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SPECIAL ARTICLE

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)☆

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Abstract The Spanish Network for the Study of Paediatric Tuberculosis has shown a lack of national consensus on the treatment of tuberculosis in children, partly due to the unavailability of paediatric presentations of antituberculosis drugs. The harmonisation of tuberculosis treatment in children is a priority in Spain. A joint action is proposed by a group of Spanish experts in childhood tuberculosis and in the area of Paediatric Pharmacology. To this end, a pTBred-led workgroup of members from five scientific bodies has been created. Drug pharmaceutical compounding in oral suspensions or oral solutions are recommended as follows: isoniazid 50 mg/mL, pyrazinamide 100 mg/mL, and ethambutol 50 mg/mL. Raw materials, period of validity, and storage conditions are specified. Recommendations for the use of fixed-dose combination drugs

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are also established. If oral solutions/suspensions or fixed-dose combination drugs are not appropriate, the use of crushed tablets is recommended. Adherence to treatment and optimal dosing of antituberculosis drugs are critical in the control and eradication of TB. This multidisciplinary document provides an opportunity to promote the appropriate treatment of paediatric tuberculosis in Spain, and should become a useful tool for paediatricians and pharmacists.

PALABRAS CLAVE
Tuberculosis;
Niños;
Guía de práctica clínica;
Fármacos antituberculosos;
Formulación magistral

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 (pTBred)

Resumen La Red Española de Estudio de la Tuberculosis Pediátrica ha evidenciado una falta de consenso nacional en la administración de antituberculosos en niños, propiciada por la escasez de presentaciones pediátricas específicas. Es prioritario homogeneizar el tratamiento de la tuberculosis en niños en nuestro país. Un grupo de expertos españoles en tuberculosis infantil y en el área de medicamentos pediátricos proponen una actuación conjunta, con la finalidad de mejorar esta situación en nuestro medio. Para ello se constituye un Grupo de Trabajo, liderado por pTBred, en el que participan otras 5 sociedades e instituciones científicas. Se proponen las siguientes fórmulas magistrales en forma de suspensión o solución oral para el tratamiento de la tuberculosis en niños: isoniacida 50 mg/ml, pirazinamida 100 mg/ml y etambutol 50 mg/ml. Se especifican materias primas, periodo de validez y condiciones de conservación y administración. Se establecen recomendaciones para el uso de fármacos combinados a dosis fijas. Si no se consigue la dosis apropiada mediante fármacos combinados a dosis fijas, y no se dispone de fórmula magistral, se recomienda la administración mediante comprimidos triturados. El adecuado cumplimiento terapéutico y la administración de dosis óptimas de los fármacos antituberculosos constituyen pilares fundamentales en el control y erradicación de la enfermedad. La oportunidad de disponer de este documento multidisciplinar en España favorecerá el correcto tratamiento de la tuberculosis pediátrica, y será una guía útil para todos los pediatras y farmacéuticos que lo precisen.

Introduction and state of the art

The formulation of paediatric drugs continues to be a world challenge, especially in diseases like tuberculosis that call for prolonged combined therapies with adequate adherence.[1] In this document, a group of Spanish experts in childhood tuberculosis and paediatric pharmacology propose several strategies that could help facilitate the treatment of children with tuberculosis in Spain.

Between February and March 2015, the Spanish Network for the Study of Paediatric Tuberculosis (Red Española de Estudio de la Tuberculosis Pediátrica [pTBred])[2] carried out the first phase of the Magistral Project,[1] a survey focused on learning how antituberculosis drugs are administered to children in Spain. The survey was sent to all the member institutions of the Network. The results evinced a lack of nationwide consensus in the administration of antituberculosis drugs in children, which was promoted by the scarcity of preparations specifically formulated for children. Most paediatricians prescribe tablets that need to be crushed and dissolved, while the rest prescribe compounded formulations (CFs) whose preparation and concentration vary between pharmacy departments in different hospitals.[1]

The heterogeneity in the administration of these drugs could compromise the strict adherence required in the treatment of tuberculosis. In light of this situation, the pTBred proposed the elaboration of a pioneering document on the administration of antituberculosis drugs in the paediatric age group, with special emphasis on children that cannot swallow solid dosage forms.[1] This document focuses on the preparation of suspensions of isoniazid, pyrazinamide and ethambutol, as liquid dosage forms are the most child-friendly. It does not include rifampicin because it is the sole first-line antituberculosis drug that is commercially available as a suspension.[3] Furthermore, this document contemplates the possibility of using paediatric dosage forms with fixed concentrations of antituberculosis agents in the doses required by children adjusted by kilogram of body weight. This document was developed and agreed on by the main experts in tuberculosis and paediatric pharmacology in Spain, and is supported by renowned scientific associations.

Compounded isoniazid formulation

Isoniazid is a drug with a high solubility in water,[4] incompatible with sugars such as sucrose,[5] and most stable at a pH of 6.[6] Supplementation with pyridoxine is recommended in children that are malnourished, HIV-positive patients, exclusively-breastfed infants and pregnant women due to the interaction of isoniazid with the metabolism of this vitamin.

Isoniazid is not commercially available as oral suspension in Spain, but it is in other countries, and it can be procured as an imported drug at a concentration of 10 mg/mL. This concentration is recommended in different formularies,[7,8] and is the one most frequently prepared in CFs. However, in children that weigh more than 5 kg and are unable to swallow commercially available tablets, this concentration results in the administration of high volumes of suspension.

The CFs included in the reference formularies in Spain use sorbitol as an excipient.[7,8] However, its use at high doses can result in intolerance and have an osmotic laxative effect.[7,9] A more concentrated formulation (50 mg/mL) would allow the administration of smaller volumes with a reduced amount of sorbitol, which would facilitate dosing and adherence while reducing the risk of potential adverse effects associated with the excipients.

Due to the ease of its preparation, its excipient compatibility and its potential to improve adherence to treatment, we recommend the preparation of the CF at a concentration of 50 mg/mL. Table 1 presents the formulation for both concentrations. The drug should be compounded using the raw chemical rather than commercially available preparations, as reduced activity has been observed with the use of the latter due to their lactose content.[10] We recommend that its administration is routinely combined with vitamin B_6 supplementation.

Table 1 Compounded isoniazid formulations. Consensus document.

Isoniazid 10 mg/mL Oral solution
Isoniazid 1 g Sorbitol 70% 50 mL solution Preserved water q.s. to 100 mL Contains sorbitol (0.35 g/mL), methylparaben and propylparaben Beyond-use date: 30 days Storage: refrigerated, protected from light and air
Isoniazid 50 mg/mL Oral solution
Isoniazid 5 g Sorbitol 70% 50 mL solution Preserved water q.s. to 100 mL Contains sorbitol (0.35 g/mL), methylparaben and propylparaben Beyond-use date: 30 days Storage: refrigerated, protected from light and air

Compounded pyrazinamide formulation

Pyrazinamide is obtained as a white crystalline powder with a low solubility in water. It forms suspensions that sediment easily and can be resuspended with shaking. Pyrazinamide is not commercially available as oral suspension in Spain,[11] but it is in other countries with a concentration of 50 mg/mL.

The preparation of a pyrazinamide suspension at a concentration of 10 mg/mL is included in some formularies,[12] although the CF provided most frequently as a reference in different formularies in Spain and other countries has a concentration of 100 mg/mL.[7,12–14] This is the CF proposed in this document (Table 2) due to its easy preparation and the vast documentation available for it. The raw chemical is the first choice for the starting material, although it could also be prepared using commercially available tablets, as has been done in stability studies of pyrazinamide formulations.[13]

Compounded ethambutol formulation

Ethambutol hydrochloride is a white crystalline powder that is hygroscopic, odourless and bitter in taste.[4,15–17] A 2% aqueous solution has a pH of 3.7–4. It is optically active, as it has two chiral carbons. Ethambutol is the name given to the dextrorotatory isomer. The levorotatory isomer is inactive and has been associated with optic neuropathy.[15] Ethambutol has displayed good bioavailability following oral intake and it is excreted in urine mostly unaltered.[16]

No oral liquid formulations are commercially available in the world. In Spain, the only commercially available formulation consists of 400 mg tablets, which are difficult to cut or disperse. Tablets containing 100 mg are available in other countries.[17]

Most CFs of ethambutol have concentrations of 25, 50 or 100 mg/mL, and are prepared with the raw powder or commercial tablets depending on the availability of these starting materials.[18–20] Table 3 presents the CF (with a concentration of 50 mg/mL) recommended in this document.[18–21]

Combined compounded formulations. Are they possible?

Due to the pathophysiology of tuberculosis, a combination of several drugs is required to cure the disease and prevent the development of drug resistance.

Table 2 Compounded pyrazinamide formulation. Consensus document.

Pyrazinamide 100 mg/mL Oral suspension
Pyrazinamide 10 g Simple syrup q.s. to 100 mL Contains sucrose (0.8 g/mL) Beyond-use date: 30 days Storage: refrigerated or at room temperature. Protected from light Shake before use

Table 3 Compounded ethambutol formulation. Consensus document.

Ethambutol 50 mg/mL Oral solution
Ethambutol 5 g Citric acid monohydrate 0.3 g Sterile water 30 mL Simple syrup q.s. to 100 mL Contains sucrose (0.6 g/mL) Beyond-use date: 30 days Storage: room temperature Shaking before use is not necessary

Promoting the development of formulations that would facilitate adherence to treatment is absolutely justified in the paediatric population. Ideally, a combined formulation of the main first-line oral antituberculosis drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) would become available. However, this objective poses numerous challenges.

Compounded formulations prepared as oral solutions have shorter beyond-use dates, as active ingredients degrade faster in solution or suspension than in solid dosage forms, and there may be problems of compatibility or interactions between their components. Currently, the number of liquid formulations with two or more active ingredients that are commercially available in the world is insignificant.

Antituberculosis drugs have different physical and chemical characteristics. Isoniazid is incompatible with sugars such as sucrose and the recommended medium is a sorbitol solution.[7,8] Its solubility in water is much higher than those of ethambutol and pyrazinamide, and it can form aqueous solutions. Pyrazinamide is the least soluble in water, and forms a suspension. Pyrazinamide and ethambutol can be prepared with sucrose.[15,22]

We did not find any evidence in the literature on the physical and chemical stability of preparations that combine three or four antituberculosis drugs in solution or suspension. These data are needed to guarantee the quality and safety of such formulations, especially in treatment regimens as complicated as those required for tuberculosis, and in populations as vulnerable as the paediatric age group.

In some countries, kits that include three drugs prepared separately in liquid form[23] are commercially available. From a compounding perspective, the preparation and standardisation in mg/mL of liquid single-component antituberculosis drugs would be the most appropriate strategy for the paediatric population, as well as the safest in terms of absorption. The challenge in this approach is the optimisation of the volumes of each drug to be administered based on the age of the patient while preserving the physical and chemical stability of each agent. Such kits are not available in Spain.

Fixed-dose combinations in paediatrics

Pharmaceutical preparations that combine two, three or four antituberculosis drugs in a single tablet (fixed-dose combinations [FDCs]) have clear advantages compared to the separate administration of individual drugs. They promote adherence and minimise dosing errors, thus decreasing the risk of treatment failure and the selection of resistant strains. However, their manufacturing poses considerable technical challenges. In recent years, it has become possible thanks to the development of sophisticated infrastructures in pharmaceutical laboratories.[24]

Several pharmacokinetic studies have shown that the dose of antituberculosis drugs per kilogram of body weight must be higher in children than the corresponding dose in adults.[25–27] These findings, along with the low toxicity of antituberculosis drugs described in the paediatric population,[28] provided the basis for the updated dosage recommendations of the WHO for the use of these agents in children in 2010[29] (Table 4). These are the doses currently recommended by the Committee on Medicinal Products of the Spanish Association of Paediatrics.[30] In 2014 the WHO updated its recommendations once again, reducing the minimum recommended dose of isoniazid to 7 mg/kg to facilitate the development of paediatric FDCs.[31]

The dosing of antituberculosis FDCs available in Spain is based on the therapeutic dosage range used in adults, and these drugs are only authorised for their use starting at a certain age and/or weight (Table 5). Their off-label use in younger children often requires cutting or crushing the tablets, which carries the risk of altering drug bioavailability and especially of administering inadequate doses—suboptimal or excessive—of some of the components.

When FDCs are used within the age and weight ranges authorised in their summaries of product characteristics,

Table 4 Paediatric doses of first-line antituberculosis drugs based on the recommendations of the WHO.

Recommended daily dose in mg/kg (range)	Dose (range) in mg/day per kg body weight						
	5 kg	10 kg	15 kg	20 kg	30 kg	40 kg	50 kg
INH 10 (7–15)	50 (35–75)	100 (70–150)	150 (105–225)	200 (140–300)	300 (210–300)	300 (280–300)	300
RIF 15 (10–20)	75 (50–100)	150 (100–200)	225 (150–300)	300 (200–400)	450 (300–600)	600 (400–600)	600
PZA 35 (30–40)	175 (150–200)	350 (300–400)	525 (450–600)	700 (600–800)	1050 (900–1200)	1400 (1200–1600)	1750 (1500–2000)
ETH 20 (15–25)	100 (75–125)	200 (150–250)	300 (225–375)	400 (300–500)	600 (450–750)	800 (600–1000)	1000 (750–1250)

ETH, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampicin.

Table 5 FDCs available in Spain.

Commercially available FDCs	2-component INH:RIF (Rifinah®)	3-component INH:RIF:PZA (Rifater®)	4-component INH:RIF:PZA:ETH (Rimstar®)
Composition (mg) INH:RIF:PZA:ETH	150:300	50:120:300	75:150:400:275
Preparation	Coated tablets	Coated tablets	Coated tablets
Indication in summary of product characteristics (age and weight)	>12 years >50 kg	>12 years	>8 years >30 kg
Tablets/day in Summary of product characteristics	2 tablets	<40 kg: 3 tablets 40–49 kg: 4 tablets 50–64 kg: 5 tablets >65 kg: 6 tablets	30–37 kg: 2 tablets 38–54 kg: 3 tablets 55–70 kg: 4 tablets >70 kg: 5 tablets

ETH, ethambutol; FDC, fixed-dose combination; INH, isoniazid; PZA, pyrazinamide; RIF, rifampicin.

only Rifinah® (isoniazid + rifampicin) is used in compliance with the paediatric doses recommended by the WHO. Conversely, the available three- and four-component FDCs do not reach the recommended dose of isoniazid, which should be corrected by the supplementary administration of this drug. Increasing the number of FDC tablets to reach the therapeutic range for isoniazid would result in the administration of excessive doses of ethambutol with Rimstar®, or rifampicin and pyrazinamide with Rifater®. In 2009, the WHO established recommendations for the use of FDCs in children based on weight, and noted that none of the combinations available at the time were appropriate for use in the paediatric age group.[32]

The development of FDCs for exclusive use in children require the adjustment of dosing to paediatric safety and efficacy ranges and to facilitate administration by the use of liquid or dispersible preparations. Liquid dosage forms are easier to administer, but dispersible tablets have advantages in areas with poor resources, as they simplify their conservation, transport and storage. The addition of sweeteners and flavourings, which is often needed to improve palatability, carries a risk of interaction with active ingredients.[33]

After resolving these problems, the TB Alliance and the WHO, in collaboration with UNITAID and USAID, promoted the development and distribution of the first FDCs appropriate for the treatment of tuberculosis[34,35] in children weighing less than 25 kg. They are dispersible tablets that contain 50 mg isoniazid, 75 mg rifampicin and 150 mg pyrazinamide for the induction phase, and the same dosing without pyrazinamide for the maintenance phase (Table 6). The tablets are small, dissolve readily in water, and have a pleasant taste. The formulation does not include ethambutol, which must be administered separately when the antibiotic susceptibility of the strain in the patient or index case is unknown. This could be solved by developing an FDC with the same doses of isoniazid, rifampicin and pyrazinamide, but with an additional 100 mg of ethambutol per tablet. Such an option would considerably improve conventional tuberculosis treatment in children.

However, these new paediatric FDCs also have their disadvantages. Their dosages are established based on broad body weight ranges, which carries a risk of overdosing, especially in smaller children. Recommendations regarding the doses to be used in children that weigh less than four kilograms have yet to be made due to the lack of pharmacokinetic data. Starting at 25 kg of body weight, the WHO recommends the administration of FDCs formulated for adults, despite the aforementioned risks of underdosing and toxicity. In our opinion, this could be resolved by administering five paediatric FDC tablets to children that weigh between 20 and 29 kg, and six tablets to children that weigh between 30 and 39 kg. Patients weighing 40 kg or more could be treated with FDCs authorised for use in adults, supplementing them with the additional administration of single-component formulations of some drugs as needed.

Table 6 New paediatric FDCs for the treatment of tuberculosis in children (WHO and TB Alliance, 2015).

Body weight range (kg)	Number of tablets	
	Induction (INH:RIF:PZA 50:75:150)	Maintenance (INH:RIF 50:75)
4–7	1	1
8–11	2	2
12–15	3	3
16–24	4	4
>25	Adult FDC	

ETH, ethambutol; FDC, fixed-dose combination; INH, isoniazid; PZA, pyrazinamide; RIF, rifampicin.

The only paediatric FDCs guaranteed to meet quality, safety and efficacy standards equivalent to those applied in the European Union are those that have been prequalified by the WHO.[36] Unfortunately, the combination of 50 mg of isoniazid and 75 mg of rifampicin (with or without 150 mg of pyrazinamide) has yet to be prequalified by the WHO, and is currently undergoing evaluation. In countries with a high prevalence of tuberculosis, these formulations are distributed by the Global TB Drug Facility of the WHO. Ideally, once they are prequalified, it should be possible to obtain these new paediatric FDCs in Spain by applying for their import as a foreign drug to the Spanish Agency of Medicines and Medical Devices.

Drug administration

Regardless of their formulation, antituberculosis drugs are ideally taken in the morning, fasting and sequentially,

Table 7 Recommended dosing of Rimstar® for children that weigh more than 30 kg.

Body weight	Combinations based on Rimstar®					Dose							
	H:R:Z:E tablets 75:150:400:275	H 50 tablets	H 150 tablets	Z 250 tablets	N. total tablets	Total H (mg)	H dose (mg/kg)	Total R (mg)	R dose (mg/kg)	Total Z (mg)	Z dose (mg/kg)	Total E (mg)	E dose (mg/kg)
30	2	0	1	1	4	300	10.0	300	10.0	1050	35.0	550	18.3
31	2	0	1	1	4	300	9.7	300	9.7	1050	33.9	550	17.7
32	2	0	1	1	4	300	9.4	300	9.4	1050	32.8	550	17.2
33	3	1	0	0	4	275	8.3	450	13.6	1200	36.4	825	25.0
34	3	1	0	0	4	275	8.1	450	13.2	1200	35.3	825	24.3
35	3	1	0	0	4	275	7.9	450	12.9	1200	34.3	825	23.6
36	3	1	0	0	4	275	7.6	450	12.5	1200	33.3	825	22.9
37	3	1	0	0	4	275	7.4	450	12.2	1200	32.4	825	22.3
38	3	1	0	0	4	275	7.2	450	11.8	1200	31.6	825	21.7
39	3	1	0	0	4	275	7.1	450	11.5	1200	30.8	825	21.2
40	3	0	0.5	0	3.5	300	7.5	450	11.3	1200	30.0	825	20.6
41	3	0	0.5	1	4.5	300	7.3	450	11.0	1450	35.4	825	20.1
42	3	0	0.5	1	4.5	300	7.1	450	10.7	1450	34.5	825	19.6
43	3	0	0.5	1	4.5	300	7.0	450	10.5	1450	33.7	825	19.2
44	4	0	0	0	4	300	6.8	600	13.6	1600	36.4	1100	25.0
45	4	0	0	0	4	300	6.7	600	13.3	1600	35.6	1100	24.4
46	4	0	0	0	4	300	6.5	600	13.0	1600	34.8	1100	23.9
47	4	0	0	0	4	300	6.4	600	12.8	1600	34.0	1100	23.4
48	4	0	0	0	4	300	6.3	600	12.5	1600	33.3	1100	22.9
49	4	0	0	0	4	300	6.1	600	12.2	1600	32.7	1100	22.4
50	4	0	0	0	4	300	6.0	600	12.0	1600	32.0	1100	22.0
51	4	0	0	0	4	300	5.9	600	11.8	1600	31.4	1100	21.6
52	4	0	0	0	4	300	5.8	600	11.5	1600	30.8	1100	21.2
53	4	0	0	0	4	300	5.7	600	11.3	1600	30.2	1100	20.8
54	4	0	0	1	5	300	5.6	600	11.1	1850	34.3	1100	20.4
55	4	0	0	1	5	300	5.5	600	10.9	1850	33.6	1100	20.0
56	4	0	0	1	5	300	5.4	600	10.7	1850	33.0	1100	19.6
57	4	0	0	1	5	300	5.3	600	10.5	1850	32.5	1100	19.3
58	4	0	0	1	5	300	5.2	600	10.3	1850	31.9	1100	19.0
59	4	0	0	1	5	300	5.1	600	10.2	1850	31.4	1100	18.6
60	4	0	0	1	5	300	5.0	600	10.0	1850	30.8	1100	18.3
61	4	0	0	1	5	300	4.9	600	9.8	1850	30.3	1100	18.0
62	4	0	0	1.5	5.5	300	4.8	600	9.7	1975	31.9	1100	17.7
63	4	0	0	1.5	5.5	300	4.8	600	9.5	1975	31.3	1100	17.5
64	4	0	0	1.5	5.5	300	4.7	600	9.4	1975	30.9	1100	17.2
65	4	0	0	1.5	5.5	300	4.6	600	9.2	1975	30.4	1100	16.9

Table 8 Recommended dosing of Rifater® for children that weigh more than 30 kg.

Body weight	Combinations based on Rifater®					Dose							
	H:R:Z tablets 50:120:300	H 50 tablets	Z 250 tablets	E 400 tablets	N total tablets	Total H (mg)	H dose (mg/kg)	Total R (mg)	R dose (mg/kg)	Total Z (mg)	Z dose (mg/kg)	Total E (mg)	E dose (mg/kg)
30	4	1	0	1.5	6.5	250	8.3	480	16.0	1200	40.0	600	20.0
31	4	1	0	1.5	6.5	250	8.1	480	15.5	1200	38.7	600	19.4
32	4	1	0	2	7	250	7.8	480	15.0	1200	37.5	800	25.0
33	4	1	0	2	7	250	7.6	480	14.5	1200	36.4	800	24.2
34	4	1	0	2	7	250	7.4	480	14.1	1200	35.3	800	23.5
35	4	1	0	2	7	250	7.1	480	13.7	1200	34.3	800	22.9
36	4	2	0	2	8	300	8.3	480	13.3	1200	33.3	800	22.2
37	4	2	0	2	8	300	8.1	480	13.0	1200	32.4	800	21.6
38	4	2	0	2	8	300	7.9	480	12.6	1200	31.6	800	21.1
39	4	2	0	2	8	300	7.7	480	12.3	1200	30.8	800	20.5
40	4	2	0	2	8	300	7.5	480	12.0	1200	30.0	800	20.0
41	5	1	0	2	8	300	7.3	600	14.6	1500	36.6	800	19.5
42	5	1	0	2	8	300	7.1	600	14.3	1500	35.7	800	19.0
43	5	1	0	2	8	300	7.0	600	14.0	1500	34.9	800	18.6
44	5	1	0	2	8	300	6.8	600	13.6	1500	34.1	800	18.2
45	5	1	0	2	8	300	6.7	600	13.3	1500	33.3	800	17.8
46	5	1	0	2	8	300	6.5	600	13.0	1500	32.6	800	17.4
47	5	1	0	2	8	300	6.4	600	12.8	1500	31.9	800	17.0
48	5	1	0	2	8	300	6.3	600	12.5	1500	31.3	800	16.7
49	5	1	0	2	8	300	6.1	600	12.2	1500	30.6	800	16.3
50	5	1	0	2	8	300	6.0	600	12.0	1500	30.0	800	16.0
51	5	1	1	2	9	300	5.9	600	11.8	1750	34.3	800	15.7
52	5	1	1	2	9	300	5.8	600	11.5	1750	33.7	800	15.4
53	5	1	1	2	9	300	5.7	600	11.3	1750	33.0	800	15.1
54	5	1	1	3	10	300	5.6	600	11.1	1750	32.4	1200	22.2
55	5	1	1	3	10	300	5.5	600	10.9	1750	31.8	1200	21.8
56	5	1	1	3	10	300	5.4	600	10.7	1750	31.3	1200	21.4
57	5	1	1	3	10	300	5.3	600	10.5	1750	30.7	1200	21.1
58	5	1	1	3	10	300	5.2	600	10.3	1750	30.2	1200	20.7
59	5	1	2	3	11	300	5.1	600	10.2	2000	33.9	1200	20.3
60	5	1	2	3	11	300	5.0	600	10.0	2000	33.3	1200	20.0
61	5	1	2	3	11	300	4.9	600	9.8	2000	32.8	1200	19.7
62	5	1	2	3	11	300	4.8	600	9.7	2000	32.3	1200	19.4
63	5	1	2	3	11	300	4.8	600	9.5	2000	31.7	1200	19.0
64	5	1	2	3	11	300	4.7	600	9.4	2000	31.3	1200	18.8
65	5	1	2	3	11	300	4.6	600	9.2	2000	30.8	1200	18.5

Table 9 Recommended dosing of Rifinah® for children that weigh more than 30 kg.

Body weight	Combinations based on Rifinah®				Administered dose							
	H:R tablets 150:200	Z 250 tablets	E 400 tablets	N. total tablets	Total H (mg)	H dose (mg/kg)	Total R (mg)	R dose (mg/kg)	Total Z (mg)	Z dose (mg/kg)	Total E (mg)	E dose (mg/kg)
30	2	4	1.5	7.5	300	10.0	600	20.0	1000	33.3	600	20.0
31	2	4	1.5	7.5	300	9.7	600	19.4	1000	32.3	600	19.4
32	2	4	1.5	7.5	300	9.4	600	18.8	1000	31.3	600	18.8
33	2	4	2	8	300	9.1	600	18.2	1000	30.3	800	24.2
34	2	5	2	9	300	8.8	600	17.6	1250	36.8	800	23.5
35	2	5	2	9	300	8.6	600	17.1	1250	35.7	800	22.9
36	2	5	2	9	300	8.3	600	16.7	1250	34.7	800	22.2
37	2	5	2	9	300	8.1	600	16.2	1250	33.8	800	21.6
38	2	5	2	9	300	7.9	600	15.8	1250	32.9	800	21.1
39	2	5	2	9	300	7.7	600	15.4	1250	32.1	800	20.5
40	2	5	2	9	300	7.5	600	15.0	1250	31.3	800	20.0
41	2	5	2	9	300	7.3	600	14.6	1250	30.5	800	19.5
42	2	6	2	10	300	7.1	600	14.3	1500	35.7	800	19.0
43	2	6	2	10	300	7.0	600	14.0	1500	34.9	800	18.6
44	2	6	2	10	300	6.8	600	13.6	1500	34.1	800	18.2
45	2	6	2	10	300	6.7	600	13.3	1500	33.3	800	17.8
46	2	6	2	10	300	6.5	600	13.0	1500	32.6	800	17.4
47	2	6	2	10	300	6.4	600	12.8	1500	31.9	800	17.0
48	2	6	2	10	300	6.3	600	12.5	1500	31.3	800	16.7
49	2	6	2	10	300	6.1	600	12.2	1500	30.6	800	16.3
50	2	6	2	10	300	6.0	600	12.0	1500	30.0	800	16.0
51	2	7	2	11	300	5.9	600	11.8	1750	34.3	800	15.7
52	2	7	2	11	300	5.8	600	11.5	1750	33.7	800	15.4
53	2	7	2	11	300	5.7	600	11.3	1750	33.0	800	15.1
54	2	7	3	12	300	5.6	600	11.1	1750	32.4	1200	22.2
55	2	7	3	12	300	5.5	600	10.9	1750	31.8	1200	21.8
56	2	7	3	12	300	5.4	600	10.7	1750	31.3	1200	21.4
57	2	7	3	12	300	5.3	600	10.5	1750	30.7	1200	21.1
58	2	7	3	12	300	5.2	600	10.3	1750	30.2	1200	20.7
59	2	8	3	13	300	5.1	600	10.2	2000	33.9	1200	20.3
60	2	8	3	13	300	5.0	600	10.0	2000	33.3	1200	20.0
61	2	8	3	13	300	4.9	600	9.8	2000	32.8	1200	19.7
62	2	8	3	13	300	4.8	600	9.7	2000	32.3	1200	19.4
63	2	2	3	11	300	4.8	600	9.5	2000	31.7	1200	19.0
64	2	2	3	11	300	4.7	600	9.4	2000	31.3	1200	18.8
65	2	2	3	11	300	4.6	600	9.2	2000	30.8	1200	18.5

without mixing them in a single glass, spoon or oral syringe.

The use of liquid formulations facilitates dosing adjustments for the administration of doses below those available in tablet form, so these formulations are the ideal and thus the first option recommended in this document, along with newly developed paediatric FDCs.

Ideally, tablets should be taken in a whole. If a patient has trouble swallowing them, all solid formulations of antituberculosis drugs can be manipulated to facilitate their administration. Tablets can be crushed and capsules can be opened.[37–39] This option should be reserved exclusively for the following cases: when the dose approximates the contents of a solid form or half a tablet, when the child rejects liquid formulations due to their organoleptic properties, or when no other formulation is available.

Crushed tablets have a stronger flavour than larger fragments.[37] This is why drugs frequently have to be mixed with foods to be given to children, although this option should be reserved only for patients with gastrointestinal intolerance. If the drug is not administered within 30 min from mixing, it should be discarded.[37–39] It must be taken into account that suspension of the crushed tablet may lead to aggregation, sedimentation or precipitation problems,[40] with a potential loss of stability.

In the case of isoniazid, the food must be low in fat, as fats slow down its absorption, and if possible low in sugars, which would inactivate it.[37–39] For infants, it can be dissolved in a spoonful of warm water and mixed with a small amount of breast milk or follow-on formula.[37–39]

Ethambutol can be administered mixed in a small volume of juice or apple sauce.[37–40] It takes 10 min to dissolve.[39] Mixing it with other fluids or syrups is not recommended, as it may not be stable, or the medium may fail to mask the bitter taste of the drug.[39,40] Last of all, there are no restrictions on the types of food that pyrazinamide crushed tablets can be mixed with for administration.

In all cases, the amount of food added should be small, guaranteeing that the child consumes the full dose.[37–39]

In case of vomiting, the dose can be retaken if less than 30 min elapsed since its administration. When a dose is skipped accidentally, the drug should be administered as soon as possible if at least 12 h remain to the next dose.[37–40]

Fixed-dose combinations for adults are prepared as coated tablets. The excipients used in the coating are widely used in tablet manufacturing processes, so it is not expected that they would interfere with drug absorption after crushing. Tables 7–9 summarise the recommended doses for the use of adult FDCs in children that weigh more than 30 kg.

Conclusions

We present a document developed by a multidisciplinary group of experts that provides recommendations for the treatment of tuberculosis in children, with especial emphasis on those that have not yet developed the ability to swallow solid dosage forms. The document proposes the preparation of CFs of isoniazid, pyrazinamide and ethambutol at the most suitable concentrations for their use in children, provides recommendations on the use of the FDCs authorised for use in Spain, and urges the competent authorities to expedite the introduction of new paediatric FDCs in Spain once they complete the prequalification process. In cases in which the use of liquid formulations is not possible, the document proposes the use of crushed tablets, to be mixed with food in patients with gastrointestinal intolerance.

We believe that this document offers an unprecedented opportunity in Spain, and that it could be very useful to paediatricians and pharmacists. Strict adherence to treatment and guaranteeing the administration of optimal doses of drugs are essential to the control and eradication of tuberculosis. Achieving these goals in the paediatric population is the ultimate purpose of this document.

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Conflict of interest

The authors have no conflict of interest to declare.

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Validation of the daily single-unit dose of isoniazid at 10 mg/kg body weight in infants aged less than 3 months. Ref. PI13/01740.

Phase IIA open clinical trial assessing the absorption of an isoniazid 10 mg/mL suspension for the treatment of tuberculosis infection in patients aged less than 6 years. Ref. ICI14/00228.

Appendix A. Working Group of the Magistral Project of pTBred

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