LUCRĂRI ORIGINALE

Romanian Anti-TB Drugs resistance surveillance 2003-2004

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REZUMAT

Ancheta 2003-2004 privind chimiorezistenţa la medicamentele antituberculoase în România

România a decis şi a iniţiat o anchetă naţională privind rezistenţa la medicamentele antituberculoase pentru care s-a folosit metodologia standardizată propusa de OMS şi UICTMR.

Protocolul a fost dezvoltat cu asistenţă tehnică din partea OMS; ancheta a început în iunie 2003 şi s-a terminat în iunie 2004. S-a testat sensibilitatea la 4 medicamente antituberculoase de linia I: Izoniazida (H), Rifampicina (R), Streptomicina (S) şi Etambutol (E).

Testarea sensibilităţii s-a făcut prin metoda concentraţiilor absolute.

Au fost incluşi în studiu 1251 pacienţi cu tuberculoză din 60 „clustere": 869 cazuri noi şi 382 anterior trataţi (retratamente). Din sistemul de penitenciare au fost incluşi 85 pacienţi, 47 cazuri noi şi 38 trataţi anterior.

Rezultate:

Populaţia generală	*Cazuri noi*	*Trataţi anterior*
• orice rezistenţă	*14.3 %*	*32.7 %*
• monorezistenţă	*8.9 %*	*12.6 %*
• MDR (H+R)	*2.9 %*	*11.0 %*
• H+E şi/sau S	*1.8 %*	*9.2 %*
• R+E şi/sau S	*0.4 %*	*0.0 %*
Sistemul de penitenciare:		
• orice rezistenţă	*17.0 %*	*42.1 %*
• monorezistenţă H	*6.0 %*	*7.9 %*
• monorezistenţă R	*6.4 %*	*7.8 %*
• MDR	*4.3 %*	*13.2 %*

S-a propus estimarea tendinţei evolutive a chimiorezistenţei la medicamentele antituberculoase în România pentru perioada următoare.

ABSTRACT

Romania decided and initiated a DRS for anti-TB drugs at national level using the standardized methodology proposed by WHO and IUATLD.

The DRS protocol was designed with technical assistance from WHO; the surveillance started in June 2003 and ended in June 2004. It was tested the susceptibility to the 4 first line anti-TB drugs: Isoniazide (H), Rifampicine (R), Streptomycine (S), Ethambutol (E).

Drug susceptibility testing used: indirect absolute concentration method.

There were included in the survey 1251 TB patients from the 60 clusters: 869 new cases and 382 previously treated. From the penitentiary system were included 85 TB patients, 47 new cases and 38 previously treated.

Results:

General population:	*New cases*	*Previously treated*
• any resistance	*14.3 %*	*32.7 %*
• monoresistance	*8.9 %*	*12.6 %*
• MDR (H+R)	*2.9 %*	*11.0 %*
• H+E and/or S	*1.8 %*	*9.2 %*
• R+E and/or S	*0.4 %*	*0.0 %*
Penitentiary system:		
• any resistance	*17.0 %*	*42.1 %*
• monoresistance H	*6.0%*	*7.9 %*
• monoresistance R	*6.4 %*	*7.8 %*
• MDR	*4.3 %*	*13.2 %*

Estimations of the trend of anti-TB drug resistance in Romania for the next period was proposed.

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I. Introduction

Drug resistance (DR) is a phenomenon that has a negative effect on the efficiency of tuberculosis (TB) treatment and on TB burden. The drug resistance surveillance (DRS) is therefore an essential tool to monitor effectiveness of TB control efforts.

Since almost a decade (1994), World Health Organization (WHO) decided to assess these phenomenon worldwide and joined forces with the International Union Against Tuberculosis and Lung Diseases (IUATLD) launching the Global Project on anti-TB Drug Resistance Surveillance[1, 2].

Romania decided to join this global project and initiated a DRS for anti-TB drugs using the same standardized methodology proposed by WHO and IUATLD[1,2, 3, 9].

The DRS protocol was designed with technical assistance from WHO; the surveillance started in June 2003 and ended in June 2004.

The susceptibility to the 4 first line anti-TB drugs was tested: Isoniazide (H), Rifampicine (R), Streptomycine (S), Ethambutol (E).

II. Background

Country profile

II.a. Geography and population

At the starting date of DRS the population of Romania was 22,835,000 inhabitants for 237,500 km^2 (21,789,842 inhabitants in 2004).

There are 41 counties and the capital city Bucharest with 2,500,000 inhabitants estimated.

II.b. TB epidemic

According to the WHO reports, Romania is one of the top five European priority countries in terms of new TB cases notification rate[4,5, 6].

In comparison with year 1985 when there was registered the lowest TB notification rate (55.8 %000), the figure doubled in 1997. In 2002 it was registered the highest TB notification rate for new cases and relapses (142.2 %000). After this year, a slightly decreasing was registered (134.6 in 2004 and 126.4 %000 in 2005)[4,5, 3, 29].

Annually there are registered over 25,000 new TB cases and relapses (79 new TB cases are notified daily). There are registered important differences in TB notification rate related to the socio-economic status of different counties (variation between <50 %000 and >200 %000)[4,5, 6, 22].

II.c. Information about the National TB Programme

The National TB Control Programme (NTP) is coordinated at central level by the Public Health Department and the National Commission of Pneumophtysiology from the Ministry of Public Health (MOPH).

The Central Unit of NTP based in "Marius Nasta" Lung Diseases Institute performs the implementation.

At the Central Unit level there is the National Supervision Commission and the TB Surveillance, human resources development, research and information- education- communication (IEC) departments.

The DOTS Strategy implementation started in Romania since 1997 and reached 100% population coverage in 2005. During the DRS the coverage was 54%.

The TB Control Programme in the penitentiary system is fully integrated in the NTP[4,5, 6, 22, 23,29].

II.d. TB laboratories network, National Reference laboratories (NRL) and connection with Supranational Reference Laboratory (SRL)

The activity of Romanian TB laboratory network is integrated in the NTP. In 2001 consisted on 181 laboratories, with one national coordinator, 41 county coordinators, and one local coordinator for each laboratory.

The TB laboratory network has 59 level I laboratories which perform only smear examination, 54 level II laboratories, which perform smear examination and culture for *M. tuberculosis*, and 75 level III laboratories which perform smear, culture and drug susceptibility tests (DST).

At the starting date of DRS in Romanian, there were 3 NRL responsible for training, supervision and quality control in their areas[22, 23].

The workload of TB Laboratories network in Romania in 2001, 2 years before starting the DRS, is presented in table I.

Since 2001, SRL from Swedish Institute for Infectious Disease Control – Stockholm, Sweden (Prof. Sven Hoffner) supervised the network activity. The first round DST proficiency testing was done in 2002. Concordance of the results obtained in Bucharest, Cluj and Iași versus Stockholm was 20/20, 20/20 respectively 20/20 for H, and 19/20, 20/20 respectively 20/20 for R.

II.e. Previous DRS

Data from previous DRS, performed in Romania in year 1995 are included in table II.

Table I.
Workload of TB laboratories network in Romania in 2001

Workload	Romania	Area of supervision for each NRL		
		Cluj	Bucharest	Iași
Total number of smear examinations	738,130	204,941	300,147	233,042
Number of smear positive examinations	81,519	17,804	41,134	22,258
Smear positive rate	11.04%	8.68%	13.87%	9.69%
Total number of cultures (Lowenstein- Jensen media)	726,599	205,599	290,980	230,020
Positive cultures	98,829	20,873	50,447	27,509
Culture positive rate	13.60%	10.15%	17.33%	11.95%
Number of drug susceptibility tests performed	18, 817	3,587	9,212	6,018

The DST for H, R, S, E were performed in Bucharest "Marius Nasta" Institute by TB Laboratory, and the External Quality Control was insured by the Antwerp Institute for Tropical Medicine, Belgium (Prof. Francoise Portaels)[7].

Table II.
Results of Romanian DRS performed in 1995

	Primary		Acquired	
	N	%	N	%
Total number of strains tested	**1636**	**100**	**1521**	**100**
Any resistance	160	9.8	552	36.3
H resistance	121	7,4	481	31,6
R resistance	55	3,4	249	16,4
Mono resistance	87	5.3	254	16.7
Multidrug resistance (MDR)	**45**	**2.8**	**219**	**14.4**
Other resistances	26	1.6	79	5.2

III. Objectives of 2003- 2004 DRS

a. To estimate the resistance level and pattern to 1st line anti-TB drugs for:

- new TB cases in Romania
- previously treated TB cases in Romania
- for new and previously treated TB cases in the penitentiary system in Romania.

b. To establish the routine DRS basis, in order to assess the trends over time of this phenomenon.

IV. Materials and Methods

a. Main characteristics of 2003- 2004 DRS:

• duration	12 months
• culture media used	Lowenstein- Jensen
• drug susceptibility testing method	Indirect absolute concentration method
• laboratory accuracy	>95% for R
• specificity for R testing	>95%
• estimated new TB cases with SS+	1020 to be included
• coverage	countrywide
• sampling method	cluster sampling
• sampling fraction	8%; 60 clusters; 17 new cases per cluster

b. It was considered acceptable a loss up to 15 % of strains

c. In order to calculate the sample size the following were taken into consideration:

- the 12.697 new cases smear positive (SS+) patients registered annually
- expected R resistance: 5%
- precision: 2
- design effect: 2 (for cluster)
- confidence interval: 95

d. in order to include the 1020 new TB cases, there were randomly selected 60 clusters (diagnostic centers) with an intake of 17 consecutive SS+ new TB cases

e. during the intake of the 17 new TB cases, there were also included all previously treated cases which fulfilled the inclusion criteria.

f. In the penitentiary system there were included all new cases and all previously treated cases with SS+ identified during the survey.

V. Intake of patients and logistics

V. a. Intake period

The total period of case intake was 12 months:

a. For the penitentiary system, the intake period started in the 1st quarter and lasted 12 months.

b. For the general population, the intake period started quarterly with 15 clusters, based on the time needed for identification of the 17 new TB cases.

V. b. Inclusion and exclusion criteria

Inclusion criteria:

For primary resistance study group:

Patients with pulmonary TB SS+ (from 1-9 AFB/100 fields to 3+ AFB) who have never been treated for TB or have been treated for less than 30 days.

For acquired resistance study group:

Patients with pulmonary re-treatment TB cases, SS+.

The main inclusion criterion was further culture confirmation (over 10 colonies growth).

Exclusion criteria:

- Smear negatives (SS -) pulmonary TB;
- extra-pulmonary TB;
- transferred cases;
- cases with address in another diagnostic center territory;
- cases with SS+ result obtained from bronchial and gastric aspirates;
- cases with SS+ already included in the survey;
- cases with SS+ sputum during monitoring treatment;
- cases with other mycobacterium than tuberculosis complex.

If, during the enclosure period some cases failed, defaulted, or become chronics and they were investigated again for the re-treatment, they were not been included a second time in the survey.

V. c. Transportation

Internal transportation

Before starting the survey, a rigorous schedule for transportation of strains in biosaftey conditions from diagnostic centers to NRL was established.

Any situation with SS+ and no grow on culture media or any loss of a strain/ sample was immediately announced to the Central Unit.

External transportation

SRL Stockholm - Sweden insured the quality control of DST, where quarterly, 25% DR strains and 10% susceptible strains were sent.

The strains to be sent for external quality control were selected strictly in test ranking, every fourth any resistant strain and every tenth susceptible strain.

The strains were retested in SRL Stockholm with Bactec 460 radiometric method.

V.d. Training

Training of participants to the DRS was considered a very important step for its success. Two weeks before the starting date of the patients intake period there were organized training sessions for lung diseases specialists and TB laboratories staff from the diagnostic centers that started the case intake.

They received information regarding organization, logistics, integration of the Romanian TB Laboratory network in the international one, about quality control of the diagnosis and its procedures.

VI. Laboratory methods

VI. a. Description of methods:

VI.a.1. Sputum collection and smear examination

Sputum collection and smear examination were performed according to the international recommendations[10, 11, 12, 13, 14, 15, 16, 17, 18].

VI. a.2. Culture

Cultures were done on Lowenstein-Jensen media. Decontamination of specimens, inoculates preparation, incubation, reading and registration of results were done according to the international standards[19, 20].

VI.a.3. Identification of the strains

During the DRS all strains were identified as belonging to the *M. tuberculosis* complex.

VI.a.4. Drug susceptibility testing

It was used indirect absolute concentration method for H 0.2 and 1 μg/ml, R 20 and 40 μg/ml, S 4 and 10 μg/ml, E 2 and 3 μg/ml [10, 11, 12,16, 18, 21].

There were analyzed results for the following concentrations: H 1 μg/ml, R 40 μg/ml, S 10 μg/ml, E 3 μg/ml.

Definition of resistance:

Sensitive - on the tubes with anti-TB drugs no growth, or growth less than 20 colonies.

Resistant – on the tubes with anti-TB drugs growth, more than 20 colonies[13, 14, 15, 19, 20,21]

VI. b. Quality control (QC) of diagnosis[14, 15]

Internal QC of susceptibility testing by using the reference *M. tuberculosis* H37Rv strain for each media batch was insured.

International QC of susceptibility testing

There were retested at SNRL Stockholm 185 sensitive and drug resistant strains, selected using the above-mentioned criteria.

VI.c. Data management and analysis

Data were kept in electronic files using in EPI-info, version SDRTB4 at the Central Unit [12, 13, 14, 15]

VII. Results

1251 TB patients were included in the survey. Their distribution by age and sex was the following:

• Patients from the 60 clusters:

New cases: 869, among them 619 (72%) were males and 250 (28%) were females. Age ranking between 14 and 88 years (40.97 average).

Retreated cases: 382 cases, among them 311 (81.42%) were males, and 71(18.58%) were females. Age ranking between 18 and 84 years (43.8 average).

• Patients from the penitentiary system:

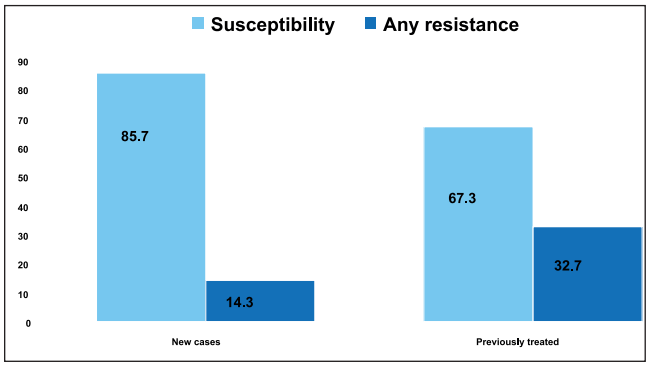
New cases: 47, among the 42 (89.3%) were males and 5 (10.6%) were females. Age ranking between 18 and 55 years (29.3 average).

Retreated cases: 38, among them 37 (97.3%) were males and 1 (2.7%) was female. Age ranking between 21 and 53 years (36,8 average).

The drug susceptibility testing of the 869 new TB cases revealed fully susceptibility to 1st line anti- TB drugs H,R, E, S, for 745 strains (85%) and drug resistance to at least one drug for 124 isolated strains (14.3%).

For the 382 strains isolated from previously treated cases fully susceptibility was met in 257 (67,3%) and drug resistance to at least one drug in 125 strains (32,7%) (figure 1).

Figure 1.
Susceptibility - Any resistance



The results of the 3 NRL showed same proportion of susceptibility and any resistance to anti- TB drugs for new cases and previously treated cases in their areas.

The highest percentages of monoresistance among new cases are registered to H and S (3.6% for each).

For previously treated cases, the isolated strains were 8.6% resistant to H. For the other anti- TB drugs the resistant of isolated strains was lower: 2.6% to S, 1.8% to R and 0% to E (Table III).

MDR (drug resistance to at least H and R) was registered for 2.9% of new cases and 11% of previously treated cases.

64% (16 out of 25 cases) from MDR among new cases were additionally resistant to other anti- TB drugs (table IV).

Table III.
Monoresistances

	New cases	%	Previously treated cases	%
Number of cases tested	869	100	382	100
H	31	31	3.6	8.1
R	13	1.5	7	1.8
E	2	0.2	0	0
S	31	3.6	10	2.6
Total	**78**	**8.9**	**48**	**12.6**

Table IV.
Resistance to HR (MDR)

	New cases	%	Previously treated cases	%
Number of cases tested	869	100	382	100
HR	9	1.0	4	1.0
HRE	2	0.2	3	0.8
HRS	4	0.5	5	1.3
HRES	10	1.2	30	7.9
Total	**25**	**2.9**	**42**	**11.0**

- Resistance to all four first line drugs was registered in 1.2% (10 cases out of 869) among new cases, and 7.9% (30 cases out of 382) among previously treated cases.
- 10 out of 25 (40%) new cases with MDR and 30 out of 42 (71%) previously treated cases were registered with resistance to all four first line drugs.

Resistance to H associated to other resistances (table V) was registered in 1.8% (16 cases out of 869) strains from new cases and 9.2% (35 cases out of 382) strains from previously treated cases. Association with resistance to S (1.5% and 3.7%) is more frequent that to E (0.2% and 0.1%)

Resistance to R is associated with resistance to S in 0.3% of strains from new cases. Association with other resistances is negligible: 0% with E and 0.1% with ES (table V).

Table V.
Resistance to H + E and/ or S
and resistance to R +E and/ or S

	New cases	%	Previously treated cases	%
Number of cases tested	869	100	382	100
H+E and/or S				
HE	1	0.1	6	1.6
HS	13	1.5	14	3.7
HES	2	0.2	15	3.9
Total	**16**	**1.8**	**35**	**9.2**
R+E and/or S				
RE	0	0	0	0
RS	3	0.3	0	0
RES	1	0.1	0	0
Total	**4**	**0.4**	**0**	**0**

Any resistance to H was found in 8.3% of strains from new cases and 28.3% from previously treated cases, and any resistance to R in 4.8% of new cases and 12.8% of previously treated cases.

Any resistance to S was 7.3% in new cases and 19.4% in previously treated cases.

Any resistance to E was 2.0% in new cases and 14.2% in previously treated cases.

The results for the strains isolated from penitentiary system cases are registered in the following table (table VI)

Table VI.
DRS results for the penitentiary system

Drug resistance pattern	New cases	Previously treated cases
Fully sensitivity	83%	57.9%
Any resistance	17.0%	42.1%
Resistance to H	0.0%	7.9%
Resistance to R	6.4%	7.8%
MDR	4.3%	13.2%
Any resistance to H	10.6%	31.6%
Any resistance to R	10.6%	21.1%
Any resistance to E	7.3%	19.4%
Any resistance to S	2.0%	14.2%

Regarding the **global prevalence of drug resistances** (cumulative for new cases and previously treated cases), the results are the following (table VII):

Table VII.
"Global" prevalence of drug resistance
(new cases and previously treated cases)

	New cases	Previously treated cases	Global prevalence %[1]
Number of cases tested	**869 (69.46%)**	**382 (30.54%)**	**100%**
Fully sensitivity	745 (85.73%)	257 (67.27%)	**82.72%**
Any resistance	124 (14.26%)	125 (32.72)	**17.28%**
Monoresistances			
Isoniazide (H)	31 (3.6%)	31 (8.1%)	**4.34%**
Rifampicine(R)	13 (1.5%)	7 (1.8%)	**1.55%**
Ethambutol (E)	2 (0.2%)	0 (0%)	**0.17%**
Streptomycine(S)	31 (3.6%)	10 (2.6%)	**3.44%**
Multiresistances			
HR (MDR)	25 (2.9%)	42 (11%)	**4.23%**
H+E or S	16 (1.8%)	35 (9.2%)	**2.34%**
R+E or S	4 (0.4%)	0 (0%)	**0.34%**
H any resistance	72 (8.3%)	108 (28.0%)	**11.52%**
R any resistance	42 (4.8%)	49 (12.6%)	**6.08%**

Drug resistance pattern analysis for previously treated cases by case category

For previously treated cases the drug resistance pattern analysis was performed by case category: relapse, retreatment for failure, retreatment after default, showing the following results: out of 382 cases analyzed, 176 were relapses, 43 retreated after default, 123 retreated for failure, and for 40 cases, the case category is unknown. The drug resistance pattern for each case category is shown in table VIII.

Table VIII.
Drug resistance pattern for previously treated cases

Total previously treated cases = 382 (40 with unknown category)												
Relapses (176)				**Defaulters (43)**				**Failures (123)**			
HR Sens	H Res	R Res	HR Res	HR Sens	H Res	R Res	HR Res	HR Sens	H Res	R Res	HR Res
131 7.4%	27 15.3%	5 2.8%	13 7.4%	35 81.4%	7 16.3%	0 0%	1 2.3%	67 54.5	27 22%	2 1.5%	27 22%

For relapses and defaulters, an important percentage of strains isolated (75-80%) preserved their sensitivity to major anti-TB drugs. Even for failures, only 45% of strains are resistant to at least one major anti-TB drug, and only 22% are resistant to both H and R. These results suggest that the treatment outcome evaluation for these cases as „failures" is sometimes not exactly; actually, they might be defaulters and not failures.

1. It has been calculated the weighted average of drug resistance prevalence, taking into consideration a number of 22,000 new cases and 4,300 relapses.

VIII. Discussions

The DRS for anti-TB drugs in Romania was necessary for evaluation of drug resistance trend in comparison with previous surveys results, and on the other hand to assess if the 10 times higher prevalence of DR phenomenon registered in this European Region than the global prevalence is at the same level in Romania, too[24, 28, 29].

The survey, performed at national level during 12 months, based on population proportionate cluster sampling, used the absolute concentration method on Lowenstein-Jensen media for testing.

The SNRL from Stockholm (Prof. Sven Hoffner) insured the quality control of the results. Accuracy and specificity for R resistance testing at >95% demonstrated previous this survey was at the same level during all its implementation period.

1251 patients were included in the study, 69.5% new cases (869 patients) and 30.5% previously treated cases (382 patients).

From the penitentiary system 85 patients were included, 53% new cases (47 patients) and 44.7% (38 patients) previously treated cases.

Drug resistance prevalence

For 745 (85.7%) strains isolated from the 869 new cases included in the study the DST revealed sensitivity for all four drugs tested (H,R,E,S), and for 124 (14.3%) at least one resistance.

Taking into consideration the WHO reports on Global Drug Resistance, in comparison with other countries from the same geographic region (Eastern Europe), the level of 15 % for "any resistance" registered in Romania is reasonable: Russian Federation 37.5%, Latvia 31.7%, Estonia 28.5%, Lithuania 29.2%, Kazakhstan 51.7% etc[25, 26, 28].

However, view the fact that annually there are registered in Romania over 22,000 new cases, we can estimate that the number of cases with at least one resistance may be up to over 3,150 cases.

For 257 (67.3%) cases, out of 382 previously treated cases included in the study, the isolated strains tested were sensitive, and for 125 (32.7%) revealed at least one resistance. Making the same comparison with the countries in the same region the DR prevalence is not very high (Latvia: 38.1%, Estonia 58.8%, Lithuania 67.9%, Uzbekistan 74.4%), but in comparison with the countries from Western Europe, the level is very high[29].

In comparison with the previous DRS (1995) the levels registered in 2003 indicate an increase of drug resistances among new cases from 9.8% to 14%, and maintenance of drug resistances among previously treated cases: 36.3% in 1995 vs. 32.7% in 2003.

One third of previously treated cases are resistant to at least one 1st line anti-TB drug[7].

The calculation of global prevalence of drug resistance (any resistance) cumulative for new cases and previously treated cases reveal the fact that 17.28% of cases registered during one year might have at least one resistance. Even this indicator in not very relevant, being only orientative, this estimation offers an overview about the importance of the phenomenon. Thus, we can estimate that for the 26,000 cases registered annually, 4,500 might have at least one resistance to 1st line anti-TB drugs.

The analysis of results from each of the 3 NRLs shows no significant differences regarding DR frequencies, both for new cases and previously treated cases, countrywide.

Monoresistance prevalence (table III)

Monoresistance to H and S for new cases registers the same value: 3.6%; for R is 1.5% and for E is 0.2%.

For previously treated cases, monoresistance to H is 8.1%, to R is 1.8%, to E is 0% and to S is 2.6%.

Globally, for all new and previously treated cases, the monoresistance stands at reasonable levels: 4.3 to H, 1.6 to R, 0.2 to E and 3.4 to H.

Overall, monoresistance was registered in 8.9% of new cases and 12.6% of previously treated cases. In 1995 survey the figures were 5.3% and 16.7% respectively[7].

Multidrugresistance prevalence (MDR) (table IV)

MDR registered among new cases stands at 2.9%, level not much different than the 1995 registered one at 2.8%. 64% of MDR cases have more resistances: three or four.

In comparison with prevalence registered in many countries from the same geographic region (Latvia, Estonia, Lithuania, Russian Federation, etc.), the level of 2.9% in Romania seems reasonable. Taking into account that the percentage of 2.9% is applicable to 22,000 new TB cases registered annually in Romania, we can estimate that the total number of new MDR-TB patients to be registered annually is over 600[29].

For previously treated cases the prevalence of MDR stands up to 11%. In comparison with other DRSs results the figure seems reasonable; however in comparison with the Western European countries, the figure is high. View the fact that annually there are registered in Romania 4,300 relapses, we can estimate that for a percentage of 11% we can register annually 470 MDR cases.

The analysis of trend of MDR among previously treated shows a slightly decreasing in comparison with the 1995 DRS: 11% *vs* 14.4%[7].

The fact that 64% of strains with MDR had resistance to E or S or both associated, is and indicator for severe prognostic of treatment outcomes for these patients.

Global prevalence of MDR (new and previously treated cases) stands up to 4.23%

View the fact that annually there are registered over 26,000 new cases and relapses we can estimate for a 4.23%, about 1,100 MDR cases to be registered annually[4,29].

Any resistance to H (28.3%) and R (12.8%) among previously treated cases is three times higher than for new cases (any resistance to H is 8.3% and to R is 4.8%).

For any resistance to S the percentage of DR is similar with the resistance to H (7.3% for new cases and 19.4% for previously treated cases).

Any resistance to E is 2.0 % for new cases and 14.2% for previously treated cases. The level of DR to E among previously treated cases is higher than the one registered during other surveys performed in WHO European Region[27, 28].

Triple resistances (to H, R and S or E) were revealed in 4 new cases (0.3%) and 15 previously treated cases (3.9%).

Resistance to HRSE with limited therapeutic possibilities was identified in 10 new cases (1.2%) and 30 previously treated cases (7.9%).

The estimation of the number of TB patients who might be registered annually with HRSE resistance, view the 22,000 new cases and 4,300 relapses stands up to 276 for new cases and 340 for previously treated cases, with a total of 616 patients with HRSE resistance annually.

The pattern analysis of the strains isolated from the patients in the penitentiary system reveal a not very different one than registered among the general/civilian population. It has been

registered sensitivity in 83% and any resistance in 17% among new cases; for previously treated cases, sensitivity was registered in 57.9% and any resistance in 42.1%.

There were registered no important differences regarding the MDR prevalence in comparison with the general/civilian population, as well: 4.3% for new cases (2.9% in the general population) and 13.2% for previously treated cases (11% in general population).

IX. Conclusions

- In Romania might be registered annually over 5,000 patients with at least one resistance to anti-TB drugs.
- The percentage of MDR among new cases is relatively low (2.9%); however, taking into consideration the high number of new TB cases registered annually (22,000) it can be estimated about 600 new MDR-TB cases to be registered annually. If we add the MDR cases registered among previously treated cases (about 470 cases - 11% from 4,300), a total number of about 1,000 MDR-TB cases to be registered annually is estimated.
- DR to all 1st line anti-TB drugs (HRSE), 1.2% among new cases and 7.3% among previously treated cases, meaning about 600 patients to be registered annually, is a severe prognostic indicator for treatment outcomes of these patients.
- The trend analysis of DR to anti-TB drugs registered in Romania since last DRS performed in 1995 shows comparable results, even the TB case notification rate had a significant increasing trend till 2002.
- In comparison with some countries in the same geographic region, the DR in Romania stands at reasonable level; however due to the high TB case notification rate the number of patients with drug resistance registered annually is high.
- The maintenance of the quality control for the bacteriological laboratories activity at same standards used during the survey is an essential condition to ensure a continuous evaluation of drug resistance trends in Romania.
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