EDITORIAL

Tuberculosis in children. Challenges and opportunities☆

Tuberculosis en niños. Retos y oportunidades

Jose A. Caminero a,b,*, Anna Scardigli c

a Servicio de Neumología, Hospital General de Gran Canaria «Dr. Negrín», Las Palmas, Spain
b Unidad de Tuberculosis Multi-drogo-resistente, División de Tuberculosis, Unión Internacional Contra la Tuberculosis y Enfermedades Respiratorias, París, France
c Fondo Mundial para la Lucha contra el Sida, la Tuberculosis y la Malaria, Ginebra, Switzerland

According to the World Health Organization (WHO), in 2014 there were 1 million of estimated cases of tuberculosis (TB) among children, representing the 10% of the global TB burden, and 136,000 children died because of TB. However, only 6.5% of the total 6 million of cases notified globally were children, thus less than 400,000 paediatric cases.1

Childhood TB in fact is a hidden epidemics: a large proportion of these cases remained undetected, or not reported, and what we see is only the top of the iceberg. For many years, TB control programs have been focused on adults with sputum microscopy smear-positive pulmonary disease, which is the main responsible of TB spread, and have not spent much attention to the unseen world of paediatric TB. Additionally, gaps in reporting paediatric TB cases from public and private health sectors, and weak national age specific surveillance systems in many settings, have contributed to maintain uncertainty about the paediatric TB burden.

The management of TB in children is challenging, first because of the limited and delayed suspicion of TB, due to the lack of specificity of signs and symptoms, and the torpid clinical evolution in this population.

Furthermore, performing an accurate diagnosis is difficult, as the disease in children is generally pauci-bacillary, the sputum is seldom produced, especially by young children, specimens are hard to obtain, and diagnostic tools have limited sensitivity. The diagnosis in most of cases is clinical, and only rarely bacteriologically confirmed. The history of contact with an adult with active disease is a useful information to support the diagnosis, and well-characterized symptoms may help the diagnostic accuracy in older children, while they may be less specific in very young children.

However, rapid molecular tests such as the geneXpert MTB/RIF, which has become widely available in the last few years, have changed the diagnostic landscape of TB. This performs the test, thanks to its sensitivity, much higher than microscopy, in a short time requested (only a couple of hours), and there is no need of sophisticated laboratory infrastructure, as compared to culture. Molecular technology can contribute to improve TB diagnostic in the paediatric population, and recent studies show that it increases two-folds the diagnosis of bacteriologically confirmed TB, compared to microscopy.2

Additionally geneXpert shows a good sensitivity also on extra-pulmonary samples – especially in lymph nodes aspirates and in cerebrospinal fluid, and can contribute to diagnose extra-pulmonary (EP) forms of TB. WHO recommends its use in children suspects of TB meningitis and other

* Corresponding author.
E-mail address: jcamlun@gobiernodecanarias.org
(J.A. Caminero).

2341-2879/© 2016 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. All rights reserved.
forms of EP TB, as lymph nodes TB. Lastly, geneXpert has
the advantage of detecting also the resistance to rifampicin,
and therefore MDR-TB, at the same time of the TB diagno-
sis, and to exclude infections caused by Mycobacteria other
than tuberculosis, since that it only detects M. tuberculosis.

The challenge of getting an appropriate sample to
test remains, but there are interesting experiences show-
ing various combinations of methods to improve specimen
collections that, together with the utilisation of PCR tech-
niques, can change significantly the chance of getting an
accurate diagnosis. In addition to the challenges to diagnose TB disease,
children face various issues also to access appropriate treat-
ment. Not only because of the difficulty in swallowing pills,
but also because of the challenges to achieve the right
dosage and blood concentration, to obtain efficacy of the
therapy and to avoid toxicity. Actually, having a very low
bacillary load, children could be cured with even only three
drugs. In fact a fourth drug, ethambutol, is recommended
only in the case of extensive lesions, and in settings where
there is high level of resistance to isoniazide or of HIV
prevalence. Even in the case of MDR-TB, in the last WHO
2016 guidelines it has been accepted that children can be
treated with a regimen that includes three new drugs, with-
out the need of the second line injectable (WHO) – except
when there is bacteriological confirmation or large lungs
involvement.

The article of Perez et al. addresses very well the chal-
lenes related to the access to appropriate TB treatment in
children, and it provides great insights on the character-
isics of first line anti-TB drugs, and on the implication of
using them in soluble version versus solid pill, and in fixed
dose combination (FDC) versus single drugs. Additionally,
the authors propose pragmatic and concrete recommendations
to make an optimal use of the existing formulations avail-
able in Spain, and advocate for early introduction of new
FDCs.

In fact, child-friendly first line TB formulations have
become recently available in the market, and through the
Global Drug Facility.

Spain reports one of the highest number of childhood TB
cases among the European Countries, with the majority of
them native born, but with an important increase of the
proportion of cases diagnosed among immigrants in the last
decades: from 2% to 46% in a thirty years review.

Knowing the TB burden in the paediatric population,
globally and at country level, is fundamental to encourage
country regulatory authorities to facilitate the process of
introduction of new drugs and preparations, as well as to
serve as an incentive for manufacturers to develop or market
appropriate paediatric formulations. In fact, appropriate
drugs to treat optimally TB in children are essential, espe-
cially in those very young or co-infected with HIV, where
there is a high risk of severe and rapidly disseminating forms
disease.

A large gap still exists in the case of multi-drug resis-
tant and extensively resistant tuberculosis (MDR/XDR-TB),
where formulations adapted to children are not available
yet. This may be not much relevant in Spain, where the per-
centage of primary MDR-TB in the native population seems
very low (0.1% vs. 2.2% of immigrants), but it is very impor-
tant in other countries of the European Region, which seem
to contribute importantly to the burden of paediatric drug-
resistant TB, based on mathematical modelling studies.

Again, a better understanding of the treatments’ needs
would help to forecast markets and to create demand.

Encouragingly, in the recent years there has been an
increased interest on paediatric TB. A roadmap of childhood
TB has been launched, new guidelines have been developed
by the WHO, the number of scientific publications
addressing children and TB is growing every year, and addi-
tionally, more clinical trials on new drugs include children at
earlier stages than before. The paper of Perez et al. con-
tributes greatly to this global interest with pragmatic and
concrete solutions.

Finally, however, it needs to be reminded that if we
want to properly treat children with TB – and to generate
demand for adequate drugs – first we need to find the paedi-
diatric cases. Addressing the challenges of TB diagnosis in
children through better access to more sensitive point of care
diagnostic tools is needed, together with better access to
appropriate treatment. The WHO End TB Strategy sets
ambitious targets, including a substantial reduction of TB
incidence and mortality, and it provides opportunities to
address paediatric TB at large scale.

Conflict of interests

The authors have no conflict of interests to declare, how-
ever the presented content of this article only expresses
the personal opinion of the authors.

References

2. Raizada N, Sachdeva KS, Nair SA, Kulsange S, Gupta RS,
   Thakur R, et al. Enhancing TB case detection: experience in
   offering upfront Xpert MTB/RIF testing to pediatric presump-
   tive TB and DR TB cases for early rapid diagnosis of drug
   http://dx.doi.org/10.1371/journal.pone.0105346.
   programmes on the management of tuberculosis in children.
   Performance of Xpert MTB/RIF and alternative specimen collec-
   tion methods for the diagnosis of tuberculosis in HIV-infected
5. WHO. WHO treatment guidelines for drug-resistant tuberculo-
6. Piñeiro Pérez R, Santiago Garcia B, Rodríguez Marrodán B,
   Baquero-Artigao F, Fernández- Llamazares CM, Gorette López-
   Ramos M, et al. Recomendaciones para la elaboración y
   administración de fármacos antituberculosos en niños. Segunda
   fase del Proyecto Magistral de la Red Española de Estudio de
   la Tuberculosis Pediátrica (pTBréd). An Pediatr (Barc).
   int/tb/areas-of-work/children/
8. Seddon J, Shingadia D. Epidemiology and disease burden of
tuberculosis in children: a global perspective. Infect Drug
Tuberculosis in children. Challenges and opportunities


