Eur Respir J 2000; 16: 200–202
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

Surveillance of antituberculosis drug resistance in Switzerland 1995–1997: the central link

P. Helbling*, E. Altpeter*, P-A. Raeber*, G.E. Pfyffer+, J-P. Zellweger#

Surveillance of antituberculosis drug resistance in Switzerland 1995–1997: The central link. P. Helbling, E. Altpeter, P-A. Raeber, G.E. Pfyffer, J-P. Zellweger. ©ERS Journals Ltd 2000.

ABSTRACT: The purpose of the present paper is to investigate the usefulness of routine notification of antituberculosis drug susceptibilities.

In Switzerland, laboratories have to report susceptibilities to isoniazid, rifampicin, ethambutol, and pyrazinamide to the Federal Office of Public Health. All clinical and laboratory information on every single tuberculosis case is routinely linked. Proportions of drug resistance were calculated and logistic regression was applied to evaluate the role of potential risk factors.

Eighty percent (1056) of all culture-positive tuberculosis cases reported between October 1995 and December 1997 were analysed. The strains of 66 (6.3%) patients had resistances to at least one drug. Risk factors identified were previous antituberculosis treatment (adjusted odds ratio 7.3, 95% confidence interval 3.9–13.6), male sex (1.4, 1.1–2.0), and age <65 yrs (1.5, 1.0–2.3). Fourteen cases (1.3%), 13 of them foreign-born, were resistant to at least isoniazid and rifampicin.

Reporting of drug susceptibilities allows routine assessment of the proportion of drug resistant tuberculosis and populations at risk. This proportion was found to be small in Switzerland. Risk factors were previous treatment for tuberculosis, male sex, and age <65 yrs. Resistance to at least isoniazid and rifampicin was predominantly found in foreign-born patients.

Eur Respir J 2000; 16: 200–202.

*Swiss Federal Office of Public Health, Bern, Switzerland. +Swiss National Centre for Mycobacteria, Dept of Medical Microbiology, University of Zurich, Zurich, Switzerland. #Swiss Lung Association, Bern, Switzerland.

Correspondence: P. Helbling
BAG
3003 Bern
Switzerland
Fax: 41 313238795

Keywords: Drug resistance
epidemiology
Europe
surveillance
Switzerland
tuberculosis

Received: October 20 1999
Accepted after revision March 7 2000

Multidrug resistant (MDR) tuberculosis (TB) is a public health threat requiring sound epidemiological data. Resistant to both isoniazid (H) and rifampicin (R), MDR-TB is difficult and costly to treat [1, 2]. To prevent the selection of resistant strains, standard combination treatment and retreatment regimens for TB are recommended [3]. Hence the need for reliable data on susceptibilities to the recommended drugs on a continuous basis. Alarmed by several reports of outbreaks of MDR-TB in the USA in the early 1990s [4, 5], the Swiss Federal Office of Public Health (SFOPH) requested in October 1995 that microbiology laboratories report results of susceptibility testing to first-line drugs. The authors present the Swiss experience in the first 2 yrs of a surveillance system that allows routine linking of all clinical and laboratory information on every single TB case.

Methods

Physicians and laboratories have to independently report all cases of TB to the SFOPH. The information collected includes the internationally recommended items; the respective case definitions are also used [6]. The information requested is a one page form to be filled in by the clinician and less than one page by the laboratory (http://www.admin.ch/bag). Information from all sources, physicians and laboratories, is centrally linked by personal identifiers and entered into the database as one record per case. As of 1 October 1995, susceptibility testing to H, R, ethambutol (E), and pyrazinamide (Z) became mandatory for all reportable TB cases. Accepted methods for antimicrobial susceptibility testing (AST) are the proportion method (including the radiometric method), the absolute concentration method, and the resistance ratio method [7]. There are nine public and seven private laboratories which perform AST for mycobacteria in the country, including the Swiss National Centre for Mycobacteria (SNCM) which receives isolates from laboratories not performing AST. The SNCM runs an external proficiency testing scheme for Switzerland which includes susceptibility testing of *Mycobacterium tuberculosis* complex and also receives all isolates resistant to R for deoxyribonucleic acid (DNA) fingerprinting by restriction fragment length polymorphism analysis based on the IS*6110* element.

The analysis presented here includes all culture-positive TB cases diagnosed between October 1995 and December 1997 and reported to the SFOPH. Cases were excluded from the analysis if results of susceptibility testing were missing or if *Mycobacterium bovis*, inherently resistant to Z, was identified. Drug susceptibility was analysed according to the standard definitions of the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) [7]. The Possibility of double entries was minimized by soundex

For editorial comments see page 195.

matching, a computer-based method of recognizing phonetically similar names in a database [8]. The analysis included descriptive statistics such as medians, ranges (where appropriate), calculations of proportions with 95% confidence intervals (95% CI), and logistic regression for risk quantification. The major outcome was resistance to any of the four first-line drugs. All analyses were performed using S+ Version 4.5 (MathSoft, Inc., Seattle, WA, USA) for Windows NT and Epi Info Version 6.04b (CDC, Atlanta, GA, USA).

Results

Between 1 October 1995 and 31 December 1997, a total of 1322 culture-positive TB cases were diagnosed and reported to the SFOPH. Thirty-three cases of *M. bovis* and one isolate of *M. tuberculosis* complex resistant to Z and, therefore, presumed to also be *M. bovis* were excluded (2.6%). A further 232 cases (17.5%) were excluded because results of susceptibility testing to one or more of the four drugs were not available for analysis. One thousand and fifty-six cases (79.9%) met the inclusion criteria. Nine hundred and fifty-six were *M. tuberculosis*, four *Mycobacterium africanum*, and 96 *M. tuberculosis* complex without further specification, but none of the latter resistant to Z. Sixty-six patients (6.3%, 95% CI 4.9–7.9) carried a strain which was resistant to any of the four drugs: 45 to H only; three to R only; three to Z only; six to H and R; two to H, R, and Z; six to H, R, E, and Z; and one to H and E. The proportion of drug resistance was elevated in patients with a history of previous treatment for TB (21 of 94: 22.3%, 14.7–32.3) compared to patients never treated before (33 of 718: 4.6%, 3.2–6.5). In patients with missing information on previous treatment, drug resistance was not elevated (12 of 244: 4.9%, 2.7–8.6).

Of the 66 subjects with drug resistance, 48 were born abroad, 50 were males, and 57 were aged <65 yrs (table 1). The most important risk factors were: 1) history of previous anti-TB treatment (adjusted odds ratio 7.3, 95% CI 3.9–13.6); 2) male sex (1.4, 1.1–2.0); and 3) age <65 yrs (1.6, 1.0–2.3). Foreign-born patients showed a slightly, but not significantly, elevated risk of resistance (1.5, 0.8–2.8); (table 2).

During the observation period, 14 cases of MDR-TB (1.3%, 0.8–2.3) were notified. Thirteen of them were foreign-born, seven of which were asylum seekers or refugees, 11 were male, and a history of previous treatment was known in nine (table 1). Their origins were Southern (3) and Eastern (2) Europe, Asia (5), Northern Africa (2) and Sub-Saharan Africa (1). Transmission among MDR patients could be excluded with all 14 TB strains displaying individual DNA fingerprints.

Table 1. – Summary statistics of antituberculosis drug resistance data, Switzerland 1995–1997

Subject characteristics	Any resistance*		MDR		Study population
	n	%	n	%	n
All origins	66	6.3	14	1.3	1056
Swiss-born	18	4.3	1	0.2	418
Previous treatment					
No	10	3.7	1	0.4	271
Yes	6	13.6	0	0.0	44
Unknown	2	1.9	0	0.0	103
Sex					
F:M	4:14		0:1		155:263
Age					
Median (range)	59 (24–90)		34 (NA)		68 (0–97)
<65 yrs	11	5.8	1	0.5	189
>64 yrs	7	3.1	0	0.0	229
Foreign-born	48	7.5	13	2.0	638
Previous treatment					
No	23	5.1	1	0.2	447
Yes	15	30.0	9	18.0	50
Unknown	10	7.1	3	2.1	141
Sex					
F:M	12:36		3:10		246:392
Age					
Median (range)	30.5 (14–71)		32 (22–71)		32 (1–99)
<65 yrs	46	7.9	12	2.1	585
>64 yrs	2	3.8	1	1.9	53
Legal status					
Swiss nationality	2	4.9	1	2.4	41
Foreign workers	19	7.0	2	0.7	273
Asylum seeker and refugees	17	8.5	7	3.5	200
Unspecified and others	10	8.1	3	2.4	124

MDR: multidrug resistance, *i.e.* resistance to at least isoniazid and rifampicin; F: female; M: male; NA: not applicable. *: to isoniazid, rifampicin, ethambutol, pyrazinamide.

Table 2. – Resistance to first-line antituberculosis drugs* (from logistic regression)

	Crude OR	95% CI	Adj. OR	95% CI
Sex				
Female	1		1	
Male	1.4	1.1–1.9	1.4	1.1–2.0
Age				
>64 yrs	1		1	
<65 yrs	1.6	1.1–2.2	1.5	1.0–2.3
Geographical origin				
Swiss-born	1		1	
Foreign-born	1.3	1.0–1.8	1.5	0.8–2.8
Previous treatment				
No	1		1	
Yes	6.0	3.3–10.9	7.3	3.9–13.6

OR: odds ratio; 95% CI: 95% confidence interval; Adj.: adjusted. *: isoniazid, rifampicin, ethambutol, pyrazinamide.

Discussion

This is the first published report on TB drug resistance from a national surveillance system with routine linking of all clinical and laboratory information of all cases notified. The representativeness of the data and their degree of completeness ensure that the situation in Switzerland is as accurately described as possible. The data demonstrate that the size of the problem has not increased in Switzerland since laboratory-based surveys conducted between 1987 and 1992 [9–10] and that the figures are comparable to those in other West European countries [11–13]. Trends over time can now be reliably followed using this surveillance system. MDR-TB among notified cases are rare and occur predominantly among immigrants, but follow-up of cases under treatment would be needed to provide

accurate information on cases becoming MDR after they are notified. In line with most studies published in this field, previous anti-TB treatment was found to be the most important predictor of anti-TB drug resistance [14]. Younger age groups, when compared to patients >64 yrs of age were also described as being at higher risk in the USA [15]. Other possible risk factors such as human immunodeficiency virus (HIV) infection could not be evaluated so far in Switzerland due to special safeguards for confidentiality in HIV infection. However, HIV-TB constitutes only a small fraction of all TB cases occurring in Western Europe [16], and it is therefore unlikely that the data are confounded by HIV infection. According to the WHO/IUATLD guidelines, the item "history of previous antituberculosis treatment" serves as a proxy for the distinction of primary and acquired drug resistance [7]. It is crucial for notifying physicians to provide this information as acquired drug resistance itself is a proxy for the quality of anti-TB treatment in the past. For the clinician, a history of previous anti-TB treatment indicates the need for a special retreatment regimen while results of susceptibility testing are pending [3].

The added value of a system yielding risk factors for drug resistance on a continuous basis is high. It allows treatment recommendations to be updated and the definition of groups in which directly observed treatment, alternative preventive treatment regimens, active screening for disease, or rapid diagnostic methods may be indicated [17].

It has been recommended that laboratories of all European countries report all isolates of *Mycobacterium tuberculosis* complex and that results be linked with clinical reports [6]. Independent mandatory case notification by physicians and laboratories minimizes underreporting. The inclusion of antimicrobial susceptibility testing results in national surveillance databases is an additional step towards a more complete picture of the epidemiology of tuberculosis. This step involves few additional resources in a country where routine susceptibility testing is performed and where a reliable surveillance system for tuberculosis already exists. As a prerequisite, legal provisions have to be made for mandatory reporting and for the use of personal identifiers to link independent reports on individual cases.

Acknowledgements. The authors thank physicians, laboratories, and regional health authorities for making tuberculosis surveillance in Switzerland possible. The authors are also indebted to H. Rieder, B. Neuenschwander, and W.J. Paget for their critical comments.

References

1. Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med* 1993; 329: 784–791.
2. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993; 328: 527–532.
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53: 536–548.
4. Centers for Disease Control and Prevention. Outbreak of multidrug-resistant tuberculosis at a hospital - New York City, 1991. *MMWR Morb Mortal Wkly Rep* 1993; 42: 427–434.
5. Centers for Disease Control. Outbreak of multidrug-resistant tuberculosis - Texas, California, and Pennsylvania. *MMWR Morb Mortal Wkly Rep* 1990; 39: 369–372.
6. Rieder HL, Watson JM, Raviglione MC, *et al*. Surveillance of tuberculosis in Europe. Working Group of the World Health Organization (WHO) and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting on tuberculosis cases. *Eur Respir J* 1996; 9: 1097–1104.
7. World Health Organization and International Union Against Tuberculosis and Lung Disease. Guidelines for surveillance of drug resistance in tuberculosis. *Int J Tuberc Lung Dis* 1998; 2: 72–89.
8. Knuth DE. The art of computer programming. 3rd edn. Reading, MA, USA, Addison-Wesley, 1997.
9. Gusset T, Rieder HL, Salfinger M. Incidence of resistance of tuberculosis bacteria in Switzerland. *Schweiz Rundsch Med Prax* 1993; 82: 1101–1104.
10. Pfyffer GE. Tuberculosis: diagnosis and incidence of resistance 1991/92. *Schweiz Rundsch Med Prax* 1993; 82: 1090–1094.
11. Irish C, Herbert J, Bennett D, *et al*. Database study of antibiotic resistant tuberculosis in the United Kingdom, 1994–6. *BMJ* 1999; 318: 497–498.
12. Schwoebel V, Decludt B, de Benoist AC, *et al*. Multidrug resistant tuberculosis in France 1992–4: two case-control studies. *BMJ* 1998; 317: 630–631.
13. Viskum K, Kok-Jensen A. Multidrug-resistant tuberculosis in Denmark 1993–1995. *Int J Tuberc Lung Dis* 1997; 1: 299–301.
14. Pablos-Mendez A, Raviglione MC, Laszlo A, *et al*. Global surveillance for antituberculosis-drug resistance, 1994–1997. World Health Organization International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 1998; 338: 1641–1649.
15. Bloch AB, Cauthen GM, Onorato IM, *et al*. Nationwide survey of drug-resistant tuberculosis in the United States. *JAMA* 1994; 271: 665–671.
16. Raviglione MC, Sudre P, Rieder HL, Spinaci S, Kochi A. Secular trends of tuberculosis in Western Europe. *Bull World Health Organ* 1993; 71: 297–306.
17. Drobniewski FA. Diagnosing multidrug resistant tuberculosis in Britain. Clinical suspicion should drive rapid diagnosis. *BMJ* 1998; 317: 1263–1264.