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Research letter

Availability of fixed-dose, child-friendly formulations of first-line tuberculosis drugs in Europe

Antoni Noguera-Julian, Danilo Buonsenso, Lindsay Mckenna, James A. Seddon, Nicole Ritz

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Availability of fixed-dose, child-friendly formulations of first-line tuberculosis drugs in Europe

[1-4]Antoni NOGUERA-JULIAN*

[5-7]Danilo BUONSENSO*

[8]Lindsay MCKENNA

[9-10]James A. SEDDON

[11-13]Nicole RITZ

*Both authors share credit for 1st authorship

[1]Infectious Diseases and Systemic Inflammatory Response in Pediatrics, Infectious Diseases Unit, Department of Pediatrics, Sant Joan de Déu Hospital Research Foundation, Barcelona, Spain.

[2]Center for Biomedical Network Research on Epidemiology and Public Health (CIBERESP), Madrid, Spain.

[3]Department of Pediatrics, University of Barcelona, Barcelona, Spain.

[4]Translational Research Network in Pediatric Infectious Diseases (RITIP), Madrid, Spain.

[5]Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.

[6]Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy.

[7]Center for Global Health Research and Studies, Università Cattolica del Sacro Cuore, Rome, Italy.

[8]Treatment Action Group, New York, United States.

[9]Department of Infectious Diseases, Imperial College, London, United Kingdom.

[10]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa.

[11]Infectious Diseases Unit and Migrant Health Service, University Children's Hospital Basel, University of Basel, Basel, Switzerland.

[12]Department of Biomedicine, University of Basel, Basel, Switzerland.

[13]Department of Paediatrics, The University of Melbourne, Parkville, Australia.

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Corresponding Author:
Dr. Nicole RITZ
University of Basel Children's Hospital, Migrant Health Service, Spitalstrasse 33, 4056 Basel, Switzerland
e-mail: nicole.ritz@unibas.ch
Phone number: +41 61 704 12 12

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"Take home" message:
The paediatric fixed-dose combinations of TB drugs are not available in Europe, where the pill burden and palatability of paediatric TB treatment is not acceptable. Facilitating the introduction of child-friendly TB drugs into Europe is urgently needed.

Introduction

The administration of drugs for the treatment of tuberculosis (TB) in children can be time-consuming and challenging, and non-adherence is a major cause of treatment failure[1]. Several factors may contribute to non-adherence, including lack of paediatric formulations, pill burden, fasting requirements, palatability, length of therapy or toxicity. Recently, the World Health Organization (WHO) has pushed for the development of child-friendly TB medicines that meet the dosage guidelines set in 2009[2]. These should include child-friendly fixed-dose combinations (pFDC) of first-line oral TB drugs, which are dispersible, palatable, simple to administer and affordable[3]. Some of these pFDC have been developed and produced by Macleods (India) and Micro Labs (India), are WHO-prequalified (WHO Prequalification of Medicines Programme, PQP) and were included in the 6th edition of the WHO Essential Medicines List for Children in 2017[4].

It is recommended that the new pFDC replace previously used medicines for children weighing less than 25 kg[3]. Countries can access these new preparations through the Global Drug Facility (GDF). Up to 116 countries from many regions in the world are already routinely treating children with the new pFDC[5,6]. However, these medicines are not licensed by the European Medicines Agency (EMA) for distribution in Europe, where pFDC could be evaluated through a centralised authorisation process, or at a national level, to be later authorised in other European Union member states.

We aimed to assess the availability of licensed first-line oral paediatric TB drug formulations in Europe, to investigate current practices regarding the choice and method of delivery of TB drugs and to assess knowledge and experience of the pFDC in Europe.

Methods

We conducted a web-based survey among the members of the Paediatric Tuberculosis Network European Trials Group (ptbnet; http://www.tb-net.org/index.php/ptbnet) based in Europe over a 2-month period (November to December 2019). At the time of the survey, most of the members (245 out of 276, 88.8%) were based in Europe. All network members were contacted by email and invited to complete the survey online. In addition, we asked a senior clinician from each European country in the ptbnet to complete a template with data on all available licensed formulations of first-line oral TB drugs in his/her country, including single drug formulations and FDC. As per Spanish regulations, Research Ethics Committee

review is not required for research involving healthcare staff recruited as research participants by virtue of their professional role.

Results

A total of 84/245 (34.3%) healthcare professionals from 26 European countries participated in the survey and answered all questions. Of the respondents, 74 (88.1%) classified themselves as 'senior doctors' (consultant or above), with 63 (75.0%) working in university hospitals.

Data on all available licensed formulations of first-line oral TB drugs were collected from 25 European countries (***Table***). Tablets were the only formulation licensed in Europe for isoniazid (dosages range: 50-300 mg), pyrazinamide (150-500mg) and ethambutol (100-500mg). A rifampicin suspension was available in 13 countries (52.0%); rifampicin was also available as tablets (75-600mg) and capsules (150-450 mg). Dispersible tablets were not available anywhere. Adult FDC were available in 19 out of 25 countries.

Regarding drug administration, respondents advised caregivers to halve or cut (78.6%), crush (76.2%), chew (21.4%) or mix the tablets with food, other than water (48.8%). A period of fasting before (75.0%; ranging from 20 minutes to overnight fasting) and after (57.1%;15-120 minutes) the administration of TB drugs was also recommended.

Other than licensed TB drug formulations, respondents used suspensions (42.9%) or weight-adapted powder capsules (13.1%) prepared *ad hoc* by pharmacies, adult FDC (39.3%) or imported dispersible drugs (13.1%). Among those prescribing adult FDC, most stated that they were using them as soon as the child was able to swallow them, irrespective of patient´s age or weight.

Most respondents (75.0%) were aware of the new dispersible pFDC and 24 (28.6%) of them had tried to obtain them. Among this group, only 7 (29.2%) had succeeded, including one institution in Bulgaria and another in the Russian Federation that had obtained pFDC through the GDF. Three institutions in the United Kingdom had managed to obtain them permanently, and one further institution in the United Kingdom and another in Austria had obtained pFDC to treat individual patients. The barriers encountered to import the pFDC included lack of support from the national TB program/drug regulators due to lack of EMA marketing

authorization, laborious import processes and paperwork, import-associated costs, long standard lead time (range: 2-6 months), and limitations on the amount of drug provided.

Discussion

Our study shows that rifampicin suspension is the only licensed child-friendly formulation available in Europe. Notably, a pharmacokinetic study has reported low drug concentrations with the use of rifampicin suspensions at recommended dosages[7]. In this context, paediatricians are forced to use several off-label alternatives to support children, which potentially lead to reduced or increased final dosage, with unknown effects on treatment outcomes and toxicity[1,8]. Unlicensed preparations of first-line TB drugs are often used, including *ad hoc* formulations prepared by pharmacies, and adult FDC[9]. Of note, the ratios of drugs dosages in adult FDC do not align with the ratios recommended in the WHO guidelines for pFDC[2].

The pill burden of licensed formulations to treat paediatric TB in Europe today is not acceptable. Our results suggest that formulations are not palatable either, although studies addressing this question are scarce. The pFDC of TB drugs have been developed to overcome these barriers and improve adherence. Treatment with pFDC consists of fewer tablets, which are dispersible but may be given in solid form, have palatable fruit flavours and facilitate the administration supported by parents or caregivers. Initial experiences with the new pFDC in South Africa have been reported favourably[10].

A key limiting factor for access to TB pFDC is related to the legislation around the licensing process for new formulations in Europe. The respondents to our survey reported lack of support from the national TB program/drug regulators, laborious administrative tasks and import-associated costs among the barriers encountered to obtain the pFDC, making the whole process "resource-intensive, complicated and unsustainable"[11]. All of these could be minimized if the formulations were licensed by the EMA. It seems paradoxical that these drugs are not licensed by the EMA, considering that Europe has pushed for and assisted with the financing of the development and pre-qualification of these new formulations through the WHO, Unitaid, and the TB Alliance. In fact, the EMA cooperates with the WHO in providing scientific opinions on high priority human medicines "to the same rigorous standards as medicines intended for use in Europe" to facilitate prequalification of the medicine by WHO

under the EU-Medicines for all procedure[12]. Therefore, the licensure of pFDC for TB treatment in Europe would seem logical and desirable.

In the past 15 years, the EMA and the United States Food and Drug administration (FDA) have been working in close collaboration on a harmonized approach to paediatric drug development plans[13]. However, the EMA, the FDA and other regulatory agencies from high-income countries (e.g. Canada, Australia and Japan) do not mutually recognise the WHO Prequalification of Medicines Programme (PQP), a process that evaluates the quality of medicines. We are not aware of any companies producing pFDC having filed an application to the EMA yet. They have instead opted only for WHO PQP, which in their view may be more cost effective and offer access to the global market. Relative to the latter, the market for pFDC in Europe is small and fragmented, existing regulatory incentives (e.g. orphan medicines status) cannot be applied to the pFDC because adult generic FDC are already available, and regulatory pathways (e.g. centralised authorization through Pediatric Use Marketing Authorization), intended to persuade manufacturers to register paediatric TB formulations in Europe, appear to have failed to overcome the required cost and efforts of doing so for the pFDC[11]. As an example of the latter, the manufacturers are asked to redevelop the products to match EMA guidelines or to adapt to individual countries requirements in terms of packaging.

To promote equitable access to the pFDC, the EMA, in coordination with other regulatory agencies and the WHO PQP, should explore the establishment of new types of reliance mechanisms for paediatric medicines as described in the draft document *WHO Good Reliance Practices in Regulatory Decision Making for Medical Products*[14], or special waivers (inclusive of any fees) for paediatric formulations not registered locally that meet predefined quality criteria. In the meantime, the EMA and the European Member States' regulatory authorities should establish easy mechanisms to facilitate the administrative procedures to request access to the pFDC where they are not yet authorized.

In conclusion, children with TB in high-income countries are unable to benefit from access to the new pFDC, mainly because of regulatory barriers. Our findings highlight the urgent need to facilitate the introduction of child-friendly TB drugs into Europe.

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References

1. Piñeiro Pérez R, Santiago García B, Fernández Llamazares CM, Baquero Artigao F, Noguera Julian A, Mellado Peña MJ. The challenge of administering anti-tuberculosis treatment in infants and pre-school children; Magistral Project of the Spanish Network for the Study of Paediatric Tuberculosis (pTBred). An Pediatr (Barc) 2016; 85: 4-12.
2. World Health Organization 2009. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. World Health Organization 2009; Geneva, Switzerland. Available at: http://www.who.int/entity/tb/challenges/interim_paediatric_fdc_dosing_instructions_sept09.pdf. Date last accessed: April 2 2021.
3. World Health Organization and UNICEF. Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children. Geneva, Switzerland: WHO, 2017. Available at: www.who.int/tb/areas-of-work/children/WHO_UNICEFchildhoodTBFDCs_ Statement.pdf. Date last accessed: April 2 2021.
4. World Health Organization 2017. WHO model list of essential medicines for children: 6th list (March 2017, amended August 2017), 6th ed. World Health Organization 2017; Geneva, Switzerland. Available at: https://apps.who.int/iris/handle/10665/273825. Date last accessed: April 2 2021.
5. Faust L, Abdi K, Davis K, He C, Mehrotra C, Stibolt E. The roll-out of child-friendly fixed-dose combination TB formulations in high-TB-burden countries: a case study of STEP-TB. J Epidemiol Glob Health 2019; 9: 210-216.
6. Maleche-Obimbo E, Wanjau W, Kathure I. The journey to improve the prevention and management of childhood tuberculosis: the Kenyan experience. Int J Tuberc Lung Dis 2015; 19: 39-42.
7. Bekker A, Schaaf HS, Draper HR, van der Laan L, Murray S, Wiesner L, Donald PR, McIlleron HM, Hesseling AC. Pharmacokinetics of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Dosed According to Revised WHO-Recommended Treatment Guidelines. Antimicrob Agents Chemother 2016; 60: 2171-2179.
8. Dooms M, Carvalho M. Compounded medication for patients with rare diseases. Orphanet J Rare Dis 2018; 13 :1.
9. Piñeiro Pérez R, Santiago García B, Rodríguez Marrodán B, Baquero-Artigao F, Fernández-Llamazares CM, Goretti López-Ramos M, Vinent Genestar J, Gómez-Pastrana Durán D, Mellado Peña MJ. Recommendations for the preparation and

administration of antituberculosis drugs in children; second phase of the Magistral Project of the Spanish Network for the Study of Paediatric Tuberculosis (pTBred). An Pediatr (Barc). 2016; 85: 323.e1-323.e11.

10. Wademan DT, Busakwe L, Nicholson TJ, van der Zalm M, Palmer M, Workman J, Turkova A, Crook AM, Thomason MJ, Gibb DM, Seeley J, Hesseling A, Hoddinott G. Acceptability of a first-line anti-tuberculosis formulation for children: qualitative data from the SHINE trial. Int J Tuberc Lung Dis 2019; 23: 1263-1268.
11. Nash M, Perrin C, Seddon JA, Furin J, Hauser J, Marais B, Kitai I, Starke J, McKenna L. Access to paediatric formulations for the treatment of childhood tuberculosis. Lancet Child Adolesc Health 2020; 4: 855-857.
12. European Medicines Agency. Medicines for use outside the EU — EU-M4all. Promoting the development of medicines and vaccines for patients in low- and EMA middle-income countries outside the European Union (EU); 2020. Available at: https://www.ema.europa.eu/en/documents/leaflet/infographic-medicines-use-outside-eu-eu-m4all_en.pdf. Date last accessed: April 2 2021.
13. Thomsen MDT. Global Pediatric Drug Development. Curr Ther Res Clin Exp 2019; 90: 135-142.
14. World Health Organization 2020. Good reliance practices in regulatory decision-making for medical products: high-level principles and considerations. Working document QAS/20.851/Rev.1; August 2020. World Health Organization 2020; Geneva, Switzerland. Available at: https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_Rev_1_Good_Reliance_Practices.pdf?ua=1. Date last accessed: May 10 2021.

Table. Licensed formulations of oral first-line anti-tuberculosis drugs available in Europe for the treatment of tuberculosis in children. Doses are in mg unless stated otherwise.

	Isoniazid (mg)	**Rifampicin (mg)**	**Pyrazinamide (mg)**	**Ethambutol (mg)**	**Fixed-dose combinations, doses in mg (age in years; weight in kg from which its use is approved)**
Austria	sTb (100)	sTb (450, 600) Tb (450) Cp (150, 300) Susp (20mg/mL)	sTb (500)	sTb (500)	H150/R300 (14; 40)
Belgium	Tb (300)	Cp (150, 300)	Tb (500)	Tb (400)	None available
Bulgaria	Tb (50, 75)	Tb (75, 150)	Tb (150, 400)	Tb (100,275)	None available
Croatia	sTb (100, 200, 300)	Cp (300)	Tb (500)	Tb (400)	H75/R150/Z400/E275 (8; 30)
Denmark	sTb (300)	Tb (150, 300) Susp (20mg/mL)	sTb (500)	Tb (400)	H75/R150/Z400/E275 (8; 30) H75/R150 (6; 30)
Finland	Tb (50) sTb (300)	Tb (450, 600) Susp (20mg/mL)	sTb (500)	Tb (100) sTb (500)	None available
France	Tb (50, 150)	Cp (300) Susp (20mg/mL)	Tb (500)	Tb (400, 500)	H50/R120/Z300 (6; 40) H150/R300 (adults only)
Germany	sTb (50, 100, 200, 300)	Tb (150, 300, 450, 600) Susp (20mg/mL)	sTb (250, 500)	sTb (100, 400)	H50/R120/Z300 (15; 30) H150/R300 (15; 40)
Greece	Tb (100)	Cp (300) Susp (20mg/mL)	sTb (500)	Tb (500)	H150/R300 (12; 50)
Iceland*	sTb (300)	Cp (150, 300)	NA	NA	None available
Ireland	NA	Cp (150, 300) Susp (20mg/mL)	NA	Tb (100, 400)	H50/R120/Z300 (adults only) H100/R150 (adults only) H150/R300 (adults only)
Italy	sTb (200)	Cp (150, 300, 450) Susp (20mg/mL)	Tb (500)	Tb (400)	H50/R120/Z300 (12; NS) H100/R150 (adults only) H150/R300 (adults only)
Latvia	Tb (100, 300)	Cp (150, 300)	sTb (500)	sTb (400)	None available
Lithuania	sTb (100)	Cp (150, 300)	sTb (500)	sTb (400)	H100/R150 (adults only) H150/R300 (adults only)
The Netherlands	Tb (200)	Tb (600) Cp (150, 300) Susp (20mg/mL)	Tb (500)	Tb (400)	H150/R300 (12; 50)
Norway	Tb (100)	Tb (150,300)	NA	NA	H75/R150/Z400/E275 (8; 30) H75/R150 (6; 30)
Portugal	sTb (50, 300)	Cp (300) Susp (20mg/mL)	sTb (500) Cp (500)	sTb (400)	H50/R120/Z300 (adults only) H100/R150 (adults only) H150/R300 (adults only)
Romania	Tb (100, 300)	Tb (150, 300)	Tb (500)	Tb (250, 400)	H150/R300 (NS; NS)
The Russian Federation	sTb (100, 150, 200, 300)	Cp (300)	sTb (500)	sTb (400)	H60/R120/Z300/E225 (13; 30) H150/R150/Z375 (13; NS) H150/Z500 (NS; NS) H150/E400 (NS; NS)
Slovakia	sTb (100)	Cp (150, 300)	Tb (500)	Tb (400)	None available
Slovenia	sTb (50)	Tb (300, 450) Cp (150, 300)	sTb (500) Tb (500)	Tb (400)	H50/R120/Z300 (adults only) H100/R150 (adults only) H150/R300 (adults only)
Spain	sTB (50, 150, 300)	Tb (300) Cp (300) Susp (20mg/mL)	Tb (250)	Tb (400)	H75/R150/Z400/E275 (8; 30) H50/R120/Z300 (NS; 40) H150/R300 (12; 50)
Sweden	sTb (300)	Cp (150, 300) Susp (20mg/mL)	sTb (500)	Tb (400)	H75/R150/Z400/E275 (8; 30) H75/R150/Z400 (NS; 30) H75/R150 (NS; 30)
Switzerland	sTb (100, 200)	Tb (100, 450, 600) Cp (150, 300)	Tb (500)	Tb (100, 400)	H75/R150/Z400/E275 (8; 30) H50/R120/Z300 (NS; 30) H75/R150 (8; 30) H100/R150 (adults only)
United Kingdom	Tb (50, 100, 300)	Cp (150, 300) Susp (20mg/mL)	Tb (500)	Tb (100, 400)	H75/R150/Z400/E275 (NS; 30) H50/R120/Z300 (adults only) H100/R150 (adults only) H150/R300 (adults only)

Abbreviations: Cp, capsule; E, ethambutol; H, isoniazid; NA, not available; NS, not specified; R, rifampicin; sTb, scored tablet; Susp, suspension; Tb, tablet; Z, pyrazinamide.
*Pyrazinamide Tb (500) and ethambutol Tb (400) are not licensed but are available for prescribing.