

# Resistance of *Mycobacterium Tuberculosis* Strains to Antituberculotics in the Czech Republic in 2003

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## ABSTRACT

**Background.** In 2003 the results of *Mycobacterium tuberculosis* susceptibility testing in 568 (84%) documented definite pulmonary TB cases in the Czech Republic were analyzed.

**Methods and Results.** Resistance to antituberculous agents was found in 4.9% of the strains. The most frequent type of resistance was resistance to one drug – isoniazid (in 1.8% pulmonary TB definite cases). In 2003 multi-drug resistant TB was found in only two patients.

**Conclusions.** The incidence of resistant strains was significantly higher in foreign-born patients – 25% of pulmonary TB patients excreted mycobacteria resistant to at least one antituberculous. *Mycobacterium tuberculosis* resistance to antituberculous was more frequent in previously treated cases of pulmonary TB, especially where a relapse has occurred within 3.5 years since the end of treatment, but it was possible to show a statistical significance of the differences due to the small number of patients.

**Key words:** tuberculosis, epidemiology, *Mycobacterium tuberculosis*, resistance, MDR.

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The World Health Organization ranks the Czech Republic among countries with a favorable TB prevalence record and effective TB surveillance (2). In the CR, TB surveillance is based on the system of Mandatory Reporting of TB Cases to the TB Patients Register. Parallel to notification of the TB Patients Register, mycobacteriological laboratories report each identified mycobacteria strain to the Bacteriological Register of Isolated Mycobacteria Strains (ISBT – Information System of Bacillary Tuberculosis). The register contains entries of both cultivation and typing results, and results of susceptibility to antituberculous (AT) drugs, thus complying with the recommendation of the WHO (5, 7) applying to first detection of *Mycobacterium tuberculosis* (MTB) before the start of treatment. The data of both registers are digital and collected by the national center. Comparison of the two registers allows control of the completeness of the notification and, by matching clinical data with susceptibility/resistance of tuberculosis strains, also the development of a more reliable TB monitoring situation and effective TB surveillance.

The degree of resistance to basic antituberculous (AT) (isoniazid, rifampicin, ethambutol, streptomycin) has a direct impact on the result of treatment; insufficient and ineffective treatment, on the other hand, prepares the conditions for the build-up of resistance (2). Resistance therefore has significance for the evaluation of the TB epidemiological situation as well as a direct impact on the treatment of individual cases. MTB resistance to AT has an unfavorable effect on the outcome of treatment. Treatment of resistant forms of TB requires the administration of very expensive drugs for longer periods than in the case of uncomplicated tuberculosis. MTB resistance thus also has a considerable economic impact.

## DATA SET AND APPLIED METHODS

Output configurations from the TB Patients Register, managed by the Institute of Health Care Data and Statistics (*Ústav zdravotnických informací*

*a statistiky ČR, ÚZIS*), were used for the analysis of TB data for 2003. Newly detected cases of TB are reported to the register by the physicians in attendance, using the Mandatory TB and Other Mycobacteria Notification system. The data are checked and supplemented with investigation results (including susceptibility results) for mycobacteria sent in by bacteriological laboratories to the Bacteriological Register of Isolated Mycobacteria Strains (ISBT), managed by the State Health Care Institute. Statistical evaluation was carried out using the  $\chi^2$  test, with Yates' correction in the case of small numbers or, where needed, Fisher's exact test. A reliability level of 95% and higher ( $p \leq 0.05$ ) was considered statistically relevant.

## RESULTS

In the CR, 660 newly detected definite cases of pulmonary TB were reported to the TB Patients Register in 2003 (Tab. 1). Of this number, cultivation results were available for 568 patients (86%) from ISBT. The results of MTB cultivations in 92 patients with bacteriologically proven pulmonary TB (14%) were not found in ISBT. Of the 568 patients with bacteriologically proven pulmonary TB, whose cultivation results were known, 556 (84%) had their susceptibility to isoniazid, rifampicin, ethambutol and streptomycin investigated. In 11 cases investigation of susceptibility was not performed, and in the case of one strain the sample had been contaminated.

In 2003 we did not find any increase in MTB resistance to AT (Tab. 2). Resistance was actually lowest for the last four years – only 27 patients. Due to the small numbers involved, it has not been possible to prove any statistical significance of the differences. The most frequently found resistance was to isoniazid, with resistance to this one drug only in 10 patients, and resistance to multiple drugs in 13 patients. In the case of other antituberculous resistance to a single drug was investigated only in individual cases; multiple resistance, besides isoniazid, was most common in streptomycin; it was confirmed in strains from 14 patients (13 were simultaneously resistant to isoniazid). Multiple-drug resistant strains (MDR resistance to isoniazid and rifampicin) were found in 2 patients only (one a Czech national, the second foreign-born).

**Table 1.** Results of bacteriological investigation according to ISBT in newly reported pulmonary TB entered into the TB Patients Register in 2003 as bacteriologically proven TB

	Number	Percentage
pulmonary TB bacteriologically proven	660	100%
cultivation result not found in bacteriological register	92	14%
cultivation result found in bacteriological register	568	86%
susceptibility to antituberculosics investigated	556	84%
susceptibility to antituberculosics not investigated	11	2%

the difference is again not statistically significant because of the low numbers (Tab. 4).

A significantly higher number of cases of pulmonary TB caused by resistant strains of mycobacteria was recorded in foreign-born persons, especially asylum-seekers. Of all the cases of bacteriologically proven pulmonary TB in foreign-born persons, 25% were caused by strains resistant to at least one AT; in the asylum-seeker group it was actually more than 33% (Tab. 5). The difference compared to our own pulmonary TB population is statistically significant ( $p < 0.0001$ ). Of the 10 foreigners with pulmonary TB and excreting MTB resistant to one or more ATs, 5 came from countries of the former Soviet Union, 4 were Vietnamese and one was born in Peru.

**Table 2.** *Mycobacterium tuberculosis* resistance to antituberculosics

	2000		2001		2002		2003	
	Number	%	Number	%	Number	%	Number	%
patients found susceptible	628	100	679	100	509	100	556	100
<i>Susceptibility results:</i>								
susceptible to all antituberculosics	598	95.2	648	95.4	476	93.5	529	95.1
resistant to one or more ATs	30	4.8	31	4.6	33	6.5	27	4.9
<i>Resistance to one drug:</i>								
isoniazid	7	1.0	9	1.3	7	1.4	10	1.8
rifampicin	4	0.6	3	0.4	2	0.4	0	0
ethambutol	1	0.1	1	0.1	1	0.2	1	0.2
streptomycin	3	0.4	2	0.3	3	0.6	2	0.4
resistance to one drug in total	15	2.1	15	2.2	13	2.6	13	2.3
<i>Resistance to multiple drugs:</i>								
multiple drug resistance (MDR)	4	0.6	9	1.3	10	2.0	2	0.4
other MDRs	11	1.8	7	1.0	10	2.0	12	2.2

The number of resistant strains is distributed evenly throughout the country, in all regions (Tab. 3). Due to the small numbers involved it has not been possible to prove statistically significant differences, although the finding of more than 15% of cases of pulmonary TB caused by resistant MTB in the Karlovy Vary region is on the border of significance ( $p = 0.11$ ). The reason is foreigners – one Ukrainian and two Vietnamese – who excreted MTB resistant to at least one AT.

From the point of view of earlier AT treatment, more resistant strains were recorded in patients treated previously with AT (for at least 4 weeks), especially if they had been treated for an earlier TB illness during the last 3.5 years – where the number of the resistant strains was more than twice higher. However,

**Table 3.** AT resistance in pulmonary TB in the CR according to region

Region	Patients with proven susceptibility	Resistant to one or more ATs	
		Abs. Number	%
Prague	125	1	0.8
Central Bohemia	72	3	4.2
South Bohemia	12	0	0
Pilsen	32	2	6.2
Karlovy Vary	26	4	15.4
Ústí upon Elbe	45	2	4.4
Liberec	13	1	7.7
Hradec Králové	31	2	6.5
Pardubice	19	0	0
Vysočina	15	2	13.3
South Moravia	44	4	9.1
Olomouc	22	0	0
Zlín	32	2	6.2
Moravian Silesia	68	4	5.9
Czech Republic (total)	556	27	4.9

## DISCUSSION

In the Czech Republic the share of definite cases of pulmonary TB reported in 2003 to the TB Patients Register, where it has been possible to retrieve the susceptibility results from the Bacteriological Register, was almost 85%. That is more than the 70% average in European countries contributing individual data to EuroTB (1). Czech Republic has thus joined the ranks of countries where susceptibility is known in 80% to 90% of definite pulmonary TBs (Germany, Latvia, Norway, United Kingdom). A similar percentage (85.4%) was found in Denmark by Thomsen (12), who compared the register of TB cases

**Table 4.** AT resistance in pulmonary TB according to earlier AT treatment

Earlier treatment	Total	Resistant to one or more ATs	
		Abs. Number	%
not previously treated with AT	496	24	4.8
treated with AT longer than 4 weeks	60	3	5
of this treated in the recent 3.5 years	17	2	11.8

**Table 5.** AT resistance in pulmonary TB according to the country of birth

Born	Total	Resistant to one or more ATs	
		Abs. Number	%
in the CR	514	17	3.3
abroad	42	10	23.8
of these asylum - seekers	17	6	35.3

with the bacteriological register of isolated MTB strains. He did not succeed in retrieving data for 14% of pulmonary TB cases indicated by clinical physicians as definite TB. This could have been due to the fact that patients were identified differently in the two registers and that it was not possible to match the patients from the TB register with the corresponding cultivation results, or to the fact that the disease was not definite albeit identified as such by the clinician.

Resistance to one or more ATs is low in the CR, concerning individual cases of pulmonary TB and fluctuating during the last four years in the region of 5%. This corresponds with the data found in targeted studies carried out by WHO (7, 8) as well as with EuroTB data (1). Compared to 1999 (8), when resistance to one or more ATs was found in 4.2% cases, the current 4.9% do not differ as far as resistance is concerned. In 1995–1997, resistance to one or more ATs was found by Helbling in 6.3% of patients in Switzerland (8) and, in 1997–1998, by Thomsen in 7.3% of patients in Denmark (6), which in both cases is more than in our study. This is proof that the TB surveillance program in the CR is effective and that intensive treatment after 1998 led to a reduction of TB sources at a time of stagnating share of resistance (1–4, 10, 11).

Most MTB strains were resistant to isoniazid, which corresponds with earlier findings (1, 7, 8, 11). These were, however, isolated cases in the context of the whole TB surveillance issue, not exceeding 3% of the detected definite pulmonary TBs. The highest resistance to a single drug – isoniazid – was found by Thomsen (6) in Denmark (1.6%) and Helbling (9) in Switzerland (4.2%).

An important circumstance is the first drop in the number of definite pulmonary TB cases caused by MDR-TB bacilli in three years (12). One case was a previously treated foreign national whose TB had been diagnosed and treated abroad; the second case was a previously treated Czech national, whose first treatment had been concluded in the prescribed manner.

The prevalence of resistance in individual regions is influenced by the low numbers, but the impact of foreigners is starting to be felt, especially in the Karlovy Vary region. The small numbers of patients also make it difficult to perform any detailed analysis of earlier treatments, which have a marked influence on the development of resistance (13, 14). The higher proportion of detected resistance in those who had been treated during the last three and a half years supports the justification of dispensary care during the first years following termination of treatment as provided in the CR for almost 20 years now, in compliance with the relevant decree (15). An essential fact is the contribution to resistance by persons born abroad (37%), coming from countries to the east of the CR, especially asylum-seekers. The trend from last year has thus been confirmed (12). The effect of foreign-born persons on resistance has been found also by Schwoebel in France (10), when in 1992–1994 almost half of MDR-TB male patients were not born in Europe. Thomsen (6) in Denmark found resistance to at least one AT in 14.6% of bacteriologically proven cases of TB in foreigners, Helbling in Switzerland gives almost 35% (9). Patients with detected MTB resistance to at least one AT usually come from countries which the WHO has designated as resistance risk countries (7,

8, 17). The question is, what will be the impact of the CR accession to the European Union on TB morbidity and on AT resistance. Should the TB problem and MTB resistance to antitubercotics of foreigners become worse, targeted measures would have to be focused on this particular population group.

## CONCLUSION

MTB resistance to AT in the CR was low in 2000–2003; in 2003 it did not exceed 5%. This is proof of the success and efficacy of treatment and of the effectiveness of the TB surveillance program in the CR. MTB strains isolated from persons born abroad account for a significant proportion of the resistance. Should this trend continue, active measures within the TB surveillance program would have to be focused on this population group.

### Abbreviations

AT	–	antitubercotics
ISBT	–	Information System of Bacillary Tuberculosis
MDR	–	multiple-drug resistance
MTB	–	<i>Mycobacterium tuberculosis</i>
TB	–	tuberculosis
ÚZIS	–	Institute of Health Care Data and Statistics

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