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Drug-resistant tuberculosis in Île-de-France children under eighteen years of age: descriptive observational retrospective study in Île-de-France over a period of five years

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**DRUG-RESISTANT TUBERCULOSIS
IN ILE-DE-FRANCE CHILDREN
UNDER EIGHTEEN YEARS OF AGE :**

**Descriptive observational retrospective study in Ile de France over a period
of five years**

THESE

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Le 23 OCTOBRE 2017

Pour obtenir le grade de

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Par

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LE 23 OCTOBRE 2017

PAR

Mme BRUNELIN-BOURASSI Annabelle

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Article soumis à publication

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RÉSUMÉ

Introduction

La tuberculose résistante (TBR) chez l'enfant est une préoccupation négligée et les recommandations, fondées sur des preuves scientifiques, concernant la conduite à tenir sont rares. Le diagnostic microbiologique de confirmation est difficile et une grande proportion des cas pédiatriques est ainsi diagnostiquée sur des critères cliniques et anamnestiques. De plus, la littérature n'offre qu'une faible évaluation de la tolérance des traitements anti-tuberculeux de deuxième-ligne chez l'enfant.

Matériel et méthodes

Dans une étude de cohorte descriptive rétrospective menée dans des hôpitaux de Paris et d'île de France, nous avons analysé les aspects démographiques, cliniques, microbiologiques et radiologiques, la prise en charge et l'évolution d'enfants traités pour une TBR. Tous les patients âgés de moins de 18 ans ayant un diagnostic confirmé ou probable ont été inclus du 1er janvier 2011 au 31 décembre 2015 avec un suivi documenté jusqu'au 31 juin 2017. Les données ont été recueillies à partir des dossiers médicaux et de la base de données microbiologiques du CNR-MyrMA. Pour chaque patient, le cas index associé, s'il existait, était décrit. Des définitions standardisées ont été utilisées pour décrire diagnostic de la maladie, effets indésirables et résultats de traitement.

Résultats

Les 24 enfants atteints de TBR inclus avaient un âge médian de 10,7 ans (IQ, 3,4-14,2 ans) avec un sexe ratio 1/1; 3 (12,5%) avaient des antécédents de tuberculose, 17 (70,9%) déclaraient être vaccinés contre le BCG, aucun n'avait le VIH. Douze patients (50,0%) étaient symptomatiques mais la plupart des cas (62,5%) ont été diagnostiqués au cours d'un dépistage systématique. Sur les 16 souches résistantes, 8 (50,0% des souches ; 10 enfants sur 24 soit 41,6%) ont été importées de pays à incidence croissante de TBR.

Treize enfants (54,2%) ont eu un diagnostic confirmé et 11 (45,8%) un diagnostic probable; 15 enfants (62,5%) étaient porteurs de souche MDR, 8 (33,3%) de souches monorésistantes (mDR) à l'isoniazide et 1 (4,2%) d'une souche pré-XDR. Le délai médian entre le diagnostic de confirmation microbiologique et le début de traitement adapté était de 78,0 jours (IQ, 40,5-119,5) pour tous les cas ; onze cas index ont été identifiés et décrits.

Dix enfants (41,7%) ont reçu un traitement injectable et la durée médiane de traitement total était de 12,0 mois (IQR 9,3-16,0) avec 18,6 mois pour le cas de souche pré-XDR, 13,3 mois (IQ, 12,0-18,0) pour les cas porteurs de souches MDR et 8,1 mois (IQ, 6.0-9.3) pour les cas porteurs de souche mDR.

Douze enfants (50,0%) ont été guéris, 11 (45,8%) ont eu une guérison probable ; 5 (20,8%) ont été perdus de vue. Aucun décès n'a été rapporté.

Conclusion

Une TBR ne peut être confirmée dans tous les cas, mais cela ne doit pas retarder le traitement chez l'enfant atteint. Le dépistage systématique autour du cas index et la surveillance des cas-contacts sont nécessaires pour la prise en charge de la TBR chez l'enfant. Plus de 90% des enfants atteints de TBR peuvent être traités avec succès ; cependant des études de pharmacocinétique manquent pour la compréhension du métabolisme de l'enfant et l'adaptation de la posologie des traitements.

ABSTRACT

Background

Paediatric drug-resistant tuberculosis (DR-TB) is a neglected concern and evidence-based guidance regarding management and outcome is lacking. Microbiologically-confirmed diagnosis is hard and a large proportion of pediatric cases is thus diagnosed on anamnestic and clinical criteria. Furthermore, literature offers limited assessment of the second-line anti-tuberculosis drugs safety in children.

Methods

In a retrospective descriptive cohort study conducted in Paris and île de France hospitals, we analysed demographic, clinical, microbiological and radiological features, management and outcome in children treated for drug-resistant tuberculosis (DR-TB). All patients under 18 years of age with a confirmed or probable diagnosis were included from 1 January 2011 to 31 December 2015, with a follow-up documented until 31 June 2017. Data were collected through folder review and CNR-MyrMA microbiological database. For each patient, the related DR-TB index case, if existed, was reported. Standardised definitions were used for diagnosis, adverse reactions and outcome.

Results

The 24 children with DR-TB included had a median age of 10,7 years old (interquartile range IQR, 3.4-14.2 years) with a sex ratio 1/1; 3 (12.5%) had tuberculosis history, 17 (70.9%) declared BCG vaccinated, none had HIV infection. Twelve patients (50.0%) were symptomatic but most of cases (62.5%) were diagnosed by systematic contact tracing. Of 16 drug-resistant strains, 8 (50.0% of strains – 10 children of 24, 41.6%) were imported from countries with an increasing incidence of DR-TB.

A confirmed diagnosis was made in 13 children (54.2%) and 11 (45.8%) had probable diagnosis; 15 children (62.5%) had multidrug-resistant (MDR) strain, 8 (33.3%) monoresistant(mDR)-to-isoniazid strains and 1 a pre-extensively drug-resistant (pre-XDR) strain. The median delay from microbiological diagnosis to onset of appropriate DR-TB treatment was 78.0 days (IQR 40.5-119.5) for all cases ; Eleven source cases were found and reported.

Ten children (41.7%) were treated with an injectable drug and the total treatment duration was a median of 12.0 months (IQR 9.3-16.0) with 18.6 months for the pre-XDR case, 13.3 months (IQR 12.0-18.0) for MDR cases and 8.1 months (IQR 6.0-9.3) for mDR cases.

Twelve children (50.0%) were cured, 11 (45.8%) probably cured. Five (20.8%) were lost to follow-up. No death was reported.

Conclusion

A confirmed diagnosis of DR-TB is not possible in all cases but should not impede the treatment of DR-TB in children. Systematic screening around source case and contact-cases follow-up is crucial for DR-TB management in paediatric cases. More than 90% of children with DR-TB can be successfully treated. However, pharmacokinetic studies are missing for the understanding of child's metabolism and the adaptation of treatment's doses.

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INTRODUCTION

The emergence and spread of bacilli resistant to first-line antituberculosis drugs - rifampicin and isoniazid, defined as multidrug-resistant (MDR) strains - and second-line - at least one fluoroquinolone and one injectable drug, defined as extensively drug-resistant (XDR) strains - bring significant challenges in disease control and management.

The World Health Organization (WHO) estimates that these strains account for 3.5% of new cases and 20.5% of previously treated cases. Access to diagnosis and treatment of these new drug-resistant tuberculosis (DR-TB) cases is still very limited and an estimated 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB) occurred worldwide by 2014 (approximately 5 % of all cases), only one quarter - or 123,000 - was detected and reported and only 50% cured **(3,6)**. More than half of these reported cases occur in India, in the People's Republic of China and in Russian Federation. However, the most affected regions today are South-East Asia, the Western Pacific and Eastern Europe **(3,7,9)** where access to screening and treatment remains limited **(7,10)**.

In France, reported tuberculosis cases' number decreased steadily for several decades. With an incidence rate of 7.5 cases per 100 000 inhabitants in 2013 **(11)**, France is considered as a low-incidence country. But strong regional and population disparities remain. Thus, incidence rates in three departments -Île-de-France, Mayotte and French Guyana- are 1.5 to 2 fold those of other french regions **(1)**. And, it's higher among people from tuberculosis high incidence regions (or with increased incidence) and homeless people **(1)**. About one hundred cases of drug-resistant tuberculosis occurred in 2012 were managed in various french hospitals.

In France, increase in primary resistance to isoniazid is confirmed. The number of MDR strains, stable from 2006 to 2010 around 35 to 49 per year, has increased since 2011 in France, even doubled between 2006 and 2013. The number of XDR strains, which was 1 to 2 per year from 2006 to 2008, has increased by 10 to 20 in 2013.

The importation's increase of strains isolated from patients born in higher MDR tuberculosis incidence countries, such as the ex-USSR **(1)**, could explain mainly these.

In children, fewer than 500 MDR-TB cases have been described in the literature (12), in small series done in the United Kingdom, the United States, Canada, Asia and South Africa (13,14,15,16). This is due, mostly, to the difficulty in obtaining drug-resistance diagnosis, which requires mycobacterial culture and drug susceptibility testing (DST), in children.

A large proportion of paediatric cases is thus diagnosed on anamnestic and clinical criteria. Indeed, obtaining respiratory secretions, such as sputum or gastric aspirates, or specimen of extrapulmonary tuberculosis, more common in young children, makes microbiological confirmation challenging, not to mention the fact that half of children with a clinical diagnosis of tuberculosis, are smear-negative or culture-negative (paucibacillary form). Also, when information is available, child is treated from index case or source case's microbiological and mycobacterial profiles (17,18).

Drug-resistant tuberculosis therapeutic management is long and complex. A confirmed microbiological diagnosis, where possible, is essential to best adapt the treatment.

Paediatric drug-resistant tuberculosis is a neglected concern, and the guidelines and recommendations about treatment are rare.

A microbiologically confirmed diagnosis is only available in 20-40% of cases. Clinicians are often reluctant to start treatment for DR-TB in children because of the lengthy use of more toxic second-line drugs, significant adverse events, and prolonged hospital admission involved.

According to the last WHO treatment guidelines for DR-tuberculosis in 2016, update of 2011, in patients with rifampicin-resistant tuberculosis (RR-TB) or MDR-TB, a regimen with at least 5 effective TB medicines during the intensive phase is recommended, including pyrazinamide (PZA) (first line oral anti-TB drug) and 4 second-line anti-TB medicines : a fluoroquinolone (later generation are preferred), an injectable agent (aminoglycoside including kanamycin, amikacin or capreomycin), and at least two drugs, among ethionamide (or prothionamide), cycloserine (or terizidone), linezolid or clofazimine ; and no more ethionamide and either cycloserine or *para*-aminosalicylic acid (PAS), as specified in 2011. Since 2016, if the minimum number of effective TB drugs cannot be composed as given above, an agent as bedaquiline, delamanid, or even PAS or others from group D3 may be added to bring the total to five (5,19,20) (*appendix*).

According to 2011 guidelines report, The best chance of drug regimens' success is observed with an intensive phase (initial part of treatment using a parenteral agent) of 8 months duration and a total treatment duration of more than 20 months (using a minimum of 3 drugs, likely to be effective, of each different class), in patients without any previous MDR-TB treatment **(6,19)**.

With 2016 update, based on a set of criteria, for those same patients, whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter regimen of 12 months may be used, with an intensive phase of 4 months (extended up to a maximum of 6 months in case of lack of sputum smear conversion), followed by a continuation phase of 5 months (using at least 4 drugs, likely to be effective). It is newly recommend that children with confirmed RR-TB or MDR-TB be given the same consideration for treatment with a shorter MDR-TB treatment regimen as adults **(20)**.

As for extensively drug-resistant tuberculosis (XDR-TB), an addition of a minimum of six anti-TB drugs, known to be effective, during the intensive phase and four anti-TB drugs during the remaining treatment time are recommended, following similar treatment durations to MDR-TB 2011 recommendations (meaning up to 9 months for the intensive phase, using parenteral agent, and over a total duration between 21 to 25 months) **(6,19)**.

A recent meta-analysis about MDR tuberculosis treatment in children, made on eight different studies including 315 children, highlighted, despite the wide variation in treatment regimens approaches and choices, the possibility to treat children successfully in similar strategies to those carried out in adults. However, no better demonstration is available to date and recommendations concerning the optimization of a child-specific treatment regimens remain largely missing. All the more so because children have a broader and more diverse spectrum of disease. Some experts suggest treating limited disease less aggressively in order to limit toxicity and long hospitalisation, but once again, the evidence supporting this theory is still too much lacking.

In France, today's litterature can not offer studies about DR-TB management and monitoring in children. Furthermore, available data regarding second-line anti-TB drugs' tolerance in this vulnerable population are scarce to date, and yet crucial to find the most appropriate treatment for these DR-TB children.

In view of uncertainties in pediatrics, a better knowledge of these drug-resistant tuberculosis remains a major challenge and, above all, a necessity for ensuring adequate management and effective treatment of children resistant tuberculosis.

In order to improve our knowledge on this subject, and to learn more about the epidemiological, clinical and radiological presentation, mycobacterial profiles of drug-resistant tuberculosis in France, we conducted an analysis to describe clinical presentation, microbiological and radiological features, management and outcome in children treated for drug-resistant tuberculosis, in hospitals in Paris and Ile-de-France.

PATIENTS AND METHODS

Study Design and Definitions.

We reviewed data from all patients under 18 years of age, diagnosed with an active (confirmed or probable) Drug-Resistant (DR)-TB, admitted in 7 Parisian and Ile de France Hospital Centers (Robert Debre Hospital, Armand Trousseau Hospital, Jean Verdier Hospital, Necker Hospital, Avicenne Hospital, Saint Camille Hospital, Delafontaine Hospital), from January 2011 to December 2015.

According to the French Agence Régionale de la Santé's (ARS) mandatory reporting criteria, microbiologically-confirmed case was defined as the presence of at least 1 clinical specimen positive for *Mycobacterium tuberculosis* (*Mtb*) on culture, or positive Acid-Fast Bacilli (AFB) smear microscopy, or 1 histology sample positive for caseating granulomas, or nucleic acid amplification test positive for *Mtb*. Also, we defined a probable case as a child with clinical symptoms, signs and/or radiology of TB, with documented close exposure to DR-TB and a decision to treat patient with anti-TB treatment.

For each patient, the reported DR-TB source case was associated, if existed. The source case was defined as a confirmed case of DR-TB with close contact to the child within the prior 24 months. Timing and duration of contact exposure should be recorded when available. As documentation of proof of exposure is often unrealistic in the field, a verbal report of close contact to a source case was acceptable.

Mycobacterial culture and drug susceptibility testing.

Mycobacterial culture (samples of affected and source cases) was completed at the Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux (CNR-MyRMA) and through the « sentinel network » (« Azay Mycobactérie ») of Microbiology Department of each hospital Center.

Microscopic examination was screening by auramine staining and confirmed by Ziehl-Neelsen staining. Primary biological samples were first decontaminated and then cultured using solid media (Löwenstein-Jensen and Coletsos solid phase medium or solid agar medium 7H10)- or liquid medium through Mycobacterial Growth Indicator Tube (MGIT) 960 system. The presence of *Mtb complex* was confirmed by PCR amplification.

Drug susceptibility was determined, through antibiogram, with use of the absolute concentration method with Löwenstein-Jensen medium. Drugs tested were isoniazid (low and high level resistance), rifampin, ethambutol, amikacin, kanamycin, moxifloxacin, ofloxacin, cycloserine, *para*-aminosalicylic acid.

Genotypic drug susceptibility testing (DST) to isoniazid and rifampicin was initially carried out using line probe assay (GenoType MTBDR_{plus}, Hain Lifescience, Nehren, Germany), according to the manufacturer's instructions. All the isolates found to be MDR or Rifampicin-resistant were tested for resistance to second-line drugs using the GenoType MTBDR_{sl} (Hain Lifesciences, Nehren, Germany) based on mutations or non-binding wild-type probes for the *gyrA* and *gyrB* gene (fluoroquinolones), the *rrs* gene (aminoglycosides/cyclic peptides), and *embB* gene (ethambutol). Further DST against other second line drugs (streptomycin, ethionamide...) were performed and eighteen antibiotics were tested to the maximum.

Mtb resistance was categorized as resistance based on isoniazid or/and rifampin resistance. Mono-resistance (mDR) was resistance to one first line anti-TB drug; multi-drug resistance (MDR) was resistance to both isoniazid and rifampin; extensively drug-resistant (XDR) was resistance to isoniazid, rifampin, and to at least one fluoroquinolone and at least one of the three main injectable agents (amikacin, kanamycin, capreomycin); the term pre-XDR resistance was used to describe resistance to isoniazid, rifampin, and to one fluoroquinolone or one of the three main injectable agents.

Data Collection.

Detailed data regarding demographic and epidemiological characteristics, medical history, BCG immunization status, mode of discovery and illness course, source of microbiological diagnosis, clinical and radiological features, microbiological findings, medical management and outcome were collected through the medical and laboratory records of the Hospital Centers.

Research was supplemented with data from the Centres de lutte antituberculeux (CLAT) of Paris and the Paris crown (Bobigny 93, Créteil 94). Finally, most biological data were transmitted from the CNR-MyRMA database.

Data, concerning patients and their source cases when available, were collected retrospectively from 1 January 2011 to 31 December 2015. This is why we based on the 2011 WHO guidelines with five groups of treatment, since the 2016 classification update was available after the start of treatment of our cases. Follow-up was documented until 31 June 2017.

Disease was classified as pulmonary if there were any chest radiographic changes attributable to tuberculosis or if any thoracic samples were positive for *Mtb*. Extrapulmonary disease was classified if any imaging demonstrated extrathoracic tuberculosis or if a microbiological sample confirmed tuberculosis at a site other than the lungs.

Outcome.

Clinical response was observed with disappearance or improvement of initial symptomatology. Delay between drug-resistance diagnosis (patient' or source case') and the beginning of the effective treatment was reported.

Adverse reactions were recorded during each child course of treatment. Following the Common Terminology Criteria for Adverse Events (CTCAE) and WHO guidelines for DR-TB, a serious adverse event (SAE) was defined, in our study, as an "adverse reaction which is fatal, life-threatening, disabling, incapacitating, or which results in or prolongs hospitalization", requiring additional care in addition to stopping drug.

Treatment outcomes were further classified into 5 items : treatment completed ; cure, defined in this study as clinical and radiological improvement with negative results of 3 consecutive respiratory cultures, with no positive culture result after the first negative result, in presence of treatment completion ; favorable course defined as cure without microbiological results' negativation ; transferred out and/or lost to follow-up and death.

Statistical analysis.

Data set was compiled anonymously into Microsoft Excel® software as a relational database. Statistics were made from Microsoft Excel® and BioStat TGV® software. Continuous variables were summarized using means, medians and interquartile ranges (IQRs, 25th-75th percentile), and categorical variables were summarized using frequencies and percentages with their 95% confidence intervals (CIs).

This study was declared to the Commission Nationale et Informatique des libertés (CNIL) and obtained a favorable opinion from the Robert Debré Hospital's Ethics Committee.

RESULTS

Demographic characteristics of study population.

Twenty-four children with drug-resistant (DR) tuberculosis (TB) were included in the analysis (*Figure 1*), with a median age of 10.7 years old (interquartile range [IQR], 3.4-14.2 years old; min-max 1.3-17.8). Ten (41.7%) were under five years of age and 9 (37.5%) were between 10 and 15.

Three patients (12.5%) had history of TB. Two of them had completed their treatment abroad and were considered as cured. In the third case, the patient was still on treatment when he arrived in France.

Among the 19 children whose vaccination status was known, 17 (89.5%) were declared BCG vaccinated. None had HIV infection. Demographic and clinical characteristics at baseline are described on *Table 1*.

Seventeen children (70.8%) had been in contact with a source case known to be infected with a drug-resistant strain. Eleven source cases were identified in the study, of which 2 were under 18 and also included as cases in the study. The median age of the source cases was 23.7 years old (IQR 21.1-37.2 ; min-max 17.7-67.3).

The relationship of source case to contact ranged between the first and the fourth degree of affinity. Eight lived in same house than the child. Duration of contact was more than 40 hours for 10 source cases. Three of them had significant comorbidities : two had HIV infection ; the last, with XDR strain, had multiples cardiovascular risk factors (with diabetes, high blood pressure and coronary artery disease).

A previous TB treatment was reported for 2 source cases, each in a country with increased incidence of DR-TB : one, 54 years before in Algeria, and one, who is also included as a case, 3 years before in India.

Seven children (29.2%) were born in countries where DR-TB's incidence is increasing (4 in Tibet, South East Asia (SEA), 3 in Romania, Eastern Europe (EE)). Of the thirteen children (54.2%) born in France and Western Europe, 2 of them (8.3% of study's cases) had source cases also born in SEA and EE. As shown on *Table 2*, 8 DR-TB strains (50.0% of study's strains), including 3 MDR-TB strains and 5 mDR-TB strains, were from countries with an increasing incidence of DR-TB.

Finally, twelve children (50.0%), representing 6 study's strains of DR-TB, were born in Maghreb or sub-Saharan African countries, or had african origin through their source case (among those born in France).

Final diagnosis of DR-TB

We identified 15 children (62.5%) with multidrug-resistant (MDR) tuberculosis, including 10 microbiologically confirmed cases (3 without source cases, 5 others related to 5 different source cases and 2 who are index cases themselves, under 18 years old) and 5 probable cases (related to 5 different source cases).

Eight (33.3%) children had monoresistant(mDR)-to isoniazid tuberculosis, including 6 probable cases related to 6 different source cases and 2 confirmed cases without a source case identified.

One patient (4.2%) was identified as a pre-XDR case, related to an XDR source case. This child had a history of tuberculous pleurisy treated 6 years before in Algeria.

Clinical and radiological findings.

Fifteen cases (62.5%), were diagnosed through systematic contact tracing. Twelve children (50.0%) were symptomatic.

Median time between onset of symptoms and onset of management was 14.5 days (IQR 11.3-21.3). Median delay from onset of symptoms to onset of appropriate treatment (adapted to the resistance pattern) was 120.0 days (IQR 81.8-159.0).

All children had chest X-ray and chest CT at diagnosis. Their main characteristics at initial presentation are summarized on *Table 1*. Five children (20.8%) with normal chest X-ray had CT performed because of the existence of a close-contact case with microbiologically proved DR-TB and a positive TST. Bronchial fibroscopy was considered necessary for 16 children (66.7%). It was described as normal in 9 cases (56.3%) and 3 children (18.8%) had partial bronchial compression with lobar orifice reduction between 10 to 50%.

Among the 21 intra-thoracic tuberculosis (87.5%), 4 (19.0%) were exclusively pulmonary, 4 (19.0%) had pulmonary localization with mediastinal and hilar lymph node involvement, 6 (28.6%) had pulmonary localization with only peri-hilar lymph node involvement, 3 (14.3%) pulmonary localization with only mediastinal lymph node involvement ; the remaining 4 children (19.0%) had exclusive lymph node involvement.

Three cases with extrapulmonary involvement

Three patients had an extra-pulmonary localization (12.5%). Two of them (8.3% - including the pre-XDR strain) had both intrathoracic and cerebral localization.

The first child, infected with a pre-XDR strain, had mediastinal and latero-tracheal lymph nodes and extensive bilateral nodules, including calcifications. Two days after onset of adapted treatment, he presented isolated paraesthesias of both hands without motor deficit with concomitant thighs myalgia. Lumbar puncture (LP) showed high WBC count (including 96% neutrophils, 2% lymphocytes, 2% other cells), low glucose level, elevated protein level ; spinal MRI showed hyperintensities of thoracic nerve roots and cerebral MRI small increase of brain volume of peri-cerebellar, peri-cerebral spaces and of the lateral and third ventricles, revealing strong suspicion of tuberculous meningitis associated.

The second child presented at initial care in Romania generalized tonic-clonic seizure and peripheral facial palsy. Meningitis was confirmed on LP and MRI. PCR done on the cerebral spinal fluid (CSF) was positive for *Mtb* with *rpoB* mutation. At arrival in France, MRI, done after two months of second-line treatment initiated in Romania, found tuberculous meningoencephalitis with basilar meningitis and several small hemispherical strokes. Then, PCR on the CSF in France was negative at that time.

The third patient presented a 5 centimeters-cervical lymphadenopathy with a phlyctenular reaction to TST. The cervical and pelvic-thoraco-abdomino CT showed under mandibular, jugular, supraclavicular (with mass effect on adjacent arteriovenous vessels), mediastinal and mesenteric multiple adenopathies. Cerebral CT and MRI performed secondarily for paralysis of the left abducens, revealed tuberculous osteomyelitis of the sella turcica. Moreover, sellar mass's biopsy completed showed typical granulomas with epithelioid and gigante-cellular cells, one containing caseous necrosis next to bone lamella, but no AFB. The PCR made on this was positive to *Mtb*. In addition, microbiological diagnosis with genotypic and phenotypic profiles was achieved through nodal puncture and sellar mass's biopsy.

Susceptibility patterns for isolates of children and source cases.

The diagnosis of active TB was microbiologically confirmed (by Ziehl–Neelsen staining, culture or PCR) in 13 cases (54.2%), with a median age of 14.1 years (IQR 13.9-15.5; min-max 3.3-17.8). In particular, culture was positive in 12 (50.0%) cases, Ziehl–Neelsen staining in 5 (20.8%) and PCR, from positive sputum smears, in 3 (12.5%) cases.

The eleven children (45.8%) with probable TB had a median age of 3.4 years old (IQR 2.1-3.4 min-max 1.3-12.3).

Among the 13 confirmed cases, 5 children (38.5%), related to 3 MDR strains, one pre-XDR strain and one mDR strain, had positive acid-fast bacilli (AFB) smears and cultures for *Mtb*; 7 children (53.8%), related to 6 MDR and 1 mDR strains, had negative AFB smears but positive cultures for *Mtb*. The last one (7.7%) was diagnosed MDR case only with a positive PCR from CSF done in Romania.

Then, among the 12 children (50.0% of cases) with positive *Mtb*-culture, 6 were related to 5 different source cases and 2 were both source and study's cases. Seven (58.3%) had positive culture obtained on respiratory sputum before or without fibroscopy. Four (33.3%) had strains isolated only on post-fibroscopy respiratory sputum, and one (8.3%) on bronchoalveolar lavage (BAL) sample.

The remaining confirmed case had only positive PCR on CSF carried out in Romania (see description above) with a positive *rpoB* mutation. Data about complete antibiogram and DST made in Romania were missing.

As shown on *Table 1*, PCR performed in 13 samples, whose 12 from confirmed cases, was positive for 10 cases (76.9% of confirmed cases) (*Table 1*) and made the diagnosis of drug-resistance in 9 cases (69.2%). Three were performed on positive sputum smear. Three PCR from positive sputum culture, one from positive BAL culture and one from bone biopsy sample were obtained before culture's results, allowing the DR's diagnosis. The last one from CSF was the only diagnosis test.

Of the 11 source cases, 2 were included cases of study. All were sputum smear positive, with cavity on thoracic CT for 8 of them (missing data for the remaining 3). Nine source cases had a culture-confirmed diagnosis (missing data for the last two).

According to DST reported, 5 sources cases (45.5%) had MDR strain, 5 (45.5%) mDR strain and the last one (9.1%) had XDR strain (*Table 1*).

Twenty-four cases and sixteen strains

Features of the 16 resistant tuberculosis strains related to the 24 cases analyzed are presented on *Table 2*.

Four of these (25.0 % of strains) were regarded as imported from Eastern Europe (in this case, Romania) and 4 others (25.0%) from South East Asia (including India), consistent with cases or source cases' place of birth. In the same way, 5 (31.3%) strains were related to sub Saharan Africa, 1 (6.3%) to North Africa, 1 (6.3%) to France, with a notion of recent travelling in Algeria for source case, and 1 (6.3%) to Caribbean (in Haïti).

Among the 5 cases related to the third strain, 3 confirmed cases had phenotypic profile showing rifampin susceptibility but genotypic DST with *rpoB* mutation involved, supporting rifampin resistance, then attesting to multidrug resistance as shown for the first and second strain.

Only one mDR case, related to strain 11, had an ethambutol resistant strain, modifying his appropriate DR-TB treatment.

Management and monitoring of children with DR-TB.

As shown on *Table 3*, all except two children were hospitalized to start treatment and during the intensive phase if an injectable agent was given. The first was a probable case with mDR strain, diagnosed through systematic contact tracing. As she was asymptomatic and her younger brother followed at hospital, she initiated her treatment at day-hospital, achieved follow-up with favorable course. Another mDR case had also his treatment initiated during day-hospital, with same favorable course.

Then, children were treated at home with regular hospital outpatient follow-up and consultation.

One MDR case was treated with aminoglycoside injections twice over two different period of three months, for a total duration of six months, decided mostly because of poor treatment compliance associated to unfavorable clinical and radiological course.

The TB drugs used and their characteristics are documented on *Table 4*.

Median delay from onset of management to onset of appropriate treatment (adapted to the resistance pattern), calculated for 22 children (because of missing data and 1 no-treated child) was 75.5 days (IQR 37.5-100.5).

Among the 15 children with MDR strains, 7 (46.7%) were treated with a combined regimen using 4 drugs from 5 different groups (2011 WHO classification) including a fluoroquinolone, an injectable drug, one or two drugs from group 4 and one from group 5 (linezolid (LZD)); 1 (6.7 %) child received the same regimen without LZD; 5 (33.3%) received a combined therapy including 4 first-line drugs and a fluoroquinolone; the last one (6.7%) received a therapy including 3 first-line drugs, one fluoroquinolone and one injectable drug (switched to rifampicin due to bad adherence).

One child was not treated but only followed. Indeed, during a first family screening, he had been treated with a first line three months tritherapy (without ethambutol) decided on a phlyctenular TST and isolated nodules on thoracic CT scan, while he was asymptomatic with normal chest X-ray.

During a second family screening revealing his sister's confirmed MDR strain, he had normal clinical examination, negative microbiological results and the repeated CT scan was normal. He was only followed clinically and radiologically for 12.1 months and considered as cured at the end of follow-up.

The case with a pre-XDR strain was treated with a 5 drugs regimen including a fluoroquinolone, an injectable agent, one drug from group 4 and 3 drugs from group 5 (including one new anti-TB drug, bedaquiline TMC207).

Of the 8 mono-resistant to isoniazid strains, two children (25.0%) were treated with first-line quadritherapy, all two considered at risk of MDR strain because of their origin from countries with increasing incidence of DR-TB ; one case (12.5%) was treated with 2 first-line drugs in addition to a fluoroquinolone because of his ethambutol resistant strain. The remaining 5 children (62.5%) were treated with a first-line tritherapy without isoniazid. None received injectable drug.

Children monitoring is described on *Table 4*. Indeed, clinical examination; Blood test following hematologic, liver, kidney and thyroid functions; hearing monitoring -performed mostly for patients treated with amikacin- ; ophtalmological supervision -done mostly for patients treated with izoniazid (INH), ethambutol (EMB) and/or linezolid (LZD)-, were carried out regularly for each patient, with weekly monitoring to monthly, then quarterly or, more rarely, semi-annual. All patients treated with ethionamid or p-aminosalicylic acid had TSH blood tests. Eighty percent of children receiving amikacin were monitored with audiogram. Then, 88.9%, 78.6% and 87.5% of patients treated with, respectively, INH, EMB, or LZD were under ophtalmological supervision.

Outcome of children with MDR-TB.

Follow-up was documented until 31 June 2017. As notified on *Table 3*, 23 patients (95.8%) have completed their treatment. The last one was lost to follow-up before completing treatment. Among them, 12 (52.2% of completed treatment cases and 50.0% of all cases) were still followed-up and 7 (30.4% of completed treatment cases and 29.2% of all cases) have completed their follow-up, at the end of the study period.

Finally, 12 children (50.0%) were cured and 11 (45.8%) had favorable course; 5 (20.8%) were lost to follow-up before completing treatment for one of them (missing data) and at the end for 4 of them. No death was reported (*Table 3*).

The median duration of respiratory isolation, estimated on 8 microbiologically-confirmed cases (66.7%) over 12 with positive culture, was 5.2 months (IQR 4.0-8.0). Two cases, whose one with positive sputum smear, were not isolated because of poor compliance ; isolation duration's data missed for the last two.

The median delay to culture conversion, estimated on 9 of the 13 confirmed cases, was 1.8 months (IQR 1.4-2.3).

Monitoring of adverse reactions is documented on *Table 4* and main adverse reactions reflected on *Table 5*.

Serious adverse events (SAE) were observed in 12 cases (50.0%), as followed.

Four cases were affected by undernutrition despite adequate nutritional management.

Over fourteen children (58.3%) treated with ethambutol (EMB), drug was interrupted for 4 and the dosage was decreased for 1 of them because of visual disturbances or visual evoked response (VER) impairment and / or pathological electroretinogram. In four out of five cases, situation normalized after the treatment was interrupted or decreased. The last one had mild impairment on VER prior to the treatment initiation, which worsened during the treatment and despite stopping it. No visual pathway impairment was individualized on MRI; however, the adverse reaction's cause was probably not related to the TB treatment itself, but worsened by the treatment. This child was still being monitored for her probably constitutional lesions that have stabilized at the end of documented follow-up.

Two other children had more or less profound hearing loss. Ototoxicity was strongly imputable to aminoglycoside use for one and to linezolid (LZD) for the second, revealed and monitored in both cases by audiogram. Hearing loss at the end of treatment is not reported for one case since he was lost to follow-up.

Among the seven children (29.2%) receiving cycloserine (CS), one child presented SEA as disabling visual and auditory hallucinations which led to treatment interruption, allowing discontinuation of adverse event.

Of 10 children (41.7%) with combined regimen including injectable drug, amikacin was stopped for only one child because of parent's patient and patient's refusal to prosecute. Finally, one patient who received LZD had to interrupt his treatment for hematologic toxicity, solved after one month.

The most commonly described clinical AR is reported as "digestive disorders", imputable to fluoroquinolones, ethionamide and PAS (Group 4), and LZD (Group 5). Half of children (50.0%) said they were prone to these as abdominal pain, diarrhea, nausea or heartburn.

During follow-up, sequelae have been reported in 11 cases (45.8%), including the lost to follow-up patient with ototoxicity described above. Among the 7 cases who have completed their follow-up, 3 (12.5% of all cases) presented sequelae as cutaneous due to nodal puncture's scar, peripheral neuropathy linked to LZD or arthralgia and tendinopathies due to fluoroquinolones (FQ).

Among the 12 still followed-up at the end of study, 7 (29.2% of all cases) presented sequelae : undernutrition for 3 of them; hematologic toxicity due to LZD and QT elongation linked to moxifloxacin (MFX) for 1; thrombosis scar of picc line and temporary tendinopathies related to MFX for another 1 ; hematologic toxicity and transitional tendinitis due to LZD for 1 ; mild impairment on VER for the child described above.

Finally, the last case with pre-XDR strain presented three severe sequelae related to treatment: migraine with phosphenes, peripheral neuropathy with dysesthesia in all limbs and ototoxicity with deafness in the treble, all two related to LZD ; and two others related to TB disease : atelectasis of both upper lobe and a stable restrictive lung disease.

Nevertheless, we noted that after discontinuation of treatment, clinical adverse reactions decreased and supplements introduced, as thyroid hormones and / or B6 vitamin and / or K vitamin would no longer be necessary.

DISCUSSION

Data on the management of drug-resistant tuberculosis (DR-TB) in children in Europe are scarce **(21)**. To our knowledge, this study is one of the only paediatric studies about this subject, particularly emphasizing on management and drug toxicity, carried out in France.

The analysis of 24 cases and 11 related source cases, brings to describe 16 DR *Mycobacterium Tuberculosis* strain with different resistance profiles (*Table 2*), in a region with one of the highest incidence rate of DR-TB in France.

As we reported, 8 DR-TB strains (50.0%) related to 10 cases (41.7% of study's cases) were described as imported from countries with an increasing incidence of DR-TB **(3,7,9)** : 4 in South East Asia (SEA), including India, and 4 in Eastern Europe (EE) ; linked to the case's or source's case place of birth.

In the same way, 5 strains (31.3%) related to 11 children (45.8 % of cases) were imported from sub Saharan Africa, 1 (6.3%), the pre-XDR strain, from North Africa and 1 (6.3%) from Caribbean. The last one (6.3%) was a "french" strain related to an index case who had only travelled in North Africa recently. In Africa (sub-Saharan and Maghreb), where the tuberculosis burden is high, data about estimated incidence of DR-TB are still disparate or missing **(1,4,9)**.

This finding is consistent with literature showing a link between increase of DR-TB strains in France and importation's increase of strains isolated from patients born in countries with a higher incidence of MDR-TB **(5,9)**. Therefore, it is essential to ask a TB-case about his origin and trips but moreover, about origins and recent trips of child's relatives.

Since microbiological confirmation is not always possible in children **(2,6,13,21)**, the current cohort would be more representative of all children with DR-TB and has greater relevance to clinicians. Our work described both 13 confirmed cases (54.2%), whose 8 had an index case (including 2 children both cases and index cases) and 11 probable cases (45.8%) each related to a source case. In addition, more children had been diagnosed through systematic contact tracing than on clinical call point (62.5% vs 33.3%).

As suggested in several reports, a significant proportion, often exceeding 50%, received a presumptive treatment, based on clinical and radiological arguments with microbiological diagnosis of a DR-TB index case or poor clinical response after first-line therapy onset **(6,10,18)**.

The broad clinical and radiological spectrum of TB presentation in children combined with the poor frequency of positive sputum smear form in young children (**2,10,13, 18**) or with the rarer extra-thoracic forms, whose investigations are hard to carry out (**21,23**), make biological confirmation diagnosis difficult.

Of the twelve symptomatic children (50.0%), 10 were confirmed cases with a median age of 14.4 years old (IQR 11.9-16.5 ; min-max 3.3-17.8) and two presumed cases, with a younger median age of 6.8 years (IQR 5.1-8.4 ; min-max 3.4-10.1).

Furthermore, a culture confirmed diagnosis was made for three asymptomatic children, with a median age of 14.0 years old (IQR 13.9-14.4). It can be seen that older child has an easier microbiological diagnosis (**13**).

Otherwise, research is currently supporting development of new biomarkers and biological molecular tests to improve microbiological diagnosis of children TB. Thus, we would avoid, on one hand, “over-diagnosis” with significant presumptive therapy use and, on the other hand, “under-diagnosis”, which is still the cause of TB morbidity and mortality (**23**).

The median delay from microbiological diagnosis to onset of appropriate DR-TB treatment was 78.0 days (IQR 40.5-119.5) for all cases, and 71.0 days (IQR 53.0-97.8) for MDR-TB cases.

According to a recent meta-analysis, published in 2012 by *D.Ettehad et al*, including eight different studies carried out in developed and developing countries, describing the treatment outcome of 315 children, this delay varied from 2 days to 46 months for the treatment of MDR tuberculosis (**21**). Then, it seems short in our territory of study, compared to other reports conducted abroad (**14,15,16,21**).

This is probably related to french systematic contact tracing around a TB case (regardless DST), allowing earlier diagnosis of children then earlier treatment with presumptive therapy, even if they are asymptomatic or probable cases. Also, a second-line treatment can be started quicker, adapted on index case's strain resistance profile, even obtaining child's own microbiological diagnosis (**21,34**).

The absence of an identified adult MDR-tuberculosis index case was strongly associated with delay in initiation of appropriate therapy in children (**13,15**). Among 8 of the 13 confirmed cases reported, with known index cases, second-line tuberculosis treatment was introduced earlier in 7 cases from the source case's resistance profile obtained before their (including two children both cases and index cases).

It shows the importance of systematic contact tracing around adult index case often smear-positive, whose microbiological confirmation diagnosis is more frequent, and also the need for a regular follow-up of contact cases, avoiding more severe diseases in children.

Moreover, for principles of good clinical practice and need for improved paediatric surveillance data, developing effective tools to enable a microbiological diagnosis in children remains crucial **(12,21)**. These missions aim to improve DR-TB treatment's adaptation and to reduce drugs' toxicity in children.

DR-TB therapeutic management in children varies widely according to literature **(6,15,21,40)** although codified according to WHO adult recommendations **(1,4,5,19,20)**. The appropriate treatment duration of DR-TB in children remains unclear given the broad spectrum of disease and the limited reports about second-line drugs toxicity in children **(21)**.

In our work, children received individualized therapy based on case's or source case's DST. Median duration of injectable drug use was 3.4 months (IQR 3.0 – 5,5), well below that recommended by the 2011 WHO adult guidelines followed during the study period **(5,19)** - except for the pre-XDR case whose median duration was 9,0 months - but close to results in previously literature reviews in children **(10,13)**. Scientific journals or expert opinion **(18)** endorse their use thanks to convincing results of MDR TB treatment in children.

All MDR children of our study were treated with an addition of four second-line anti-TB drugs including at least one later generation fluoroquinolone with injectable drug for 60.0% of them.

Regimen for pre-XDR case included a new therapeutic agent, as Bedaquilin TMC207, usually less available in children and being studied in recent clinical trials **(16)**.

Before last 2016 update, the advice from the WHO and most TB programmes is that all patients newly diagnosed with DR-TB (i.e. not previously treated dor MDR-TB) are treated for a standardised (long) duration over 20 months for MDR and XDR cases **(5,19)**.

According to the meta-analysis by *D.Ettehad et al*, treatment duration ranged from 6 to 34 months, but for most studies included, treatment was given for a minimum of 18 months **(21)**. Regardless of the strain's resistance, the median duration of treatment reported in our work was shorter than recommended in adult, before 2016 **(1,5,6,19)**.

The median duration result of 13.3 months (IQR 12.0-18.0) for MDR cases is similar in comparison to the 2013 descriptive cohort study of 149 children started on MDR-TB treatment from Cape Town **(13)**. A majority of 95.8% cases were regarded as treated successfully, including the 12 children cured and the 11 with favorable course.

In this regard, consideration are underway to reduce the long duration of treatment in early and limited forms of the children disease, in the future, if adequate evidence from clinical studies becomes available.

However, last WHO policy recommendations, in 2016, report that in second-line drug naïve MDR-TB patients, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens, with a first intensive phase of 4 months, extended to 6 months, following early results from observational studies **(20, 47-50)**.

As adults, it is recommended that MDR-TB children be given the same consideration for a shorter treatment regimen **(20)**.

Even if this conditional recommendation has low certainty in the evidence, treatment-shortening strategies and the use of fewer drugs in children with non-severe DR-TB is a significant aim in therapeutic DR-TB management in children.

However, it should be considered in conjunction with obtaining a complete resistance profile of the children's or source case's strain and close follow-up showing treatment effectiveness in these vulnerable patients.

Furthermore, future controlled studies should further assess the potential for shorter treatment as a method to limit public health costs and adverse events, especially because improvements in diagnostics might increase the number of individuals needing treatment **(43)**.

We also reported different combined regimen for our mDR-TB study's cases, including 25.0% of those (2 cases) treated with first line quadritherapy because of clinicians' reported "high risk of MDR strain", which leads to a poignant question of mDR-TB treatment. Favorable course or cure were described for 87.5% of them.

More and more current studies show the proven incidence increase of monoR strains with isoniazid (INH) in particular in young patients, indicating the presence of recent circulation's strains **(51,52)**. However, few recommendations on diagnosis and treatment are available, while it is crucial not to increase the risk of multiresistance.

A 2017 Lancet infectious disease meta-analysis report that isoniazid resistance is associated with increased acquired multi-drug resistance in patients treated with regimen containing only first-line TB drugs (whom WHO-recommended regimen for new and previously-treated cases) **(53)**.

Thus, first-line quadritherapy is not so protective against the risk of MDR than expected. This has important implications in our country where mDR-TB increases **(51)** but where WHO-recommend treatment is used empirically without drug-susceptibility testing, particularly in children, whose confirmed diagnosis is more difficult.

Thus, *Gegia M. et al* concludes that regimen of 6-9 months of rifampicin, pyrazinamid and ethambutol (EMB) had reasonable treatment outcomes and, also, suggests that use of fluoroquinolones, as an alternative, for 2 or 4 months merits consideration for treatment of INH-resistant strains **(53)**. That's why, first-line tritherapies without EMB should not be considered anymore for INH-R-TB cases or patients at risk.

In previous reports, moderate anti-TB drug toxicity was observed in 40% of children **(10)**. As described by *D.Ettehad et al*, more than one-third of children had moderate adverse events, with the most common as nausea **(20)**.

In our study, they were observed at most in 50.0 % of cases as other digestive disorders particularly abdominal pain, diarrhea, nausea and heatburn.

Nevertheless, we described serious adverse reactions (AR) in 12 (50.0%) children, including 7 cases (29.2%) with treatment interrupted and 2 (8.3%) hearing loss linked to amikacin.

Adverse reactions' collection is not always reported in most studies and the attribution of one to a single drug is hard **(14,15,21)**.

These significant figures lead one to wonder about the development of effective and more "child-friendly" medicines and an improved understanding of pharmacokinetics and dynamics of second-line drugs in children.

Older studies have reported less incidence of AR of second-line anti-TB drugs in adults than in children **(21,44)**. Today, it is harder to compare the prevalence of AR between DR-TB children and adults because a summary estimate is poorly available in adults **(41)**.

Young children also have a different metabolism than adults of anti-TB drugs **(13,18,23)**. More than half of cases were monitored with drug dosages of second-line anti-TB drugs, when available. According to assay's cut off given by french pharmacology laboratories, we have mainly observed underdosing in treated children. However, in comparison to the WHO 2011 guidelines and recent literature recommendations about anti-TB drug's doses in children **(10, 19)**, second-line treatment's doses were prescribed at recommended upper cut off or above them for fluoroquinolones and linezolid (group 5 of 2011 WHO Drug Grouping) or as recommended for cycloserine (group 4). Nevertheless, mainly overdoses with amikacin were observed with drugs' doses at recommended lower cut off or below them.

These results, associated with a 95.8% treatment success, raise once again a huge lack of understanding of second-line treatment's pharmacology and metabolism in DR-TB children, with a toxicity's risk and overdose still widely known.

Median duration of follow-up was 22.7 (IQR 19.0-28.3) and 10.1 months (IQR 7.9-14.7) estimated respectively for 13 MDR (54.2%) and 7 mDR (29.2%) cases with treatment completed. Previous reports described quite disparate median duration results between 12 months and 36.7 months **(18)**. Most patients initiated treatment at hospital, as found in other clinical journals **(12,13,18)**.

Poor or doubtful compliance has been described in 21.7% of children including only one for whom treatment duration had been extended and who needed secondary hospitalisation in long-stay center to improve treatment intake. Other compliance problems were especially related to the handicap of the multiple daily intake, digestive adverse reactions, and also to respiratory isolation constraint for two cases.

Improvement in follow-up and compliance with TB treatments is largely supported by the WHO-initiated Directly-Observed Therapy (DOT) strategy. This plays a major role in reducing the global morbidity of the disease and is a key component of treatment success in DR-TB children **(8)**.

Our cure rate of 95.8 % (confirmed and favorable course) is better than that literature offers for the MDR-TB adults' treatment. Many other reports of DR-TB in adults have shown a success rate between 54 to 69% of cases **(41,42)**, with bad outcome for malnourished, alcoholic, XDR strains patients, patients with standardized treatment (in contrast with individualized treatment), with short duration treatment and male.

This difference can be explained with the shorter diagnosis delay, shorter treatment duration, less extensive disease patterns, probably faster childhood bacillus clearance than in adults due to the paucibacillary nature of the disease and with closer follow-up in children than in adults **(20)**.

A limitation of this study is its retrospective nature and the small number of patients, inherent in french low incidence's pathologies and the very short time period of study. As a result, it is impossible to obtain statistical conclusion on causation even if descriptive analysis does provide much information. Another limitation of our study is the low proportion of children who had their follow-up completed, even if treatment was completed. Only 29.2% (7 cases) have completed their follow-up, underestimating the rate of sequelae and making our median duration of follow-up poorly interpretable.

A prospective study extended throughout France, would provide more information in the future on long-term outcome of children with DR-TB.

In conclusion, bacteriological confirmation of DR-TB remains difficult in children because of the wide spectrum of clinical and radiological presentation of the disease and the frequency of paucibacillary forms. Nevertheless, this fact should not delay appropriate treatment onset to improve treatment success with the least adverse reaction as possible. Contact tracing around index cases remain essential, as follow-up of children-contacts.

Then, greater priority should be placed both on developing studies about second-line treatment's pharmacology and metabolism in DR-TB children and on limiting multidrug-resistance risk with rapid, accurate and effective treatment of INH-R-TB which increased in younger in France.

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TABLES AND FIGURES

Figure 1. Flowchart of study selection.

Abbreviations : MDR-TB, multidrug-resistant tuberculosis ; LTI, latent tuberculosis infection ; UHC, University Hospital Center ; N.E.M., Necker-Enfants-Malades hospital.

* Others stands for Avicenne, Bligny, Saint Camille, Delafontaine hospitals centers.

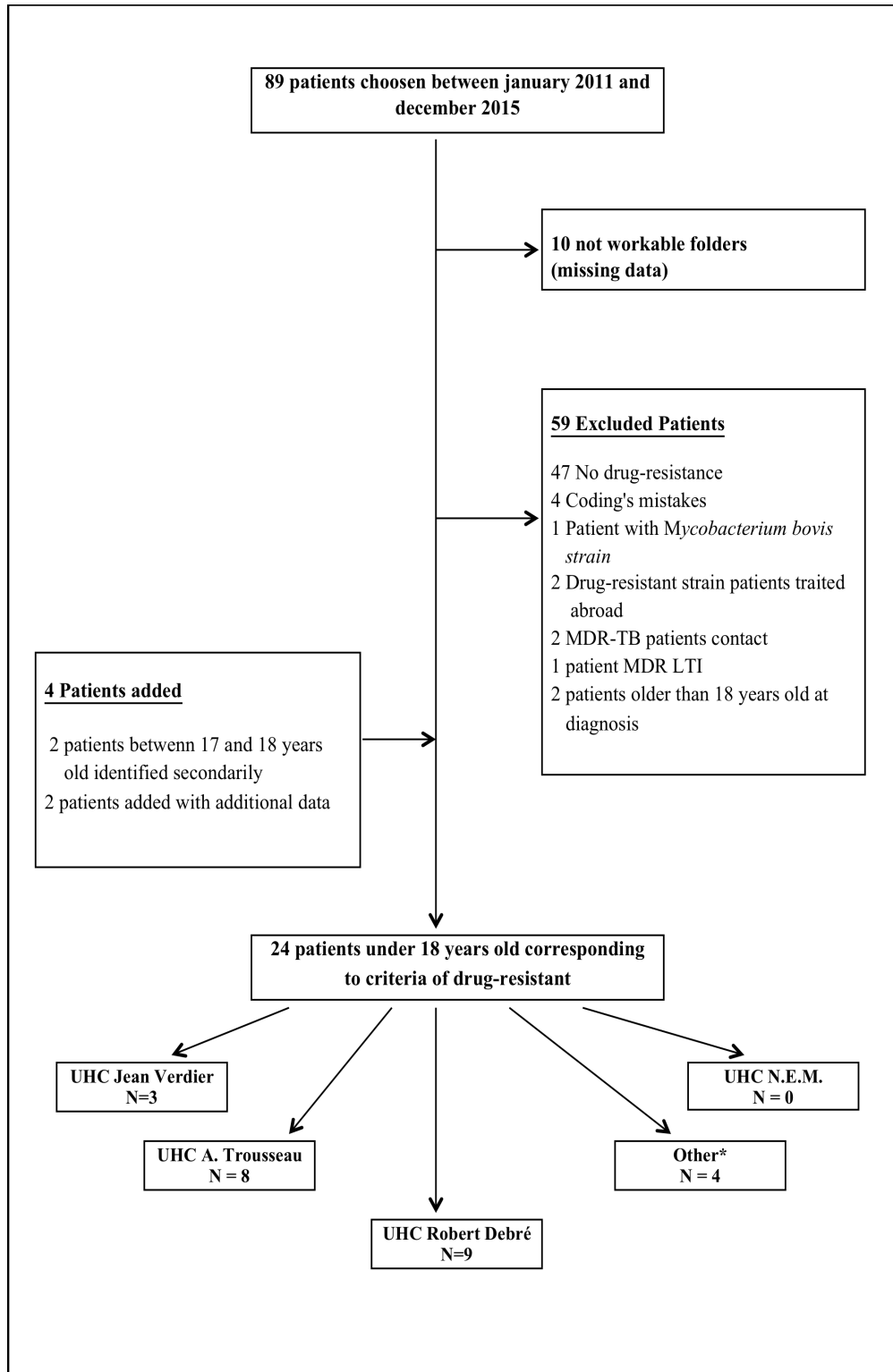


Table 1. Baseline demographic, clinical, microbiological and radiological characteristics of 24 children treated for DR-TB (n=24 unless otherwise stated)

Characteristic	Variable	Pre-XDR case (n=1)	MDR case (n=15)	mDR case (n=8)	all cases (n=24) ^a
Age, y	≤ 2y	NA	2 (8.3)	1 (4.2)	3 (12.5)
	2 - 5 y	NA	2 (8.3)	5 (20.8)	7 (29.2)
	5 - 10 y	NA	1 (4.2)	0 (0.0)	1 (4.2)
	10 - 15 y	1 (4.2)	6 (25.0)	2 (8.3)	9 (37.5)
	15 - 18 y	NA	4 (16.7)	0 (0.0)	4 (16.7)
Sex	Male	NA	8 (33.3)	4 (16.7)	12 (50.0)
	Female	1 (4.2)	7 (29.2)	4 (16.7)	12 (50.0)
Weight	Less than -2 SD for age	NA	0 (0.0)	1 (4.2)	1 (4.2)
	-2 to + 1SD for age	1 (4.2)	13 (54.2)	6 (25.0)	20 (83.3)
	More than +1 SD for age	NA	2 (8.3)	1 (4.2)	3 (12.5)
Medical history					
	BCG vaccination (n=19)	0 (0.0)	11 (57.9)	6 (31.5)	17 (89.5)
	History of TB treatment	1 (4.2)	2 (8.3)	0 (0.0)	3 (12.5)
Source case (n=11) ^b	None identified	NA	3 (12.5)	2 (8.3)	5 (20.8)
	INH-R-TB	NA	0 (0.0)	5 (45.5)	5 (45.5)
	MDR-TB	NA	5 (45.5)	0 (0.0)	5 (45.5)
	XDR- TB	1 (9.1)	0 (0.0)	0 (0.0)	1 (9.1)
Case's place of birth	France and Western Europe	NA	8 (33.3)	5 (20.8)	13 (54.1)
	Eastern Europe	NA	1 (4.2)	2 (8.3)	3 (12.5)
	South East Asia (SEA)	NA	4 (16.7)	0 (0.0)	4 (16.7)
	Africa (sub-Saharan and North Africa)	1 (4.2)	1 (4.2)	0 (0.0)	2 (8.3)
	USA	NA	0 (0.0)	1 (4.2)	1 (4.2)
	Haiti (Caribbean)	NA	1 (4.2)	0 (0.0)	1 (4.2)
	France	NA	2 (25.0)	0 (0.0)	2 (25.0) ^c
Source case's place of birth (if case was born in France) (n=8) ^c	Africa (sub-Saharan)	NA	2 (25.0)	2 (25.0)	4 (50.0)
	SEA	NA	0 (0.0)	1 (12.5)	1 (12.5)
	Eastern Europe	NA	0 (0.0)	1 (12.5)	1 (12.5)
Mode of disease discovery	Systematic screening (around a case or minor newcomer)	NA	10 (41.7)	5 (20.8)	15 (62.5)
	Clinical call point	1 (4.2)	4 (16.7)	3 (12.5)	8 (33.3)
	First-line treatment failed	NA	1 (4.2) ^d	0 (0.0)	1 (4.2) ^d
Number of symptomatic patients		1 (4.2)	8 (33.3)	3 (12.5)	12 (50.0)
Positive TST (n=19) ^e		1 (5.3)	11 (57.9)	7 (36.8)	19 (100.0)
Positive QuantiFERON-TB (n=13) ^e		1 (7.7)	7 (53.8)	5 (38.5)	13 (100.0)
Type of TB	Intrathoracic	NA	13 (54.2)	8 (33.3)	21 (87.5)
	Extrathoracic	1 (4.2)	2 (8.3)	0 (0.0)	3 (12.5)
Extrapulmonary involvement (more than one possible ; n=3)	TB meningitis	1 (4.2)	1 (4.2)	0 (0.0)	2 (8.3)
	Peripheral lymph node TB	0 (0.0)	1 (4.2)	0 (0.0)	1 (4.2)
	Sphenoid bone TB	0 (0.0)	1 (4.2)	0 (0.0)	1 (4.2)
Final diagnosis of DR-TB	Confirmed	1 (4.2)	10 (41.7)	2 (8.3)	13 (54.2)
	Probable	NA	5 (20.8)	6 (25.0)	11 (45.8)
Positive smear microscopy result for respiratory samples		1 (4.2)	3 (12.5)	1 (4.2)	5 (20.8)
Positive culture result for respiratory samples		1 (4.2)	9 (37.5)	2 (8.3)	12 (50.0)
<i>M. Tuberculosis</i> PCR result (n=13) ^f	From positive sputum smear	NA	2 (15.4)	1 (7.7)	3 (23.1)
	From positive sputum culture	1 (7.7)	3 (23.1)	0 (0.0)	4 (30.8)
	From BAL fluid/ CSF / bone biopsy	NA	3 (23.1)	0 (0.0)	3 (23.1)
Chest radiograph features at baseline	Normal	0 (0.0)	4 (16.7)	1 (4.2)	5 (20.8)
	Perihilar/Hilar lymphadenopathy or airways compression	1 (4.2)	10 (41.7)	4 (16.7)	15 (62.5)
	Lobar/segmental collapse or opacification	0 (0.0)	0 (0.0)	1 (4.2)	1 (4.2)
	Alveolar opacities	1 (4.2)	5 (20.8)	5 (20.8)	11 (45.8)
	Pleural effusion	0 (0.0)	1 (4.2)	0 (0.0)	1 (4.2)
	Tuberculous cavern	1 (4.2)	2 (8.3)	0 (0.0)	3 (12.5)
Thoracic CT scan features at baseline	Necrotic lymphadenopathy	0 (0.0)	6 (25.0)	3 (12.5)	9 (37.5)
	Isolated nodules	0 (0.0)	8 (33.3)	1 (4.2)	9 (37.5)
	Extensive nodular ranges (bilateral or not)	1 (4.2)	3 (12.5)	3 (12.5)	7 (29.2)
	Presence of cavity	1 (4.2)	3 (12.5)	2 (8.3)	6 (25.0)
	Parenchymal calcifications	1 (4.2)	1 (4.2)	2 (8.3)	4 (16.7)

Abbreviations : DR, drug-resistant ; TB, tuberculosis ; NA, not applicable ; SD, standard deviation ; BCG, Bacillus Calmette-Guerin ; HIV, human immunodeficiency virus ; IQR, interquartile range ; TST, tuberculin skin test ; PCR, polymerase chain reaction ; BAL, bronchoalveolar lavage ; CSF, cerebrospinal fluid ; CT, computerized tomography.

^a Data represent Number (N.) of patients unless otherwise noted.

^b Among the 11 source cases identified (n=11), 2 of them were also included as cases of the study.

^c Of the 11 source cases, 8 had child contact cases born in France ; One of these two source cases is an included case born in France.

^d For this case only, a first-line anti-tuberculosis treatment had been started then adapted (to the PCR detection of cerebral spinal fluid from a strain resistant to rifampicin) in Romania, two months before his arrival in France. This second-line treatment of pulmonary and cerebral tuberculosis was followed for two months in Romania but stopped before arriving in France for second opinion. The adapted treatment then chosen in France hospital was different from the first one instituted in Romania.

^e 19 children of 24 cases had tuberculin skin test ; data are missing for the five last cases / 13 children of 24 had quantiFERON-tb test ; data are missing for the 11 last cases.

^f Of the 24 cases, 13 are known to have had PCR ; those PCR were made on samples of smear microscopy, culture, bronchoalveolar lavage fluid, cerebrospinal fluid (CSF) or bone biopsy ; it called positive to the *Mycobacterium tuberculosis complex*. The case with positive PCR made on CSF sample was carried out in Romania ; the positive PCR on bone biopsy was made on sphenoid bone biopsy.

Table 2. Features of the 16 resistant tuberculosis strains related to the 24 cases of the study

STRAINS	Number of related cases	Drug-resistance	Genotypic DST with mutation involved	Phenotypic profile (antibiogram)	Strain's case Origin	Source case origin, family link
strain 1	1	MDR	rpoB + (in Romania)	/	Romania (EE)	/
strain 2	1	MDR	rpoB+ (cocci bacterial contamination)	<i>no data</i>	Tibet (SEA)	/
strain 3	5 including the source case	MDR	inhA+(LL) katG- (HL) rpoB+ rrs- ethA- ethR- katG+ inhA- rpoB+ embB+ rrs- gyrA-	INH-R (HL) RMP-R (IL) SM-R PTO-R INH-R, RMP-R EMB-R SM-R ETO-R	France Parents born in Mali	Brother, France Recent trip in Mali (A)
strain 4	1	MDR	katG+ inhA- rpoB+ embB+ rrs- gyrA-	INH-R (HL) RMP-R EMB-R SM-R ETO-R	Haïti (Caribbean) /	
strain 5	3 including the source case	MDR	katG+ inhA- rpoB+ embB+ ethA+ ethR+ pncA+ inhA+ katG+ rpoB+ embB+ rrs - ethA+ ethR-	INH-R (HL) RMP-R EMB-R ETO-R INH-R (HL) RMP-R EMB-R SM-R PTO-R	Tibet (SEA)	Brother, Tibet (SEA)
strain 6	1 + 1 source case	MDR	inhA+ katG- rpoB+ embB+ rrs - ethA+ ethR-	INH-R (HL) RMP-R EMB-R SM-R PTO-R	France	Mother, France Recent trip in Algeria
strain 7	2 + 1 source case	MDR	inhA+ katG- rpoB+ embB+ ethA- ethR- inhA+ katG- rpoB+ embB+ rrs- ethA- ethR-	INH-R (HL) RMP-R EMB-I PTO-R INH-R (HL) RMP-R EMB-R SM-R PTO-R	Cameroon + France	Cousin, Cameroon (A)
strain 8	1 + 1 source case	MDR	inhA+ katG- rpoB+ embB+ rrs- ethA- ethR-	INH-R (HL) RMP-R EMB-R SM-R PTO-R	France	Father, Republic of Congo (A)
strain 9	1 + 1 source case	pre XDR with XDR source case	inhA+ katG+ rpoB+ embB+, gyrB+, rrs- ethA+, ethR+	INH-R (HL) RMP-R EMB-R FQN-R ETO-R	Algeria	Grand Mother, Algeria
strain 10	1	MonoR INH	katG+ inhA- rpoB- embB-	INH-R (HL)	Romania (EE)	/
strain 11	1	MonoR INH	katG+ inhA- embB+ rpoB-	INH-R (HL) EMB-R SM-R	USA Parents born in India	/
strain 12	1 + 1 source case	MonoR INH	katG+ inhA- rpoB- embB-	INH-R (HL) SM-R	France	Father, Romania (EE)
strain 13	1 + 1 source case	MonoR INH	katG- inhA- rpoB-	INH-R (LL) (EMB-S, SM-S)	France	Cousin, China (SEA)
strain 14	2 + 1 source case	MonoR INH	katG+ inhA- rpoB-	INH-R (HL) (EMB-S)	France	Uncle, Republic of Congo (A)
strain 15	1 + 1 source case	MonoR INH	<i>no data</i>	INH-R	Romania (EE)	Brother, Romania (EE)
strain 16	1 + 1 source case	MonoR INH	<i>no data</i>	INH-R (LL)	France Parents born in Mali	uncle, Mali (A)

Abbreviations : MDR-TB, multidrug-resistant ; R, resistance ; I, intermediate resistance ; S, susceptible ; DST, Drug Susceptibility Testing ; RMP, rifampin ; INH, isoniazid ; EMB, ethambutol ; PZA, pyrazinamide ; AK, amikacin ; SM, streptomycin ; MFX, moxifloxacin ; LFX, levofloxacin ; PTO, prothionamide ; ETO, ethionamide ; CS, cycloserine ; PAS, p-aminosalicylic acid ; LZD, linezolid ; FQN, fluoroquinolone ; LL, low level ; IL, intermediate level ; HL, high level ; EE, Eastern Europe ; SEA, South East Asia ; A (Africa).

Table 3. Management and outcome in children treated for DR-TB (n=24 unless otherwise stated)

Management and Outcome	Number of cases (N, %), unless over indicated			
	Pre-XDR case (n=1)	MDR cases (n=15)	mDR cases (n=8) ^a	all cases (n=24)
Admitted to hospital	1 (4.2)	15 (62.5)	6 (25.0)	22 (91.7)
Median duration of hospitalisation (days, IQR) (n=22)	41.0	20.0 (12.5-58.0)	16.0 (10.0-20.5)	19.5 (10.8-40.3)
Number of cases with C+ in respiratory isolation (n=12) ^b	1 (8.3)	7 (58.3)	2 (16.7)	10 (83.3)
Median duration of respiratory isolation (months, IQR) (n=8) ^b	6.0	5.2 (4.5-12.0) ^b	1.2 ^b	5.2 (4.0-8.0)^b
Median delay to culture conversion (month, IQR) (n=9) ^b	1.8	2.0 (1.5-3.0)	1.1	1.8 (1.4-2.3)
Treated with injectable antibiotic ^c (WHO grouping 2)	1 (4.2)	9 (37.5)	0 (0.0)	10 (41.7)
Median duration of injectable antibiotic (months, IQR)	9.0	3.0 (3.0-4.4)	/	3.4 (3.0-5.5)
Median duration of total treatment (months, IQR)	18.6	13.3 (12.0-18.0) ^d	8.1 (6.0-9.3)	12.0 (9.3-16.0)^d
Median delay from microbiological diagnosis of DR-TB to start of appropriate DR-TB treatment (days, IQR) ^e	2110.0	71.0 (53.0- 97.8)	85.0 (11.8-158.3)	78.0 (40.5-119.5)
Median delay from onset of symptoms to onset of appropriate treatment (days, IQR) (n=12) ^f	159.0	120.0 (95.8-137.3)	26.0 (17.5-100.0)	120.0 (81.8-159.0)
Median duration of follow-up (months, IQR) (n=21) ^g	23.3	22.7 (19.0-28.3)	10.1 (7.9-14.7)	19.0 (13.8-23.8)
Outcome				
Treatment Completed	1 (100.0)	14/15 (93.3)	8/8 (100.0)	23 (95.8)
Treatment stopped before ending	NA	1/15 (6.7)	NA	1/15 (6.7)
Cure	1 (100.0)	10/15 (66.7)	1/8 (12.5)	12 (50.0)
Favorable Course ^h	NA	5/15 (33.3)	6/8 (75.0)	11 (45.8)
Lost to follow up	0 (0.0)	2/15 (13.3)	3/8 (37.5) ^g	5 (20.8)^g
Died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: DR, drug-resistant ; TB, tuberculosis ; Pre-XDR, pre-extensively drug resistant, term used to describe resistance to isoniazid, rifampin, and to one fluoroquinolone or one of the three main injectable agents ; MDR, multidrug resistant ; mDR, monoresistant ; C+, culture-positive sample ; WHO, World Health Organization ; IQR, interquartile range, NA, not applicable.

^a Monoresistant to isoniazid.

^b Among the 12 cases with respiratory samples' positive culture, 2 MDR cases were not in isolation for lack of compliance.

^b Data missed for isolation duration for one mDR case and one MDR case.

^b Over the 12 children with culture-positive samples, data missed for 2 MDR and 1 mDR cases.

^c Injectable means intravenously (IV), intramuscular (IM) subcutaneously (SC). One case received IV then SC injections and another case only IM injections.

^d Among the MDR cases, one child was not treated, only followed ; for another case, data on follow-up and treatment durations were missing. Thereby, 13 cases of the 15 study's MDR cases and 22 cases of all study's cases were selected for calculations.

^e Results obtained with 23 cases of the 24 study's cases. One patient was not treated, only followed up. Also, we considered 14 cases of the 15 MDR cases, all the mDR and pre-XDR cases for calculations.

^f Results calculated taking into account the number of symptomatic patients : 12 of all cases, 8 cases among MDR cases, and 3 cases of mDR cases.

^g It corresponds to the delay between the date of hospitalization admission and the end of follow-up (or date of last visit). It was estimated in children who had their treatment completed without missing datas : n= 21 for all cases ; n=1 for pre-XDR case who has ended her treatment ; n=13 for MDR cases ; n=7 for mDR cases.

^h Favorable course concentrated here cured cases without bacteriological evidence, with good clinical and radiological evolution.

ⁱ Two mDR cases, with favorable course, were lost to follow-up just after treatment completion, one just before last consultation. The two last MDR cases were lost to follow up before end of treatment but with culture conversion obtained.

Table 4. Drug therapy characteristics and monitoring for children treated for DR-TB (n=24 unless otherwise stated).

WHO's Grouping treatments	N° treated (%) ^a	Median duration in months of treatment (IQR)		N° monitored by dosages (%)	N° with poor or doubtful compliance (%)	N° monitored with drug dosages performed for poor adherence	Origin of Treatment modifications		N° monitored by blood, liver and kidney function tests (%)	N° monitored by TSH blood samples (%)	N° monitored by audiogram (%)	N° under ophthalmological supervision (color vision) (%)
		mDR	MDR/PreXDR				Overdose	Underdosing				
		Group 1										
INH ^a	9 (39.1)	4.9 (4.3-5.4)	12.3 (12.0 - 13.1)	7 /9 (77.8)	1 /9	0	2	4	8 /9 (88.9)^d	0 /9 (0.0)	1 /9 (11.1)	8 /9 (88.9)
RMP ^a	14 (60.9)	9.0 (6.0-9.5)	12.0 (12.0-12.5)	7 /14 (50.0)	1 /14	1	1	6	12 /14 (85.7)	0 /14 (0.0)	1 /14 (7.2)	10 /14 (71.4)
PZA ^a	15 (65.2)	3.9 (3.1-6.8)	12.3 (12.0-15.6)	3 /15 (20.0)	2 /15	1	0	0	13 /15 (86.7)	1 /15 (6.7)	1 /15 (6.7)	10 /15 (66.7)
EMB	14 (60.8)	4.1 (3.5-7.6)	7.4 (5.6-11.2)	4 /14 (28.6)	2 /14	1	0	1	12 /14 (85.7)	1 /14 (7.1)	1 /14 (7.1)	11 /14 (78.6)
Group 2												
AK	10 (43.5)	/	3.4 (3.0-4.5)	8 /10 (80.0)	2 /10	1	6	1	10 /10 (100.0)	9 /10 (90.0)	8 /10 (80.0)	8 /10 (80.0)
Group 3												
LFX	9 (39.1)	7.4 (n=1)	12.3 (12.0-14.8)	8 /9 (88.9)	2 /9	2	0	5	9 /9 (100.0)	3 /9 (33.3)	4 /9 (33.3)	7 /9 (77.8)
MFX	7 (30.4)	/	18.0 (14.5-18.5)	7 /7 (100.0)	1 /7	1	0	1	7 /7 (100.0)	6 /7 (85.7)	5 /7 (71.4)	6 /7 (85.7)
Group 4												
ETO	1 (4.3)	/	13.3 (n=1)	0 (0.0)	0	/	/	/	1 /1 (100.0)	1 /1 (100.0)	0 /1 (0.0)	1 /1 (100.0)
CS	7 (30.4)	/	17.5 (13.3-18.0)	7 /7 (100.0)	2 /7	2	4	2	7 /7 (100.0)	7 /7 (100.0)	7 /7 (100.0)	5 /7 (71.4)
PAS	8 (34.8)	/	16.9 (13.7-18.0)	0 (0.0)	2 /8	0	/	/	8 /8 (100.0)	8 /8 (100.0)	8 /8 (100.0)	6 /8 (75.0)
Group 5												
LZD	8 (34.8)	/	11.1 (9.0-16.5)	7 /8 (87.5)	2 /8	2	1	2	8 /8 (100.0)	8 /8 (100.0)	7 /8 (87.5)	7 /8 (87.5)
CFZ	1 (4.3)	/	10.8 (n=1)	0 (0.0)	0	/	/	/	1 /1 (100.0)	1 /1 (100.0)	1 /1 (100.0)	1 /1 (100.0)
TMC207	1 (4.3)	/	18.5 (n=1)	0 (0.0)	0	/	/	/	1 /1 (100.0)	1 /1 (100.0)	1 /1 (100.0)	1 /1 (100.0)
All Regimen therapy	23^a (100.0)	8.1 (6.0-9.3)	13.8 (12.1-18.0)^b	18 /23 (78.3)	5 /23 (21.7)	3^c	/	/	22^a (95.7)	9^a (39.1)	10^a (43.5)	16^a (69.5)

Abbreviations : DR-TB, drug-resistant tuberculosis ; WHO, world health organization ; N°, number of cases ; TSH, thyroid stimulating hormone ; INH, Isoniazid ; RMP, Rifampicin ; PZA, Pyrazinamide ; EMB, Ethambutol ; AK, Amikacin ; LFX, Levofloxacin ; MFX, Moxifloxacin ; ETO, Ethionamide ; CS, Cycloserine ; PAS, p-aminosalicylic acid ; LZD, Linezolid ; TMC207, Bedaquiline ; CFZ, Clofazimine ; IQR, Interquartile range ; Pre-XDR, pre-extensively drug resistant, term used to describe resistance to isoniazid, rifampin, and to one fluoroquinolone or one of the three main injectable agents ; MDR, multidrug resistant ; mDR, monoresistant to isoniazid.

According to 2011 WHO guidelines : Group 1 = First-line oral anti-TB drugs ; Group 2 = Second-line injectable agents (Group B of 2016 WHO classification) ;

Group 3 = Fluoroquinolones (Group A of 2016 WHO classification) ;

Group 4 = Oral bacteriostatic second-line anti-TB drugs (Group C of 2016 WHO classification except PAS in Group D3) ;

Group 5 = Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (mix of Group C and D2 of 2016 WHO classification).

(See the appendix)

^a A MDR case had been treated with preventive triple therapy (INH-RMP-PZA) for three months, after the first family screening. He was not included in the statistics since he was not treated but only followed at the time of the second family screening and treatment. Thereby n=23 for calculations in this table.

^b Calculated for 22 cases of the 24 study's cases, due to the non treated case (iea) and missing data about duration treatment for a second MDR case.

^c Dosages were performed for all drugs of the 3 cases' regimen therapy except PAS (for those who took it).

^d Data missed for the last case.

Table 5. Adverse reactions in children treated for DR-TB.

Adverse reaction	Number of cases (N,%)	Drugs involved (WHO's Grouping Drug)				
		Group 1	Group 2	Group 3	Group 4	Group 5
Clinical events						
Skin side effects						
<i>Acne</i>	1 (4.2)	RMP,PZA		LFX		
<i>Eczema</i>	1 (4.2)			LFX	CS, PAS	
Gastrointestinal symptoms						
<i>Vomiting</i>	2 (8.3)	EMB			PAS	
<i>Anorexia, undernutrition</i>	6 (25.0)			LFX, MFX	CS, PAS	LZD
<i>Other digestive disorders^a</i>	12 (50.0)	INH		LFX, MFX	ETO, PAS	LZD
Mucosal involvement						
<i>Mycosis, candidiasis</i>	1 (4.2)					LZD
<i>Coloring of secretions</i>	3 (12.5)	RMP				
Ophthalmological						
<i>Visual impairment</i>	2 (8.3)	EMB				
Neurological						
<i>Dizziness</i>	3 (12.5)	INH			CS	LZD
<i>Visual, auditory hallucinations</i>	1 (4.2)				CS	
<i>Migraine with visual aura</i>	1 (4.2)					LZD
<i>Headache</i>	1 (4.2)					LZD
<i>Paresthesias</i>	1 (4.2)			MFX		
<i>Peripheral neuropathy</i>	2 (8.3)			MFX		LZD
Cardio-Vascular						
<i>QT elongation</i>	1 (4.2)			MFX		
<i>Peripheral superficial thrombosis</i>	1 (4.2)		AK (picc line)		PAS	
Rheumatologic						
<i>Joint, muscle, bone pain</i>	4 (16.7)			LFX, MFX		
Biological events						
Hematologic toxicity^b	8 (33.3)					LZD
Hemostasis disorders^c	5 (20.8)				PAS	
Hypothyroidism	2 (8.3)				PAS	
Vitamin B6 deficiency	7 (29.2)	INH			CS	
Renal toxicity	1 (4.2)		AK			
Hepatotoxicity	0 (0.0)					
Paraclinical events						
Abnormalities of visual evoked response	4 (16.7)	EMB				
Hearing loss	1 (4.2)		AK			
Treatment interrupted	7 (29.2)	EMB	AK		CS	LZD ^d

Abbreviations : DR-TB, drug-resistant tuberculosis ; WHO, World Health Organization ; RMP, rifampicin ; INH, isoniazid ; EMB, ethambutol ; PZA, pyrazinamide ; AK, Amikacin ; MFX, moxifloxacin ; LFX, levofloxacin ; ETO, ethionamide ; CS, cycloserine ; PAS, p-aminosalicylic acid ; LZD, linezolid.

^a including abdominal pain, diarrhea, nausea, heatburn.

^b anemia and/or neutropenia and/or lymphopenia, leukocytosis for one case.

^c abnormal platelet aggregation test and/or decrease in P.T. and dependent vitamin K factors.

^d One month of interruption because of hematologic toxicity.

APPENDIX

From *Classification of drugs to treat multidrug-resistant tuberculosis (MDR-TB): evidence and perspectives*.

Rendon A. et al ; J Thorac Dis. 2016 Oct; 8(10): 2666–2671. doi: 10.21037/jtd.2016.10.14

WHO 2011 TB drugs classification		WHO 2016 TB drugs classification	
GROUP 1. First-line oral anti-TB drugs	Isoniazid Rifampicin Ethambutol Pyrazinamide	GROUP A Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
GROUP 2. Injectable anti-TB drugs (injectable or parenteral agents)	Streptomycin Kanamycin Amikacin Capreomycin	GROUP B Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)
GROUP 3. Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin Ofloxacin	GROUP C Other Core Second-line Agents	Ethionamide/ Prothionamide Cycloserine/Terizidone Linezolid Clofazimine
GROUP 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide/Prothionamide Cycloserine/Terizidone p-aminosalicylic acid (Bedaquiline) (Delamanid)	GROUP D Add-on agents (not core MDR-TB regimen components)	D1 Pyrazinamide Ethambutol High-dose isoniazid
GROUP 5. Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB	Linezolid Clofazimine Amoxicillin/Clavulanate Imipenem/Cilastatin Meropenem High-dose isoniazid Thioacetazone Clarithromycin		D2 Bedaquiline Delamanid D3 p-aminosalicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

Anti-TB drugs with future potentialities for upgrade: linezolid, delamanid, bedaquiline, carbapenemics

UFR SCIENCES MEDICALES HYACINTHE BASTARAUD

SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, en présence des maîtres de cette école et de mes condisciples, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité qui la régissent.

Mon premier souci sera, de rétablir, de préserver ou de promouvoir la santé dans tous les éléments physiques et mentaux, individuels collectifs et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou dignité.

Même sous la contrainte, je ne ferai usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients de décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer leurs consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai influencer ni par la recherche du gain ni par la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me sont confiés.

Reçu à l'intérieur des maisons, je respecterai les secrets des foyers.

Et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances, sans acharnement.

Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.

Que je sois modéré en tout, mais insatiable de mon amour de la science.

Je n'entreprendrai rien qui ne dépasse mes compétences ; je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses,

Que je sois déshonoré et méprisé si j'y manque.

NOM : BRUNELIN

PRENOM : Annabelle

Sujet de la thèse : Drug-resistant Tuberculosis in Ile-de-France children under eighteen years of age

Thèse : Médecine - Université des Antilles et de la Guyane

Année 2017

Numéro d'identification :

MOTS-CLES : Tuberculosis, drug-resistant, children, treatment outcome, France.

Introduction

La tuberculose résistante (TBR) chez l'enfant est une préoccupation négligée et les recommandations, fondées sur des preuves scientifiques, concernant la conduite à tenir sont rares. Le diagnostic microbiologique de confirmation est difficile et une grande proportion des cas pédiatriques est ainsi diagnostiquée sur des critères cliniques et anamnestiques. De plus, la littérature n'offre qu'une faible évaluation de la tolérance des traitements anti-tuberculeux de deuxième-ligne chez l'enfant.

Matériel et méthodes

Dans une étude de cohorte descriptive rétrospective menée dans des hôpitaux de Paris et d'île de France, nous avons analysé les aspects démographiques, cliniques, microbiologiques et radiologiques, la prise en charge et l'évolution d'enfants traités pour une TBR. Tous les patients âgés de moins de 18 ans ayant un diagnostic confirmé ou probable ont été inclus du 1er janvier 2011 au 31 décembre 2015 avec un suivi documenté jusqu'au 31 juin 2017. Les données ont été recueillies à partir des dossiers médicaux et de la base de données microbiologiques du CNR-MyrMA. Pour chaque patient, le cas index associé, s'il existait, était décrit. Des définitions standardisées ont été utilisées pour décrire diagnostic de la maladie, effets indésirables et résultats de traitement.

Résultats

Les 24 enfants atteints de TBR inclus avaient un âge médian de 10,7 ans (IQ, 3,4-14,2 ans) avec un sexe ratio 1/1; 3 (12,5%) avaient des antécédents de tuberculose, 17 (70,9%) déclaraient être vaccinés contre le BCG, aucun n'avait le VIH. Douze patients (50,0%) étaient symptomatiques mais la plupart des cas (62,5%) ont été diagnostiqués au cours d'un dépistage systématique. Sur les 16 souches résistantes, 8 (50,0% des souches ; 10 enfants sur 24 soit 41,6%) ont été importées de pays à incidence croissante de TBR.

Treize enfants (54,2%) ont eu un diagnostic confirmé et 11 (45,8%) un diagnostic probable; 15 enfants (62,5%) étaient porteurs de souche MDR, 8 (33,3%) de souches monorésistantes (mDR) à l'isoniazide et 1 (4,2%) d'une souche pré-XDR. Le délai médian entre le diagnostic de confirmation microbiologique et le début de traitement adapté était de 78,0 jours (IQ, 40,5-119,5) pour tous les cas ; onze cas index ont été identifiés et décrits.

Dix enfants (41,7%) ont reçu un traitement injectable et la durée médiane de traitement total était de 12,0 mois (IQR 9,3-16,0) avec 18,6 mois pour le cas de souche pré-XDR, 13,3 mois (IQ, 12,0-18,0) pour les cas porteurs de souches MDR et 8,1 mois (IQ, 6,0-9,3) pour les cas porteurs de souche mDR.

Douze enfants (50,0%) ont été guéris, 11 (45,8%) ont eu une guérison probable ; 5 (20,8%) ont été perdus de vue. Aucun décès n'a été rapporté.

Conclusion

Une TBR ne peut être confirmée dans tous les cas, mais cela ne doit pas retarder le traitement chez l'enfant atteint. Le dépistage systématique autour du cas index et la surveillance des cas-contacts sont nécessaires pour la prise en charge de la TBR chez l'enfant. Plus de 90% des enfants atteints de TBR peuvent être traités avec succès ; cependant des études de pharmacocinétique manquent pour la compréhension du métabolisme de l'enfant et l'adaptation de la posologie des traitements.

JURY :

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SUJET DE LA THESE : Drug-resistant Tuberculosis in Ile-de-France children under eighteen years of age**THESE : MEDECINE****Qualification : Médecine spécialisée : Pédiatrie****ANNEE : 2017****NUMERO D'IDENTIFICATION : 2017ANTI0205****MOTS CLEFS :****Tuberculosis, drug-resistant, children, treatment outcome, France.****RESUME****Introduction**

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