Tuberculosis in childhood: a systematic review of national and international guidelines

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**Abstract**

Background: Paediatric tuberculosis (TB) represents a major public health concern worldwide. About 1 million children aged less than 15 years develop TB each year, contributing to 3-25% of the total TB caseload. The aim of this review is to evaluate national and international guidelines concerning tuberculosis in childhood and compare them in terms of diagnosis and treatment strategies.

Methods: A literature search of the Pubmed database was performed from January 2000 to August 2013, using the terms “tuberculosis” and “children”. The search was limited to guidelines and consensus conferences, human species and full text availability, with no language restrictions.

Results: Twenty-seven national and international guidelines are identified. Several discrepancies on the diagnosis workup of TB are underlined. The main points of disagreement are represented by the interpretation of tuberculin skin test (TST) result and the recommendations on the use of TST and/or interferon-gamma release assay (IGRA) for the diagnosis of TB infection. Otherwise, all guidelines are in agreement that a microbiological confirmation should always be sought. Similarly, susceptibility drug testing and genotyping should be performed whenever it is possible on the basis of resources availability. On the contrary, the use of nucleic acid amplification tests (NAATs) for the *M. tuberculosis* detection is still controversial. A general consensus exists, otherwise, on TB treatment and only minor discrepancies are evidenced, such as the recommendations on daily or intermittent treatment regimens.

Conclusions: Despite advances in TB diagnostic tools have been reached during the last decade, a lack of uniformity in their availability, indication and interpretation has relevant consequences for clinical practice. Further studies need to be performed to clarify this issue and identify a reliable and reproducible diagnostic workup. Moreover, future studies should analyze the drug metabolism and the efficacy of intermittent dosing regimes in childhood, as well as new treatment regimens in order to improve the therapy compliance.

Background

Paediatric tuberculosis (TB) represents a major public health concern worldwide. The World Health Organization (WHO) reported that about 9 million people develop TB each year, and of whom about 1 million (11%) occur in children aged less than 15 years. Children contribute to 3–6% of the total TB caseload in developed countries and to more than 25% of the burden of TB disease in developing countries [1]. Nonetheless, paediatric TB has been relatively neglected for several years, mainly due to difficulties in mycobacterium isolation in children. Novel developments in diagnosis and treatment of paediatric TB have been carried out and, more recently, the definition of an adequate management of TB in childhood has become one of the main aspects of the global TB control efforts [1-4].

The aim of the present systematic review is to evaluate and compare national and international guidelines concerning diagnosis and treatment strategies in paediatric TB.

Methods

A literature search of the Pubmed database was performed from January 2000 to August 2013, using the terms “tuberculosis” and “children” as key words. The search was limited to type of article, guideline and consensus conference, human species and full text availability, with...
no limits of language. The results were also restricted on
the basis of title and abstract. Therefore, 23 articles were
identified and of those 17 were considered relevant to the
goal of the research.

In order to verify the completeness of the Pubmed
database, a literature search of other databases (Web
of Science, Embase, Pascal and National Guideline
Clearinghouse) was also conducted, but the results
were virtually overlapping.

Additionally, the websites of relevant government
organizations and professional societies were reviewed
for documents of interest (WHO, Center for Disease
Control and Prevention - CDC, European Center for
Disease Control and Prevention - ECDC, National Insti-
tute for Health and Care Excellence - NICE, American
Academy of Pediatrics - AAP, International Union
Against Tuberculosis and Lung Disease - IUATLD,
American Thoracic Society - ATS, Canadian Thoracic
Society - CTS). All reference lists were examined in
order to identify pertinent publications, which were
added in the review.

All the results were closely evaluated and the papers
that were not pertinent or redundant were excluded. In
particular, our search was limited to guidelines developed
at national or international levels, excluding local or
regional recommendations, and overall 27 articles were
included in this review.

Results
The twenty-seven guidelines identified through the search
strategy are listed in table 1. Twelve guidelines regard
exclusively paediatric TB [1,5,9,12,23-26,28-30], whereas
15 guidelines analyze the management of TB in both
adults and children [6-8,13-22,27,31]. The majority of the
guidelines were focused on restricted fields concerning
paediatric TB, as diagnostic tools or treatment strategies,
whereas eight guidelines discuss extensively all aspects
related to the management of TB in childhood
[1,9,12,18,22,28,29,31].

Diagnostic tests for *M. tuberculosis* infection
The demonstration of *M. tuberculosis* infection is a rele-
vant part of the diagnosis of both TB disease and latent
TB infection (LTBI). LTBI is defined as *M. tuberculosis*
complex infection without clinical features or radiographic
findings of TB disease [1,12,21,29]. Children with LTBI are
at increased risk of developing active TB and becoming
infectious. Therefore the identification of children latently
infected with *M. tuberculosis* represents an important
issue of TB preventive strategies.

Tuberculin skin test (TST) and interferon-gamma
release assays (IGRAs) are immune-mediated methods
currently available for identifying *M. tuberculosis* infection
[1,6,9-12,14,16,19,21-23,28,29,31]. However, TST and
IGRA are not able to distinguish between latent TB infec-
tion and active disease, and a negative result does not
exclude the possibility of *M. tuberculosis* infection. There-
fore, according to the AAP [12], both TST and IGRAs
should not be considered a gold standard for the diagnosis
of LTBI.

The TST is based on the evidence that *M. tuberculosis*
infection promotes a delayed-type hypersensitivity reac-
tion to antigenic components isolated from tubercle bacilli
culture by protein precipitation (PPD), also known as
tuberculin. All guidelines recommend that TST should
be performed only in children who are at increased risk
of *M. tuberculosis* infection (i.e. contact with people with
contagious TB, HIV-infected children) or children with
suspected TB disease. The preferred method of PPD
administration is represented by Mantoux technique,
which consists of an intradermal injection of 5 tuberculin
units of PPD (0.1 ml) into the volar surface of the fore-
arm, using a 27-gauge needle. The test should be read
between 48 and 72 hours after the injection, measuring
the transverse diameter of the induration. However, the
interpretation of TST results is still controversial. The
majority of the guidelines [1,9-11,23,28,31] affirms that
TST should be considered positive if the diameter of the
induration is > 10 mm in any child and > 5 mm in high
risk children, including HIV-infected children and
severely malnourished children. Otherwise the American
guidelines [12,14] recommend three different cut-points.
Five millimetres should be considered positive in high-
risk children, including close contact with contagious
people with TB, suspect of TB disease (i.e. chest
radiograph suggestive of active or previous TB) and
immunodeficiency (i.e. HIV-infected children, children
receiving immunosuppressive therapy). In children at
increased risk of disseminated TB disease (i.e. children
younger than 4 years, children with other medical condi-
tions) and children with likelihood of being infected with
*M. tuberculosis* (i.e. children born in high prevalence
regions or children who travel to high prevalence regions)
the cut-off proposed is 10 mm. Eventually, TST > 15 mm
is positive in children aged 4 years or older without any
risk factors. All the guidelines agree that the TST result
should be interpreted as positive regardless of Bacille
Calmette-Guérin (BCG) vaccination, because there is no
way of distinguishing between a positive TST due to
*M. tuberculosis* infection and that caused by BCG
vaccination.

Over the last decade new diagnostic tests have been
developed for the detection of TB infection measuring,
ex-vivo, the interferon-gamma released by T-cells in
response to mycobacterial antigens (IGRAs) [32], Quan-
tiFERON-TB Gold-In tube (Cellestis, Victoria, Australia)
and T-SPOT.TB (Immunejct, Oxford, United Kingdom)
have been approved by the United States Food and
Table 1 National and international guidelines concerning paediatric tuberculosis.

| Guideline Title [Reference] | Guideline Developer(s) | Countries or Regions | Year | Target Population | Guideline Fields |
|-----------------------------|------------------------|----------------------|------|-------------------|-----------------|
| Guidance for national tuberculosis programmes on the management of tuberculosis in children [1] | WHO | International | 2006 | Children | Diagnosis, Treatment |
| Rapid advice: Treatment of tuberculosis in children [5] | WHO | International | 2010 | Children | Treatment |
| Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement [6] | WHO | International | 2011 | Adults, Children | Diagnosis |
| Policy statement: automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system [7] | WHO | International | 2011 | Adults, Children | Diagnosis |
| Guidelines for the programmatic management of drug-resistant tuberculosis [8] | WHO | International | 2011 | Adults, Children | Treatment |
| Desk-guide for diagnosis and management of TB in children [9] | IUATLD | International | 2010 | Children | Diagnosis, Treatment |
| Evaluation of Tuberculosis Diagnostics in Children [10,11] | Expert Panel | International | 2012 | Children | Diagnosis |
| Tuberculosis (in: Red Book 2012) [12] | ATS CDC IDSA | U.S. | 2012 | Children | Diagnosis, Treatment |
| Treatment of Tuberculosis [13] | ATS CDC IDSA | U.S. | 2003 | Adults, Children | Treatment |
| Diagnostic Standards and Classification of Tuberculosis in Adults and Children [14] | ATS CDC IDSA | U.S. | 2000 | Adults, Children | Diagnosis |
| Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis [15] | CDC | U.S. | 2009 | Adults, Children | Diagnosis |
| Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection [16] | CDC | U.S. | 2010 | Adults, Children | Diagnosis |
| Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection [17] | CDC | U.S. | 2011 | Adults, Children | Treatment |
| European Union Standards for Tuberculosis Care [18] | ECDC ERS | Europe | 2012 | Adults, Children | Diagnosis, Treatment |
| Use of interferon-gamma release assays in support of TB diagnosis [19] | ECDC | Europe | 2011 | Adults, Children | Diagnosis |
| Management of contacts of MDR TB and XDR TB patients [20] | ECDC | Europe | 2012 | Adults, Children | Diagnosis, Treatment |
| LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement [21] | TBNET | Europe | 2009 | Adults, Children | Diagnosis |
| Clinical diagnosis and management of tuberculosis, and measures for its prevention and control [22] | NICE | U.K. | 2011 | Adults, Children | Diagnosis, Treatment |
| Diagnosis of tuberculosis in pediatrics. Consensus document of the Spanish Society of Pediatric Infectology (SEIP) and the Spanish Society of Pediatric Pneumology (SENP) [23] | SEIP SENP | Spain | 2010 | Children | Diagnosis |
| Consensus document for the treatment of pulmonar tuberculosis in children [24] | SEIP | Spain | 2007 | Children | Treatment |
| Recommendations of the Spanish Society for Pediatric Infectious Diseases (SEIP) on the management of drug-resistant tuberculosis [25] | SEIP | Spain | 2009 | Children | Treatment |
| Consensus document on treatment of tuberculosis exposure and latent tuberculosis infection in children [26] | SEIP | Spain | 2006 | Children | Treatment |
| Recommendations for Therapy, Chemoprevention and Chemoprophylaxis of Tuberculosis in Adults and Children [27] | D2K DGP | Germany | 2012 | Adults, Children | Treatment |
| Childhood tuberculosis guidelines of the Southern African Society for Paediatric Infectious Diseases [28] | SASPID | South Africa | 2009 | Children | Diagnosis, Treatment |
| Consensus Statement on Childhood Tuberculosis [29] | IAP | India | 2010 | Children | Diagnosis, Treatment |
Drug Administration [19] and licensed for commercial distribution in Europe [16] and several other countries [28,29,31]. All the recent guidelines are in agreement that IGRAs represent a relevant diagnostic tools for the identification of M. tuberculosis infection, except for one [9] which do not discuss the role of IGRAs in the diagnosis of TB infection. The CDC, the ECDC and the WHO have published specific recommendations focusing on the use of IGRAs in TB and LTBI diagnosis [6,16,19]. They analyze the sensitivity and specificity of the test, the costs and the role of IGRAs in the diagnosis of TB infection both in adults and children. Whereas the guidelines developed in high-income settings discuss extensively the use of IGRAs [21-23,31], those from middle or low-income countries only mention IGRAs [28,29].

All guidelines underline that few data concerning the use of IGRAs in childhood are available, but the IGRAs seem to perform well in children aged 5 years or older. The sensitivity of IGRAs for detecting TB infection in childhood is generally similar to TST, according also to recent meta-analysis [32-34]. The IGRAs specificity seems to be higher than TST, because the antigens used are absent in most pathogenic non-tuberculous mycobacteria, as well as in BCG strains. This characteristic explains the IGRAs advantage over TST in identifying a natural M. tuberculosis infection in settings with high non-tuberculous mycobacteria exposure and high BCG vaccination coverage [21,35]. Moreover boosting does not occur when the test is repeated, being particularly useful in BCG-vaccinated children. Anyway the IGRA tests have a reduced accuracy for the detection of M. tuberculosis infection in high-burden TB settings compared with low-burden TB settings [33,35]. Indeed IGRAs are unsuitable for resource-limited settings, being expensive and requiring sophisticated laboratory support and trained personal for accurate performance. According to that, the WHO [6] strongly recommends that IGRAs should not replace the TST for the detection of TB infection in children in low or middle-income countries, regardless of HIV status. On the contrary, the NICE guidelines [22] encourage the use of IGRAs and suggest considering those for all children aged 5 years or older whose TST shows positive results. Differently, European [19], Spanish [23], Canadian [31] and American [12,16] guidelines affirm that the selection of the most suitable test or combination of tests should be based on clinical data, as BCG status, history of contact with active TB or other risk factors for infection or progression of the disease (table 2).

**Diagnostic tools for TB disease**

All guidelines [1,9-12,14,18,22,23,28,29,31] agree that the isolation of M. tuberculosis complex from different specimens as sputum (natural or induced), gastric aspirates, bronchial washings, pleural fluid, cerebrospinal fluid, urine or biopsy tissue is the gold standard for the diagnosis of TB. Older children and adolescents frequently can produce sputum spontaneously or by induction with aerosolized hypertonic saline. Otherwise early-morning gastric aspirate, collected on three separate days, represents an option for young children and any child in whom sputum cannot be obtained. All guidelines underline that a microbiological confirmation should always be sought using all the resources available, although it is well known that children are generally paucibacillary.

The first bacteriological evidence of the presence of mycobacteria in a clinical specimen is the detection of acid fast bacilli (AFB) in stained smears examined microscopically. This test gives an estimation of the numbers of bacilli excreted and therefore of the patient’s infectiousness. However, the results of AFB smears of gastric aspirates are often negative and also the presence of non-tuberculous mycobacteria, can cause false-positive results [12,31]. For these reasons all clinical specimens should be inoculated into culture media. Despite culture is the gold standard for laboratory confirmation of TB disease, M. tuberculosis is isolated from less than 50% of children and 75% of infants with pulmonary tuberculosis [12,31,36]. In low-income settings, where the facilities and resources are limited, bacteriological confirmation should
be prioritized in children who have HIV infection, complicated or severe disease or suspected drug-resistant TB [1,28]. Moreover, the growth of the mycobacteria in culture is required not only for confirming the diagnosis and determining the mycobacteria species, but also for genotyping and drug susceptibility testing, according to all guidelines. Although all guidelines underline the importance of genotyping and drug susceptibility testing, only American and Spanish guidelines describe the methods used [14,23].

A relevant improvement in the direct identification of \textit{M. tuberculosis} resulted from the introduction of nucleic acid amplification test (NAAT). The CDC [15] and the WHO [7] have recently published an updated guidelines for the use of NAAT in the diagnosis of TB in both children and adults, although some guidelines only explain briefly their potential implications [12,18,22,23,28,31], and other do not consider this topic [9-11]. The NAATs are rapid and accurate methods. They can provide the results within 24–48 hours, one or more weeks earlier than culture. Global sensitivity is greater than 95% in AFB-microscopy positive respiratory specimens and ranges between 50-80% in AFB-smear negative specimens [15]. Currently several assays are available, including line probe assays (LPAs) and NAATs using polymerase chain reaction (PCR). Real-time PCR is becoming increasingly available and several guidelines purpose its use for \textit{M. tuberculosis} detection in respiratory specimens [7,12-15,18,22,23,28,31]. The CDC [15] recommends the use of NAAT in any patient with signs and symptoms of pulmonary TB, for whom a diagnosis has not yet been established or for whom the test result would change the case management. The NICE guideline [22], on the contrary, limits NAAT use only to sputum smear positive persons for whom the rapid confirmation of TB diagnosis would change their care. Other guidelines [23,28,31] underline the useful of NAAT, but they do not provide specific indications. However, all guidelines agree that

| Table 2 Recommendations for the use of Tuberculin Skill Test (TST) and Interferon-gamma Release Assay (IGRA) in children |
|---------------------------------------------------------------|
| WHO [6] | TST alone | IGRA alone | both TST and IGRA |
| | • Any child, irrespective of HIV status, in low and middle-income countries | • BCG vaccinated children (> 5 years of age) | • Children > 5 years of age whose TST is positive |
| NICE [22] | • Children younger than 5 years | • Children > 5 years of age, in an outbreak situation | |
| American [12,16] | • Children younger than 5 years | • BCG vaccinated children (> 5 years of age) | • The initial and repeat IGRA are indeterminate |
| | • Before initiation of immunosuppressive therapy | • Children > 5 years of age who are unlikely to return for TST reading | • The initial test (TST or IGRA) is negative and: |
| | | • Before starting immunosuppressive therapy | • clinical suspicion for TB disease is moderate to high |
| | | | • Children > 5 years of age who have received BCG vaccine |
| | | | • Non-tuberculous mycobacterial disease is suspected |
| | | | • Additional evidence are needed to increase compliance |
| European [19] | • Children younger than 5 years | • BCG vaccinated children (> 5 years of age) | • HIV-infected children |
| | • Children > 5 years who are: | • Before starting immunosuppressive therapy (anti-TNFalfa inhibitor therapy) | |
| | - not HIV-infected | | • The initial TST is negative and: |
| | - not BCG vaccinated | | • Immunocompromised children |
| | | | • High risk of infection, of progression to disease and of a poor outcome |
| | | | • The initial TST is positive and: |
| | | | • BCG vaccinated children |
| | | | • Risk factors are negative |
| Spanish [23] | • Any child | • People who have received BCG vaccination | • High risk of infection, of progression to disease and of a poor outcome |
| | | • People from groups that historically have poor rates of return for TST reading. | • The initial and repeat IGRA are indeterminate |

Note. WHO: World Health Organization; BCG: Bacille Calmette-Guèrin
NAATs do not replace AFB smear and culture, which should be always performed. Moreover the NAATs should not be used for treatment monitoring as they persist positive for long periods after therapy, being unable to distinguish live from dead bacilli.

However, evidence concerning NAATs accuracy for non-respiratory specimens are limited. Further research is needed before NAATs can be recommended for the diagnosis of TB in children who cannot produce sputum [12,15]. The NAATs are also able to detect drug resistance. If the AFB-smear is negative, as it frequently occurs in children, the NAAT of choice is the Xpert-MTB/RIF (Cepheid, Sunnyvale, California, USA) which is a real-time PCR assay detecting the 81-bp-core region of the RNA-polymerase b-subunit gene. This region, which is closed to M. tuberculosis specific DNA sequences, accounts for more than 95% of rifampicin (RIF) resistance. Therefore the Xpert-MTB/RIF can be used for the detection of RIF-resistance [37,38]. Additionally, given that rifampicin resistance is usually accompanied by isoniazid resistance, it can be used also as a rapid marker of multi-drug resistant (MDR) TB. According to these findings, the WHO [7,8] recommends the Xpert-MTB/RIF as the initial diagnostic test in children and adolescents suspected of having multidrug-resistant (MDR)-TB or HIV-associated TB. The WHO also suggests to consider it as a follow-on test to microscopy in settings where MDR-TB or HIV are of lesser concern, especially in further testing of smear-negative specimens. The ECDC guidelines [18] confirm the WHO recommendations.

Among radiological tools, all guidelines [1,9-12,18,22,23,28,29,31] are in agreement that chest radiography is an important part of the diagnostic workup of TB and should be performed in any child with suspected TB. Chest radiographic features vary widely, showing normal findings as well as lymphadenopathy, atelectasis, cavitary lesions, miliary disease and pleural effusion. There are no pathognomonic radiological sings of TB, but some radiological lesions strongly suggest TB, as miliary disease, hilar and paratracheal lymphadenopathy or cavitary lesions.

A general consensus exists also concerning the use of chest CT only for complicated cases, considering the high level of radiation exposure and the high costs related to its use. The CT, as well as magnetic resonance, may also be very helpful in the evaluation of TB meningitis, osteoarticular disease, intra or extra-thoracic lymphadenopathy and pericardial TB.

### Treatment for TB disease

The major goals of anti-TB treatment are to cure the patient by eliminating most of the bacilli, prevent the development of drug resistance by using a drug combination regimen, prevent TB relapse by eliminating the quiescent bacilli and, finally, decrease the TB transmission to others.

The poor adherence to the anti-TB therapy represents the main contributor factor to treatment failure and emergence of TB drug-resistance. In order to improve the compliance to the treatment, all guidelines [1,5,9,12,13,18,22,24,25,27-31] emphasize the widespread use of the directly observed therapy (DOT), a patient-centred strategy in which patients are observed to ingest each dose of anti-TB drugs.

All guidelines are also in agreement that TB treatment should include an initial intensive phase, when three to four drugs are used in order to kill the majority of bacilli and prevent the emergence of drug resistance, and a continuation phase, when fewer drugs are given in order to eradicate quiescent bacilli. The first-line anti-TB drugs, their dosages and adverse events are summarized in table 3. The guidelines considered in the present review recommend the same standard treatment regimen for pulmonary TB (table 4). Children living in settings were HIV prevalence is high or isoniazid (INH)-resistance is high, or both, should be treated with a four drugs regimen (INH, RIF, pyrazinamide-PZA and ethambutol-EMB) for 2 months, followed by a two drugs regimen (INH, RIF) for 4 months. However, if the risk of drug-resistance and the HIV prevalence are low, EMB can be omitted, considering that it can cause retrobulbar neuritis and could be difficultly monitoring in children. Despite two recent systematic reviews [39,40] show that an

| **Table 3 First-line drugs used for treatment of tuberculosis in childhood [1,9,12,13,24,27-31]** |
|---------------------------------------------------------------|
| **Daily dosage (maximum dosage)** | **Twice-thrice weekly dosage (maximum dosage)** | **Adverse Reactions** |
| Isoniazid (INH) | 10-15 mg/kg (300 mg) | 20-30 mg/kg (900 mg) | Hepatotoxic effects, such as mild hepatic enzyme elevation and hepatitis, gastrointestinal neuropathy, hypersensitivity |
| Rifampicin (RIF) | 10-20 mg/kg (600 mg) | 10-20 mg/kg (600 mg) | Orange discoloration of secretions and urine, vomiting, hepatitis, influenza-like reaction, thrombocytopenia |
| Pyrazinamide (PZA) | 30-40 mg/kg (2 g) | 50 mg/kg (2 g) | Hepatotoxic effects, hyperuricemia, arthralgia, gastrointestinal tract disturbances |
| Ethambutol (EMB) | 15-25 mg/kg (2.5 g) | 50 mg/kg (2.5 g) | Optic neuritis with decreased red-green colour discrimination and visual acuity, gastrointestinal disturbances, hypersensitivity |
intermittent short course of therapy is less likely to cure tuberculosis in childhood compared to daily therapy, several guidelines [1,5,9,12,13,22,24,27,30,31] propose both daily and intermittent (twice or thrice weekly) dosing regimens, and major discrepancies are evidenced. The AAP [12], the ATS along with the CDC [13], as well as the APRG along with ASID [30] recommend a daily or twice-weekly regimen in both intensive and continuation phases. The NICE [22], otherwise, excludes the use of twice-weekly regimen for the treatment of active TB, suggesting a thrice-weekly intermittent regimen only for patients receiving DOT. The WHO [1], the IUATLD [9] and the CTS [31] limit a thrice-weekly regimen to children known to be HIV uninfected and living in settings with well established DOT, and they allow an intermittent regimen only during the continuation phase. Finally Spanish guidelines [24] agree that children who are known to be reliable with DOT may be considered for both twice and thrice-weekly regimens.

A general consensus exists concerning treatment regimens for extra-pulmonary TB (table 4): except for meningitis and osteoarticular TB, the standard recommended regimen (INH + RIF + PZA + EMB for 2 months, followed by INH + RIF for 4 months) should be started. Otherwise, the guidelines strongly recommend 12 months of therapy for meningeal TB [1,5,9,12,13,22,27,30,31] and osteoarticular TB [1,5,9,22,27,30,31]. Among drug-resistance TB, only few guidelines [1,8,12,25,30,31] provide specific recommendations, probably due to the lack of evidence concerning this issue in childhood. Recommended regimens [8,12,25,30,31] for INH-monoresistance and RIF-monoresistance TB are listed in table 4. Despite the evidence concerning safety and efficacy in TB treatment of fluoroquinolones in children are few, all guidelines recommend their introduction in the treatment of monodrug-resistance TB, considering the indirect evidence from cystic fibrosis and osteomyelitis treatment in children.

The AAP [12] define the MDR as a TB infection or disease caused by a strain of M. tuberculosis complex that is resistant to at least INH and RIF. For MDR-TB cases, all guidelines [1,8,12,25,30,31] are in agreement that the treatment should be based on the drug susceptibility pattern of the M. tuberculosis isolated from child specimens or, more frequently, from the source case specimens.

### Table 4 Recommendations for treatment of TB in childhood [1,8,9,12,13,17,18,21,22,24,27-31]

| TB disease (except meningitis and osteoarticular TB) in HIV-uninfected children with low risk of INH-resistance | Intensive phase (duration) | Continuation phase (duration) |
|---|---|---|
| INH + RIF + PZA (2 months) | INH + RIF (4 months) |

| TB disease (except meningitis and osteoarticular TB) in HIV-infected children and/or children with high risk of INH-resistance | INH + RIF + PZA + EMB (2 months) | INH + RIF (4 months) |

| Meningitis and osteoarticular TB | INH + RIF + PZA + EMB (2 months) | INH + RIF (10 months) |

| INH-mono resistance TB | RIF + PZA + EMB (2 months) | RIF + PZA + EMB (4-7 months) |
|---|---|---|
| RIF + PZA + EMB (2 months) | RIF + EMB (10 months) |
| RIF + PZA + EMB + FQN (2 months) | RIF + EMB + FQN (4-7 months) |

| Rif-mono resistance TB | INH + PZA + EMB + FQN (2 months) | INH + EMB + FQN (10-16 months) |
|---|---|---|
| INH + PZA + EMB (2 months) | INH + EMB (16 months) |

| MDR-resistance TB | Treatment regimens should be based on the drug susceptibility pattern of the M. tuberculosis isolated from child specimens or, more frequently, from the source case specimens. |

| LTBI | INH (6-9 months) |
|---|---|
| INH + Rif (3 months) |
| INH + Rifabutin (weekly for 12 weeks) |

| INH-mono resistance LTBI | Rif (4-6 months) |

Note: § recommended regimen; # alternative regimen; TB: Tuberculosis; INH: Isoniazid; RIF: Rifampicin; PZA: Pyrazinamide; EMB: Ethambutol; FQN: Fluoroquinolones; MDR: Multi-Drug Resistance; RPT: Rifabutin.
certain to be effective [30]. Additionally, treatment duration should be prolonged and ranges from 12 to 24 months in the different guidelines [1,8,18,12,25,30,31].

Second-line drugs used in pediatric TB are listed in table 5.

### Treatment for LTBI

After exposure to an active case, children are more likely to develop tuberculosis than adults, hence contact screening and chemoprophylaxis are particularly important. Several guidelines discuss LTBI and its treatment [1,12,13,17,18,21,26-31] and all of those are in agreement that any child who has a history of TB exposure, positivity of TST and/or IGRA, but not evidence of active tuberculosis, should start the treatment for LTBI (table 4).

Isoniazid represents the preferred drug for children with LTBI, unless INH-resistance is suspected, and the efficacy approaches about 100% if the adherence to therapy is adequate [12]. All guidelines [1,12,13,17,18,21,26-31] suggest using isoniazid alone for LTBI treatment in childhood although minor differences concern the treatment duration, which ranges from 6 months [1,22,26,28-30] to 9 months [12,13,17,21,27,31]. Additionally, the Southern African [28] guidelines propose 3 months of INH and RIF as alternative therapy regimen. Recently, the CDC has published recommendations for the use of a new combination regimen of rifapentin (RPT) and INH to be administered weekly for 12 weeks as DOT [17]. Although the evidence on tolerability and efficacy of this combination in childhood is lacking, it can be considered in selected cases, if the compliance to treatment is low and the hazard of TB is high.

### Conclusions

The present systematic review has identified 27 national and international guidelines concerning the management of pediatric tuberculosis [1,5-31]. There are several discrepancies on the diagnosis workup of TB. Major differences concern the TST interpretation. Most of the guidelines [1,9-11,23,28,31] establish a cut-point of 10 mm for any child and 5 mm for high-risk children, although the American guidelines [12,14] increase the cut-point to 15 mm for children without any risk factors and to 10 mm for children with minor risk factors, maintaining the diameter of 5 mm only for high-risk population. Considering that TST sensitivity and specificity are influenced by the cut-off used [21], differences among guidelines are not merely academic but have important consequences for clinical practice. Recommendations also differ substantially regarding the use of TST and IGRA for the diagnosis of TB infection. The guidelines from high-income countries [12,16,22,23,19,31] widely promote the IGRA use, whereas the WHO [6] strongly recommends that IGRA should not replace the TST for the detection of TB infection in children in low or middle-income countries. These findings could be explained considering that IGRA has a reduced accuracy in high-burden TB settings compared with low-burden TB

### Table 5 Second-line drugs used for TB treatment in children [8,12,13,25,27,30,31]

| Drug                  | Daily dosage (maximum dosage) | Adverse Reactions                                      |
|-----------------------|-------------------------------|--------------------------------------------------------|
| Streptomycin          | 20-40 mg/kg/ (1 g)            | Auditory, vestibular and renal toxicity, rash          |
| Amikacin              | 15-30 mg/kg/ (1 g)            | Auditory, vestibular and renal toxicity                |
| Kanamycin             | 15-20 mg/kg/die, given in 2-3 divided doses (1 g) | Hepatotoxic effects, gastrointestinal tract disturbances, neurotoxicity, hypersensitivity and hypothyroid |
| Capreomycin           | 15-30 mg/kg/die, given in 2-4 divided doses (10 g) | Hepatotoxic effects, gastrointestinal tract disturbances, hypersensitivity |
| Ethionamide           | 10-20 mg/kg, given in 2-divided doses (1 g) | Psychosis, personality changes, seizure, rash     |
| Para-amino salicylic acid | 200-300 mg/kg/die, given in 2-4 divided doses (10 g) | Hepatotoxic effects, gastrointestinal tract disturbances, hypersensitivity |
| Cycloserine           | 10 mg/kg/ (400 mg)            | Theoretical effect on growing cartilage, gastrointestinal tract disturbances, rash, headache, restlessness |
| Moxifloxacin          | 10 mg/kg/ (1 g)               | Inflammation, gastrointestinal tract disturbances, hypersensitivity |
| Levofloxacin          | 10 mg/kg/ (1 g)               | Inflammation, gastrointestinal tract disturbances, peripheral neuropathy, thrombocytopenia |
| Linezolid             | 10 mg/kg/ (1,2 g)             | Inflammation, gastrointestinal tract disturbances, peripheral neuropathy, thrombocytopenia |

Rifampicin alone for 4-6 months is recommended for the treatment of LTBI if a resistance to INH is strongly suspected or demonstrated [1,12,13,21,26,27,30,31]. However, on the basis of the currently available evidences, second-line drugs are not recommended for the chemoprophylaxis in MDR-TB contacts.
settings [33,35], is expensive and requires sophisticated laboratory support and trained personal [6,16,21].

A general consensus exists, on the contrary, on the microbiological confirmation of TB diagnosis, despite in low-income settings the mycobacterial culture is not performed routinely and is limited to HIV-infected children or severe disease. Although all guidelines underline the importance of susceptibility drug testing and genotyping, the guidelines from low-income countries do not strongly recommend these tests routinely to all patients, probably because of costs and lack of facilities. Finally the use of NAATs for the direct detection of *M. tuberculosis* is still controversial. Whereas the CDC [15] and the WHO [7] have recently published an updated guidelines focusing on the use of NAATs, the majority of guidelines [12,18,23,28,29,31] do not provide specific recommendations on their use. Moreover, evidence concerning NAATs accuracy for non-respiratory specimens are limited and further research is needed before NAATs can be recommended for the diagnosis of TB in children who cannot produce sputum [12,15].

Despite advances in TB diagnostic tool have been reached over the last decade, a lack of uniformity in their availability, indication and interpretation has relevant consequences for clinical practice. Further research is needed to identify a reliable and reproducible diagnostic workup not only to improve individual case management, but also to provide a valid basis for epidemiological data analysis, drug efficacy evaluation and improving clinical trials.

The recommendations on TB treatment are otherwise homogeneous and only minor discrepancies are evidenced in the present review. The main point of disagreement is represented by the daily and intermittent (twice or thrice weekly) regimens recommended, which vary widely between different guidelines. The lack of evidence among the drugs metabolism and the efficacy of intermittent treatment regimes in childhood is probably the main reason of this finding. Further studies need to be performed in order to clarify this issue. Finally, the poor adherence to the therapy, which is often too long, represents a relevant concern, especially in low-income settings where DOT is not always guaranteed. The combination regimen of RPT and INH, recently proposed by the CDC for LTBI, could be a valid alternative in these patients. Data on efficacy and safety of this combination are needed before address new recommendations. Moreover, new treatment regimens, indicated also for active TB, should be analyzed in future studies in order to improve the treatment compliance.

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**List of abbreviations used**

AAP: American Academy of Pediatrics; AFB: Acid Fast Bacillus; APRG: Australasian Paediatric Respiratory Group; ASD: Australasian Society for Infectious Diseases; ATS: American Thoracic Society; BCG: Bacille Calmette-Guérin; CDC: Center for Disease Control and Prevention; CLA: Canadian Lung Association; CTS: Canadian Thoracic Society; DGP: German Respiratory Society; DOT: Directly Observed Therapy; DZK: German Central Committee against Tuberculosis; ECDC: European Center for Disease Control and Prevention; EMB: Ethambutol; ERS: European Respiratory Society; FQN: Fluoroquinolones; IAP: Indian Academy of Pediatrics; IDSA: Infectious Diseases Society of America; IGRA: Interferon-gamma Release Assays; INH: Isoniazid; IUATLD: International Union Against Tuberculosis and Lung Disease; LPA: Line Probe Assays; LTBI: Latent Tuberculosis Infection; MDR: Multi Drug Resistance; NAAT: Nucleic Acid Amplification Test; NICE: National Institute for Health and Care Excellence; PCR: Polymerase Chain Reaction; PHAC: Public Health Agency of Canada; PPD: Purified Protein Derivate, Tuberculin; PZA: Pyrazinamide; RIF: Rifampicin; RPT: Rifabutin; SAPID: Southern African Society for Paediatric Infectious Diseases; SEIP: Spanish Society for Paediatric Infectious Diseases; SNP: Spanish Society for Paediatric Respiratory Disease; TB: Tuberculosis; TST: Tuberculin Skin Test; WHO: World Health Organization

**Competing interests**

The authors declare that they have no competing interests.

**Declarations**

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