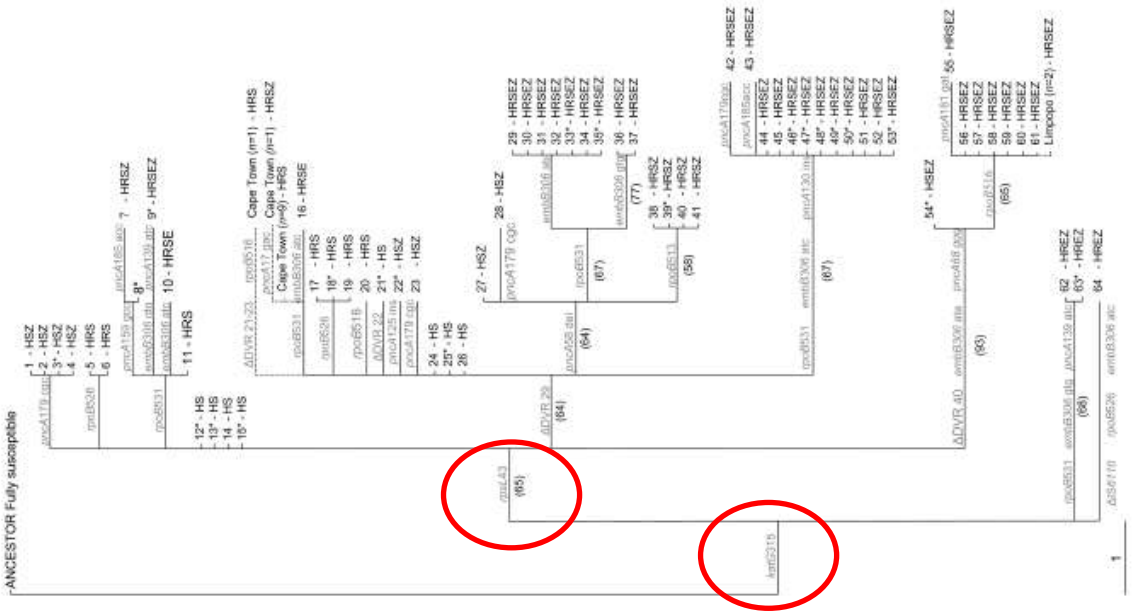
FIG 1 Frequency distribution of major MDR genotypes in four South African provinces. The proportion of isolates belonging to the Beijing, LAM4, S, T1, X1, or other genotypes is indicated in different shades of gray. The proportion of typical and atypical Beijing strains among the Beijing strains in Western Cape, Eastern Cape, and Gauteng Provinces is shown in Table 2. Beijing strains from KwaZulu-Natal were not available for further characterization. LAM4 is also commonly referred to as F15/LAM4/KZN.

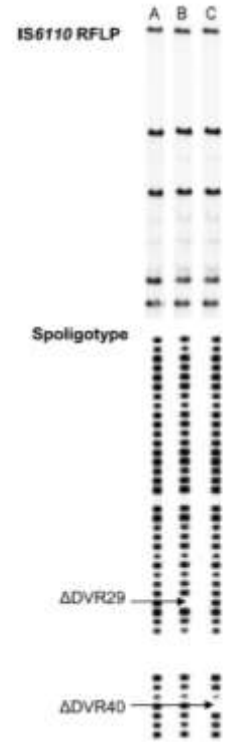
Int J Tuberc Lung Dis. 2007 Feb;11(2):195-201.

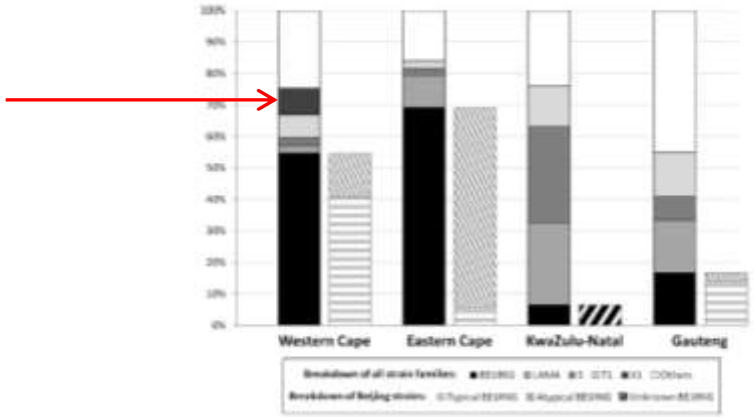
Spread of an emerging Mycobacterium tuberculosis drug-resistant strain in the western Cape of South Africa.

Victor TC, Streicher EM, Kewley C, Jordaan AM, van der Spuy GD, Bosman M, Louw H, Murray M, Young D, van Helden PD, Warren RM.

Department of Science and Technology/National Research Foundation (DST/NRF) Centre for Biomedical TB Research/ Medical Research Council (MRC) Centre for Molecular and Cellular Biology, Stellenbosch University, Tygerberg, South Africa. tv@sun.ac.za







Int J Tuberc Lung Dis. 2010 Jan;14(1):119-21.

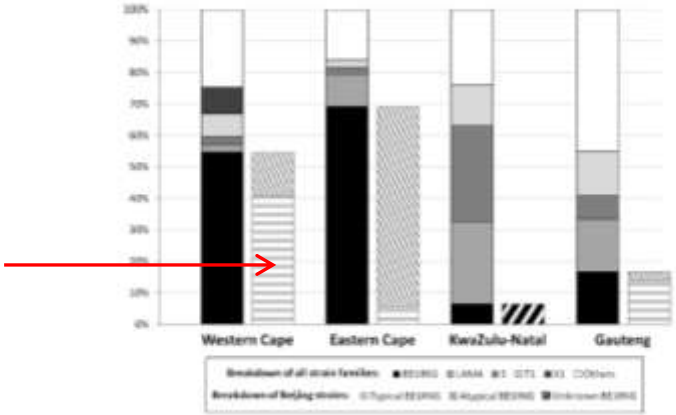
Drug-resistant tuberculosis epidemic in the Western Cape driven by a virulent Beijing genotype strain.

Johnson R, Warren RM, van der Spuy GD, Gey van Pittius NC, Theron D, Streicher EM, Bosman M, Coetzee GJ, van Helden PD, Victor TC.

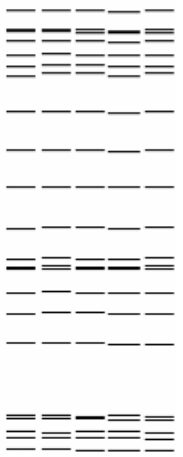
Division of Molecular Biology and Human Genetics, Department of Biomedical Science, Stellenbosch University, Tygerberg, South Africa.

Table Demographic, phenotypic and genotypic data of drug-resistant TB cases diagnosed in the two study periods

	Period 1 January 2001–December 2002 *n* (%)	Period 2 January 2005–December 2006 *n* (%)	OD ratio	95%CI	*P* value	Doubling time*
Demographics†						
Cases†	438	652				8.2
Average age, years	36	34				NA
Male sex	265 (60.5)	387 (59.4)	0.95	0.7–1.2	0.71	NA
Smear-positive	397 (90.6)	579 (88.8)	0.8	0.5–1.2	0.24	NA
Drug resistance						
INH monoresistance	176 (40.2)	229 (35.1)	0.8	0.6–1.0	0.1	13.3
RMP monoresistance	14 (3.2)	24 (3.7)	1.2	0.6–2.3	0.7	5.6
MDR-TB	199 (45.4)	396 (60.7)	1.9	1.5–2.4	<0.0001	4.0
Polyresistance	49 (11.2)	3 (0.5)	0.04	0.01–0.1	<0.0001	−4.3
Genotype						
Beijing	118 (26.9)	238 (36.5)	1.6	1.2–2.0	0.001	3.9
Haarlem	10 (2.3)	12 (1.8)	0.8	0.3–1.9	0.7	20.0
LAM	74 (16.9)	106 (16.3)	0.96	0.7–1.3	0.8	9.3
X1	111 (25.3)	166 (25.5)	1.0	0.8–1.3	1	8.1
Other	125 (28.5)	130 (19.9)	0.6	0.5–0.8	0.001	100
MDR-TB						
Beijing	57 (28.6)	160 (40.4)	1.7	1.2–2.4	0.005	2.2
Haarlem	7 (3.5)					
LAM	29 (14.6)					
X1	58 (29.1)					
Other	48 (24.1)					
Clone R220						
Cases	53 (12.1)					
INH monoresistance	23 (45.1)					
MDR-TB	28 (54.9)					
Polyresistance	2 (3.8)					



Beijing R220 Clone



-15 *inhA* promoter mutation

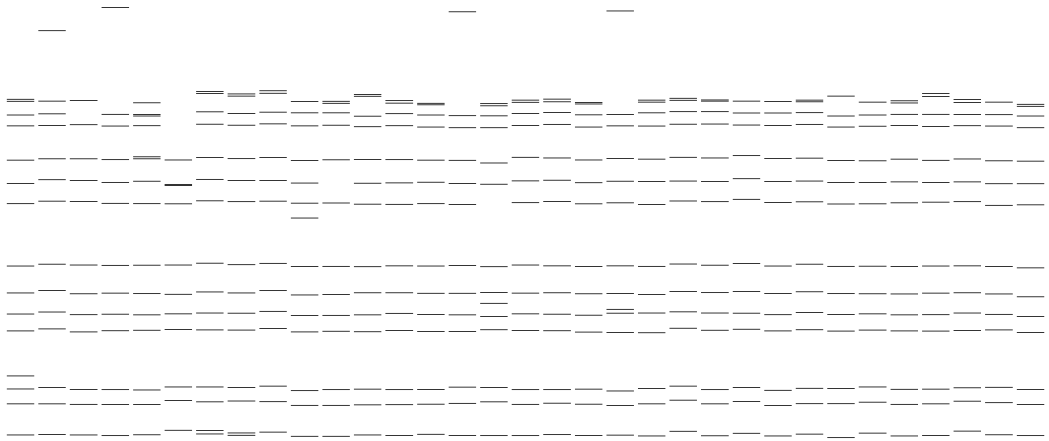
J Clin Microbiol. 2008 Apr;46(4):1514-6. Epub 2008 Feb 13.

Spread of a low-fitness drug-resistant Mycobacterium tuberculosis strain in a setting of high human immunodeficiency virus prevalence.

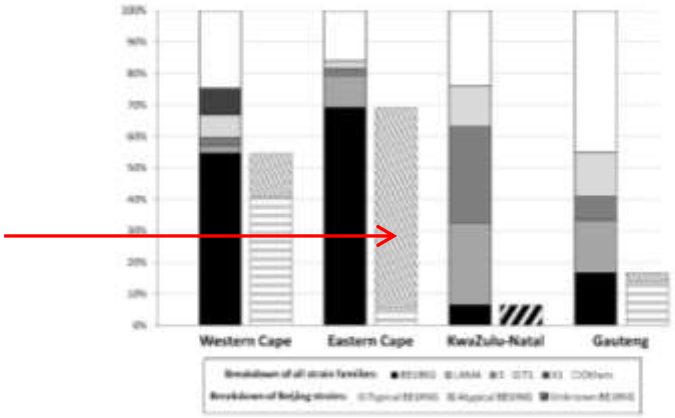
Strauss OJ, Warren RM, Jordaan A, Streicher EM, Hanekom M, Falmer AA, Albert H, Trollip A, Hoosain E, van Helden PD, Victor TC.

DST/NRF Centre of Excellence for Biomedical Tuberculosis Research/ MRC Centre for Molecular and Cellular Biology, Division of Molecular Biology and Human Genetics, Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa.

Atypical Beijing Clone



rpoB 516 mutation

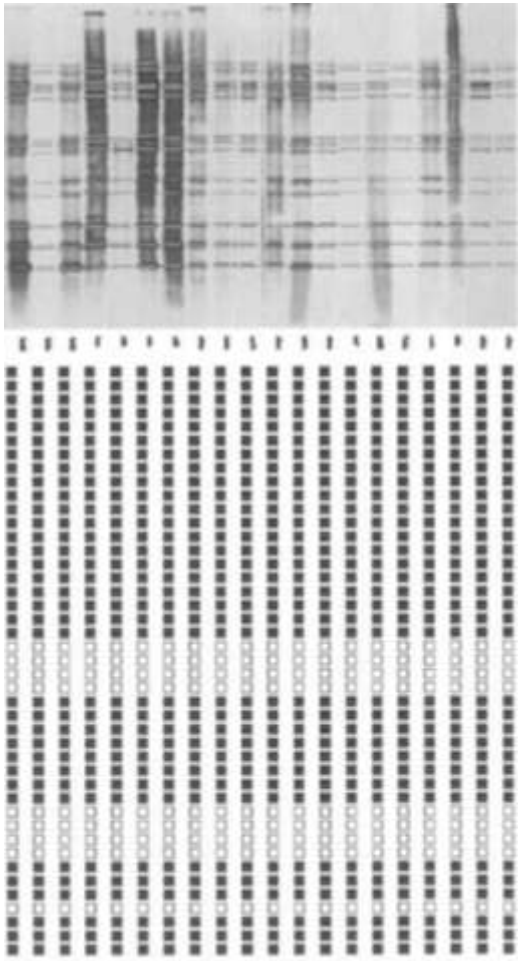


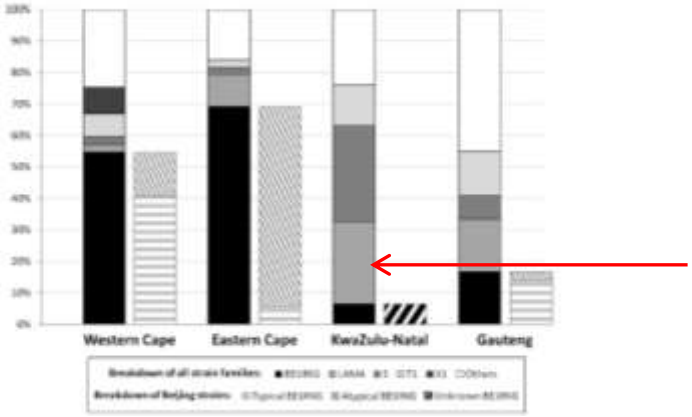
Clin Infect Dis. 2007 Dec 1;45(11):1409-14. Epub 2007 Oct 22.

Evolution of the extensively drug-resistant F15/LAM4/KZN strain of Mycobacterium tuberculosis in KwaZulu-Natal, South Africa.

Pillay M, Sturm AW.

Department of Medical Microbiology, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, South Africa.





Lancet. 2006 Nov 4;368(9547):1575-80.

Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa.

Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, Zeller K, Andrews J, Friedland G.

AIDS Program, Section of Infectious Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA. negandhi@montefiore.org

Abstract

BACKGROUND: The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

METHODS: We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

RESULTS: From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR tuberculosis had never been previously treated for tuberculosis; 67% (28 of 42) had a recent hospital admission. All 44 patients with XDR tuberculosis who were tested for HIV were co-infected. 52 of 53 patients with XDR tuberculosis died, with median survival of 16 days from time of diagnosis (IQR 6-37) among the 42 patients with confirmed dates of death. Genotyping of isolates showed that 39 of 46 (85%, 95% CI 74-95) patients with XDR tuberculosis had similar strains.

CONCLUSIONS: MDR tuberculosis is more prevalent than previously realised in this setting. XDR tuberculosis has been transmitted to HIV co-infected patients and is associated with high mortality. These observations warrant urgent intervention and threaten the success of treatment programmes for tuberculosis and HIV.

	Number (%)
Tuberculosis characteristics (n=53)	
Pulmonary tuberculosis alone	40 (75%)
Pulmonary and extrapulmonary tuberculosis	13 (25%)
Sputum-smear positive	42 (79%)
Sputum-smear negative	11 (21%)
Previous tuberculosis treatment (n=47)	
No previous treatment	26 (55%)
Previous treatment: cure or completed treatment	14 (30%)
Treatment default or failure	7 (15%)
Previous admission in past 2 years (n=42)	
Admitted for any cause	28 (67%)
No previous admission	14 (33%)
HIV characteristics (n=44)	
HIV-infected	44 (100%)
On antiretroviral therapy	15 (34%)

Table 2: **Characteristics of patients with XDR tuberculosis**

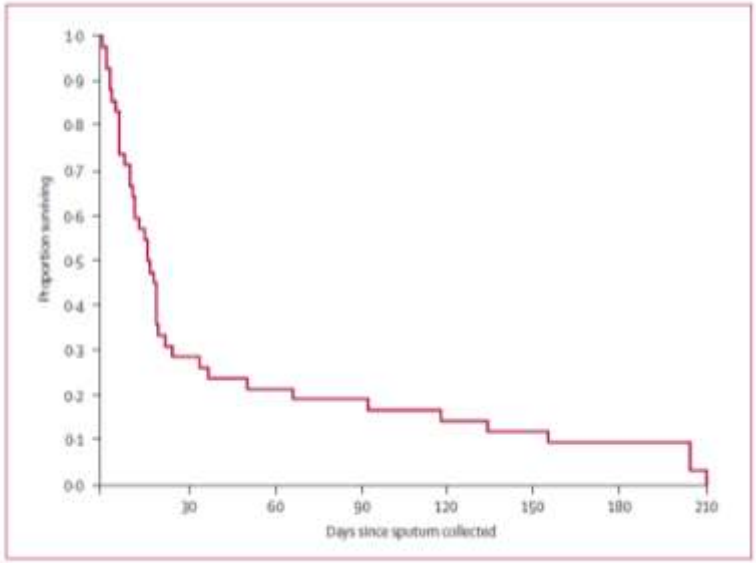


Figure: **Survival after sputum collection in patients with XDR tuberculosis with confirmed dates of death (n=42)**

Int J Tuberc Lung Dis. 2008 Jan;12(1):99-104.

Genotypic diversity of extensively drug-resistant tuberculosis (XDR-TB) in South Africa.

Mlambo CK, Warren RM, Poswa X, Victor TC, Duse AG, Marais E.

Clinical Microbiology and Infectious Disease, National Health Laboratory Services, University of the Witwatersrand, Johannesburg, Gauteng, South Africa.

Abstract

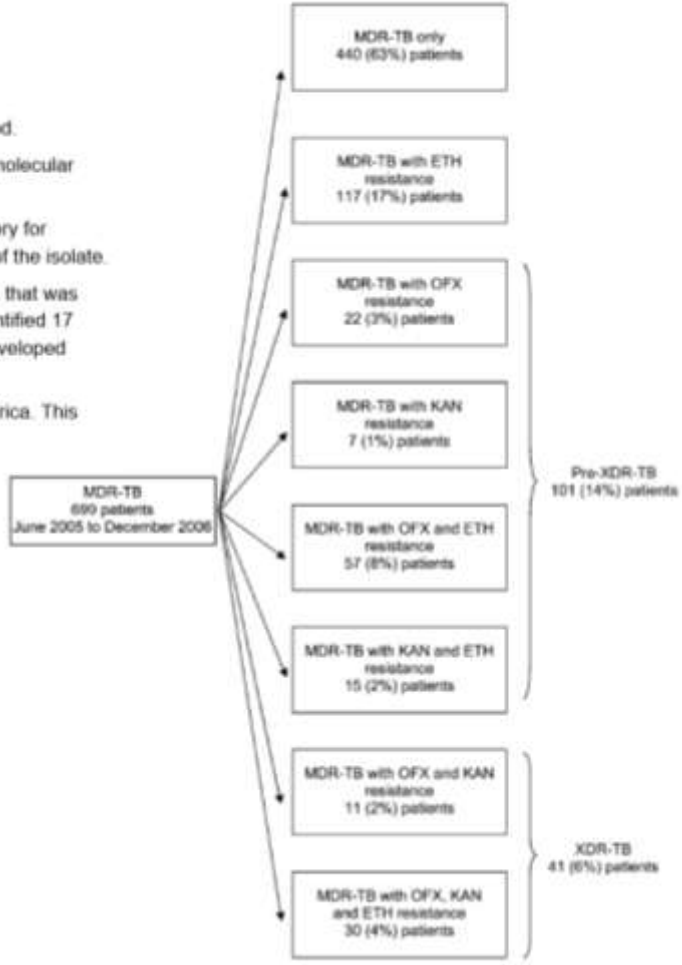
SETTING: The epidemiology of extensively drug-resistant tuberculosis (XDR-TB), an emerging threat to TB control, is not well understood.

OBJECTIVE: To gain insight into the genotypic population structure of XDR Mycobacterium tuberculosis strains in South Africa using a molecular approach and thereby determine whether XDR-TB is mainly acquired or transmitted.

DESIGN: Sputum isolates from patients with multidrug-resistant tuberculosis (MDR-TB) were submitted to the National Referral Laboratory for second-line drug susceptibility testing. The XDR-TB isolates were spoligotyped and these data were compared to the geographic origin of the isolate.

RESULTS: Of the 699 MDR-TB isolates submitted for testing between June 2005 and December 2006, 101 (17%) patients had a culture that was resistant to either ofloxacin or kanamycin, and 41 (6%) were resistant to both drugs (XDR-TB). Spoligotyping of the XDR-TB isolates identified 17 genotypes. As a result of the high genotypic diversity and geographical distribution, we estimate that between 63% and 75% of cases developed XDR-TB through acquisition.

CONCLUSION: Acquisition of extensive drug resistance appears to be the primary mechanism driving the XDR-TB epidemic in South Africa. This urgent TB control issue has to be addressed to prevent the spread of this potentially incurable disease.



Spoligotype family	Sublineage/ST	*n* (%)	Spoligotype patterns	Province	Isolates *n*	Clinics *n*
Beijing	1	14 (34)		N. Cape	5	4
				N. West	4	3
				Limpopo	3	1
				Gauteng	2	1
LAM	LAM4/60	3 (7)		Gauteng	2	2
				Limpopo	1	1
	LAM9/42	2 (5)		Gauteng	2	2
EAI1	EAI1_SOM/48	2 (5)		N. West	1	1
				Limpopo	1	1
	EAI1_SOM/806	2 (5)		Gauteng	1	1
				N. West	1	1
T	T1/53	2 (5)		Gauteng	1	1
				N. West	1	1
	T2/52	1 (2)		Gauteng	1	1
	T3/37	1 (2)		N. West	1	1
H	H1/47	1 (2)		N. West	1	1
	H3/50	1 (2)		Gauteng	1	1
X	X3/92	1 (2)		N. West	1	1
S	71	1 (2)		N. West	1	1
Not in SpolDB4	Type A, possible H	6 (14)		N. West	6	1
		1 (2)		Gauteng	1	1
		1 (2)		Gauteng	1	1
	Possible LAM	1 (2)		Limpopo	1	1
	Possible LAM	1 (2)		Limpopo	1	1
Total		41			41	

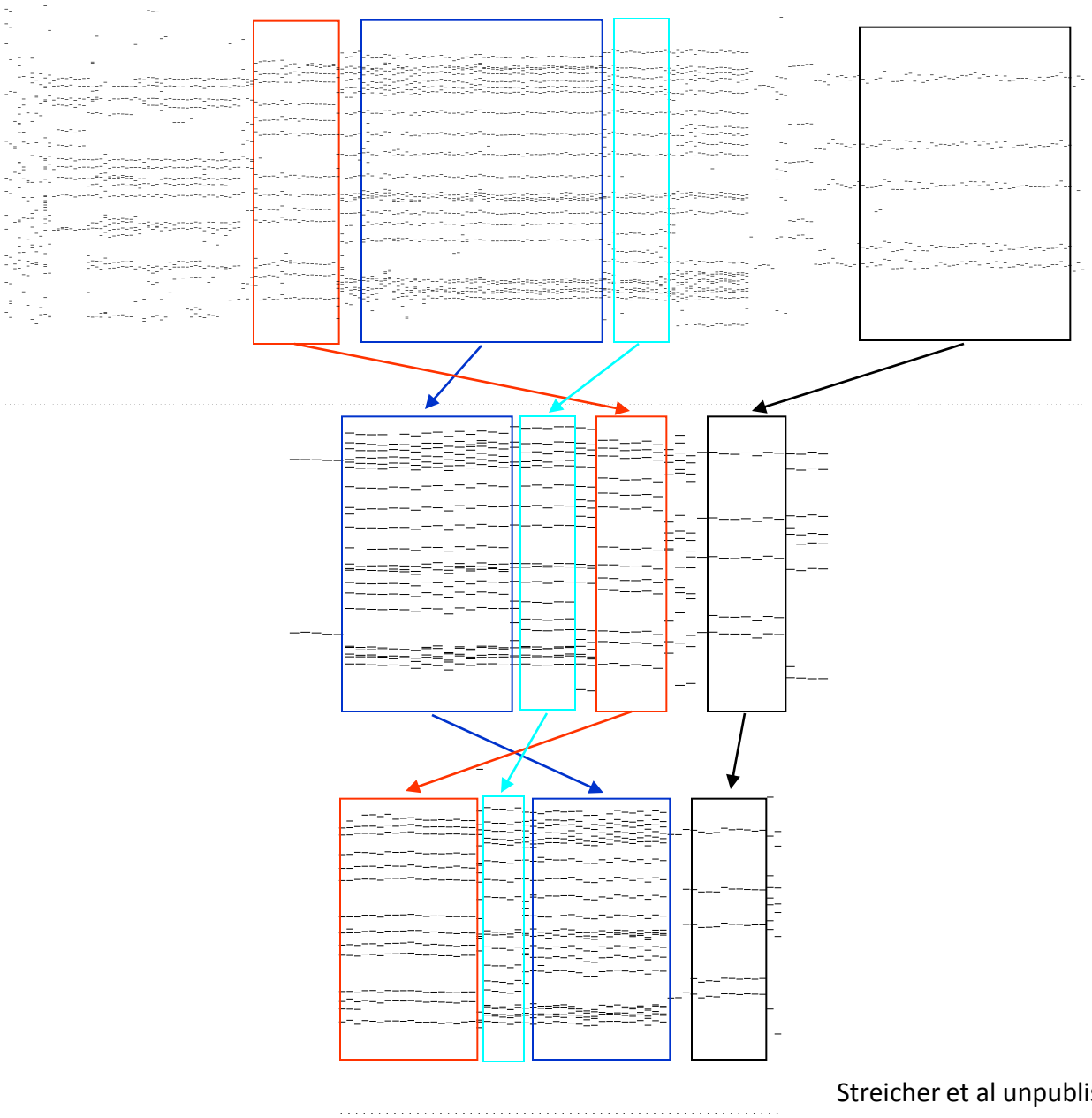
Figure 3 Spoligotype family assignment of XDR-TB isolates showing the province of origin and the number of clinics in which each spoligotype was identified. XDR-TB = extensively drug-resistant tuberculosis; ST = spoligotype; N. Cape = Northern Cape Province; N. West = North West Province; LAM = Latino-American-Mediterranean family; EAI1 = East-African-Indian.

XDR-TB in the Western Cape

MDR-TB

Pre XDR-TB

XDR-TB



Streicher et al unpublished data

A historical review of XDR tuberculosis in the Western Cape province of South Africa

Gregory Symons, Karen Shean, Elize Pietersen, Richard van Zyl Smit, Lititia Pool, Malika Davids, Paul Willcox, Keertan Dheda

There are limited data on the temporal relationship between the regional introduction of multidrug-resistant tuberculosis (MDR-TB) treatment and the subsequent development of extensively drug-resistant TB (XDR-TB). The first XDR-TB case in the Western Cape province of South Africa was recorded in 1992, approximately 5 - 7 years after the regional introduction of MDR-TB-like treatment. Between 1990 and 2002 we identified 48 patients with XDR-TB in the Cape Metropole region of the Western Cape province. Patients were predominantly HIV-uninfected and median survival was 10.8 months. XDR-TB has therefore been present in the Western Cape at least since 1992. These data inform public health policy relevant to the introduction of new anti-TB drug regimens.

S Afr Med J 2011;101:

"XDR-TB has therefore been present in the Western Cape at least since 1992."

"Patients were predominantly HIV-uninfected and median survival was 10.8 months"

Clin Infect Dis. 2007 Dec 1;45(11):1409-14. Epub 2007 Oct 22.

Evolution of the extensively drug-resistant F15/LAM4/KZN strain of Mycobacterium tuberculosis in KwaZulu-Natal, South Africa.

Pillay M, Sturm AW.

Department of Medical Microbiology, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, South Africa.

Abstract

BACKGROUND: Although several hot spots of multidrug-resistant tuberculosis have been identified on the African continent, extensive drug resistance (XDR) has not been reported until recently, when a large number of XDR cases were identified in KwaZulu-Natal. The majority of the patients involved were infected with the same strain of Mycobacterium tuberculosis (F15/LAM4/KZN). We report this strain's development from multidrug resistance to XDR.

METHODS: We searched databases for studies performed during the period 1994-2005 that involved the resistance patterns of isolates of M. tuberculosis with the F15/LAM4/KZN strain fingerprint.

RESULTS: As early as 1994, the F15/LAM4/KZN strain was responsible for a number of cases of multidrug-resistant tuberculosis, indicating the ability of the strain to cause cases of primary resistant tuberculosis. Some of the isolates were also resistant to streptomycin. From 1994 onwards, multidrug-resistant isolates with resistance to additional drugs were found, and the first XDR isolate was discovered in 2001.

CONCLUSIONS: Drug resistance to as many as 7 drugs developed in a local strain of M. tuberculosis in slightly more than a decade. This coincided with the introduction of the directly observed therapy-based and directly observed therapy-plus-based tuberculosis-control programs. It is postulated that the introduction of these programs in the absence of susceptibility testing or drug resistance surveillance has been instrumental in the development of XDR in this highly transmissible F15/LAM4/KZN strain. The expanding pool of human immunodeficiency virus-infected, tuberculosis-susceptible individuals has likely contributed to this development.

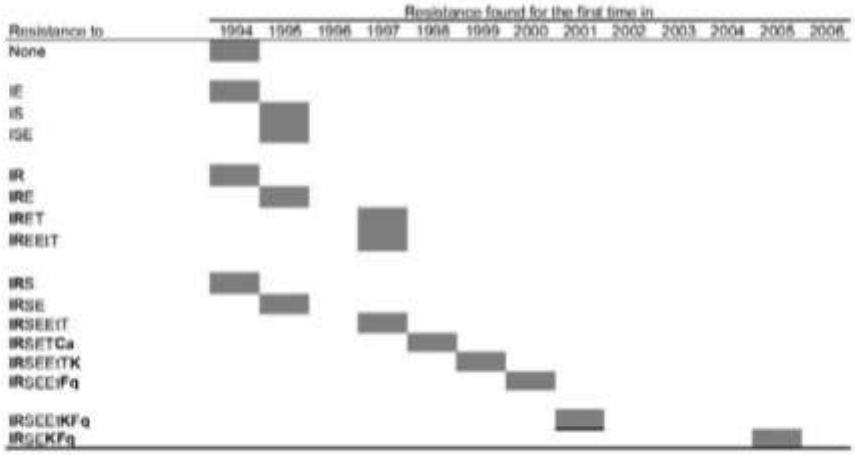


Figure 1. Development of drug resistance in the KwaZulu-Natal family of strains of *Mycobacterium tuberculosis* during the period 1994–2006. Ca, capreomycin; E, ethambutol; Et, ethionamide; F, fluoroquinolones; I, isoniazid; K, kanamycin/amikacin; R, rifampicin; S, streptomycin; T, thiacetazone.

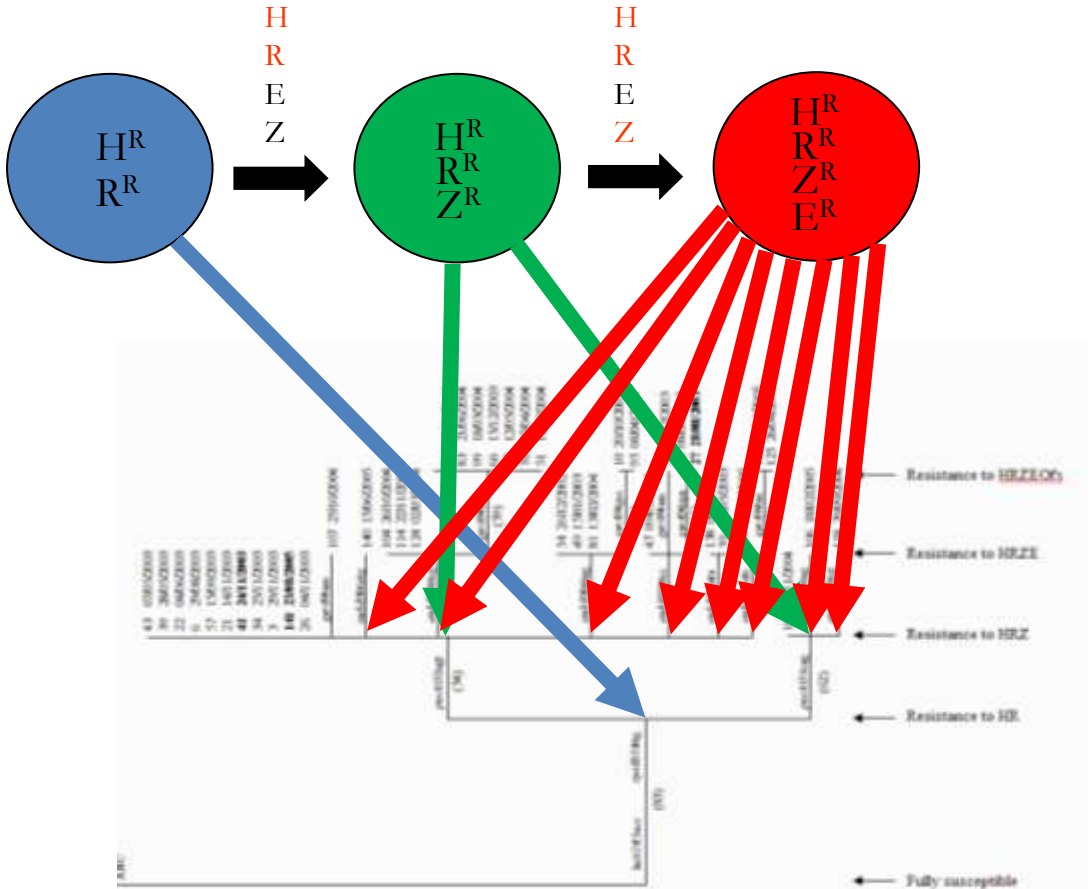
Emerg Infect Dis. 2010 Feb;16(2):264-71.

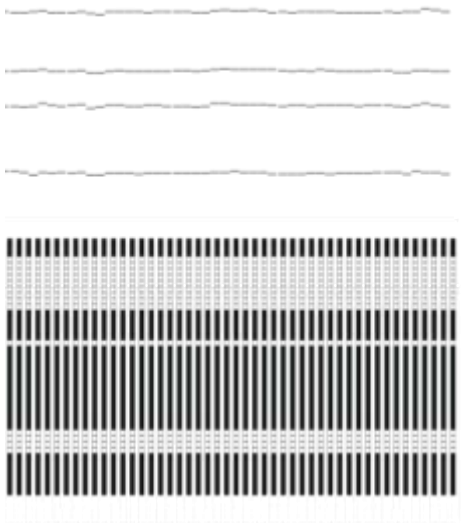
Emergence of increased resistance and extensively drug-resistant tuberculosis despite treatment adherence, South Africa.

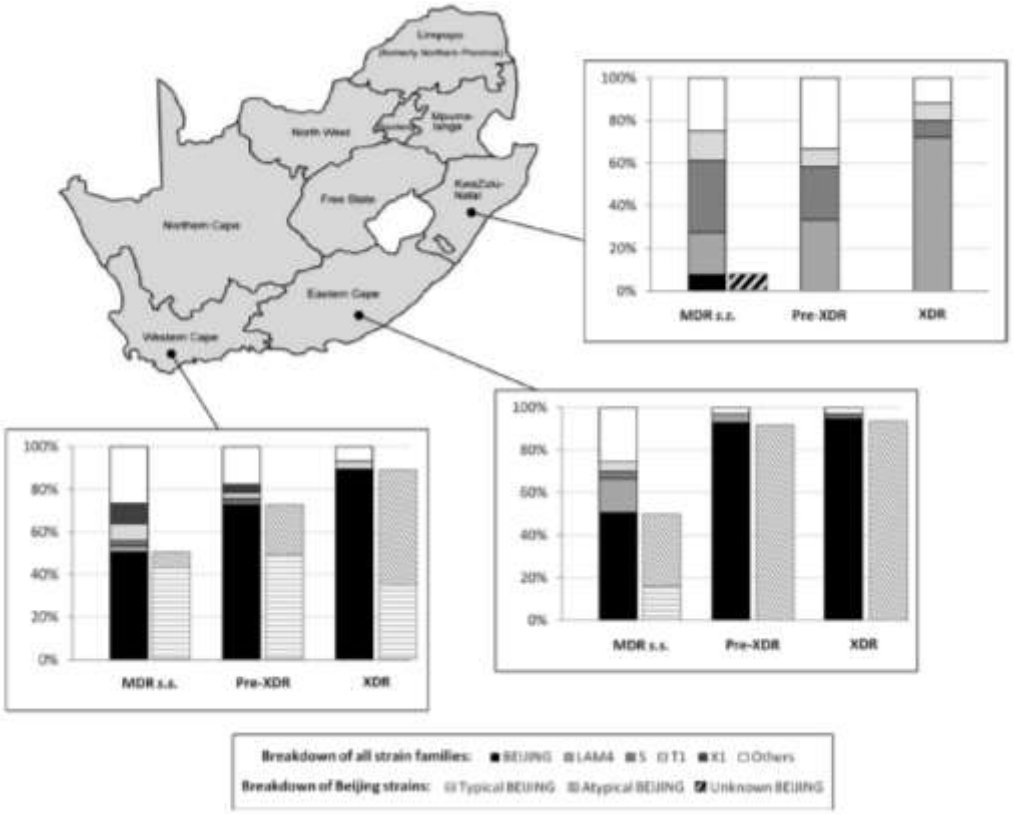
Calver AD, Falmer AA, Murray M, Strauss OJ, Streicher EM, Hanekom M, Liversage T, Masibi M, van Helden PD, Warren RM, Victor TC.
West Vaal Hospital, Orkney, South Africa.

Abstract

We investigated the emergence and evolution of drug-resistant tuberculosis (TB) in an HIV co-infected population at a South African gold mine with a well-functioning TB control program. Of 128 patients with drug-resistant TB diagnosed during January 2003-November 2005, a total of 77 had multidrug-resistant (MDR) TB, 26 had pre-extensively drug-resistant TB (XDR TB), and 5 had XDR TB. Genotyping suggested ongoing transmission of drug-resistant TB, and contact tracing among case-patients in the largest cluster demonstrated multiple possible points of contact. Phylogenetic analysis demonstrated stepwise evolution of drug resistance, despite stringent treatment adherence. These findings suggested that existing TB control measures were inadequate to control the spread of drug-resistant TB in this HIV co-infected population. Diagnosis delay and inappropriate therapy facilitated disease transmission and drug-resistance. These data call for improved infection control measures, implementation of rapid diagnostics, enhanced active screening strategies, and pharmacokinetic studies to determine optimal dosages and treatment regimens.







Int J Tuberc Lung Dis. 2011 Mar;15(3):344-51.

inhA promoter mutations: a gateway to extensively drug-resistant tuberculosis in South Africa?

Müller B, Streicher EM, Hoek KG, Tait M, Trollip A, Bosman ME, Coetzee GJ, Chabula-Nxiweni EM, Hoosain E, Gey van Pittius NC, Victor TC, van Helden PD, Warren RM.

Department of Science and Technology/National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research/Medical Research Council Centre for Molecular and Cellular Biology, Division of Molecular Biology and Human Genetics, Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa. bmuller@sun.ac.za

Emerg Infect Dis. 2011 Mar;17(3):510-3.

Increasing drug resistance in extensively drug-resistant tuberculosis, South Africa.

Shah NS, Richardson J, Moodley P, Moodley S, Babaria P, Ramtahal M, Heysell SK, Li X, Moll AP, Friedland G, Sturm AW, Gandhi NR.

Tugela Ferry Care and Research Collaboration, Tugela Ferry, South Africa. saritashah2@gmail.com

Abstract

We expanded second-line tuberculosis (TB) drug susceptibility testing for extensively drug-resistant Mycobacterium tuberculosis isolates from South Africa. Of 19 patients with extensively drug-resistant TB identified during February 2008-April 2009, 13 (68%) had isolates resistant to all 8 drugs tested. This resistance leaves no effective treatment with available drugs in South Africa.

Table 1

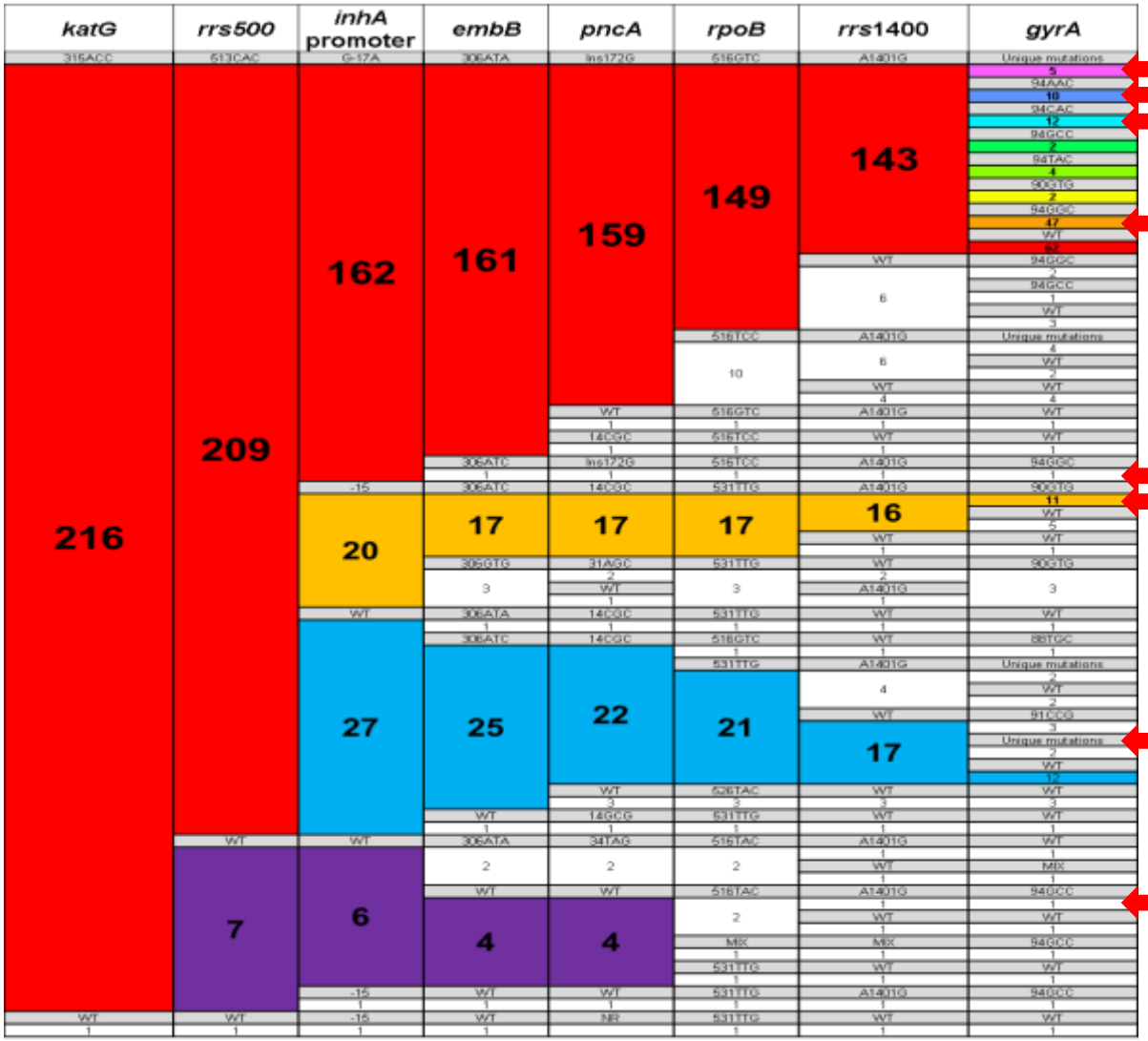
Drug susceptibility test results for 19 XDR TB patients, South Africa*

Drug resistance pattern (antibiogram)	No. (%) patients
INH, RIF, EMB, SM, OFL, KM	2 (11)
INH, RIF, EMB, SM, OFL, KM, CAP	4 (21)
INH, RIF, EMB, SM, OFL, KM, CAP, ETO	13 (68)
Total	19 (100)

Emergence of TDR in South Africa?

July 2008 and July 2009

INH^R Sm^R Eth^R EMB^R PZA^R RIF^R Am^R Km^R Cm^R Ofx^R



PAS^R

PAS^R

PAS^R

PAS^R

PAS^R

Klopper et al (accepted EID)

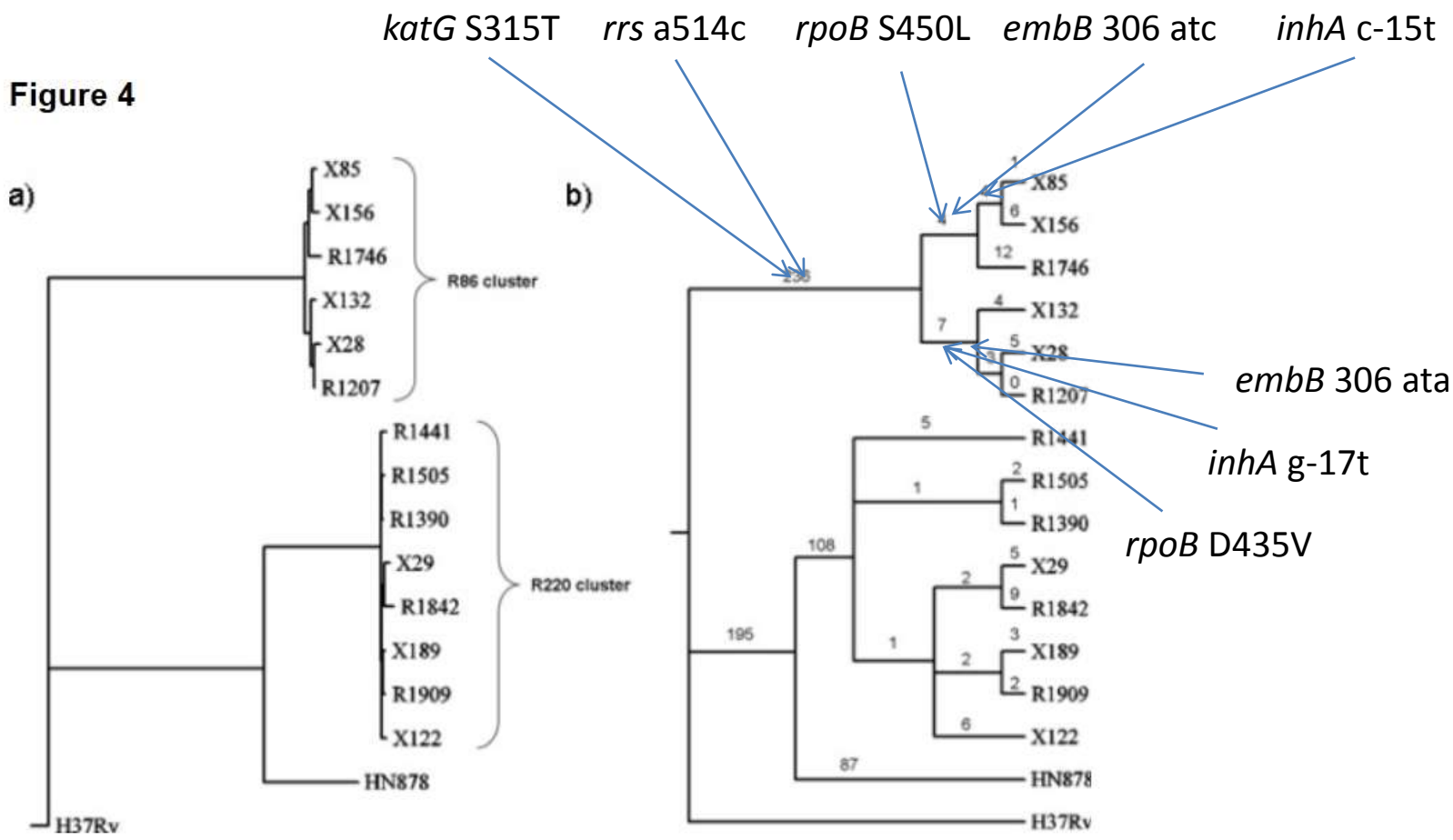
BMC Genomics. 2010 Nov 26;11:670.

The non-clonality of drug resistance in Beijing-genotype isolates of Mycobacterium tuberculosis from the Western Cape of South Africa.

Ioerger TR, Feng Y, Chen X, Dobos KM, Victor TC, Streicher EM, Warren RM, Gey van Pittius NC, Van Helden PD, Sacchettini JC.
Department of Computer Science and Engineering, Texas A&M University, College Station, TX, USA. ioerger@cs.tamu.edu

Abstract

Figure 4



Phylogenetic tree constructed from 727 SNPs (excluding those related to drug resistance) by maximum parsimony (a), and also displayed as a cladogram (b) showing the number of changes (unique SNPs) associated with each branch.

J Acquir Immune Defic Syndr. 2011 Jun 1;57(2):146-52.

Extensively drug-resistant TB in Eastern Cape, South Africa: high mortality in HIV-negative and HIV-positive patients.

Kvasnovsky CL, Cegielski JP, Erasmus R, Siwisa NO, Thomas K, der Walt ML.

Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, USA. ckvasnovsky@smail.umaryland.edu

Abstract

BACKGROUND: Tuberculosis is a leading cause of morbidity and mortality worldwide. Patients with extensively drug-resistant tuberculosis (XDR-TB) have had high mortality rates, especially when coinfected with HIV.

METHODS: A retrospective cohort study of the first 206 patients treated for XDR-TB in Eastern Cape Province, South Africa, October 2006 to January 2008, a province that has treated multidrug-resistant tuberculosis since 2000. All 206 patients were hospitalized for treatment until monthly sputum specimens were culture negative.

RESULTS: Sixty-five patients diagnosed with XDR-TB died before XDR-TB treatment start. Among 195 patients starting treatment with a known HIV status, 108 (55.4%) were HIV positive, and 86 patients (44.1%) died during the first year of treatment. HIV-positive patients receiving antiretroviral treatment (ARVs) fared and HIV-negative patients, and more of both these groups survived than HIV-positive patients not on ARVs. However, HIV-negative patients experienced more serious adverse events requiring the withdrawal of medications than did HIV-positive patients, regardless of the use of ARVs.

CONCLUSIONS: Experience in Eastern Cape Province, South Africa, suggests that patients can be treated for both XDR-TB and HIV. We have also shown that such combination therapy can be well tolerated by patients.

“8.4% converted to negative sputum culture in a median of 143 days (IQR 90-207.5 days).”

“patients received an average of only 1.7 drugs considered “effective”.”

“58.4% diagnosed with XDR-TB did not survive 1 year.”

Lancet. 2010 May 22;375(9728):1798-807.

Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study.

Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L, Willcox P, John MA, Reubenson G, Govindasamy D, Wong M, Padanilam X, Dziwiecki A, van Helden PD, Siwendu S, Jarand J, Menezes CN, Burns A, Victor T, Warren R, Grobusch MP, van der Walt M, Kvasnovsky C.

Lung Infection and Immunity Unit, Division of Pulmonology and University of Cape Town Lung Institute, Department of Medicine, Cape Town, South Africa. keertan.dheda@uct.ac.za

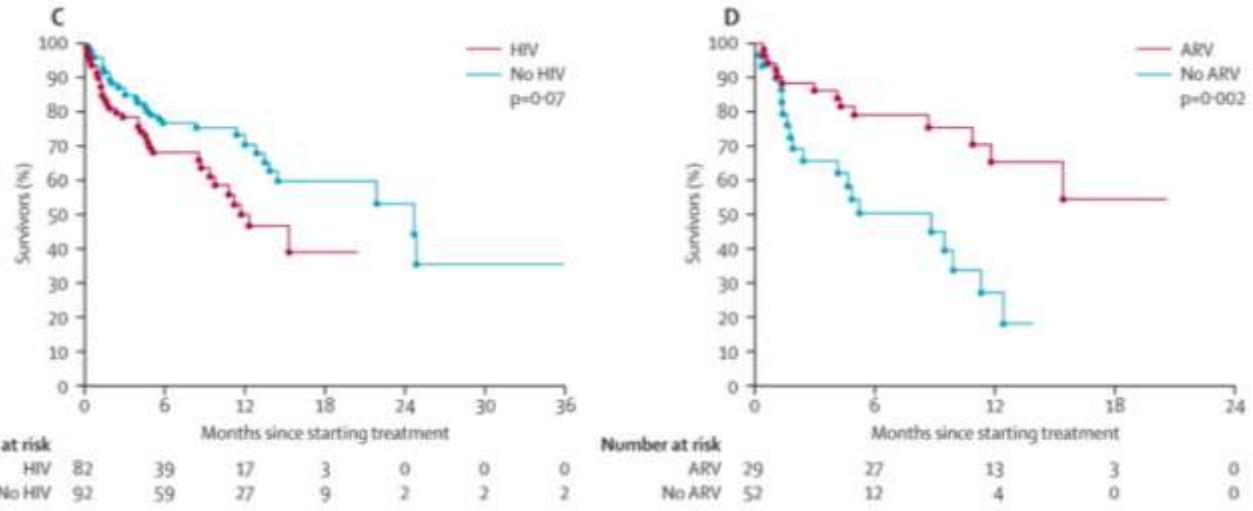
Abstract

BACKGROUND: Data from Kwazulu Natal, South Africa, suggest that almost all patients with extensively drug-resistant (XDR) tuberculosis are HIV-positive, with a fatal outcome. Since, there are few data for the treatment-related outcomes of XDR tuberculosis in settings with a high HIV prevalence, we investigated the associations of these diseases in such settings to formulate recommendations for control programmes.

METHODS: In a retrospective cohort study, we analysed the case records of patients (>16 years old) with XDR tuberculosis (culture-proven at diagnosis) between August, 2002, and February, 2008, at four designated provincial treatment facilities in South Africa. We used Cox proportional hazards regression models to assess risk factors associated with the outcomes-mortality and culture conversion.

FINDINGS: 195 of 227 patients were analysed. 21 died before initiation of any treatment, and 174 patients (82 with HIV infection) were treated. 62 (36%) of these patients died during follow-up. The number of deaths was not significantly different in patients with or without HIV infection: 34 (41%) of 82 versus 28 (30%) of 92 (p=0.13). Treatment with moxifloxacin (hazard ratio 0.11, 95% CI 0.01-0.82; p=0.03), previous culture-proven multidrug-resistant tuberculosis (5.21, 1.93-14.1; p=0.001), and number of drugs used in a regimen (0.59, 0.45-0.78, p<0.0001) were independent predictors of death. Fewer deaths occurred in patients with HIV infection given highly active antiretroviral therapy than in those who were not (0.38, 0.18-0.80; p=0.01). 33 (19%) of 174 patients showed culture conversion, of which 23 (70%) converted within 6 months of initiation of treatment.

INTERPRETATION: In South Africa, patients with XDR tuberculosis, a substantial proportion of whom are not infected with HIV, have poor management outcomes. Nevertheless, survival in patients with HIV infection is better than previously reported. The priorities for the country are still prevention of XDR tuberculosis, and early detection and management of multidrug-resistant and XDR tuberculosis through strengthened programmes and laboratory capacity.



Summary

1) Drug resistance has been in SA for >60 years.
2) Spectrum of different DR Strains.
3) Beijing genotype dominates in certain settings.
4) Transmission drives the DR-TB epidemic.
5) Failure to diagnose – amplification and transmission.
6) XDR-TB is everywhere in SA.
7) "TDR" is evolving.
8) Need to recognize mycobacterial pharmacogenetics.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J Clin Microbiol. 2004 Feb;42(2):891-4.

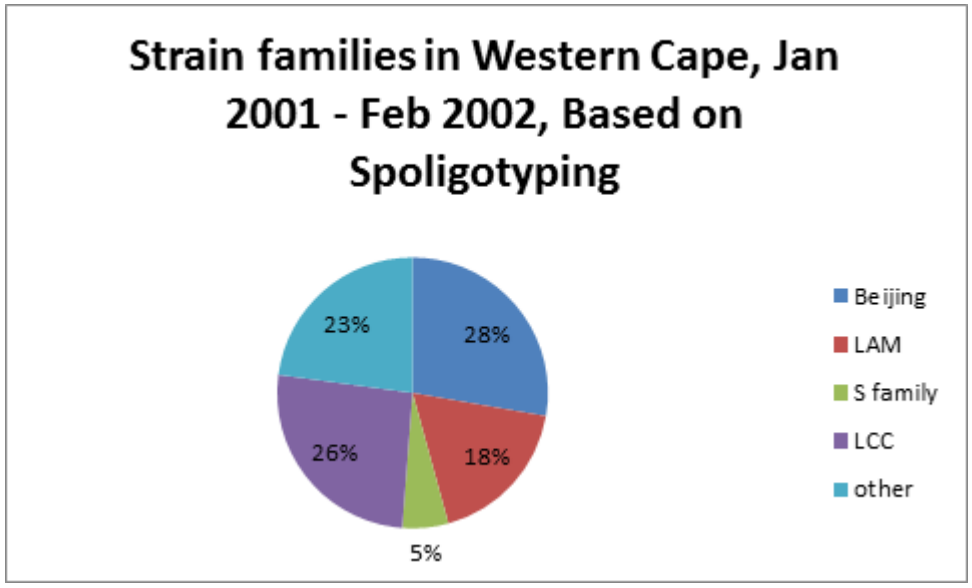
Genotypic and phenotypic characterization of drug-resistant Mycobacterium tuberculosis isolates from rural districts of the Western Cape Province of South Africa.

Streicher EM, Warren RM, Kewley C, Simpson J, Rastogi N, Sola C, van der Spuy GD, van Helden PD, Victor TC.

MRC Centre for Molecular and Cellular Biology, Department of Medical Biochemistry, University of Stellenbosch, Tygerberg, South Africa.

Abstract

Genotypic and phenotypic analysis of drug-resistant Mycobacterium tuberculosis isolates from the Western Cape Province of South Africa showed that drug resistance is widespread and recently transmitted. Multidrug-resistant (MDR) isolates comprise 40% of this collection, and a large pool of isoniazid monoresistance may be a future source of MDR tuberculosis.



Infect Genet Evol. 2012 Jun;12(4):686-94. Epub 2011 Aug 4.

Emergence and treatment of multidrug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in South Africa.

Streicher EM, Müller B, Chihota V, Mlambo C, Tait M, Pillay M, Trollip A, Hoek KG, Sirgel FA, Gey van Pittius NC, van Helden PD, Victor TC, Warren RM.

DST/NRF Centre of Excellence for Biomedical TB Research/MRC Centre for Molecular and Cellular Biology, Division of Molecular Biology and Human Genetics, Faculty of Health Sciences, Stellenbosch University, South Africa. lizma@sun.ac.za

Abstract

Drug resistant tuberculosis (TB) has reached alarming proportions in South Africa, draining valuable resources that are needed to fight drug susceptible TB. It is currently estimated that 9.6% of all TB cases have multi-drug resistant (MDR)-TB, thereby ranking South Africa as one of the highest MDR-TB burden countries in the world. Molecular epidemiological studies have demonstrated the complexity of the epidemic and have clearly shown that the epidemic is driven by transmission as a consequence of low cases detection and diagnostic delay. The latter has in turn fueled the amplification of drug resistance, ultimately leading to the emergence of extensively drug resistant (XDR)-TB. Despite the introduction of new drugs to combat this scourge, culture conversion rates for XDR-TB remain below 20%. Failure to achieve cure may be explained from DNA sequencing results which have demonstrated mutations in 7 genes encoding resistance to at least 8 anti-TB drugs. This review shows how molecular epidemiology has provided novel insights into the MDR-TB epidemic in South Africa and thereby has highlighted the challenges that need to be addressed regarding the diagnosis and treatment of MDR-TB. An important step towards for curbing this epidemic will be collaboration between clinicians, laboratories and researchers to establish scientific knowledge and medical expertise to more efficiently guide public health policy.