

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA  
DOCTORAL SCHOOL**

**EPIDEMIOLOGICAL AND CLINICAL CONSIDERATIONS OF  
EXTRARESPIRATORY TUBERCULOSIS IN THE ACTUAL CONTEXT  
OF THE TUBERCULOSIS ENDEMY EVOLUTION IN DOLJ COUNTY**

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# **GENERAL PART**

# I. INTRODUCTION

Tuberculosis is an infectious and contagious disease with chronic evolution, widely spread in general population (present in the vast majority of countries of the world), which, untreated or improperly treated, has an important fatality. Most commonly affects the adult population in the most productive years of life, causing serious economic and social consequences.<sup>[209]</sup>

In the last two decades there has been a progressive increase in the number of cases of tuberculosis throughout the world, even in the most developed countries due to the increased incidence of HIV infection, immigration, low economic status of some countries and the emergence of strains of tubercle bacilli resistant to anti-tuberculosis drugs.<sup>[497]</sup>

Currently, about one third of the world population is infected with the tubercle bacillus; 47% of the infected population lives in southeast Asia, 95% of tuberculosis cases occurring in developing countries.<sup>[161][172][534]</sup>

Of those who are infected with bacillus Koch a percentage between 5% and 10% develop the disease tuberculosis.<sup>[173]</sup>

Estimated, it is considered that in the last decade of the twentieth century became ill about 32 million people, the number of deaths reaching almost 10 million cases. Annually, around 8.8 million people worldwide are diagnoses with tuberculosis and another 1.4 million die from this disease.

In Romania, tuberculosis is a major public health problem.

DOTS strategy recommended by WHO for TB control since 2005 has national coverage of 100%. In this respect, the National Strategy for Tuberculosis Control in Romania 2015-2020 was developed and then implemented through the National Program for Tuberculosis Prevention, Surveillance and Control based on the documents developed by the European Center for Disease Control (ECDC) and WHO regarding tuberculosis control.

In our country, the global incidence (new and recurrent cases of tuberculosis) is the largest in the European Union and one of the largest in the Europe-WHO region.

The number of new cases and recurrences recorded annually decreased progressively from 30.984 in 2002 to 17.694 in 2011, reaching 12.836 in 2016.<sup>[211]</sup>

The National Program for the Prevention and Control of Tuberculosis in Romania aims to reduce the transmission, morbidity and mortality of tuberculosis until it is no longer a national public health problem.

To achieve this goal, the PNPSCT has the following objectives:

- ensuring universal access to rapid techniques for diagnosing tuberculosis and identifying the strength profile;
- diagnosis of at least 85% of the estimated cases of tuberculosis;
- achieving the 90% therapeutic success rate in new cases of bacteriologically confirmed pulmonary tuberculosis;
- achieving a 75% therapeutic success rate in new cases of MDR TB;
- reducing the mortality rate by tuberculosis to 5.4%;
- decrease the overall incidence of tuberculosis to 55.51‰<sub>000</sub>.

These targets are set to be achieved by 2020.<sup>[211]</sup>

The purpose of the National Tuberculosis Control Strategy is to eliminate this disease in Romania until 2050, meaning the presence of less than one case of positive microscopy tuberculosis per million inhabitants per year.<sup>[462][629]</sup>

## 1. Etiology of tuberculosis

Tuberculosis is an infectious disease produced by *Mycobacterium tuberculosis* (MT). Tuberculosis Bacillus was identified in 1882 by Robert Koch.<sup>[441]</sup> The name of the genus *Mycobacteria* comes from Greek "myces" meaning mushroom, mold and "bacterian" = stick. On the liquid medium, the *M. tuberculosis* culture appears as a "mold", hence the name of mycobacteria proposed by Lehmann and Newmann in 1896.

## 2. Sources of tuberculosis infection

The main sources of tuberculosis infection are as follows:

- patients with pulmonary tuberculosis that eliminate bacilli in sputum (called bacilli dispersers). The maximum potential for transmission of tuberculosis infection is for those with identifiable bacilli in the microscopic sputum examination;
- patients with extra-respiratory tuberculosis with active, open, fistulising lesions (lymph nodes, uro-genital, osteo-articular, cutaneous, etc.);
- sick animals of tuberculosis, more commonly bovine animals that spread *M. bovis* infection through their natural and pathological products (milk, urine, faeces). Occasional contamination may occur from wild animals (wild boars), domestic animals (dogs, cats) or laboratory animals suffering from tuberculosis.<sup>[160]</sup>

## 3. Tuberculosis transmission pathways

The main route of transmission of tuberculosis is airborne (95% of cases) through "Pflüger's drops". Pflüger's drops containing tuberculous bacilli are expelled by patients with active tuberculosis by coughing, sneezing, talking and singing. By inhalation of these drops infection of healthy people from diseased (bacilli) is infected.

The most contagious forms of tuberculosis are those with endobronchial and laryngeal localization.

Digestive transmission is achieved through milk from bovine with mammary tuberculosis. Because of the gastric juice, a larger amount of infective bacilli is required to cross the digestive barrier and infect the body. The incriminated agent is *M. bovis*. Digestive transmission is common in children (consumers of unpasteurized milk) and in workers in zootechnical farms (sheds with diseased animals) who inject particles from the animals of diseased animals. The frequency of tuberculosis with *M. bovis* is currently low compared to the last century.<sup>[459]</sup>

Skin transmission occurs in those who work with pathological products from tuberculosis patients (laboratory workers, anatomopathologists).

Other ways of transmitting tuberculosis are: *the conjunctival pathway* (the infectious particles are projected in the conjunctiva), *the transplacental pathway* (hematogenous spread), *the intrapartum* (fetus can aspirate or swallow amniotic fluid) and *the instrumental pathway*.<sup>[160]</sup>  
[209]

## 4. Receptivity

The human species is considered to have a natural resistance to tuberculous mycobacteria. Factors influencing antituberculous immunity are: genetics, magnitude of infection and its type.<sup>[459]</sup>

## **5. Tuberculosis infection risk factors**

The occurrence of tuberculosis is influenced by a number of factors.

The risk of tuberculosis infection is influenced by the quality of the sources of infection (maximum risk for those eliminating bacilli -identifiable by microscopic examination), pathogenicity and virulence of strains, the duration and continuity for spreading bacilli and the amount of germs produced by the patient with tuberculosis.<sup>[459]</sup>

## **6. Tuberculosis infection**

Tuberculosis infection is the condition where viable tuberculous bacilli are present in a body without signs or symptoms of disease. This represents latent infection with tuberculous bacilli. In Romania the vast majority of the population is infected with *Mycobacterium tuberculosis*. Infected organisms can present this condition for life, in the absence of immunodepression factors. In about 10% of cases, infection progresses to illness within the first two years of exposure (6-24 months).<sup>[60]</sup>

## **7. Tuberculous disease**

Tuberculosis is the disease produced by *Mycobacterium tuberculosis* that progressively invades one or more organs. Depending on the organ affected tuberculosis is pulmonary, renal, lymph node etc. This disease is manifested by constitutional symptoms or by signs and symptoms specific to each organ.

## **9. Extra Respiratory Tuberculosis**

### ***9.1. Definition***

Extra-respiratory tuberculosis is the form of tuberculosis that occurs in places other than the lung. Patients with two coexisting forms of tuberculosis, pulmonary and extra-respiratory, will be considered according to WHO rules as pulmonary tuberculosis.<sup>[393]</sup>

Among the factors that contributed to the increase in the cases of extra-respiratory tuberculosis are: the increase in the number of immunosuppressed persons, the increase of the number of inhabitants of the terrestrial (especially the elderly), the increase of the medical staff who are exposed to this disease.<sup>[221]</sup> Excessive respiratory tuberculosis is more common in children than in adults.<sup>[440]</sup>

Although the preferred location for tuberculosis is pulmonary, it may be located in any organ in the human body.<sup>[171][183][287]</sup>

### ***9.2. Immune mechanisms in extra-respiratory tuberculosis***

During the course of the infection, the Koch bacillus spreads throughout the body and can be located in any organ in the human body and leading to secondary outbreaks of infection. These may become endogenous reactivation outbreaks - extra-respiratory tuberculosis forms. Approximately 15% of patients with active tuberculosis have an extra-respiratory localization.<sup>[88]</sup>

### ***9.3. Epidemiology of extra-respiratory tuberculosis***

Prior to the occurrence of HIV infection, the worldwide extra-respiratory tuberculosis represented approximately 15-20% of all cases of tuberculosis.<sup>[495][540][609][711]</sup>

16.116 cases of extra-respiratory tuberculosis were reported in the European Union in 2011. This number represents 22% of the total number of tuberculosis cases reported in the European Union.<sup>[565]</sup>

In 2011, 2.781 cases of extra-respiratory tuberculosis were diagnosed in Romania, representing 14% of all cases of tuberculosis. The notification rate was 13 cases per 100.000 inhabitants. Between 2002 and 2011, the proportion of cases of extra-respiratory tuberculosis increased from 11% (2002) to 14% (2011)<sup>[612]</sup>

### ***9.4. The characteristics of tuberculosis cases***

In women, extra-respiratory tuberculosis was reported more frequently than pulmonary tuberculosis (46.4% of cases versus 32.5%). Also distribution by age groups was different. In children (age group 0-14 years), extra-respiratory tuberculosis was reported more frequently than pulmonary tuberculosis (7.7% of cases compared to 3.1%). Moreover, extra-respiratory tuberculosis was reported more frequently (37.9% of cases) compared to pulmonary tuberculosis (17.7% of cases). The proportion of cases of extra-respiratory tuberculosis among immigrants in low-incidence countries increased significantly from 48.5% in 2002 to 61.1% in 2011 ( $p < 0.01$ ). In contrast, in countries with high incidence, the proportion of extra-respiratory tuberculosis among migrants decreased from 4.1% in 2002 to 3.2% in 2011.<sup>[565]</sup>

In Romania, the most frequent locations of extra-respiratory tuberculosis in 2011 were pleural with 1.606 cases (58%) and lymph node with 535 cases (19%), followed by tuberculosis of the spine and tuberculous meningitis, both representing for 129 cases.<sup>[612]</sup> (table 3)

Country	Site of extrapulmonary tuberculosis									
	Lymphatic N (%)	Pleural N (%)	Urogenital N (%)	Bone N (%)	Spinal N (%)	Gastro-intestinal N (%)	Meningal N (%)	Disseminated N (%)	CNS other N (%)	Other extra-pulmonary N (%)
Austria	65 (48)	20 (15)	16 (12)	8 (6)	3 (2)	8 (6)	1 (1)	2 (1)	2 (1)	11 (8)
Czech Republic	34 (44)	16 (21)	6 (8)	2 (3)	6 (8)	0 (0)	0(0)	0(0)	2 (3)	12 (15)
Germany	431 (47)	147 (16)	90 (10)	67 (7)	34 (4)	43 (5)	22 (2)	13 (1)	9 (1)	70 (8)
Malta	6 (55)	1 (9)	1 (9)	0 (0)	1 (9)	0 (0)	1 (9)	0 (0)	0 (0)	1 (9)
Netherlands	225 (51)	64 (15)	19 (4)	11 (2)	26 (6)	33 (7)	3 (1)	0 (0)	7 (2)	53 (12)
Poland	149 (25)	214 (36)	68 (11)	40 (7)	35 (6)	12 (2)	10 (2)	16 (3)	2 (0)	53 (9)
Romania	535 (19)	1,606 (58)	117 (4)	89 (3)	129 (5)	65 (2)	129 (5)	0 (0)	3 (0)	108 (4)
Slovakia	20 (32)	18 (29)	7 (11)	0 (0)	13 (21)	1 (2)	0 (0)	0 (0)	0 (0)	3 (5)
Slovenia	10 (37)	11 (41)	1 (4)	1 (4)	1 (4)	3 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Sweden	139 (61)	15 (7)	2 (1)	11 (5)	19 (8)	20 (9)	5 (2)	0 (0)	3 (1)	14 (6)
United Kingdom <sup>a</sup>	2,360 (49)	492 (10)	130 (3)	181 (4)	320 (7)	349 (7)	150 (3)	89 (2)	61 (1)	647 (14)

CNS: central nervous system.

<sup>a</sup> United Kingdom data were provided by the Health Protection Agency and data were provided for all sites of extrapulmonary tuberculosis for a case. The 4,313 extrapulmonary tuberculosis cases had 4,779 sites of disease.

Table 3. Diagnosis type and percentages of extra-respiratory tuberculosis in 11 countries in the European Union in 2011.<sup>[612]</sup>

### 9.5. Extra-respiratory tuberculosis and HIV infection

HIV-tuberculosis coinfection occurs when there is concurrent HIV infection and latent or active tuberculosis. In 2011, around 430,000 people with HIV-TB coinfection died worldwide, while 990,000 of those who died had tuberculosis alone.<sup>[216]</sup> In the same year, about 1.7 million people died with HIV alone.<sup>[689]</sup> Also in 2011, it was estimated that there were 8.7 million new cases of active tuberculosis globally. Of these, 1.1 million (13%) were considered to have HIV infection. Around 79% of HIV cases associated with tuberculosis were in Africa.<sup>[216]</sup>

### 9.7. Clinical manifestations of extra-respiratory tuberculosis

Excessive respiratory tuberculosis, known as disseminated tuberculosis or miliary tuberculosis, refers to all types of tuberculosis except pulmonary tuberculosis. It is the type of tuberculosis that does not affect the lungs and the main form is pleural tuberculosis.<sup>[163]</sup>

The general symptom of extra-respiratory tuberculosis is similar to pulmonary tuberculosis (fever, inappetence, fatigue, weight loss, nocturnal sweating). There may be also site-specific symptoms.<sup>[218]</sup>

Fever of unknown origin without other signs or clinical symptoms may be the only sign of an extra-respiratory tuberculosis without a clear location.<sup>[588]</sup>

Among the clinical features of extra-respiratory tuberculosis are: lymphocytic predominant ascites and negative bacterial cultures; chronic lymphadenopathy (most commonly cervical); protein growth, glucose lowering and lymphocytic pleocytosis in the CSF; gastro-intestinal symptoms similar to Crohn's disease and amebiasis; the appearance of a pleural exudate with lymphocytic predominance, negative cultures and pleural thickening; the occurrence of HIV infection; the appearance of joint inflammation with negative bacterial cultures; the appearance

of sterile pyuria despite antibiotic treatments; the occurrence of unexplained pericardial effusion, constrictive pericarditis and pericardial calcifications and the occurrence of osteomyelitis involving thoracic vertebrae.<sup>[218]</sup>

# **SPECIAL PART**

## II. OBJECTIVES

The objectives I pursue in this paper are found throughout each chapter.

They consist of:

- identification of the main characteristics of tuberculosis with extrapulmonary location in Dolj County;
- determining the location and importance of localizing forms of extra-respiratory tuberculosis;
- description of the spectrum of clinical-evolutionary aspects in the extra-respiratory locations of tuberculosis;
- comparative study of patients with extra-respiratory tuberculosis with / without associated HIV infection;
- description of the evolution of endemic extra-respiratory tuberculosis under antibacterial treatment;
- assessing the impact of tuberculosis outbreaks on the quality of life as well as on their socio-economic aspects.

We considered that an analysis of the current situation of the extra-respiratory tuberculosis status in Dolj County in the context of a descending trend of tuberculosis endemicity in our country can provide epidemiological and clinical evidence of a true reflection of this form of tuberculosis and can also provide solutions that would better integrate the management of these localizations in the present tuberculosis control program.

## III. MATERIAL AND METHOD

A personal concern in the field has been materialized over the past years by research on morbidity and mortality data and clinical particularities of extra-respiratory tuberculosis in Dolj County.

The place of the study was Clinical Hospital of Infectious Diseases and Pneumofiziologie "Victor Babeş" Craiova, respectively TB Ambulatory Clinic of Craiova.

The research was carried out without additional financial support. Documentation has been used for official records / documents, most of which are current working tools in the control of tuberculosis.

The research carried out under the guidance of the two scientific advisors assumed a retrospective analysis of cases of tuberculosis at the TB Ambulatory Clinic of Craiova for an 8-year period (01.01.2005 - 31.12.2012). Due to the fact that this is a descriptive study, the evolution of the patients' disease included in this survey was not influenced. Also, the "Ethics Committee" of the "Victor Babeş" Craiova Hospital for Infectious Diseases and Pneumofiziologie Hospital was not needed for this analysis.

Returning to the 1.120 patients with extra-respiratory tuberculosis registered at the level of TB Craiova Dispensary during the 8 years of study, they were predominantly male (58%) (Figure 3), 60% from the urban environment (Table 6, Figure 4). The population in Dolj county is made up of 49% men and 51% women, we can state that there is a significant difference between these proportions and those calculated for the number of cases with ex-respiratory TB, the value of  $p < 0.001$ . The percentage of men with extra-respiratory TB diagnosed in Dolj county, between 2005-2012, is significantly higher than the proportion of men in the county population.

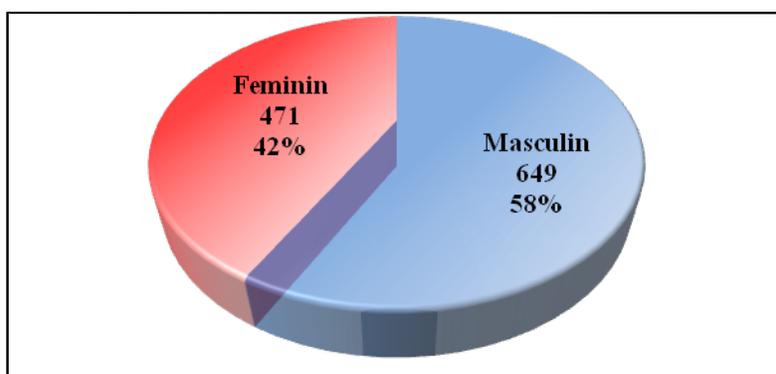


Figure 3. Distribution of the study group by sex.

Origin	No. patients	%
Rural	446	40
Urban	674	60
<b>Total</b>	<b>1.120</b>	

Table 6. Distribution of the study group by place of origin.

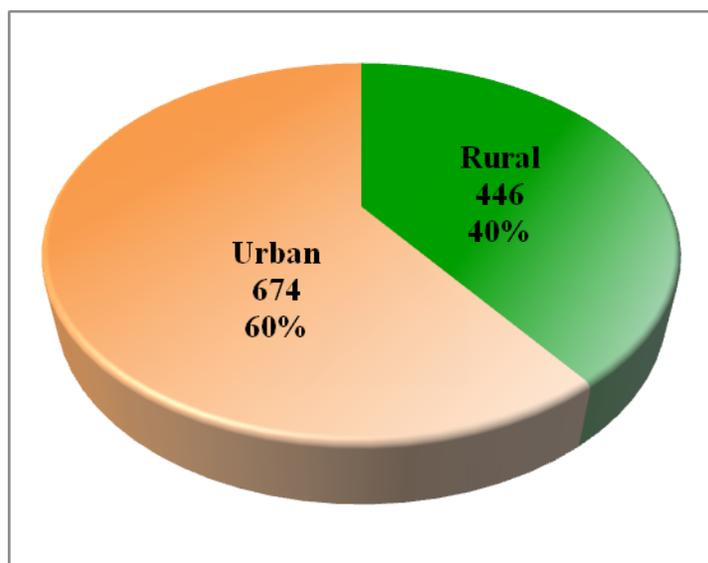
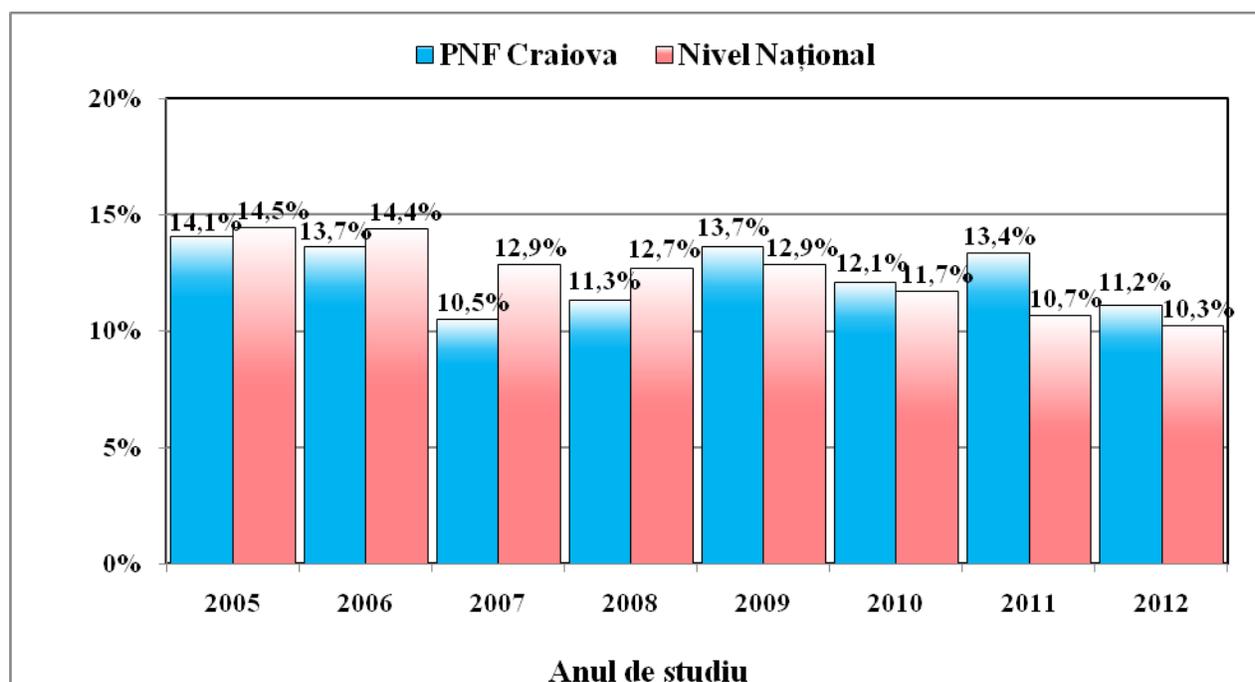


Figure 4. Distribution of the study group by place of origin.

At national level the number of outbreaks of tuberculosis decreased constantly after 2006 and at the level of TB Ambulatory Clinic of Craiova the same aspect was registered. We have found that there are statistically significant differences between the distribution of cases of extra-respiratory tuberculosis identified at the level of the TB Ambulatory Clinic of Craiova and the national one,  $p = 0.29 < 0.05$ . Although the percentages differences are small (the maximum differences being 2.3% for 2007 and 2.7% for 2011), these percentages are reported for thousands of cases, making the differences statistically relevant. (Table 134, Figure 27)

Register	Year								Total
	2005	2006	2007	2008	2009	2010	2011	2012	
TB Ambulatory Clinic of Craiova	158	153	118	127	153	136	150	125	<b>1.120</b>
National	3.765	3.756	3.351	3.310	3.351	3.058	2.781	2.669	<b>26.041</b>

Table 134. Number of patients with extrarespiratory localizations from all cases of Tuberculosis.



p Chi pătrat 0,02946734

Figure 27. TB extra-respiratory localizations at the level of TB Ambulatory Clinic of Craiova and National.

Extra-respiratory Tuberculosis is more rarely discussed in medical literature. However there are some reports of clinical cases and a series of articles published about patients describing various forms of Extra-respiratory Tuberculosis.<sup>[68,345,716]</sup> In these articles, extra-respiratory tuberculosis is perceived more as a clinical particularity and less as a public health problem. One of the likely reasons why extra-respiratory tuberculosis is not on the order of public health priorities is because transmission of the disease is quite low due to localizations. The same reasoning is also used in childhood tuberculosis.<sup>[563,564]</sup> At international level, patients with extra-respiratory tuberculosis do not receive special attention in tuberculosis control strategies.<sup>[182,624]</sup> However, these extra-respiratory tuberculosis contributes significantly to the tuberculosis morbidity, which can cause complications, sequelae that can persist throughout life and may produce deformities, sometimes severe.<sup>[150,329,372,395]</sup>

Among the factors that have contributed to the increase in cases of extra-respiratory tuberculosis are: increasing number of immunodepressed people, increasing number of inhabitants of the Earth (especially the elderly) and increasing number of medical staff exposed to this disease.<sup>[221]</sup> Extra respiratory tuberculosis is more common in children than in adults.<sup>[440]</sup>

Although the preferred location of tuberculosis is pulmonary, it can affect any organ in the human body.<sup>[171,186,287]</sup>

## IV. CONCLUSIONS

1. In the group of 1120 patients with extrapulmonary tuberculosis registered in the eight years of study in TB Craiova Dispensary, 40% come from the rural area and 60% from the urban area.

Most patients enrolled in each study year came from urban areas.

2. Cases of extra-respiratory TB recorded in the TB Ambulatory Clinic of Craiova in the period 2005-2012 don't follow the descending trend of the total number of tuberculosis cases registered here as well as at the national level.

3. The percentage of patients in the urban area is significantly higher than their percentage in the population of Dolj County ( $p < 0.0001$ ).

4. By dividing the batch of the patients we considered, we observe the predominance of the male (58%). The percentage of men with extra-respiratory tuberculosis diagnosed in Dolj County between 2005-2012 is significantly higher than the proportion of men in the Dolj County population ( $p < 0.0001$ )

57% of male patients and 64.5% of females come from urban areas.

5. The age group breakdown of the study group shows a bimodal distribution of data: a peak in the age group of 21-30 years and another at 51-60 years. This suggests that there are different predisposing factors to the extra-respiratory localization of tuberculosis in certain age groups.

6. Although there are some differences between the two sexes in the age group distribution, they are not statistically significant because the Chi square test result exceeded the maximum statistical significance limit ( $p = 0.070 > 0.05$ ).

7. Rural patients are higher in age groups of 0-15 years and 61-70 years, and those in the urban area are significantly more numerous in the 21-30 years, 31-50 years

8. Although there are differences in the 143 histopathological confirmations between the study years, they are not statistically significant ( $p = 0.759 > 0.05$ ).

Because of the small number of histopathologically confirmed cases in each study year, the Chi square test does not detect a significant gender difference in histopathological confirmations ( $p = 0.810 > 0.05$ ) and in the distribution on their residence environment ( $p = 0.125 > 0.05$ ).

9. Due to the small number of cases confirmed by cultures (61), the statistical analysis of the distribution by sex and residence area is not relevant.

10. By comparing the distribution of bacteriologically and histopathologically confirmed cases over the years of study (attention: not percentages of total cases, histopathological confirmations being obviously more numerous), we did not identify statistically significant differences, the Chi square result being well above the maximum admissible limit for statistical significance ( $p = 0.670 > 0.05$ ).

11. Bacteriological confirmation was present in higher percentage in males than in females, while histopathological confirmation prevailed in females ( $p = 0.0013 < 0.05$ ).

12. Most disease confirmations were found in the 21-60 age group.
13. We did not identify significant differences between years of study in the percentage of new cases of extra-respiratory TB, ranging from 85% to 95% (p Chi square = 0.999 > 0.05).
14. There are no significant differences between the study years in the percentage of those with complete treatment, of all cases with extra-respiratory TB; they varied between 70% and 80% (p Chi square = 0.992 > 0.05).
15. By comparing the proportion of new cases for each of the dispensary groups, we found that there were no significant differences in the percentage of new cases in the different categories analyzed, the Chi square result being  $p = 0.989 > 0.05$ .
16. After pleural tuberculosis, present in 58% of cases, more frequent locations for tuberculosis were in the laterocervical lymph nodes, vertebral, meningeal, pericardial or peritoneal locations.
17. If ganglion and pericardial locations predominated in women, the other predominated in males. Exceptions are made for skin and epitrochlear lymph node localizations encountered only in women.
18. Lymph nodes, meningeal, peritoneal, and polyserosity sites predominate in age groups up to 40 years of age and the rest at age 40; tuberculous pericarditis and vertebral tuberculosis predominate at the age of 60 years.
19. Pleural, meningeal, laterocervical and urogenital lymph nodes have benefited from the most bacterial confirmations.
20. 90% of the cases included in the study were new cases of tuberculosis and the number of failures and therapeutic cessation was very low (4 cases, 9 cases respectively).
21. 75% of the patients underwent complete treatment, 6% were registered with therapeutic cessation, 5% were evaluated with for further treatment and 3% died.
22. Of the whole group of patients with extra-respiratory tuberculosis 6 localizations received full treatment.

**Key words: extrapulmonary tuberculosis, TB Ambulatory Clinic of Craiova, patients**

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