TRENDS IN INCIDENCE OF EXTRAPULMONARY TUBERCULOSIS IN CHILDREN IN THE CZECH REPUBLIC IN THE PAST 35 YEARS

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SUMMARY

Objective: Extrapulmonary tuberculosis (EPTB) in children globally represents a proportion of all cases of tuberculosis, reaching 20% according to published reports. Children are at a higher risk for disseminated TB and extrapulmonary forms. The most prevalent clinical presentations of EPTB in children worldwide are peripheral lymphadenitis and osteoarticular TB. Peritoneal, urogenital, or meningeal tuberculosis is less frequent, and their diagnosis is often difficult. The aim of the study was the determination of EPTB incidence in children in a low-prevalence region over 35 years.

Methods: Descriptive retrospective study of the incidence of EPTB in children and adolescents (aged 0–18 years) in the Czech Republic in the years 1987–2021 as reported in the tuberculosis register.

Results: Total amount of EPTB cases was 95. The most prevalent form was extrathoracic lymph node TB. The median age was 10 years. Most patients (84%) were Czechs. None of them died. The ratio of pulmonary and extrapulmonary TB was 79.8% to 20.2%.

Conclusion: The low incidence of EPTB in Czech children is congruent with a low incidence of TB in the Czech Republic. Our study confirms that the most frequent form of EPTB is peripheral lymph node TB. Our study did not prove a significant change in the trend of EPTB after the cessation of the mandatory Bacillus Calmette–Guerin (BCG) vaccination programme.

Key words: tuberculosis, extrapulmonary, TB peripheral lymphadenitis, osteoarticular TB, uropoetic

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INTRODUCTION

From the global point of view, tuberculosis is a "top killer" pathogen on WHO's list (1). TB is the 13th leading cause of death, and at the time of publication the second leading infectious killer after COVID-19 (above HIV/AIDS). Annually, tuberculosis afflicts around 10 million people, of which approximately 1.5 million dies (1).

Pulmonary TB (PTB) is more frequent than extrapulmonary TB (1). The proportion of extrapulmonary tuberculosis (EPTB) is highly variable from one country to another (2). From 2002 to 2011 in the European Union, extrapulmonary TB without pulmonary involvement represented 19% of all new tuberculosis cases, whereas extrapulmonary TB with pulmonary involvement accounted for 6%. Therefore, the proportion of newly notified tuberculosis cases with pulmonary involvement alone was 75% (2). There are just several studies regarding EPTB in children (3–7).

The epidemiological situation regarding the incidence of TB in the Czech Republic (3.4 per 100,000 inhabitants in the year 2020) is one of the lowest among the neighbouring EU countries (8). Only 44 cases of extrapulmonary TB were reported in 2020 which represents an incidence of 0.41/100,000.

The purpose of the study is to monitor the incidence rate and obtain a comprehensive picture of the total number of cases and their precise description according to other determinants (clinical presentation, bacteriological verification, age, sex, ethnicity, etc.).

MATERIALS AND METHODS

For our work, we used only retrospective collection of registered data with respect to patient anonymity and GDPR. Data from the tuberculosis register were obtained with the consent of the National Tuberculosis Surveillance Unit. We did not require Ethics Committee approval for our study.

Searching for Cases

For the purposes of this study, we used data from the tuberculosis register. The register has existed in the Czech Republic since the 1950s (9). Reporting new disease cases and relapses of tuberculosis is a legal obligation. The data regarding all reported cases are held centrally and monitored. The data have been in

digital form since 1996. Previous data are not digitalized. We obtained data from 1987 to 1995 from the archive paper copies of unified forms of obligatory reports of cases to TB register from a single centre that follows up on most paediatric cases in the Czech Republic and digitalized them for the purpose of this study. From 1996 to 2021, we obtained data from electronic databases of the tuberculosis register. These data are used to count proportion of PTB to EPTB, trends and gender distribution.

TB Diagnostics

The diagnosis of TB was made in accordance with the World Health Organization and American Thoracic Society criteria (10, 11). All analyses included children aged < 18 years with TB who had either bacteriologically confirmed TB (biological specimen positivity determined via culture, smear microscopy) or clinically diagnosed TB (bacteriological criteria were not fulfilled, but a clinician made a diagnosis of active TB). This definition included case diagnoses which were based on X-ray abnormalities or suggestive histology and EPTB cases without laboratory confirmation. Concurrent extrapulmonary and pulmonary TB (combined TB) was defined as any case of TB that involved both the lungs and organs other than the lungs. In some studies (6), extrapulmonary tuberculosis comprises also the affection of intrathoracic lymph nodes and pleura. This study will not consider the affection of intrathoracic lymph nodes and pleura.

Evaluation of Data from TB Register

The forms of obligatory reports include multiple variables which we evaluated in our study. Firstly, we assessed the diagnosis according to the 10th International Classification of Diseases (ICD). For this study, we chose diagnoses reported in the tuberculosis register under codes A17 and A18 (Table 1) consisting of tuberculous involvement of lymph nodes, bone, skin, central nervous system, gastrointestinal system and peritoneum, eye, ear, genitourinary system, and adrenal glands. Diagnoses from older reports were recorded in relevance to previous ICDs. In these cases, in relation to the verbally written diagnosis, we consolidated all diagnoses according to ICD-10th revision. In this study, we decided to focus on extrathoracic localizations of TB and we did not involve TB of the pleura, intrathoracic lymph node, or miliary TB. As a part of the final data processing, we sorted the data into subgroups according to the organ affected. These subgroups were further analysed conforming to other determinants. Secondly, the general characteristic of the patient included gender, age, country of origin, and ethnicity. Concerning the age, we included children from birth up to and including seventeen years of age. From the questionnaire, it is possible to determine whether the patient is of Roma ethnicity. Therefore, we focused on this ethnicity; belonging to other ethnicities is rare in the Czech Republic and was not monitored in our study. Thirdly, the patient's medical characteristics were Bacillus Calmette–Guerin (BCG) vaccination and comorbidities. The presence of other known disease (comorbidities) or other important related facts shall be entered on the uniform TB register reporting form. Fourthly, the methodology of assignment of the diagnosis of TB was based on the positive culture of acid-resistant bacillus (ARB) in samples obtained from affected tissues or histologic, clinical findings. Exposure to tuberculosis bacillus was investigated through tuberculin skin tests (TST) – "Mantoux" method.

Table 1. *Codes from the 10th Classification of Diseases used in our study*

A17.0	Tuberculous meningitis (G01*)
A17.1	Meningeal tuberculoma (G07*)
A17.8	Other tuberculosis of nervous system
A17.9	Tuberculosis of nervous system, unspecified (G99.8*)
A18	Tuberculosis of other organs
A18.0	Tuberculosis of bones and joints
A18.1	Tuberculosis of genitourinary system
A18.2	Tuberculous peripheral lymphadenopathy
A18.3	Tuberculosis of intestines, peritoneum and mesenteric glands
A18.4	Tuberculosis of skin and subcutaneous tissue
A18.5	Tuberculosis of eye
A18.6	Tuberculosis of ear
A18.7	Tuberculosis of adrenal glands (E35.1*)
A18.8	Tuberculosis of other specified organs

Codes with asterisks refer to alternative coding option for selected disease.

Statistical Analysis

We used the exact test for proportions in binomial distribution and/or corresponding confidence interval for inference on proportions. Equal representation of individual subtypes of EPTB across age groups was studied by means of chi-square test. The trends in time were modelled via Poisson regression. Segmented regression was used for testing a change in the trends. All the statistical tests were performed on significance level $\alpha = 0.05$ and we report 95% confidence intervals. The data were evaluated using software R, version 4.0.4 (12).

RESULTS

The number of tuberculosis cases and incidence of tuberculosis in the Czech Republic show a continually decreasing trend. In the early 2000s, the incidence of TB was around 13/100,000 population. Since 2013, the incidence has remained below 5/100,000 population. The incidence of TB in children and adults both decreased. In the early 2000s, the number of cases among children and adolescent patients was up to 20 per year. The declining trend of TB incidence in the Czech Republic is reflected in the declining trend of EPTB cases (13). In our data set, we have a total of 95 cases of EPTB. The most prevalent diagnosis – 67 cases (71%) was tuberculosis of lymph nodes, the second most prevalent diagnosis – 11 cases (12%) was bone tuberculosis and the third – 6 cases (6%) was uropoetic TB. Other localisations were present in single units: tuberculous meningitis – 4 cases (4%), meningeal tuberculoma – 1 case (1%), TB of the ear – 3 cases (3%), 2 cases of gastrointestinal TB, 1 case of skin TB, and 3 cases of non-specified EPTB.

Gender Distribution

In our data set, cases of EPTB were slightly more frequent in female patients, forming 53.7% of the cases. However, equal representation of genders cannot be rejected (p = 0.54).

Distribution According to Country of Origin

Most cases (84%) occurred among Czech citizens, 4% came from Vietnam and 3% from Mongolia. We had patients from Europe, Asia, America, and Africa. Above Vietnam and Mongolia, those were just single units.

Distribution According to Ethnicity

Just 6 cases from 95 (6%) were children of Roma ethnicity.

Distribution According to Vaccination History

Almost 70% (65 cases) of children were BCG vaccinated, 15% were not vaccinated, and in 15% the BCG vaccine was not reported.

Age Distribution

The average age was 11.6 years. The median age was 10.0 years. Three-year-olds were the most numerous group, followed by ten-year-olds. The smallest group were children aged four. Lymphatic TB and osteoarticular were equally represented in all age groups. TB of the central nervous system was most frequent in the youngest age group. Uropoetic TB was also referred in the youngest age group but was most frequent in adolescents (Fig. 1, Table 2).

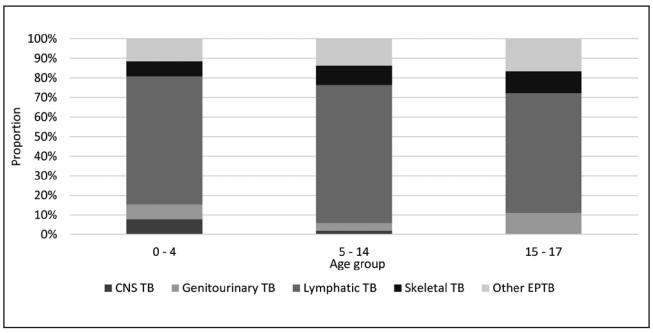

Fig. 1. *Proportion of EPTB diagnoses.*

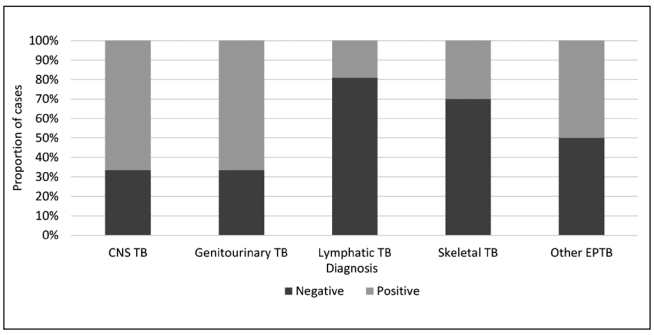

Fig. 2. *Proportion of culture status by diagnosis.*

Method of Diagnosis

Just 28.7% (27 out of 94 with known culture status) cases turned out to be culture positive. For the most common lymphatic TB, the proportion was 19%. The counts are too small for proportions and confidence intervals for other diagnoses to provide

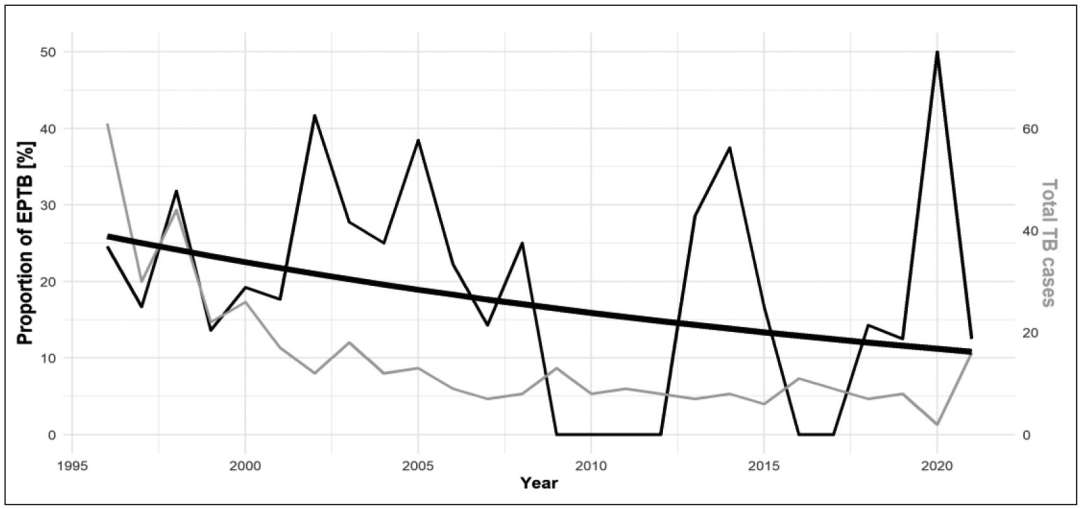

Fig. 3. *Proportion of extrapulmonary TB in time.*

The trend in proportion of extrapulmonary TB out of all TB cases is significantly negative (p = 0.034).

Table 2. *Percentage representation of selected EPTB diagnoses by age group*

Age group	CNS TB (%)	Genitourinary TB (%)	Lymphatic TB (%)	Skeletal TB (%)	Other EPTB (%)	Total EPTB (%)
0–4	1.69	0.85	9.32	0.85	2.54	15.25
5–14	0.65	1.29	20.00	2.58	4.52	29.03
15–17	0.00	0.85	9.32	1.69	1.69	13.56
All	0.77	1.02	13.55	1.79	3.07	20.20
p-value	0.320	0.913	0.011	0.562	0.377	0.002

EPTB – extrapulmonary tuberculosis; CNS – central nervous system

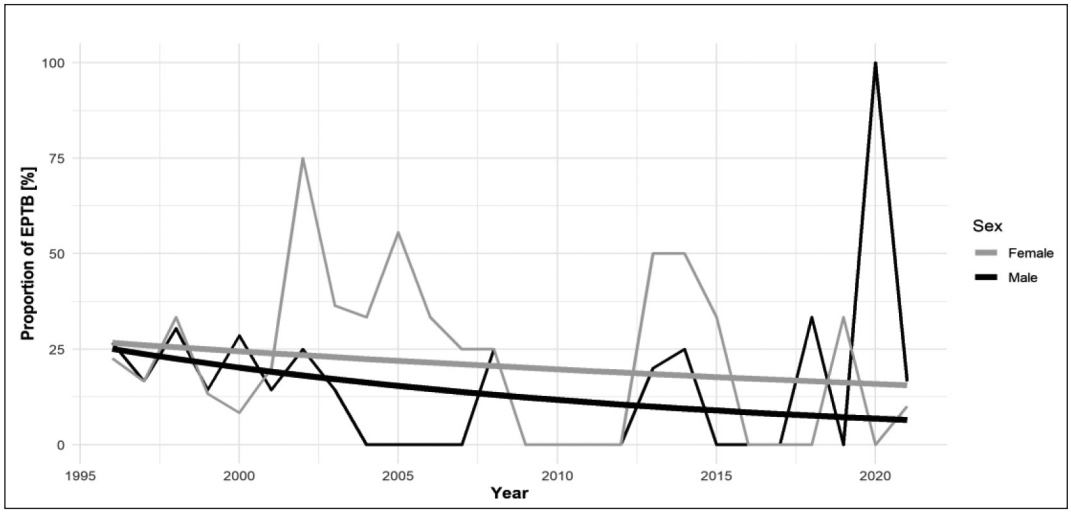

Fig. 4. *Difference of trends between boys and girls.*

Although it seems that the proportion of extrapulmonary TB decreases faster in time for boys, the difference in trends is not statistically significant (p = 0.338).

helpful information. On the other hand, 98.3% (59 out of 60) cases were histologically positive (Fig. 2).

In 14% of cases in our study, the TST result was not available, 20% of subjects had an anergic TST. The highest TST was in gastrointestinal TB, and the lowest was in osteoarticular TB.

Ratio of PTB to EPTB

The ratio of pulmonary and extrapulmonary TB in our data set was 79.8% to 20.2%.

Trends

The trend in the proportion of EPTB out of all TB cases is significantly negative (p = 0.034). Difference of trends between boys and girls is not conspicuous. There is no significant change in the trend after the cessation of the vaccination programme in 2010 (p = 0.750) (Fig. 3, Fig. 4).

Clinical Features According to Localization

TB Peripheral Lymphadenitis

TB peripheral lymphadenitis is the most common form of extrapulmonary TB. We proved it also in our study with 67 cases (71%) of peripheral lymphadenitis; 10.6% were combined with pulmonary forms. The female gender slightly predominated (55%). The median age was 10 years. Most cases came from the Czech Republic. Single units of patients came from Afghanistan, Mongolia, India, Niger, Somalia, and Vietnam; 68% of the cases were BCG-vaccinated; 26% of the subjects had a positive culture, and 71% had positive histopathology confirming the specific type of TB inflammation. TST results were available in 54 cases (82%). The average TST value was 11.5 mm. The maximal TST value was 30 mm; 10 cases (15%) had an anergic TST (Table 3).

Osteoarticular Tuberculosis

Our study comprises 11 cases of osteoarticular TB, 73% were boys. The median age was 8.5 years. In relation to the country of origin, 7 were Czechs and others came from Africa (country not specified), Afghanistan, India, and Vietnam; 20% had EPTB combined with pulmonary form. Just 3 cases were ART positive (one from the articular fluid and two from the gastric lavage); 60% were BCG vaccinated, and 40% were BCG status unknown. In 10 cases the localization was in one or several vertebrae, one in the hip joint. Unfortunately, just half of those patients had a panelled result of TST in the form. From those 6, 4 were positive (7, 15, 16, 20 mm) and 2 were anergic (Table 3).

Uropoetic Tuberculosis

There were 6 cases of uropoetic TB in our study. None of them were combined with the pulmonary form of TB; 5 cases represented TB of the kidneys; one case was epididymal TB. The patients were of ages 0, 3, 3, 6, 12, and 13 years. According to gender: 4 were girls and 2 were boys. Half of them were BCG vaccinated. Anergic TST was detected in two cases, the maximum TST result was 17 mm; 50% were confirmed by the histopathologist, and just 30% were confirmed by positive culture from the urine. Epididymal TB is very rare in children, it was represented in just

Table 3. *Clinical features according to localization (N = 95)*

Locality	n	%	Males/females (%)	Age (years)	TST (mm)
LN TB	67	71	45/55	10	10.6
OA TB	11	12	73/27	8.5	9.6
UP TB	6	6	40/60	6.1	6.8
CNS TB	4	4	25/75	6.5	1.5

LN – lymph node; OA – osteoarticular; UP – uropoetic; CNS – central nervous system; TST – tuberculin skin test

one case in our collection. The diagnosis was made histopathologically, TST, IGRA test and culture were negative (Table 3).

Central Nervous System TB

In our data collection there were 4 cases of basilary meningitis. Their clinical features were different. Three of 4 simultaneously had a pulmonary form of TB. The ages were 1, 1, 5, and 13 years. Female gender dominated, 3 to 1. Two patients were Czechs, one from Mexico, one from Mongolia; 75% of the cases had a positive TST, and 25% had an anergic TST; 75% had a positive ART culture from the CSF. Two children were BCG vaccinated, 1 was not BCG vaccinated, and 1 had an unknown vaccination status. No comorbidities were reported. We had just one case of central nervous system tuberculoma in a 1-year-old girl from India – in this case, pulmonary TB, osteoarticular TB, and tuberculoma were combined. None of them died (Table 3).

DISCUSSION

Our retrospective study monitored a period of 35 years. In this time period the total amount of EPTB cases reported in the TB register was 95 and the most prevalent form of EPTB was extrathoracic lymph node TB.

The historical background of the monitored time period has dramatically evolved. In the second half of the 1980s' former Czechoslovakia was a homogenous country with shallow migration. This situation changed after the end of the communist era in 1989. From the beginning of the 21st century, with EU citizenship and the opening of the borders of the Schengen area, the spectrum of TB patients changed with a massive growth of imported infection in foreigners. Those changing conditions did not significantly alter that most registered EPTB cases are Czech citizens, followed by Vietnamese patients. Although this information may be biased by the fact that a child has Czech citizenship, but their parents may be foreigners from countries with a high incidence of TB, which the data collection method does not reveal to us. This situation may change soon with a high migration from Ukraine due to the war.

Another changing condition during the years of our study was the BCG vaccination policy. Compulsory universal mass Bacillus Calmette–Guerin vaccination programmes were introduced in Czechoslovakia in 1953 and abolished in 2010, and then changed to a selective vaccination programme for infants at high risk of contracting tuberculosis. The Czech Republic already had an experience discontinuing BCG vaccinations in three regions (approximately one-third of the country) between 1986 and 1992 (16, 17) which is the exact time of our study's beginning. Even those changing conditions did not significantly influence the incidence of EPTB or its clinical presentations.

Our study aimed to monitor trends in EPTB in a low TB incidence country. We have concluded three crucial outcomes of this study:

- The incidence of EPTB in children in the Czech Republic is very low and its decreasing trend corresponds with the decreasing trend of TB incidence. We have to admit that we cannot explain why the proportion of EPTB in the total amount of TB cases has decreased. The question is whether some of the children included in the peripheral lymph node TB cohort and diagnosed on the basis of histopathology were in fact avian mycobacteriosis.
- The ratio of pulmonary and extrapulmonary TB in our data set was 79.8% to 20.2%. This well-known distribution has been repeatedly published in studies on children and adults (3–6, 15, 18, 19).
- The distribution of EPTB diagnosis (peripheral lymph node TB, osteoarticular TB and uropoetic TB) corresponds with other published works (4, 6 ,7).

Other interesting observations are that the verification of the diagnosis per culture was very low. Just 28.7% (27 out of 94 with known culture status) cases turned out to be culture positive (CI: 19.9–39.0). This is congruent with other published works that also mentioned a lower sensitivity of non-invasive diagnostic tests in non-pulmonary specimens (11, 15). The verification of the diagnosis per histopathology was 98.3%. These observations correspond to the work of Pakistani authors, where 89.6% of patients with TB peripheral lymphadenitis were diagnosed based on suggestive histopathology (20). Unfortunately, in 14% of cases in our study, the TST result was not available; 20% of the subjects had an anergic TST. Auld et al. published a work on the association between the TST and TB in which 14% of extrapulmonary and 23% of pulmonary and extrapulmonary forms were associated with negative TST (21). Another work by Steiner et al. dedicated to negative TST in children performed Mantoux tests on 200 children with culture-proven *Mycobacterium tuberculosis* infections; 14% had an anergic tuberculin skin test (22).

In several studies, the female gender is a defined risk factor for EPTB in adults. In contrast, the predominance of the female sex is not described in childhood (19, 23, 24). Even in our study, the sex ratio is almost equal with only a slight female predominance (53.7%).

Roughly 3% of the Czech population claim to be of Roma ethnicity. The representation of Roma children in our study was 6%, which is doubly higher. This is even more pronounced in the case of pulmonary forms of tuberculosis, where Roma children are represented in almost 30% of cases (13).

We should take the proportion of vaccinated to unvaccinated with a grain of salt. The vaccination strategy changed throughout our study. Therefore, we should consider that until 2010 almost all children were vaccinated, while from 2010 onwards, all children were unvaccinated.

Strength and Limitations

TB in children has unique features different from adults, making the diagnosis more challenging. TB in children is often paucibacillary. The symptoms of TB in children have a broad spectrum ranging from asymptomatic clinical features and non-specific symptoms to severe clinical presentations. Diagnosis is based on epidemiological co-occurrence of TB in the household, tuberculin skin test, IGRA test, imaging methods, microbiological cultures, and histopathology (11, 14, 15).

The strength of our study is the long-term design monitoring for the last 35 years in the whole country.

Our study has several limitations. The design of our study is a retrospective analysis of data evaluated by other researchers. This type of study may be burdened by observer bias. First, data from 1987 to 1995 are not available in an electronic form from

the TB register. For this period, we obtained data from copies of TB reports to the TB register from a single centre that traditionally takes care of most TB cases in the Czech Republic. We acknowledge that data collection for this period, where data are not obtained from the TB registry, may be underestimated. Finally, new diagnostic tools such as IGRAs and molecular assays were not widespread during the whole study period. Thus, we do not mention IGRA and PCR tests in our findings.

CONCLUSION

The low incidence of EPTB in Czech children is congruent with a low incidence of TB in the Czech Republic (8). Our study confirms that the most frequent form of extrapulmonary TB is peripheral lymph node TB. Our study did not prove a significant change in the trend of EPTB after the cessation of the mandatory BCG vaccination programme.

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Conflict of Interests

None declared

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REFERENCES

1. World Health Organization. Tuberculosis [Internet]. Geneva: WHO; 2022 [cited 2022 Oct 6]. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis.
2. Sandgren A, Hollo V, van der Werf MJ. Extrapulmonary tuberculosis in the European Union and European Economic Area, 2002 to 2011. Euro Surveill. 2013 Mar 21;18(12):20431. doi: 10.2807/ese.18.12.20431-en.
3. Chu P, Chang Y, Zhang X, Han S, Jin Y, Yu Y, et al.; Futang Research Center of and Pediatric Development (FRCPD). Epidemiology of extrapulmonary tuberculosis among pediatric inpatients in mainland China: a descriptive, multicenter study. Emerg Microbes Infect. 2022 Dec;11(1):1090-102.
4. Kaba Ö, Kara M, Odacılar CA, Kamer İ, Sütçü M, Demir SÖ, et al. Evaluation of cases of pediatric extrapulmonary tuberculosis: a single center experience. Turk Pediatri Ars. 2019 Jul 11;54(2):86-92.
5. Wang MS, Wang JL, Liu XJ. Epidemiological trends in the form of childhood tuberculosis in a referral tuberculosis hospital in Shandong, China. Biomed Res Int. 2020 Aug 8;2020:6142567. doi: 10.1155/2020/6142567.
6. Maltezou HC, Spyridis P, Kafetzis DA. Extra-pulmonary tuberculosis in children. Arch Dis Child. 2000 Oct;83(4):342-6.
7. Santiago-García B, Blázquez-Gamero D, Baquero-Artigao F, Ruíz-Contreras J, Bellón JM, Muñoz-Fernández MA, et al. Pediatric extrapulmonary tuberculosis. Pediatr Infect Dis J. 2016 Nov 1;35(11):1175-81.
8. Institute of Health Information and Statistics of the Czech Republic. Basic overview of tuberculosis epidemiology in the Czech Republic in 2020 [Internet]. Prague: IHIS CR; 2021 [cited 2022 May 5]. Available from: https://www.uzis.cz/res/f/008358/tbc2020-en.pdf.
9. Institute of Health Information and Statistics of the Czech Republic. Register of Tuberculosis [Internet]. Prague: IHIS CR [cited 2020 Oct 26]. Available from: https://www.uzis.cz/index.php?pg=registry-sber-dat--ochrana-verejneho-zdravi--registr-tuberkulozy. (In Czech.)
10. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis - rapid diagnostics for tuberculosis detection, 2021 update. Geneva: WHO; 2021.
11. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017 Jan 15;64(2):111-5.
12. The R Foundation. The R Project for Statistical Computing [Internet]. [cited 2022 May 15]. Available from: https://www.r-project.org/.
13. Doležalová K, Göpfertová D. Ten years' experience with the discontinuation of the Bacillus Calmette-Guérin vaccination in the Czech Republic. Int J Mycobacteriol. 2021 Apr-Jun;10(2):193-8.
14. Doležalová K. Actual trends in tuberculosis in childhood and adolescence. Pediatr Praxi. 2019 Jun 20;20(3):152-6. (In Czech.)
15. Natali D, Cloatre G, Brosset C, Verdalle P, Fauvy A, Massart JP, et al. What pulmonologists need to know about extrapulmonary tuberculosis. Breathe (Sheff). 2020 Dec;16(4):200216. doi: 10.1183/20734735.0216-2020.
16. Trnka L, Danková D, Svandová E. Six years' experience with the discontinuation of BCG vaccination. 1. Risk of tuberculosis infection and disease. Tuber Lung Dis. 1993 Jun;74(3):167-72.
17. Trnka L, Danková D, Svandová E. Six years' experience with the discontinuation of BCG vaccination. 2. Cost and benefit of mass BCG vaccination. Tuber Lung Dis. 1993 Aug;74(4):288-92.
18. Mazza-Stalder J, Nicod L, Janssens JP. Extrapulmonary tuberculosis. Rev Mal Respir. 2012 Apr;29(4):566-78. (In French.)
19. Sreeramareddy CT, Panduru KV, Verma SC, Joshi HS, Bates MN. Comparison of pulmonary and extrapulmonary tuberculosis in Nepal - a hospital-based retrospective study. BMC Infect Dis. 2008 Jan 24;8:8. doi: 10.1186/1471-2334-8-8.
20. Sarfaraz S, Iftikhar S, Memon Y, Zahir N, Hereker FF, Salahuddin N. Histopathological and microbiological findings and diagnostic performance of GeneXpert in clinically suspected tuberculous lymphadenitis. Int J Infect Dis. 2018 Nov;76:73-81.
21. Auld SC, Click ES, Heilig CM, Miramontes R, Cain KP, Bisson GP, et al. Association between tuberculin skin test result and clinical presentation of tuberculosis disease. BMC Infect Dis. 2013 Oct 4;13:460. doi: 10.1186/1471-2334-13-460.
22. Steiner P, Rao M, Victoria MS, Jabbar H, Steiner M. Persistently negative tuberculin reactions: their presence among children with culture positive for Mycobacterium tuberculosis (tuberculin-negative tuberculosis). Am J Dis Child. 1980 Aug;134(8):747-50.
23. Yang Z, Kong Y, Wilson F, Foxman B, Fowler AH, Marrs CF, et al. Identification of risk factors for extrapulmonary Tuberculosis. Clin Infect Dis. 2004 Jan 15;38(2):199-205.
24. Lin CY, Chen TC, Lu PL, Lai CC, Yang YH, Lin WR, et al. Effects of gender and age on development of concurrent extrapulmonary tuberculosis in patients with pulmonary tuberculosis: a population based study. PLoS One. 2013 May 22;8(5):e63936. doi: 10.1371/journal.pone.0063936.

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