Clinical presentation, diagnostics, and outcomes of infants with congenital and postnatal tuberculosis: a multicentre cohort study of the Paediatric Tuberculosis Network European Trials Group (ptbnet)

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Summary

Background According to estimates, globally more than 200,000 pregnant women develop tuberculosis (TB) annually. Despite this, data on perinatal TB remain scarce. This study aimed to describe perinatal TB, comprising congenital (cTB) and postnatal (pTB) TB, in a European setting.

Methods Retrospective cohort study via the Paediatric Tuberculosis Network European Trials Group (ptbnet) capturing and comparing cases of cTB and pTB diagnosed at 104 participating European healthcare institutions between 1995 and 2019.

Findings Forty-six cases reported by 20 centres were included in the final analysis (cTB, n = 27; pTB, n = 19). Median age at symptom onset was one week in cTB (IQR: 0–1 weeks), and 12 weeks in pTB patients (IQR: 5–18 weeks). Prematurity was more common in cTB than pTB patients [57.9% (11/19); 95% CI: 36.3–76.9% vs. 21.1% (4/19); 95% CI: 8.5–43.3%; p = 0.049], and the average birth weight was significantly lower [1680 g; IQR: 932–2805 g vs. 2890 g; IQR: 2461–3400 g; p = 0.0043]. Microbiological confirmation was achieved in most patients [85.2% (23/27); 95% CI: 67.5–94.1% vs. 78.9% (15/19); 95% CI: 56.7–91.5%; p = 0.70]. The sensitivity of interferon-gamma release assays was poor in both groups [25.0% (3/12) 95% CI: 8.9–53.2% vs. 35.7% (5/14) 95% CI: 16.3–61.2%; p = 0.68]; in contrast, the sensitivity of the tuberculin skin tests (at 5 mm cut-off) was significantly higher in pTB patients [16.7% (2/12) 95% CI: 4.7–44.8% vs. 66.7% (10/15); 95% CI: 41.7–84.8%; p = 0.0185]. Approximately half of the patients required intensive care support [51.9% (14/27) 95% CI: 34.0–69.3% vs. 47.4% (9/19); 95% CI: 27.3–68.3%; p > 0.99]. Four (4/46; 8.7%) patients died, and four (4/46; 8.7%) had severe long-term sequelae.

Interpretation There was substantial mortality and morbidity in this patient cohort, despite the high-resource setting. cTB was associated with premature birth and low birth weight. In contrast to microbiological tests, immunological tests perform poorly in perinatal TB, and should therefore not be used as rule-out tests.

Funding No study-specific funding.

Keywords: TB; Europe; Congenital; Perinatal; Interferon-gamma release assay; Diagnostics

Introduction

It is estimated that 10.6 million people developed tuberculosis (TB) in 2022, resulting in approximately 1.3 million fatalities. The global figure of individuals with latent TB (LTBI) is however far greater, with recent estimates suggesting that around a quarter of the world's population are infected with *Mycobacterium tuberculosis*.[1]

The risk of progression from LTBI to TB disease (TBD) is substantially higher in pregnancy with an estimated 216,500 pregnant women developing TBD each year globally.[1,2] In a recent UK study, the incidence of TB during pregnancy and subsequent 6 months was 15.4 per 100,000 compared to only 9.1 per 100,000 in non-pregnant women.[3] Globally, significant underreporting of TBD in pregnancy and in infancy is highly likely.[4–7]

Perinatal tuberculosis has traditionally been classified into congenital TB (cTB), caused by *in utero* mother-to-child transmission via haematogenous transmission, ingestion/aspiration of infected amniotic fluid or intrapartum via ingestion/aspiration of infected genital secretions, and postnatal TB (pTB), caused by inhalation of infectious respiratory droplets from the mother or another infectious index case.[4]

To date, fewer than 500 cases of cTB have been reported in the literature.[5,6,8] A recent systematic review on the management of infants born to mothers with TBD highlighted the urgent need for additional data to inform practice guidelines.[7] Although currently no robust data exist, some reports from low-resource, high TB prevalence settings indicate that the case fatality rate (CFR) of cTB may be as high as 50%.[4,5,9,10] Data from high-resource settings are even more limited.

Historical diagnostic criteria for cTB, originally proposed by Beitzke in 1935, included proof of a primary hepatic complex obtained through a surgical procedure or autopsy.[11] Cantwell's revised criteria in 1994 required 'proven tuberculous lesions' and at least one of the following: i) lesions in the first week of life; ii) a primary hepatic complex or caseating hepatic granulomas; iii) tuberculous infection of the placenta or the maternal genital tract; or iv) exclusion of the possibility of postnatal transmission by a thorough investigation of

Research in context

Evidence before this study

We searched MEDLINE and Embase via the OVID interface for publications since January 1, 1954, on September 14, 2024, using the search algorithm "congenital tuberculosis OR perinatal tuberculosis", limiting search results to English language and human/humans, which produced 474 results, reduced to 309 unique publications after removal of duplicates. Of the matches, 38 publications were unrelated to the topic, one was a book chapter, 13 were conference abstracts, 5 editorials, 10 letters, 25 reviews, and 217 case reports and case series. The large majority of the latter reported a single case or fewer than 5 cases. The literature reviews with the largest number of patients are those by Li et al. and Peng et al., which included 92 and 170 cases, respectively. The largest reports presenting original cases were two papers from China by Zhang et al. and Zhou et al., which included 26 and 33 infants with congenital TB, respectively.

Added value of this study

To our knowledge, this is the first multinational multi-centre study on congenital and postnatal TB to date. Our report provides detailed data on the clinical presentation, diagnostic results, treatment and outcome of infants with congenital or postnatal TB. The data highlight the limitations of immune-based TB diagnostics in this age group, as well as the substantial morbidity and mortality associated with TB disease in those infants. Our data also underscore the limitations of the commonly used Cantwell criteria for congenital TB.

Implications of all the available evidence

Our observations will help to raise awareness of an uncommon condition, which is likely considerably under-recognised and under-reported. In addition, our data will help clinicians providing care for young infants to diagnose and manage patients with congenital or postnatal TB more efficiently. Based on our observations, we are proposing modified criteria for congenital TB, which are less restrictive than the Cantwell criteria.

contacts.[9,11] However, several reports indicate that a substantial proportion of cTB cases present far later than the first week of life, with some patients being diagnosed at several months of age.[4,12] Also, data from a literature review on cTB that included 170 cases published between 1946 and 2009 suggest that a diagnosis of genital TB is established in only a quarter of the mothers of infants with cTB. Finally, unless maternal TBD is known or suspected, the placenta has typically been discarded by the time most infants with cTB become symptomatic.[13]

The primary aim of this multicentre study was to describe confirmed and probable cTB and pTB cases diagnosed at European healthcare institutions, with a focus on the clinical presentation, diagnostics and outcomes. The secondary aim was to assess the suitability of the Cantwell criteria in this cohort of children to inform future perinatal TB guidelines.

Methods

Initial survey

This study was conducted by the Paediatric Tuberculosis Network European Trials Group (ptbnet), a research network of clinicians and researchers with interest in paediatric TB.[14–16] In 2019, ptbnet had 239 active members, primarily based at tertiary and quaternary healthcare institutions (n = 104) across 32 European countries. A pre-study survey was sent to all ptbnet members in March 2019 asking collaborators to report all infants with cTB and pTB diagnosed at their institution from January 1995 to December 2019. Clinicians who reported cases were then invited to provide detailed, anonymized data for each case.

Inclusion and exclusion criteria

Data were collected on all reported cases with suspected cTB or pTB. For the purpose of this study, cTB was defined as an infant with microbiologically-confirmed TBD or probable TBD and at least one of the following criteria: i) microbiologically-confirmed urogenital TB infection in the mother, ii) microbiologically-confirmed placental TB infection, iii) presence of granuloma(s) in the child's liver on imaging and/or histopathology, iv) presence of symptoms in the first week of life. pTB was defined as an infant ≤6 months of age with microbiologically-confirmed or probable TBD who did not fulfil the criteria for cTB and in whom the mother was deemed to be the index case (as indicated by contact tracing).

Study definitions

Definite TBD was defined as a symptomatic individual with microbiologically-confirmed TB infection with positive culture and/or polymerase chain reaction (PCR) results. Probable TBD was defined as a symptomatic individual fulfilling at least two of the following four criteria: a) symptoms and signs consistent with TBD (chronic cough, persistent fever, night sweats, weight loss/failure to thrive, severe malaise/listlessness, meningism or reduced level of consciousness), b) radiological findings suggestive of TBD, c) presence of risk

	Congenital TB (n = 27)	Postnatal TB (n = 19)	p-value
Age at symptom onset, median (IQR)	1 (0–1)	12 (5–18)	<0.0001
<1 week	20/27 (74.1)	0/19 (0)	<0.0001
1–<4 weeks	3/27 (11.1)	1/19 (5.3)	0.63
4–<12 weeks	3/27 (11.1)	8/19 (42.1)	0.0322
12–26 weeks	1/27 (3.7)	10/19 (52.6)	0.0002
Male sex	14/27 (51.8)	12/19 (63.2)	0.55
Gestation at birth (weeks), median (IQR)[a]	32 (26–38)	38 (37–40)	0.0065
Gestation at birth (weeks), median (IQR)[b]	34 (31–40)	38 (37–40)	0.13
Prematurity[b]	11/19 (57.9)	4/19 (21.1)	0.0489
Birth weight (grams), median (IQR)[c]	1680 (932–2805)	2890 (2461–3400)	0.0043
Ethnicity			
White Caucasian	14/27 (51.8)	11/19 (57.9)	0.77
Black African	6/27 (22.2)	2/19 (10.5)	0.44
Black Caribbean	0/27 (0)	0/19 (0)	>0.99
Indian subcontinent	3/27 (11.1)	1/19 (5.3)	0.63
Other Asian	2/27 (7.4)	0/19 (0)	0.50
Middle Eastern/Arabic	2/27 (7.4)	1/19 (5.3)	>0.99
Latin-American	0/27 (0)	4/19 (21.1)	0.0238
HIV status			
Perinatally-acquired HIV	2/27 (7.4)	0/19 (0)	0.50
BCG-vaccinated	2/26 (7.7)	0/19 (0)	0.50
Presenting symptoms/signs[d]			
Fever (temperature >38.5 °C)	16/27 (59.3)	9/19 (47.4)	0.55
Poor feeding	13/24 (54.2)	10/19 (52.6)	>0.99
Poor weight gain	10/24 (41.7)	7/19 (36.8)	>0.99
Irritability	11/26 (42.3)	4/19 (21.1)	0.20
Respiratory symptoms/signs	23/27 (85.2)	15/19 (78.9)	0.70
Hepatomegaly	9/27 (33.3)	7/19 (36.8)	>0.99
Splenomegaly	8/27 (29.6)	5/19 (26.3)	>0.99
Gastrointestinal symptoms/signs	7/27 (25.9)	2/19 (10.5)	0.27
TB disease focus[e]			
Pulmonary	23/27 (85.2)	19/19 (100)	0.13
Miliary	8/27 (29.6)	9/19 (47.4)	0.35
Abdominal (incl. hepatic focus)	8/27 (29.6)	3/19 (15.8)	0.32
Central nervous system	7/27 (25.9)	6/19 (31.6)	0.75
Peripheral lymph nodes	4/26 (15.4)	1/18 (5.6)	0.63
Other TB disease[f]	2/27 (7.4)	2/19 (10.5)	>0.99

BCG, Bacille Calmette Guérin; IQR, interquartile range; TB, tuberculosis. Figures shown are numbers and percentages, unless stated otherwise. [a]4 pairs of twins in the cTB group. [b]Adjusted for twin pregnancy (n = 4). [c]Data missing in two patients in cTB group and one patient in postnatal TB group. [d]Some patients had more than one symptom or sign. [e]Some patients had more than one disease focus. [f]cTB group: ophthalmic (n = 1), middle ear (n = 1); pTB group: ophthalmic (n = 1), renal (n = 1).

Table 1: **Demographic and clinical characteristics of the study population.**

factors for TB infection (maternal TBD or birth in a high TB prevalence country, defined as an annual incidence >40/100,000), d) positive immune-based test for TB infection (i.e. tuberculin skin test (TST) or interferon-gamma release assay (IGRA)). These criteria are more stringent than the criteria proposed by the American Thoracic Society and the Centres for Disease Control and Prevention.[17] Reported cases fulfilling neither of these two definitions were excluded from the analyses. In this study, two cut-offs for TST positivity were analysed: i) ≥ 5 mm induration and ii) ≥ 10 mm induration at 48–72 h.

Data collection

The standardised, password-protected Excel data collection form comprised a total of 155 items capturing infant and maternal data, including demographics, clinical data, radiological investigations, IGRA and TST results, blood test and microbiological results, treatment, details related to the Cantwell criteria and outcomes. No personal or identifiable data were collected during this study.

Statistical analysis

Non-parametric two-tailed Mann Whitney *U* tests were used to compare continuous variables and chi-square or Fisher's exact tests for categorical variables. p-values <0.05 were considered statistically significant. For missing data, an available case analysis approach was used. Analyses were performed and all figures were constructed with Prism (V9.0; GraphPad, La Jolla, U.S.) and SPSS (V28.0, IBM, Armonk, U.S.).

Ethical considerations

The study was reviewed and approved by the ptbnet steering committee, and conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Depending on national laws and regulations, local ethics committee approval was obtained, if required. Informed consent was obtained from the parents/guardians of the patients prior to inclusion, if required by laws and regulations. No personal or identifiable data were collected or processed during the conduct of this study.

Role of the funding source

There was no specific funding for this study.

Results

Demographic and clinical characteristics

A total of 46 infants with cTB or pTB disease were reported from 20 healthcare institutions based in 11 European countries (Figure S1): Austria (n = 1), Belgium (n = 3), Bulgaria (n = 2), Finland (n = 1), Germany (n = 5), Italy (n = 9), Spain (n = 14), Sweden (n = 3), Switzerland (n = 2), Ukraine (n = 1) and United Kingdom (n = 5). All cases reported met the inclusion criteria.

Based on the study definitions, there were 27 (58.7%) cTB cases and 19 (41.3%) pTB cases, including four pairs of twins with cTB. Twenty-three (85.2%) of the cTB cases and 15 (78.9%) of the pTB cases had definite TBD; the remaining cases were classified as probable TBD. The majority of infants were white Caucasian and 54.3% were male (Table 1). The age at symptom onset was lower in the cTB group than in the pTB group (Fig. 1).

Approximately one quarter (25.9%) of the cTB cases did not have symptoms during the first week of life; four (15%) of the infants with cTB developed TB symptoms at four or more weeks of age (Table 1). The oldest infant with cTB developed symptoms at 29 weeks, was diagnosed at 37 weeks of age and died 17 days after commencement of treatment. TB transmission in this infant occurred via the maternal genital tract, subsequently confirmed by mycobacterial cultures of the endometrium; the mother had no evidence of pulmonary TBD (unremarkable chest x-ray, sputum PCR- and culture-negative). Approximately half (47.4%) of the infants with pTB developed symptoms in the first three months of life.

The proportion of premature deliveries (<37 weeks of gestation) was significantly higher in the cTB group, even when the pairs of twins were excluded from the analysis ($p = 0.0023$ and 0.0489, respectively). Infants with cTB also had significantly lower birthweights than infants with pTB (Table 1; $p = 0.0043$). Two children with cTB had been vaccinated with BCG before TB-related symptoms evolved. Respiratory symptoms were the most common presenting feature in both groups, followed by fever and poor feeding, with no significant difference in the clinical features at presentation between the patient groups. Fever was an inconsistent feature that was present in only approximately half of the patients. Approximately a third of the patients in each group had hepatomegaly and/or splenomegaly. Pulmonary TB was the most common diagnosis in both groups, but miliary TB, abdominal TB and central nervous system (CNS) TB were also relatively common (Table 1).

Two infants in the cTB group were also diagnosed with perinatally-acquired HIV infection. One of them developed Immune Reconstitution Inflammatory Syndrome (IRIS). Both completed TB treatment without sequelae.

Radiological findings

The most common investigations were chest x-ray (CXR), abdominal ultrasound scan (USS) and cranial USS (Table 2). Only a minority of the patients underwent computed tomography (CT) or magnetic resonance imaging (MRI).

The proportion of patients with CXR changes suggestive of TBD was lower in the cTB group than in the pTB group (66.7% vs. 94.4% respectively; $p = 0.0343$). In both groups the most common radiological findings on

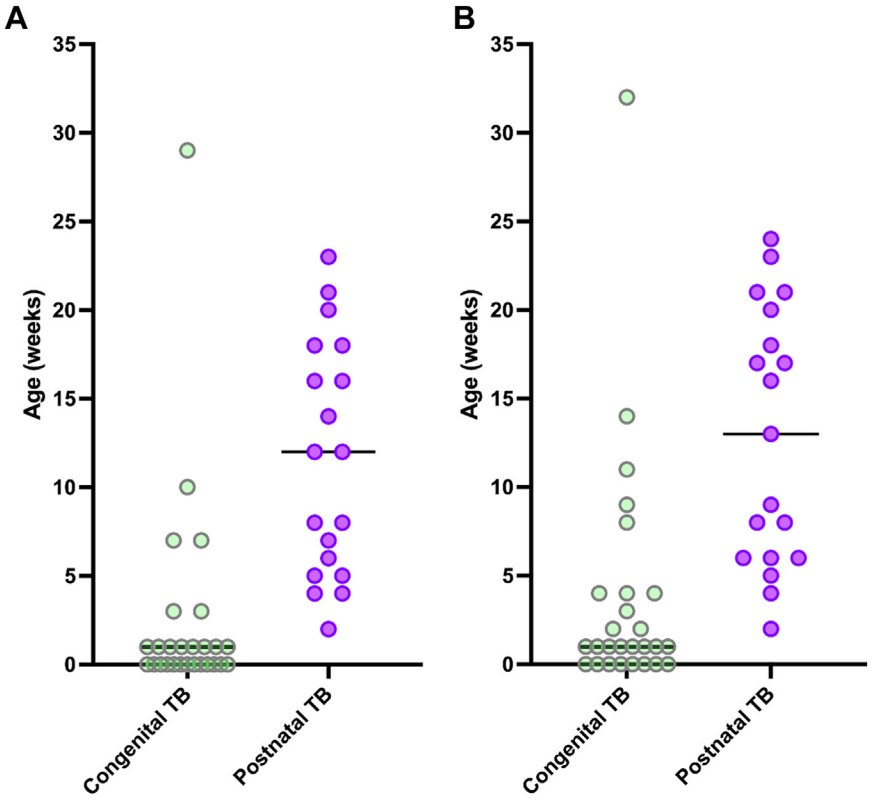

Fig. 1: **Dot plot diagram showing the age at symptom onset (A) and the age at presentation (B) in infants with congenital and postnatal tuberculosis.** Each dot represents one patient; the horizontal lines indicate the medians.

	Congenital TB (n = 27)	Postnatal TB (n = 19)	p-value
Chest x-ray			
Suggestive of TBD	18/27 (66.7)	17/18 (94.4)	0.0343
Abnormal, not suggestive of TBD	5/27 (18.5)	1/18 (5.6)	
No abnormalities detected	4/27 (14.8)	0/18 (0)	
Chest CT			
Suggestive of TBD	5/5 (100)	11/11 (100)	>0.99
Abnormal, not suggestive of TBD	0/5 (0)	0/11 (0)	
No abnormalities detected	0/5 (0)	0/11 (0)	
Chest imaging (x-ray OR chest CT) suggestive of TBD	23/27 (85.2)	19/19 (100)	0.13
Abdominal x-ray			
Suggestive of TBD	2/16 (12.5)	1/6 (16.7)	>0.99
Abnormal, not suggestive of TBD	4/16 (25.0)	0/6 (0)	
No abnormalities detected	10/16 (62.5)	5/6 (83.3)	
Abdominal ultrasound scan			
Suggestive of TBD	9/22 (40.9)	6/15 (40.0)	>0.99
Abnormal, not suggestive of TBD	2/22 (9.1)	0/15 (0)	
No abnormalities detected	11/22 (50.0)	9/15 (60.0)	
Abdominal CT			
Suggestive of TBD	3/4 (75.0)	0/0	>0.99
Abnormal, not suggestive of TBD	0/4 (0)	0/0	
No abnormalities detected	1/4 (25.0)	0/0	
Abdominal MRI			
Suggestive of TBD	2/2 (100)	1/2 (50.0)	>0.99
Abnormal, not suggestive of TBD	0/2 (0)	0/2 (0)	
No abnormalities detected	0/2 (0)	1/2 (50.0)	
Cranial ultrasound scan			
Suggestive of TBD	2/21 (9.5)	3/13 (23.1)	0.35
Abnormal, not suggestive of TBD	6/21 (28.6)	2/13 (15.4)	
No abnormalities detected	13/21 (61.9)	8/13 (61.5)	
Cranial CT			
Suggestive of TBD	2/6 (33.3)	1/3 (33.3)	>0.99
Abnormal, not suggestive of TBD	0/6 (0)	0/3 (0)	
No abnormalities detected	4/6 (66.7)	2/3 (66.7)	
Cranial MRI			
Suggestive of TBD	4/9 (44.4)	3/5 (60.0)	>0.99
Abnormal, not suggestive of TBD	2/9 (22.2)	1/5 (20.0)	
No abnormalities detected	3/9 (33.3)	1/5 (20.0)	
Abnormalities on chest imaging[a]			
Pulmonary consolidation	12/19 (63.2)	11/19 (57.9)	>0.99
Atelectasis	9/19 (47.4)	5/19 (26.3)	0.31
Pleural effusion	1/19 (5.3)	2/19 (10.5)	>0.99
Airway compression	2/19 (10.5)	6/19 (31.6)	0.23
Hilar/mediastinal lymphadenopathy	7/19 (36.8)	14/19 (73.7)	0.0489
Calcifications	1/19 (5.3)	0/19 (0)	>0.99
Pulmonary cavities/bullae	0/19 (0)	3/19 (15.8)	0.23
Emphysema	0/19 (0)	2/19 (10.5)	0.49
Miliary infiltrates	8/19 (42.1)	5/19 (26.3)	0.50
Abnormalities on abdominal imaging[a]			
Hepatomegaly	7/10 (70.0)	6/7 (85.7)	0.60
Hepatic abnormalities[b]	6/10 (60.0)	2/7 (28.6)	0.33
Splenomegaly	6/10 (60.0)	5/7 (71.4)	>0.99
Splenic abnormalities[b]	6/10 (60.0)	2/7 (28.6)	0.33
Intraabdominal lymphadenopathy	4/10 (40.0)	2/7 (28.6)	>0.99
Ascites	4/10 (40.0)	2/7 (28.6)	>0.99
Abnormalities on cranial imaging[a]			
Meningeal enhancement	2/5 (40.0)	2/4 (50.0)	>0.99
Cerebral infarcts	2/5 (40.0)	0/4 (0)	0.44

(Table 2 continues on next page)

chest imaging were pulmonary consolidation, hilar or mediastinal lymphadenopathy, atelectasis and miliary changes. Hilar and/or mediastinal lymphadenopathy (36.8% vs. 73.7%; p = 0.0489) and pulmonary cavitation/bullae (0% vs. 15.8%, respectively; p = 0.23) were more common in the pTB group.

Among patients who had a cranial USS, 9.5% in the cTB group had intracranial changes suggestive of TBD, compared with almost one quarter (23.1%) in the pTB group (Table 2). Chest CT had a high diagnostic yield, identifying changes suggestive of TBD in every patient who underwent this investigation (n = 16). Fewer than half of the cTB cases (9/22; 40.9%) who underwent an abdominal USS had intraabdominal changes suggestive of TBD. Of those nine cases, only six (6/22; 27.3%) had changes consistent with a primary hepatic complex.

Laboratory findings

The most common laboratory abnormalities comprised hepatic transaminitis and anaemia (Table S1). No significant differences were observed between the two groups in any of the blood parameters included in the analyses.

Immune-based and microbiological TB tests

The majority (83.3%) of infants in the cTB group who underwent a TST had a negative test result, even at the 5 mm cut-off (Table 3). In contrast, two thirds (66.7%) of children who had a TST in the pTB group had a positive result. The sensitivity of interferon-gamma release assays was poor in both groups (25.0% vs. 35.7%; p = 0.68). Notably, indeterminate IGRA results were common in the cTB, but not in the pTB group.

Overall, microbiological confirmation of TBD was achieved by culture and/or PCR in the majority of cTB and pTB patients (85.2 and 78.9%, respectively; p = 0.70). The sample types with the highest yield for microbiological confirmation were gastric aspirates and bronchoalveolar lavage fluid (Table 3). *M. tuberculosis* was identified in cerebrospinal fluid by culture or PCR in a small proportion of infants who underwent a lumbar puncture. Mycobacterial blood cultures also had a low yield, but had only been obtained in a few patients.

Treatment and outcome

Approximately a third of the patients received an anti-TB treatment regimen other than isoniazid, rifampicin, pyrazinamide with or without ethambutol, for a variety of reasons, including prematurity and suspected drug-resistance (Table 4). The median treatment duration in both groups was considerably longer than the standard 6-month therapy (cTB: 40 weeks; pTB: 36 weeks). A significant proportion of patients developed complications secondary to TBD or TB treatment (Table 4). Intensive care unit (ICU) admission was required by 41.7% cTB patients that initiated treatment within the first week after symptom onset, whereas 61.5% of the patients with delayed treatment initiation needed ICU

support (p = 0.43). A similar trend was observed in the pTB patients. In the entire cohort, four patients died of TBD. A further four (8.7%) infants had long-term sequelae at discharge, including hemiparesis (n = 2) and neurodevelopmental delay (n = 2); all four had evidence of CNS TBD (Table 4).

Performance of the Cantwell criteria

Of the cTB cases, 85.2% fulfilled the Cantwell criteria (Table 5). Four (14.8%) did not meet the criteria due to lack of microbiological confirmation, despite extensive investigations. However, all four infants had symptom onset during the first week of life. Case 1 was an infant in whom TB was identified in placental tissue; in case 2 TB was found in amniotic fluid and the maternal peritoneum; both had twin siblings diagnosed with microbiologically-confirmed TB. Case 3 was born to a mother with pulmonary TB, and case 4 to a mother with abdominal and genitourinary TB (TB confirmed on endometrial and placental tissue); both presented with respiratory distress and CXR changes at birth.

Importantly, more than one quarter (25.9%) of the cTB cases did not develop symptoms in the first week of life, and fewer than a third (27.3%) who underwent abdominal imaging had a primary hepatic complex or caseating granulomas (Table 5).

Maternal demographic and clinical characteristics

There was limited accessible documentation regarding TB-related clinical features, investigations and outcomes in several mothers. There was no difference between the cTB and pTB patient groups regarding the maternal age at delivery (Table S2). Most mothers originated from Europe, followed by Africa and Asia. Two mothers had undiagnosed HIV infection and infants with perinatally-acquired HIV and cTB. Only half (52.9%) of the mothers in the cTB group retrospectively reported having symptoms during pregnancy or during labour; only four (18.2%) were investigated for TB during pregnancy, and all four were screened due to clinical symptoms. Two mothers had pulmonary TB, one CNS TB and one miliary TB. In about half of the mothers, investigations for TB were only initiated because TB was suspected in their infant. Extrapulmonary TB was significantly more common in the cTB group (75.0% vs. 8.3%; p = 0.0006). Miliary TB was also more commonly observed in the cTB group, but this did not reach statistical significance (22.7% vs. 7.1%; p = 0.37). Twelve mothers of children in the cTB group were diagnosed with TB of the genital tract. In both groups microbiological confirmation of TB was achieved in the majority of mothers (cTB: 87.0%, pTB: 85.7%; Table S3).

Discussion

To our knowledge this is the first European multinational, multi-centre study on perinatal TB, which was

	Congenital TB (n = 27)	Postnatal TB (n = 19)	p-value
(Continued from previous page)			
Tuberculomas/granulomas	2/5 (40.0)	2/4 (50.0)	>0.99
Hydrocephalus	1/5 (20.0)	2/4 (50.0)	0.52
Calcifications	1/5 (20.0)	1/4 (25.0)	>0.99

CT, computer tomography; MRI, magnetic resonance imaging; TBD, tuberculosis disease. Figures shown are numbers and percentages. [a]Includes only children with abnormal findings suggestive of TBD in the respective radiological investigation. [b]Abnormalities comprised: granulomas, calcifications, infarcts and miliary infiltrates.

Table 2: **Summary of radiological investigations performed in the study population.**

	Congenital TB (n = 27)	Postnatal TB (n = 19)	p-value
Immune-based tests (at presentation)			
Tuberculin skin test			
TST induration diameter, median (IQR)	0 (0–5.0)	8.0 (0–15.0)	0.0363
Positive (at 5 mm cut-off)	2/12 (16.7)	10/15 (66.7)	0.0185
Negative (at 5 mm cut-off)	10/12 (83.3)	5/15 (33.3)	
Positive (at 10 mm cut-off)	1/12 (8.3)	7/15 (46.7)	0.0433
Negative (at 10 mm cut-off)	11/12 (91.7)	8/15 (53.3)	
QuantiFERON-TB Gold assay[a]			
Positive	3/10 (30.0)	4/10 (40.0)	>0.99
Negative	3/10 (30.0)	5/10 (50.0)	
Indeterminate[b]	4/10 (40.0)	1/10 (10.0)	
T-SPOT.TB assay			
Positive	0	1/4 (25.0)	>0.99
Negative	1/2 (50.0)	3/4 (75.0)	
Indeterminate[b]	1/2 (50.0)	0	
Microbiological investigations			
Nasopharyngeal aspirate			
AFB staining positive	1/5 (20.0)	2/3 (66.7)	0.55
Mycobacterial culture positive	0/5 (0)	2/3 (66.7)	0.44
Mycobacterial PCR positive[c]	0/2 (0)	1/3 (33.3)	>0.99
Gastric aspirate			
AFB staining positive	8/19 (42.1)	3/18 (16.6)	0.15
Mycobacterial culture positive	19/21 (90.5)	10/18 (55.6)	0.025
Mycobacterial PCR positive[c]	14/16 (87.5)	10/13 (76.9)	0.63
Bronchoalveolar lavage fluid			
AFB staining positive	4/7 (57.1)	2/6 (33.3)	0.59
Mycobacterial culture positive	5/7 (71.4)	4/6 (66.7)	>0.99
Mycobacterial PCR positive[c]	3/6 (50.0)	4/5 (80.0)	0.55
Cerebrospinal fluid[d]			
AFB staining positive	0/16 (0)	0/12 (0)	>0.99
Mycobacterial culture positive	2/20 (10.0)	1/12 (8.3)	>0.99
Mycobacterial PCR positive[c]	1/11 (9.1)	1/10 (10.0)	>0.99
Blood			
Mycobacterial culture positive	2/10 (20.0)	0/2 (0)	>0.99
TBD confirmed by mycobacterial culture	22/27 (81.5)	11/19 (57.9)	0.10
TBD confirmed by PCR[c]	17/27 (63.0)	12/19 (63.2)	>0.99
Overall TBD microbiologically-confirmed	23/27 (85.2)	15/19 (78.9)	0.70

AFB, acid fast bacilli; IQR, interquartile range; PCR, polymerase chain reaction; TBD, tuberculosis disease; TST, tuberculin skin test. Figures shown are numbers and percentages, unless stated otherwise. [a]Comprising QuantiFERON-TB Gold assay (cTB: n = 1; pTB: n = 1), QuantiFERON-TB Gold in-Tube assay (cTB: n = 4; pTB: n = 6), and QuantiFERON-TB Gold Plus assay (cTB: n = 4; pTB: n = 1); in some patients the QuantiFERON-TB version was not known (cTB: n = 1; pTB: n = 2). [b]Indeterminate and negative results were grouped together for statistical comparisons. [c]A variety of different commercial and in-house PCR assays were used across the participating centres. [d]Lumbar puncture was performed in 17 (63.0%) children in the cTB group, and 13 (68.4%) in the pTB group.

Table 3: **Summary of immune-based tuberculosis tests and microbiological investigations performed in the study population.**

	Congenital TB (n = 27)	Postnatal TB (n = 19)	p-value
Treatment			
Time from first symptoms to treatment initiation in days, median (IQR)	10 (0–17)	10 (0–21)[a]	>0.99
ICU admission	14/27 (51.9)	9/19 (47.4)	>0.99
Patients requiring ICU admission according to treatment delay			
<1 week	5/12 (41.7)	2/6 (33.3)	>0.99
1–<4 weeks	8/13 (61.5)	5/10 (50.0)	0.69
4–<12 weeks	1/2 (50.0)	2/2 (100)	>0.99
>12 weeks	0/0 (0)	0/1 (0)	–
Primary regimen: HRZE	12/27 (44.4)	9/19 (47.4)	>0.99
Primary regimen: HRZ	5/27 (18.5)	3/19 (15.8)	>0.99
Primary regimen other than HRZ(E)	10/27 (37.0)[b]	7/19 (36.8)[c]	>0.99
Change or interruption of the primary treatment regimen	5/27[d] (18.5)	0/18[e] (0)	0.07
Duration of treatment in weeks, median (IQR)	40 (36–52)	36 (20–48)	0.07
Completion of treatment	26/27 (96.3)	15/18 (83.3)[e]	0.29
Drug-resistance identified during TB treatment	2/27 (7.4)	2/18 (11.1)[e]	>0.99
Outcome			
Complications secondary to TB	5/27 (18.5)	6/18 (33.3)[e]	0.30
Complications secondary to TB treatment	4/27 (14.8)	2/18 (11.1)[e]	0.99
Long-term sequelae (excluding death)	2/27 (7.4)	2/18 (11.1)[e]	>0.99
Death	1/27 (3.7)	3/18 (16.7)[e]	0.29

HIV, human immunodeficiency virus; HRZ, isoniazid, rifampicin and pyrazinamide; HRZE, isoniazid, rifampicin, pyrazinamide and ethambutol; ICU, intensive care unit; IQR, interquartile range, TB, tuberculosis. Figures shown are numbers and percentages, unless stated otherwise. [a]In 4 patients, treatment was initiated before onset of symptoms due to maternal TB diagnosis. [b]Reasons for alternative treatment regimens: suspected drug-resistant TB (n = 2); severity of the disease or only intravenous drug administration possible (n = 8). [c]Reasons for alternative treatment regimens: suspected drug-resistance TB (n = 2); severity of the diseases (n = 5). [d]Reasons for change or interruption: drug resistance (n = 2), side effects (n = 3). [e]One patient lost to follow-up.

Table 4: **Summary of treatment and outcome in the study population.**

facilitated by a well-established collaborative research network – ptbnet – currently the largest paediatric TB research network globally. Only a limited number of cases were identified across a considerable number of tertiary and quaternary centres providing healthcare for children with TB, indicating that cTB and pTB are rare entities in Europe. However, our data suggest that opportunities to timely diagnose maternal and perinatal TB were frequently missed.

	Congenital TB (n = 27)
Proven TB of the placenta or maternal genital tract	16/24 (66.7)[a]
Primary hepatic complex or caseating granulomas (on imaging)	6/22 (27.3)[b]
Symptoms in 1st week of life	20/27 (74.1)
Exclusion of postnatal transmission	22/27 (81.5)[c]
Microbiologically-confirmed TB in the child	23/27 (85.2)
Fulfilling the Cantwell criteria	**23/27 (85.2)**

TB, tuberculosis. Figures shown are numbers and percentages. [a]Comprises the following: Genital tract TB (n = 12); placental TB (n = 4). Only 12 mothers underwent investigations for genital tract TB (data missing in n = 3, including n = 1 with *M. tuberculosis* detected in the mother's urine and peritoneum). [b]No abdominal imaging performed in n = 5. [c]In n = 1 the child developed symptoms in the first week of life and a primary hepatic complex was found, but the mother was only diagnosed with pulmonary TB and a miliary pattern was observed on the chest x-ray; in n = 2 information about contact tracing was limited but the children (twins) both developed symptoms during the first week of life and the mother was diagnosed with abdominal TB as a peritoneal tissue sample was PCR- and culture-positive and pulmonary TB in the mother was ruled out with sputum samples and an unremarkable chest x-ray; in n = 1 the mother had pulmonary TB and a miliary pattern in the chest x-ray as well as osteoarticular TB and the child developed TB symptoms (miliary TB) in the first week of life; in n = 1 the mother was only diagnosed with microbiological confirmed pulmonary TB but the child developed symptoms at 3 weeks of life and showed calcifications in the liver as well as hepatic granuloma.

Table 5: **Summary of the frequency of features required by the original Cantwell criteria in the subgroup of children with congenital tuberculosis.**

Our study has several key findings. Firstly, the data show that symptoms and signs classically associated with TBD are often absent in infants with cTB or pTB. Only approximately half of the patients had fever at presentation, and even fewer had a history of poor weight gain. Secondly, a considerable proportion of those patients had severe variants of TBD, such as miliary TB or CNS TB. This aligns well with data from a recent publication from China, which reported that 78.8% of patients with cTB in their cohort had disseminated TB.[18] Considering the high proportion of CNS TB in our cohort, all children with suspected cTB or pTB should undergo lumbar puncture to rule out meningitis. Thirdly, a substantial proportion of the pTB cases unexpectedly had pulmonary cavitation/bullae at presentation, despite TB-induced cavitation being a very rare event in pre-adolescent children.[19]

In paediatric practice, TSTs and IGRAs are commonly used as adjunctive tools in the diagnostic workup of suspected TBD.[20] Several studies have conclusively shown that IGRAs perform less well in young children than in adolescents and adults.[21–23] However, the literature remains very limited with regards to the performance of those immune-based tests in neonates.[20] We found that even at the lower (5 mm induration) TST cut-off the majority (83.3%) of infants in the cTB group had a negative test result, contrasting with infants with pTB of whom 66.7% had a positive TST result. IGRAs performed equally poorly in both subgroups, with fewer than half of the patients having a positive test result. A further striking finding was the high proportion (40.0%) of indeterminate QuantiFERON-TB Gold assay results observed in cTB cases. Similarly, in the aforementioned report from China, where ELISPOT assays were used instead of the QuantiFERON assay, only 52.4% of the patients with congenital TB had positive IGRA test results.[18] Considering the poor sensitivity of both TST and IGRAs in this setting, we believe that both tests should be used in parallel in patients with suspected cTB or pTB to increase the diagnostic yield, particularly as result discordance between immune-based tests is common in children.[24,25]

Another noteworthy observation is the high proportion of microbiological confirmation achieved in both the cTB and the pTB subgroup (85.2% and 78.9%, respectively), contrasting with the lower confirmation rates in most paediatric studies, which typically range from 10% to 60%.[26–28] Although the basis of this observation is uncertain, this may reflect the immaturity

of the neonatal host defense-system,[21] resulting in a reduced capacity to contain the causative agent. A reduced ability in cTB and pTB patients to mount an effective immune response against *M. tuberculosis* would also at least partially explain why immune-based TB tests perform so poorly in those patients.

While our data underscore the severity of cTB and pTB, with approximately half of the infants in each group requiring ICU admission, the combined CFR of 8.9% was considerably lower than the CFR of up to 50% suggested by the literature.[4,5,8,10] Notably, the CFR in our study does not differ substantially from the overall CFR of 8.4% for TB disease in EU/EEA countries.[29] The comparatively low mortality observed may be due to access to a wider range of diagnostics, as well as high-level ICU support. However, TBD and anti-TB treatment had a significant impact on the survivors in our cohort. Almost a quarter developed complications secondary to TB, and more than one in ten developed adverse drug events. Also, close to one in ten patients developed long-term neurological sequelae.

We found that over 80% of the cTB cases in our cohort met the Cantwell criteria.[9] However, our data highlight the limitations of those criteria. Only 74.1% of the cTB cases were symptomatic in the first week of life, with the remaining patients developing symptoms later. Also, fewer than a quarter of cTB patients who had undergone abdominal imaging had evidence of a primary hepatic complex or caseating granulomas. Based on our observations, we propose modified criteria for cTB (Table 6), which are designed to be less restrictive.

Although not the main focus of our study, there were also several interesting findings related to the mothers of infants with cTB. Surprisingly, only approximately half were symptomatic during pregnancy and fewer than a quarter were screened for TB during that period. In about half of the mothers TB investigations were initiated solely on the basis of their baby being suspected of having TBD. Those observations highlight that, firstly, obstetricians should have a low threshold to initiate investigations for TBD even in oligosymptomatic mothers, and, secondly, that clinicians should not discard cTB as a potential differential diagnosis in sick infants purely on the basis that TB symptoms are absent in the mother. Pregnancy-induced immunosuppression, a well-documented phenomenon, may be playing a significant role allowing dissemination of infection while the manifestation of symptoms of TBD is reduced.[30,31] This would also partly explain the remarkably high proportions of extrapulmonary and miliary TB observed in those women (75.0% and 22.7%, respectively).

The main limitation of this study lies in its retrospective nature, resulting in some data not being available due to lack of documentation, especially with regards to maternal data. Furthermore, there is the inherent potential for recall and selection bias, i.e. it is possible that more severe cases were more likely to be reported. However, considering how uncommon perinatal TB is in Europe, it appears unlikely that a meaningful prospective study could be performed. Despite conducting the study via a dedicated research network that currently comprises more than 400 members, only a limited number of patients fulfilling the inclusion criteria were identified, precluding more detailed statistical analyses. A further limitation is that only approximately two thirds of the patients underwent lumbar puncture, and that presence of meningitis can therefore not be ruled out in the remaining children. Finally, the study team had to rely on the imaging reports from local radiologists, who may have had limited experience with TBD in children.

In conclusion, our data suggest that cTB and pTB are rare disease entities in the European setting. Severe variants of TBD and disseminated TB are common, with approximately half of the infants requiring ICU support. Particularly in infants with cTB, immune-based tests (TST and IGRA) perform poorly. Although lower than previously reported, the morbidity and mortality are substantial in both patient groups, despite the high-resource setting. TB symptoms in the mother are often absent, but this should not discourage clinicians from performing investigations for TB in the infant. Also, clinicians should consider the possibility of cTB even if the Cantwell criteria are not fulfilled. Finally, the similar clinical features and outcomes in both groups in our study suggest that cTB and pTB represent a

Infant with confirmed OR probable TBD	No. of cases in this cohort fulfilling each criterion
And at least one of the following criteria	
Presence of symptoms in the first week of life	20/27 (74.1%)
Microbiologically-confirmed urogenital TB infection in the mother	9/13 (69.2%)
Microbiologically-confirmed TB infection of the placenta or amniotic fluid	7/12 (58.3%)
Presence of granuloma(s) in the child's liver on imaging and/or histopathology	6/22 (27.3%)
Cases fulfilling 1 criterion	14/27 (51.9%)
Cases fulfilling 2 criteria	12/27 (44.4%)
Cases fulfilling 3 criteria	1/27 (3.7%)
Cases fulfilling all 4 criteria	0/27 (0%)
Fulfilling the modified criteria (overall)	27/27 (100%)

Confirmed TBD is defined as microbiologically-proven infection with *M. tuberculosis* based on culture or polymerase chain reaction testing.
Probable TBD is defined as a symptomatic individual fulfilling at least two of the following four criteria: a) symptoms and signs consistent with TBD (chronic cough, persistent fever, night sweats, weight loss/failure to thrive, severe malaise/listlessness, meningism or reduced level of consciousness), b) radiological findings suggestive of TBD, c) presence of risk factors for TB infection (maternal TBD or birth in a high TB prevalence country), d) a positive immune-based test for TB infection (i.e. tuberculin skin test or interferon-gamma release assay).

TB, tuberculosis; TBD, tuberculosis disease.

Table 6: **Modified criteria for congenital tuberculosis.**

continuum rather than two clearly-defined, separate disease entities.

Contributors

NMA conceived of the study. FG, AAC, MT and NMA designed the study. FG and MT cleaned and analysed the data, constructed the figures. FG, AAC, MT and NMA wrote the first draft of the manuscript. All authors contributed data to the study, contributed to the data interpretation, critically reviewed the manuscript, and approved the final manuscript for submission.

Data sharing statement

The authors will consider any justified requests to share data from academic researchers. The data will only be shared in a de-identified and anonymised format.

Editor note

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Declaration of interests

FG has received speaker fees and remuneration for advisory work from bioMérieux, and has received support for conference attendance from Pfizer. MT has received laboratory materials from Cellestis/Qiagen at reduced pricing and free of charge for other TB-related studies, and has received support from Cepheid for an unrelated TB diagnostics study. NMA has received support for conference attendance from AstraZeneca. ALV received grant support from Merck Sharp &Dohme, and consulting fees from Angelini Pharma. The manufacturers had no influence on the conduct of this study, or the decision to submit for publication. ANJ was supported by a research grant from the Carlos III Institute of Health, Ministry of Economy and Competitiveness (Spain), reference PI22/00766, and by the Spanish Society of Pneumology and Thoracic Surgery, grant number 169-2022. RS has received grant support by the United States National Institutes of Health (NIH). ME has received grant support by the European Union's Horizon 2020 research and innovation programme, grant number 848196. AB received fixed term consultancy fees by WHO relating to antimicrobial resistance in children and antibiotic prioritisation, is member of the scientific steering committee of the Paediatric European Network for Treatment of AIDS—Infectious Diseases (PENTA-ID) and chair of the European Paediatric HIV treatment guidelines working group (PENTA/European AIDS Clinical Society). SW holds a part-time contract with PENTA, is a committee member for the British Association for Paediatric Tuberculosis (BAPT), steering committee member of ptbnet, guideline committee member for the Children's HIV Association (Chiva) and Clinical Specialist Advisor to the British Thoracic Society MDR TB Clinical Advice Service. BKL is member of a patient advocacy group for Cystic Fibrosis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101303.

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