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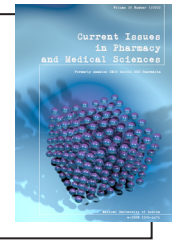

Peculiarities of the detection and course of the pediatric extrapulmonary tuberculosis taking into account drug resistance

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ABSTRACT

Pediatric tuberculosis is a health problem of special significance because it is a marker for current transmission of tuberculosis in society. The research aimed at analyzing the peculiarities of detection and course of pediatric extrapulmonary tuberculosis (EPTB) taking into account the profile of drug resistance. A retrospective study of medical charts of children with EPTB (n = 47; 1st group) and pulmonary tuberculosis (PTB) (n = 49; 2nd group) aged 0-15 for 2013-2020 has been conducted. 2 subgroups with EPTB were identified separately: resistant (EPRTB) (n = 23) and sensitive (EPSTB) (n = 24). Results and discussion. The frequency of EPTB was 9.8%. Tuberculosis of peripheral LN (40.5%), CNS (27.7%), bones and joints (23.4%) was significantly more often diagnosed, than other lesions. Almost half of children with EPTB had a miliary distribution. In 44.7% of children with EPTB contact with a patient with tuberculosis was not established. EPRTB was significantly more common among children under 1 and up to 3 years of age than EPSTB. The resistance to combination of HR (73.6%) was found more often than to HRES (10.5%), HRS, H and Z (5.3% each; $p<0.01$). In 73.9% of children with EPRTB was detected when seeking medical care, in 13.0% the time to diagnosing lasted 6 months. Among children with EPRTB, gradual course was more frequent and in 47.8% intoxication syndrome was dominating. 78.3% of children with EPRTB were not vaccinated.
Conclusion. The above indicates the need to intensify preventive measures against tuberculosis among children, especially at risk groups, make monitoring of contacts and their treatment.

INTRODUCTION

Today, tuberculosis (TB) is one of the major health and social challenges in the world. Thus, in 2016, the World Health Organization (WHO) defined a new strategy to combat TB which is called "Unite to End TB!". This strategy was intended to be applied until 2035 and foresaw a reduction in morbidity by 80% and mortality by 90% [1]. However, as a result of the global COVID-19 pandemic, the progress made in 2020 was lost (from 7.1 million new cases of the disease in 2019 to 5.8 million in 2020), and program performance declined [2]. Restrictions on access to TB diagnosing and treatment have led to an increase in TB mortality worldwide. According to approximate estimation, as of 2020, there were 1.5 million TB deaths annually. Other global consequences of the pandemic include a reduction in the number of people with drug-resistant TB (DRTB) who were registered and treated from 2018 to 2020. This was 482 683 cases, which is only 32% of the 5-year target of 1.5 million. Including children in particular, the total number was 12 219 cases, which is only 11% of the 5-year plan of 115 000 [3].

Today, Ukraine remains in the top 10 countries with the burden of DRTB in the world. Still, the number of reports of DRTB in Ukraine in 2020 decreased by 47%, when compared with 2019 [3].

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The effectiveness of any program can be assessed by benchmarks in the weakest and the most vulnerable groups, which include children. According to the WHO, it is necessary to detect TB in children annually at a level of at least 5% in the country. Thus, in 2019, the percentage of TB cases among children under the age of 15 in Ukraine was 3.4% of the total number of TB cases. The emergence of DRTB, which poses a major threat to global TB prevention and treatment, also affects children [2]. There are two main factors regarding the risk of disease progression: age and the condition of the immune system [4-7]. Although pulmonary TB (PTB) is the most common localization of a specific process, extrapulmonary generalized lesions account for a quarter of the total number of cases [8, 9] among which resistant forms are found [10,11]. Diagnosing of TB in children is difficult and time consuming, and the presence of non-specific symptoms which are distinctive to other common diseases lead to late diagnosing [12] and untimely and incorrect treatment.

The research on the main components of TB control (detection, diagnosis, treatment and prevention) is one of the «links» of the WHO strategy. Given the above, the study and the analysis of clinical and microbiological features of detection, the course of pediatric extrapulmonary TB (EPTB) to optimize tactics to prevent the spread of specific lesions as a result of timely diagnosing and prescribing TB therapy and chemoprevention is relevant and promising.

AIM

Our research aimed at analyzing the peculiarities of detection and the course of pediatric EPTB, taking into account the profile of drug resistance.

MATERIAL AND METHODS

A retrospective study of medical data was conducted to examine TB-specific symptoms among all hospitalized children. We analyzed all medical charts (MCs) of children aged 0 to 15 who were treated from local forms of TB at the Lviv Anti-TB hospital (Lviv, Ukraine) from 01/2013 to 01/2020. From 478 MCs of children hospitalized in the pediatric department, we selected medical documents of all patients with EPTB and randomly selected 49 patients with PTB.

In Ukraine, a case of TB disease is determined by a physician on review of the clinical, laboratory, radiologic and/or histopathologic test results. EPTB is defined as identification of *Mycobacterium tuberculosis* in a tissue or specimen from a site other than lung parenchyma, in association with clinical and/or imaging findings compatible with local infection. In contrast, PTB is defined as having TB disease with lung and intrathoracic lymphatic nodes (ILN) involvement.

In our study, patients with TB were divided into two groups: with EPTB (n=47; 1st group) and PTB without generalization (n=49; 2nd group; control). To study some peculiarities of TB, 2 subgroups of patients with EPTB were identified: with resistant (EPRTB) (n=23; 1a subgroup) and sensitive forms of the disease (EPSTB) (n=24; 1b subgroup).

Patients of the researched population underwent microscopic (according to Ziel-Nielsen), molecular genetic (GeneXpert MTB/RIF), culture studies on solid (Levenstein-Jensen) and liquid (BACTEC MGIT 960) nutrient media and linear probe analysis (Hain Lifesciences using of hybridization of GenoType MTBDR plus/sl and determination of susceptibility of Mycobacterium TB (MBT) to anti-tuberculous drugs (ATD) of the I line (H – isoniazid, R – rifampicin, E – ethambutol, S – streptomycin, Z – pyrazinamide) of biopsy, resection materials, cerebrospinal fluid and other fluids in accordance with current standards.

In addition, we used visualizing diagnostic methods to examine the organs of the chest, abdomen, CNS, musculoskeletal system (radiography, computed tomography, ultrasound, MRI), spinal puncture with examination of cerebrospinal fluid, morphological examination of biopsy, resection material and other examinations according to the affected organ.

The following information was analyzed: age, profiles of resistance of MBT to ATD, clinical forms of PTB and EPTB, variants of a course of the disease, the method of detection and the duration of a specific process before diagnosing, the condition at the time of admission to a specialized medical institution. Vaccine status was assessed as follows: in the absence of scar after BCG vaccination or its size within 1-3 mm, children were considered ineffectively vaccinated.

In the study, a person who had excretion of *Mycobacterium tuberculosis* as determined by the applied laboratory methods was defined as a 'bacterial excretor'. A 'nonbacterial excretor' was a person who did not excrete *Mycobacterium tuberculosis*.

All characteristics were collected and entered into a custom-built electronic data collection tool. Digital results were processed by methods of variational statistics using Student's t-test, the data were considered significant at $p<0.05$. The results are given in the form of mean values and standard error of mean values (M±m).

RESULTS

It was established that during the study period, local forms of EPTB were found among 9.8±1.8% of hospitalized children ($p<0.01$).

The average age of children in the 1st and 2nd groups was 3.8 and 5.5 years old, and in the 1a and 1b subgroups – 2.5 and 5.1 years old (all $p>0.05$). More importantly is that in the 1st group, significantly less often than in the 2nd one, children under 3 years of age were observed (61.7±7.1% *vs*. 38.8±6.9%; $p<0.05$), including children under 1 year of age (38.3±11.5% *vs*. 10.2±4.3%, $p<0.05$). The same trend was observed in the 1a subgroup, compared to the 1b (78.3±8.6% *vs*. 45.8±10.2%; 56.5±10.3% *vs*. 20.8±8.3%; all $p<0.05$).

Determination of the profile of resistance of MBT to ATD among patients of the 1a subgroup showed that in the vast majority of cases, resistance to R was found (43.5±10.3%), less often – multidrug-resistant TB (MDRTB) wherein the risk of MDRTB among children from the focies of MDRTB infection being 30.4±9.6% and 17.4±7.9%, and the least commonly − monoresistant TB (8.6±5.8%). We found that in the vast majority of cases (73.6±10.1%), there

was resistance to the combination of HR, which is significantly more common than resistance to combinations of HRES (10.5±7.0%), HRS and resistance to H and Z (both 5.3±5.1%; all p<0.01).

The analysis of the structure of clinical forms of EPTB (Fig. 1) among children of the 1st group was conducted and it was found that TB of peripheral lymph nodes (LN) (40.5±7.2%), meninges and CNS (27.7±6.5%), bones and joints (23.4±6.2%) occur significantly more commonly than TB of the intestine, skin and eyes (4.2±2.9%; 2.1±2.1%; 2.1±2.1%; all p<0.01). TB of bones and joints was also probably more often observed than the latter (23.4±6.2%; p<0.05). It is important to note that three children of the 1st group of the first year of life died: two were diagnosed with meningoencephalitis, in one case – combined with miliary PTB, in the other – with primary tuberculous complex (PTC). The third dead child had TB of mesenteric and axillary LN combined with miliary PTB. These children were diagnosed with MDRTB.

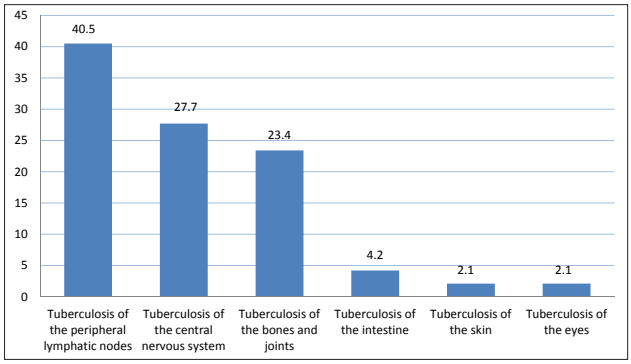
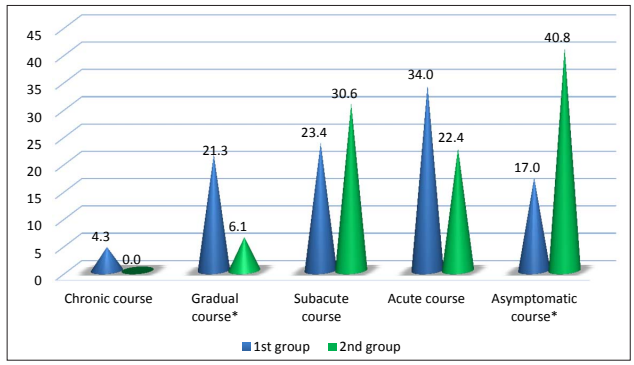


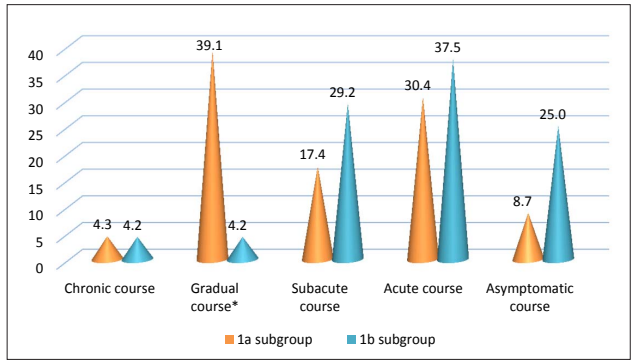
Figure 1. Frequency of detection (%) of different clinical forms of extrapulmonary TB among children of the 1st group during 2013-2020.



Note: * marked signs, between which there is a significant difference (p<0.05)

Figure 2. Variants of the course of tuberculosis among children of the researched groups (%)

A similar analysis in subgroups has shown that children in the 1a subgroup had a significantly more gradual course of the disease (Fig. 3), comparing with the 1b subgroup (39.1±10.2% *vs*. 4.2±4.1%; p<0.01).



Note: * marked signs, between which there is a significant difference (p<0.05)

Figure 3. Variants of the course of tuberculosis among children 1a and 1b subgroups (%)

At the same time, we did not find significant differences in the frequency of detection of clinical forms of TB in 1a and 1b subgroups. However, in the 1a subgroup, TB of meninges and CNS was observed a little more often (9/39.1% *vs*. 4/16.7%), as well as in the 1b subgroup − TB of bones and joints (8/33.3% *vs*. 3/13.0%; all p>0.05). It should be noted that only 2 cases (8.7%) from the 1a subgroup were diagnosed with intestinal TB and only 1 case (4.2%) with TB of eye and skin was detected in the 1b subgroup.

The structure of clinical forms of PTB has shown that in the 1st group, in which it was expected less often than in 2nd one, we observed TB of intrathoracic LN and PTC (17.0±5.5% *vs*. 38.8±7.0%; 25.5±6.4% *vs*. 61.2±7.0%; all p<0.05), but significantly more often – miliary PTB (46.8±7.3% *vs*. 0; p<0.01). The frequency of detection of different clinical forms in 1a and 1b subgroups did not differ significantly.

We found that among children of the 1st group, the acute course prevailed (34.0%), while in children of the 2nd group – asymptomatic (40.8%; Fig. 2). There was a statistically significant difference between the frequency of asymptomatic and subacute courses in the 1st and 2nd groups (17.0±5.5% *vs*. 40.8±7.0%; 21.3±6.0% *vs*. 6.1±3.4%; both p<0.05).

Research has indicated that one of the main risk factors for the development of TB is the presence of children in contact with a TB patient. We found that children of the 1st group had the same frequency of contact with a bacterial excretor and an undetected contact (44.7%), while in the 2nd group, the most frequent contact was with a nonbacterial excretor (51.0%). Importantly is that the contact with the nonbacterial excretor was significantly more common in the 2nd group compared to the 1st one (51.0±7.1% *vs*. 10.6±4.5%; p<0.05), while the undetected contact was probably more common in the 1st group compared to the 2nd one (44.7±7.3% *vs*. 20.4±5.8%; p<0.05).

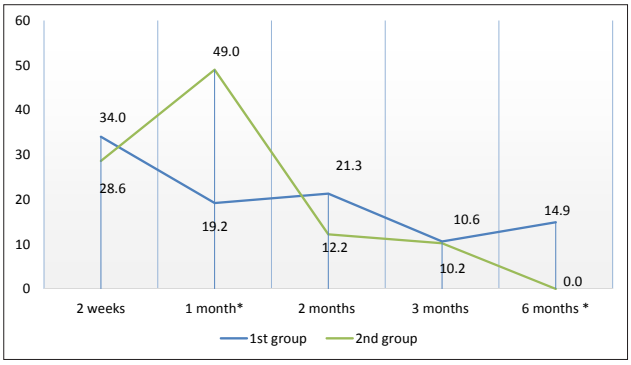
In 1a and 1b subgroups, an undetected contact with a TB patient occurred with the same frequency (43.5±10.3% and 45.8±10.2%), while a contact with a bacterial excretor in 1a subgroup occurred 1.4 times more often (52.2±10.4% *vs*. 37.5±9.9%), and with a nonbacterial excretor – 3.9 times less often (4.3±4.2% *vs*. 16.7±7.6%; all p>0.05). It was found that only half of the children of 1a subgroup had contact with a bacterial excretor, which confirmed the resistance of MBT, and a comparative analysis of the resistance profiles of the bacterial excretor has shown a coincidence with the resistance profiles of children.

We also noted that the diagnosis of TB among children of the 1st group was significantly more frequently found while

seeking medical care compared to the 2nd group (66.0±6.9% *vs*. 38.8±7.0%; p<0.05). At the same time, children of the 2nd group were diagnosed with TB more often during contact and preventive examinations compared to the 1st group (46.9±7.1% *vs*. 29.8±6.7%; 14.3±5.0% *vs*. 4.2±2.9%; all p>0.05).

In the 1a subgroup, the diagnosis was most often made when seeking medical care (73.9±9.2%), significantly less often at contact or preventive examinations (26.1±9.2% and 0; both p<0.01). In the 1b subgroup, the diagnosis was probably more often detected when seeking medical care (58.3±10.1%) and during contact examinations (33.3±9.6%) than during preventive examinations (8.3±5.6%; p<0.01 and p<0.05). We did not find significant differences in a certain method of detection of TB in 1a and 1b subgroups.

We analyzed the time of TB process from the first symptoms to an establishing specific diagnosis and showed the results in Figure 4. We saw that TB among children of the 1st group, compared to the 2nd, was significantly less diagnosed within 1 month (19.2±5.7% *vs*. 49.0±7.1%, p<0.01), and almost the same amount − during the first two weeks, 2 and 3 months (all p>0.05). It should be noted that only in the 1st group, TB was diagnosed within 6 months (14.9±5.2% *vs*. 0; p<0.05).



Note: * marked signs, between which there is a significant difference (p<0.05)

Figure 4. Duration of the tuberculosis process before establishing a specific diagnosis in children of the researched groups (%)

Among children of 1a and 1b subgroups, the specific process from the first symptoms to diagnosis mostly lasted up to 2 weeks (39.1±10.2% *vs*. 29.2±9.3%; p>0.05). In addition, in the 1a subgroup, lesions were diagnosed slightly more often up to 2 months (30.5±9.6% *vs*. 12.5±6.7%) and slightly less often up to 1 month (8.7±5.9% *vs*. 29.2±9.3%), compared to the 1b subgroup, but did not reach the level of probability (all p>0.05).

On admission to a specialized medical hospital, patients from the 1st group more often than the 2nd had the predominance of intoxication syndrome (51.1±7.3% *vs*. 30.6±6.6%; p<0.05), while in the 2nd group – bronchopulmonary (40.8±7.0% *vs*. 17.0±5.5%, p<0.05). The combination of these syndromes was more common in the 1st group compared to the 2nd (31.9±6.8% *vs*. 12.2±4.7%; p<0.05). The absence of clinical manifestations was characteristic only of the 2nd group (16.3±5.3% *vs*. 0; p<0.01).

Significant differences between the frequency of detection of these syndromes among the children of 1a and 1b subgroups were not detected, as manifestations of intoxication (47.8±10.4% and 54.2±10.2%), bronchopulmonary (21.8±8.6% and 12.5±6.7%) syndromes and their combination (30.4±9.6% and 33.3±9.6%) were equally frequent (all p>0.05).

At the time of hospitalization, the children of the 1st group, compared to the 2nd, were significantly more likely to show severe (36.2±7.0% *vs*. 0; p<0.01) and moderate (40.4±7.1% *vs*. 16.3±5.3%; p<0.05) conditions, while satisfactory conditions were significantly more common among children of the 2nd group (83.7±5.3% *vs*. 23.4±6.2%; p<0.01). No significant differences between the frequency of detection of a certain degree of severity on admission in 1a and 1b subgroups were found.

Patients of the 1st group were more often unvaccinated (61.7±7.1% *vs*. 24.5±6.1%; p<0.01) and significantly less often - effectively vaccinated (10.6±4.5% *vs*. 34.7±6.8%; p<0.05) than patients of the 2nd group. It is important that concomitant pathology was significantly more often diagnosed among children of the 1st group than the 2nd (51.1±7.3% *vs*. 30.6±6.6%; p<0.05). These results may be related to interruptions in vaccine supply and parental refusal to vaccinate.

We also found out that the patients in the 1a subgroup were significantly more likely to be unvaccinated, than in the 1b (78.3±8.6% *vs*. 45.8±10.2%; p<0.05), and the patients of 1b subgroup were significantly more likely to be ineffectively vaccinated (33.3±9.6% *vs*. 4.3±4.2%; p<0.05).

DISCUSSION

Leading scientists emphasize that the problem of childhood TB in different countries around the world is insufficiently studied [13,14] due to difficulties in diagnosing the disease, oligobacillary, and variations in the clinical and physical manifestations of the disease in different age groups [15]. Taking into account the main aspects of childhood TB, our study focuses on severe, common processes, the share of which was almost 10% of the total number of cases of local forms of TB during 2013-2020.

Belogortseva *et al*. [10] reported an increase in the percentage of severe, common clinical forms of TB and the number of bacterial excretors among children in Ukraine. The researchers noted an increase in the proportion of patients with R resistance, among which cases of risk of MDRTB (46.4%) and MDRTB (30.4%) predominated. In contrast, we found that the most common type of resistance among children with EPTB was resistance to R (43.5%), in a third of cases (30.4%) − MDRTB and only in 17.4% – risk of MDRTB.

In the publication of Sakhelashvili *et al*. [16], it is stated that the children from MDRTB focies were most often resistant to a combination of HRES (40%) and slightly less often – to HR (25%). In our study, most children were found to be resistant to the combination of HR (73.6%) and only 10.5% – to HRES. This may indicate the peculiarities of the distribution of these variants of resistant strains of MBT among children in the Lviv region, which led to generalization.

The analysis of scientometric databases has shown that the majority of studies focus on the adult population [17-19]. Pediatric TB is a direct consequence from the adult, and

is a marker of the current transmission of TB infection in society [2]. The researchers point out that drug resistance in children is mostly due to primary transmission, rather than the influence of previous specific treatment, which means the transmission of an already stable strain of MBT through a family contact with adults [20,21]. According to our data, 52.2% of all children with EPRTB were in contact with a bacterial excretor, but only half of them had contact with a bacterial excretor with resistant strains of MBT. At the same time, the resistance profiles of children with EPRTB coincided with the resistance profiles of their bacterial excretor source. These data coincide with the data of other scientists who studied clinical and microbiological parameters among children and adolescents with PTB with MDRTB focies [16].

According to WHO recommendations, one of the key areas of TB prevention and treatment is contact tracking. This makes possible to identify cases of TB, as well as to identify people with latent TB infection (LTBI), who are at risk of developing the disease in the future [22]. However, according to our data, in 43.5% of all children with EPRTB, the contact with a TB patient was not established, and in 73.9% of all children, EPRTB was diagnosed while seeking medical care and only 26.1% of children were diagnosed during contact examination. In South Africa, for example, a 30-month study was conducted to assess the prevalence of TBI and morbidity among 125 children who came into household contact with MDRTB patients. According to this study, 78% of children were infected or ill [23]. Thus, the presence of MDRTB in a child usually indicates presence of the disease within other family members, so a family-oriented approach should be applied in treatment.

Children with TB are often not covered by Anti-TB services because they usually have nonspecific symptoms. We found that almost half (47.8%) of all children with EPRTB were dominated by intoxication syndrome, and in 39.1%, the specific process was gradual, hence, in one third of all children with EPRTB disease, the duration from the first manifestations to diagnosis was 2 months, and in 13.0% – up to 6 months. In addition, 40% of all children with EPRTB were diagnosed with a severe condition at the time of hospitalization in an Anti-TB hospital, and in three cases, the specific process was lethal. This indicates the need to focus the attention of health professionals on the clinical peculiarities of TB among children, which will improve the diagnosing and speed up the start of treatment [12].

Thus, the results demonstrate the importance of further improvement of measures to detect, diagnose, treat and prevent TB not only among children, but also among adults. This is because children are an important and sensitive indicator of the prevalence of TB in the population and their incidence depends on the incidence of adults.

CONCLUSIONS

1. During the study period (2013-2020), the frequency of extrapulmonary TB in children was 9.8%. Moreover, children under 1 and under 3 years old were significantly more likely to predominate in the group with EPRTB, compared to the group with EPSTB (56.5% *vs*. 20.8%; 78.3% *vs*. 45.8%, all $p<0.05$).
2. Among children with EPTB, resistance to the combination of HR (73.6%) was found more often than to HRES (10.5%), HRS and resistance to H and Z (5.3% each; all $p<0.01$). What is more, 30.4% of all patients with EPRTB had MDRTB.
3. Among clinical forms of EPTB, children were significantly more often diagnosed with TB of peripheral LN (40.5%), meninges and CNS (27.7%), bones and joints (23.4%) than other lesions (all $p<0.05$). Almost half of the children with EPTB had miliary PTB ($p<0.01$). In 51.1% of all patients, EPTB was diagnosed as a concomitant pathology.
4. In almost half of the children with EPTB, contact with a patient with TB was not established (44.7%). In 66.0% of all cases, EPTB (73.9% in the case of EPRTB) was detected when seeking medical care. In 14.9% of all patients with EPTB, the time to diagnosing lasted 6 months.
5. In children with EPRTB, compared to the children with EPSTB, a gradual course of the disease was probably more often observed (39.1% *vs*. 4.2%; $p<0.01$). In 47.8% of all patients with EPRTB, the intoxication syndrome was dominating. In three patients with MDRTB, the process was lethal.
6. A significant difference was found in the detection of the frequency of severe (36.2% *vs*. 0; $p<0.01$) and moderate (40.4% *vs*. 16.3%; $p<0.05$) conditions in children with EPTB, compared to children with PTB. The vast majority of children with EPRTB were not vaccinated, in contrast to patients with EPSTB (78.3% *vs*. 45.8%; $p<0.05$).
7. The above indicates the need to intensify preventive measures against TB among children (especially those who are at risk), to ensure control over vaccination, to undertake regular screening and monitoring of contacts among adults and apply control treatment, as well as to apply increasing vigilance and knowledge of physicians in nonspecific manifestations of TB lesions.

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