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The background and rationale for a new fixed-dose combination for first-line treatment of tuberculosis in children

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SUMMARY

In 2010, the World Health Organization revised the recommendations for the treatment of tuberculosis (TB) in children. The major revision was to increase isoniazid, rifampicin and pyrazinamide dosages according to body weight in children. The recommendations for higher dosages are based on consistent evidence from 1) pharmacokinetic studies suggesting that young children require higher dosages than adolescents and adults to achieve desired serum concentrations; and 2) observational studies reporting that the higher dosages would not be associated with increased risk of toxicity in children. However, national tuberculosis programmes faced unforeseen challenges in implementing the revised recommendations. The main difficulty was to adapt the revised dosages for the treatment of children with drug-susceptible TB using available fixed-dose combinations (FDCs). A more suitable FDC for the intensive and continuation phases of treatment has now been developed for planned implementation in 2015. This paper explains the background and rationale for the development of a new FDC tablet for children with drug-susceptible TB.

KEY WORDS: isoniazid; rifampicin; pyrazinamide; ethambutol; dosages; toxicity; children; FDCs; pharmacokinetic

THE WORLD HEALTH ORGANIZATION (WHO) estimates that 10% of the 9.6 million cases of tuberculosis (TB) worldwide in 2014 occurred in children aged 0–14 years, and that there were around 136 000 TB-related deaths among children.[1] The true burden of child TB is not known due to recognised challenges in accurate diagnosis and under-reporting, and may be greater than WHO estimates.[2] The burden is highest in TB-endemic, resource-limited settings, where children constitute a large proportion of the population and where there is often a high prevalence of risk factors for infection and disease.[3] Important risk factors associated with susceptibility to TB and TB-related mortality in children include young age, malnutrition and HIV infection.[4–7] It is therefore important to ensure optimal use of anti-tuberculosis treatment in young and immunosuppressed children.

The recently launched WHO End TB Strategy, which provides global targets and strategy for TB control after 2015, includes the ambitious target of reducing deaths due to TB by 95% between 2015 and 2035.[8] This global strategy includes child TB to a greater extent than previous strategies, and urges greater collaboration with the child health sector where children with TB are clinically managed and cared for. The Roadmap for Childhood Tuberculosis, launched in 2013 by the WHO and its partners, specifically defines steps to achieve these ambitions and urges greater inclusion of children in the development of new tools for treatment, policy development and research.[9] We aim to explain the background and rationale for the recent development of a fixed-dose combination (FDC) that is suitable for the treatment of young children with drug-susceptible TB.

PRINCIPLES IN THE TREATMENT OF CHILDHOOD TUBERCULOSIS

The principles of treatment of TB are essentially the same for children as they are for adults. Effective regimens require a combination of antimicrobials with activity against *Mycobacterium tuberculosis* aiming to eliminate replicating and dormant or near-dormant mycobacteria, prevent

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Table 1 Recommended treatment regimens for new patients (WHO, 2014)[13]*

TB disease category	Recommended regimen	
	Intensive phase	Continuation phase
Non-severe forms of TB (smear-negative PTB, intrathoracic lymph node TB, peripheral lymph node TB) in low HIV prevalence and low INH resistance settings	2HRZ	4HR
Non-severe forms of TB (smear-negative PTB, intrathoracic lymph node TB, peripheral lymph node TB) in HIV-endemic† or high INH resistance‡ settings	2HRZE	4HR
More severe forms of PTB and EPTB, except TB meningitis and osteoarticular TB	2HRZE	4HR
TB meningitis and osteoarticular TB	2HRZE	10HR

* Numbers before the letters indicate the duration in months of the phase of treatment. Streptomycin is no longer recommended for children with TB.
† Countries where HIV prevalence among adult pregnant women is ⩾1%, or ⩾5% among TB patients.
‡ The WHO does not define a threshold for high levels of prevalence of INH resistance; this is left to the discretion of the national TB programmes of individual countries.
WHO = World Health Organization; TB = tuberculosis; PTB = pulmonary TB; HIV = human immunodeficiency virus; H, INH = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; EPTB = extra-pulmonary TB.

the emergence of drug-resistant organisms, and achieve this with a minimum of toxicity.[10,11] Isoniazid (INH, H) and rifampicin (RMP, R) are potent bactericidal drugs that are included in first-line regimens for the entire treatment duration.[12,13] RMP and pyrazinamide (PZA, Z) are first-line sterilising drugs that aim to eradicate organisms that are less metabolically active in an acidic environment to prevent relapse. Protection against the emergence of drug-resistant organisms is achieved by combining effective early bactericidal activity to reduce the microbial load with effective sterilising activity of more slowly replicating organisms. Ethambutol (EMB, E) is primarily used as a fourth drug, in combination with INH, RMP and PZA, to prevent or delay the emergence of resistant strains.[10–13]

Table 1 lists the regimens by disease category as currently recommended by WHO for new TB cases in children with presumptive drug-susceptible TB.[13] The regimens recommended and used in children and adolescents are consistent with those recommended for adults.[12] The most common diagnostic category for TB in children is smear-negative (or smear not performed) pulmonary TB.[1] The most common regimen used in children worldwide is 2HRZ/4HR (i.e., a 2-month intensive phase of daily INH, RMP and PZA, followed by a 4-month continuation phase of daily INH and RMP). In principle, a three-drug regimen can be used during the initial phase of treatment in the majority of young children, as the disease is often paucibacillary; the risk of developing drug resistance is therefore lower than for adolescents or adults with TB. The risk of relapse following treatment completion with a three-drug regimen (HRZ) in the intensive phase is very low in children.[14,15]

RATIONALE FOR THE INCLUSION OF AND DOSAGES FOR ETHAMBUTOL IN CHILDREN

A fourth drug is recommended for the 2-month intensive phase combination in addition to INH, RMP and PZA in case of TB characterised by a large bacillary load, such as pulmonary TB that is sputum smear-positive or extensive parenchymal involvement, in order to reduce the risk of the development of drug resistance.[10–12] The fourth drug that is currently recommended for this purpose, including in children, is EMB.[13] EMB is also currently recommended for inclusion in the intensive phase of treatment for new TB cases in children in settings with 'high HIV prevalence or high INH resistance or both' (Table 1).[13] A high HIV prevalence setting is defined as a setting where the HIV prevalence among adult pregnant women is ⩾1%, or ⩾5% among TB patients. The WHO has not defined a threshold for high levels of prevalence of INH resistance, which is left to the discretion of the national TB programmes (NTPs) of individual countries.[12,13] This is a challenge for implementation, as many TB-endemic countries do not have drug resistance surveillance data. It is well known that INH-resistant TB is common worldwide,[1,16] and that the addition of a fourth drug will lower the risk of treatment failure by using at least three effective drugs in the intensive phase.[17] It is likely that INH-resistant TB is also common in children.[18] However, the efficacy of adding EMB in preventing the acquisition of RMP resistance in cases with pre-treatment INH resistance is recognised as a priority for research, as the evidence for this is currently weak.[12]

For many years, EMB was not recommended, but contraindicated, for use in young children (<5 years of age). The concern was that EMB might cause optic neuritis in children who were too young to report the early visual symptoms, which could thus lead to

Table 2 Recommended first-line drug dosages for children as currently and previously recommended by the World Health Organization

Drug	Currently recommended[13] Daily dosage (dose range) mg/kg	Previously recommended[41] Daily dosage (dose range) mg/kg
Isoniazid	10 (7–15)	5 (4–6)
Rifampicin	15 (10–20)	10 (8–12)
Pyrazinamide	35 (30–40)	25 (20–30)
Ethambutol	20 (15–25)	15 (15–20)

irreversible blindness. Reconsidering the use of EMB was prompted by the HIV epidemic, which required the urgent need to replace thioacetazone as the previously recommended fourth drug during the intensive phase. Thioacetazone caused frequent, severe and often fatal reactions in HIV-infected adults and children.[19,20] Streptomycin was not considered an ideal alternative, as its use required hospitalisation for the intensive phase of 2 months, and hospitals had become overburdened. With the introduction of EMB as the recommended fourth drug during the intensive phase in adults, there was a need to reconsider its use in children.[21,22]

A very extensive review on behalf of the WHO included a careful examination of the pharmacokinetic and safety data on EMB in children.[23] Reviews of the use of EMB in children of all ages, including infants, using a wide range of dosages and providing careful evaluation of visual side-effects, reported that toxicity was dose-related and related to the duration of treatment.[21,22,24] It was concluded that the risk of toxicity was negligible if recommended dosages were adhered to.[23,24] It was also noted that the duration of treatment with EMB as first-line treatment is limited to 2 months. The review highlighted the fact that dosages recommended by WHO at the time (15–20 mg/kg)[25] resulted in lower peak serum concentrations of EMB in children than in adults, especially in young children aged <5 years. Peak serum concentrations were in fact at such low levels that they might be inadequate for effective treatment. As a result, the WHO advised that the recommended dosages for EMB be increased for children, being careful to ensure that the upper limit of the recommended dose range had an excellent safety profile.[26]

RATIONALE FOR THE INCREASED DOSES OF ISONIAZID, RIFAMPICIN AND PYRAZINAMIDE

The focus on the safety and dosage issues for EMB use in children highlighted the general lack of pharmacokinetic data on anti-tuberculosis drugs in children. Dosage recommendations in children in mg/kg were the same as for adults and had largely been informed by pharmacokinetic studies in adults. However, rates of drug metabolism, distribution and clearance are different in children and adults, especially infants and young children.[27] Pharmacokinetic studies in children over the last decade have shown that age is a determinant of serum levels for all first-line anti-tuberculosis drugs. Infants and young children have lower peak serum levels than older children or adults.[28–34] Peak serum levels of INH, RMP, PZA and EMB were also lower in HIV-infected children not receiving antiretroviral therapy than in non-HIV-infected children, although this difference did not reach statistical significance.[32–34]

Pharmacokinetic data for INH, RMP and PZA in children were reviewed, as was the risk of toxicity in children at different dosages of INH, RMP and PZA. Hepatotoxicity is the major drug-related adverse event of concern and is occasionally reported.[35,36] There is already a large amount of previous evidence of treatment success and low risk of toxicity with the use of the new WHO-revised dosages in children, including reports from populations in countries where TB is still endemic.[14,37–39] An extensive review of this evidence concluded that increasing the dosages to those now recommended would not be associated with an increased risk of hepatotoxicity.[39] Following the review of toxicity and consultation, the WHO revised and increased the recommended dosages for RMP, INH and PZA in 2010 to add to the earlier revision for EMB.[40] The revised recommended dosages are listed in Table 2, along with the previous dosage recommendations for comparison. Recent pharmacokinetic data from children in South Africa and Malawi provide supportive evidence for the revised dosages.[42,43]

WHY THE NEED FOR A REVISED FIXED-DOSE COMBINATION?

Increasing the dosages proved a major challenge for implementation using the available FDCs.[44,45] FDC tablets have some advantages over individual drugs, as they lessen the pill burden and the likelihood of prescription errors. As FDCs also avoid selective non-adherence, they lessen the risk of the emergence of drug resistance, even when this risk is lower in young children. The challenge was that the FDCs of first-line drugs for children that were the most readily available comprised RHZ 60:30:150 for the intensive phase and RH 60:30 for the continuation phase.[41] These combinations were suitable for young children using the previous dosage recommendations for INH 5 mg/kg and RMP 10 mg/kg (Table 2), because the ratio of RMP:INH was 2:1, i.e., R:H 60:30. However, the R:H ratio required to use the revised dosages of 15 mg/kg RMP and 10 mg/kg INH is now 3:2.[13] The implementation of the revised dosages was further complicated by the 2010 update of the guidelines, which recommended an INH dosage range of 10–15 mg/kg.[40] The changes in the recommendations made

Table 3 A summary of the main issues considered and the recommendations developed from an informal WHO consultation meeting held in 2012

Issues considered	Considerations and discussion	Decision
Recommendation for optimal FDCs for children	Ratio of RMP to INH in FDCs needs to be 3:2 to align with current recommended dosages Dosage in mg in the FDC needs to be low enough to avoid the need to break the FDC tablet for the majority of children Limited size of the potential market an obstacle to the development of a wider range of options	RHZ 75:50:150 in the intensive phase RH 75:50 in the continuation phase
Further revision of the INH dose range following 2010 recommendations	Recommendation of 10 mg/kg for INH with a range of 10–15 mg/kg a major barrier to the use of FDCs (either 60:30:150 or 75:50:150) Pharmacokinetic data indicate that the previously recommended range of 4–6 mg/kg was inadequate in infants and young children Pharmacokinetic data show higher and adequate levels are achieved with a dose of >7 mg/kg	Range for INH: 7–15 mg/kg
The addition of EMB to FDC	Addition of EMB would result in a considerably larger and more unstable FDC EMB not indicated for the majority of TB cases in young children (<25 kg) globally; limited size of the potential market an obstacle to the development of a wider range of options Persistent concerns among clinicians and NTPs leading to reluctance to use EMB in young children Uncertainty as to whether EMB would continue to be the recommended fourth drug in the medium or long term	EMB not included in the FDC EMB 100 mg single drug preparation is available
The cut-off weight at which children should receive adult preparations	Dosage decisions for treatment should be by weight and not by age Dosage in mg in the FDC needs to be low enough to avoid the need to break FDC tablets for the majority of children Use of low-dose FDCs for children associated with increase in pill burden as weight increases Pharmacokinetic data in older children and adolescents of ⩾25 mg more similar to adolescents and adults than to infants and young children	Weight bands for FDC of up to 25 kg At ⩾25 kg, change to adult dosage guidelines and preparations
Availability of suitable single-dose INH preparations	Availability of FDCs for the treatment of TB associated with reduced availability or procurement of single-drug INH preparations Single-drug INH required to implement INH preventive therapy in eligible young child contacts and HIV-infected children Dosage in mg in INH preparations needs to be low enough to avoid the need to break tablets, including in infants	Continue to provide INH preparations of 50 mg and 100 mg
Child-friendly preparations	Recognised difficulty for infants and young children to swallow tablets Liquid preparations less readily transported and stored than solid preparations in resource-limited settings	Dispersible, flavoured preparation preferred

WHO = World Health Organization; FDC = fixed-dose combination; RMP, R = rifampicin; INH, H = isoniazid; Z = pyrazinamide; EMB = ethambutol; NTP = National TB Programme.

it very difficult to use the current FDCs of RHZ 60:30:150 for the intensive phase and RH 60:30 for the continuation phase and simultaneously remain within the recommended dosage ranges for all three first-line drugs. Although the WHO developed interim dosage tables to facilitate implementation that required additional INH single-dose preparations of 100 mg tablets, the dosing had become more complicated, causing confusion and a higher risk of dosing error.

A survey of 34 NTPs in early 2012 in five different global regions and including 10 high TB burden countries highlighted these challenges.[45] Of 31 respondents, 19 reported using the revised 2010 dosages, while 12 reported continued use of the 2006 guidelines with the previous drug dosages. According to those who had changed, implementing the 2010 guidelines was complicated and challenging. The survey made a number of additional observations: not all NTPs were comfortable using EMB in young children despite the 2006 WHO guidelines, and with the implementation and wide use of FDCs, single-dose INH was often no longer available. The latter observation clearly had implications not only in

Table 4 Example of a suitable weight-band table for the recently developed fixed-dose combination

	Numbers of tablets		
	Intensive phase		Continuation phase
Weight bands kg	RHZ 75:50:150	E 100	RH 75:50
4–7	1	1	1
8–11	2	2	2
12–15	3	3	3
16–24	4	4	4
⩾25	Go to adult dosages and preparations		

R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol.

trying to boost the INH dose to adjust for revised recommendations, but also for the implementation of INH preventive therapy.

OUTCOME OF A CONSULTATION TO ESTABLISH AN OPTIMAL FIXED-DOSE COMBINATION

In response to the challenges created by the 2010 dose revision,[40] an informal consultation was organised by the WHO and held in May 2012 in Stellenbosch, South Africa. A range of experience and expertise was represented, including global experts in pharmacokinetics, formulation and regulatory process for anti-tuberculosis medication in children. The main issues considered and discussed are listed in Table 3, along with the final recommendations for each issue. Important decisions to inform the future development and implementation of a suitable FDC were to recommend RHZ 75:50:150 as the preferred FDC and to widen the recommended range for INH to 7–15 mg/kg. These recommendations were supported by pharmacokinetic and safety data.[34,37] Table 4 provides an example of a suitable weight-band table for the implementation of the new FDC.

CHALLENGES TO PROVIDING ANTI-TUBERCULOSIS TREATMENT FOR CHILDREN

There are ongoing challenges to the logistics of providing anti-tuberculosis treatment for children.[41,44] The production and provision of anti-tuberculosis drug preparations has largely focused on treatment in adults. Securing more than one pharmaceutical company to produce FDCs for children may be challenging, due to the limited market. Although liquid formulations might be easier to administer to small children, in reality, in many settings, children of all ages with TB receive treatment in the form of tablets or portions of tablets. Tablet portions are often well taken and tolerated by children and have some advantages in resource-poor settings, as they are more readily transported and stored than liquid preparations. However, the use of tablets means that a fixed-dosage amount is supplied within a certain weight band, and this can lead to a broad range of actual dose received in mg/kg. This is especially problematic in younger children in the lower weight bands.[46] Furthermore, weight gain in response to anti-tuberculosis treatment can be such that the child moves to another weight band during treatment, requiring a higher dosage, which may not be noted. Neonates (usually <4 kg), for whom drug pharmacokinetics are relatively poorly documented, deserve special attention; the use of FDC tablets is thus more challenging and requires frequent adjustments. Although neonates are treated with standard regimens, drug dosages need careful consideration and regular review. Finally, the adoption and use of FDC medication makes it challenging to manage a possible adverse reaction to one of the drugs included in the FDC, especially when single-drug preparations of the drugs included in the FDC are no longer readily available.

Principles that should be applied in the development of new anti-tuberculosis drugs for children should include determining the correct dosage and developing preparations that are child-friendly.[47] Previous experience has demonstrated additional challenges to the implementation of any new formulation such as the recently developed FDC. These challenges include procurement and distribution of a new drug, requiring revised guidelines for use, training for correct use and monitoring for drug-related toxicity following release. The details of the preparation required and logistical issues for implementation of the new FDC for first-line treatment of TB in children is addressed in detail in an accompanying paper in this supplement.

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RESUME

En 2010, l'Organisation Mondiale de la Santé a révisé les recommandations relatives au traitement de la tuberculose (TB) de l'enfant. La révision majeure a consisté à augmenter la dose en fonction du poids de l'isoniazide, de la rifampicine et du pyrazinamide pour les enfants. Ces recommandations en faveur de doses plus élevées sont basées sur des preuves cohérentes émanant : 1) des études de pharmacocinétique qui montrent que les jeunes enfants ont besoin de doses plus élevées que les adolescents et les adultes pour aboutir à la même concentration sérique ; et 2) des études d'observation qui montrent que ces doses plus élevées ne sont pas associées à un risque accru de toxicité chez les enfants. Cependant, ces nouvelles recommandations ont créé des défis imprévus à leur mise en œuvre pour les programmes nationaux TB. La difficulté principale a été d'adopter les doses révisées pour le traitement de la TB pharmacosensible chez les enfants recevant les combinaisons à dose fixe disponibles (FDC). A présent, des FDC mieux adaptées à la phase intensive et à la phase d'entretien ont été créées en vue d'être introduites en 2015. Cet article explique le contexte et la justification de l'élaboration de nouveaux comprimés FDC pour traiter la TB pharmacosensible de l'enfant.

RESUMEN

En el 2010, la Organización Mundial de la Salud revisó las recomendaciones sobre el tratamiento de la tuberculosis (TB) en los niños. La principal modificación consistió en aumentar la posología pediátrica en función del peso corporal de la isoniazida, la rifampicina y la pirazinamida. La recomendación de administrar dosis más altas se basó en datos fidedignos provenientes de dos fuentes: 1) los estudios farmacocinéticos según los cuales los niños precisan dosis más altas que los adolescentes y los adultos con el fin de alcanzar la concentración sanguínea prevista; y 2) los estudios de observación que revelan que dosis más altas no se asociarían con un mayor riesgo de toxicidad en los niños. Sin embargo, la aplicación de las recomendaciones revisadas planteó problemas imprevistos a los programas nacionales contra la TB. La principal dificultad consistió en aplicar las posologías revisadas al tratamiento de la TB normosensible en los niños, utilizando las asociaciones en dosis fijas de medicamentos (FDC) existentes. En la actualidad, se han desarrollado FDC mejor adaptadas para la fase intensiva y la fase de continuación del tratamiento y se planea su introducción en el 2015. En el presente artículo se explica la información previa y el fundamento del desarrollo de las nuevas asociaciones en FDC destinadas a la TB normosensible en los niños.