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EDITORIAL

Tuberculosis in children. Challenges and opportunities☆

Tuberculosis en niños. Retos y oportunidades

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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

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forms of EP TB, as lymph nodes TB.[3] Lastly, geneXpert has the advantage of detecting also the resistance to rifampicin, and therefore MDR-TB, at the same time of the TB diagnosis, 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 showing various combinations of methods to improve specimen collections that, together with the utilisation of PCR techniques, can change significantly the chance of getting an accurate diagnosis.[4]

In addition to the challenges to diagnose TB disease, children face various issues also to access appropriate treatment. Not only because of the difficulty in swelling 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.[3] 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, without the need of the second line injectable (WHO) – except when there is bacteriological confirmation or large lungs involvement.[5]

The article of Perez et al.[6] addresses very well the challenges related to the access to appropriate TB treatment in children, and it provides great insights on the characteristics 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 available 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.[7]

Spain reports one of the highest number of childhood TB cases among the European Countries, with the majority of them native born,[8] 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.[9]

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.[10] In fact, appropriate drugs to treat optimally TB in children are essential, especially in those very young or co-infected with HIV, where there is a high risk of severe and rapidly disseminating forms of disease.

A large gap still exists in the case of multi-drug resistant 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 percentage of primary MDR-TB in the native population seems very low (0.1% vs. 2.2% of immigrants),[11] but it is very important 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.[12]

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,[4] the number of scientific publications addressing children and TB is growing every year, and additionally, more clinical trials on new drugs include children at earlier stages than before.[13] The paper of Perez et al.[6] contributes 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 paediatric 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[14] sets ambitious targets, including a substantial reduction of TB incidence and mortality, and it provides opportunities to address paediatric TB at large scale.[15]

Conflict of interests

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

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