GIORNATE INFETTIVOLOGICHE
"LUIGI SACCO" 2022

BEST PAPERS IN INFECTIOUS DISEASES 2022

UNIVERSITÀ DEGLI STUDI DI BRESCIA

Dr. Luca Rossi

LATENT TUBERCULOSIS INFECTION (LTBI)

A state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB.

1,7 billion

Asymptomatic and not infectious

5-10%

Risk for active TB disease

Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy

Mass, population-wide LTBI testing and treatment are not feasible (imperfect tests, risks of side-effects, high cost)

WHO Latent tuberculosis infection: updated and consolidated guidelines for programmatic management

LTBI SCREENING AND TREATMENT

WHO recommendations

AT-RISK POPULATION GROUPS

- people living with HIV
- household contacts of TB cases
- anti-TNF treatment
- dialysis
- organ or haematologic transplantation
- silicosis

IN COUNTRIES WITH LOW TB INCIDENCE

- immigrants from countries with a high TB burden
- health workers
- prisoners
- homeless people
- drug-abusers

LTBI SCREENING AND TREATMENT

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- health workers
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- homeless people
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< 2% estimated prevalence

LTBI SCREENING AND TREATMENT

WHO recommendations

Need to extend screening and treatment to other at-risk groups

AT-RISK POPULATION GROUPS

- people living with HIV
- household contacts of TB cases
- anti-TNF treatment
- dialysis
- organ or haematologic transplantation
- silicosis

IN COUNTRIES WITH LOW TB INCIDENCE

- immigrants from countries with a high TB burden
- health workers
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- homeless people
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< 2% estimated prevalence

BMJ Open

The relationship between mental health and risk of active tuberculosis: a systematic review

Sally E Hayward ,[1,2] Anna Deal ,[1,2] Kieran Rustage ,[1]
Laura B Nellums ,[1,3] Annika C Sweetland,[4] Delia Boccia,[2] Sally Hargreaves ,[1]
Jon S Friedland [1]

The first systematic review to examine mental health as a risk factor for active TB

10 studies
607 184 subjects

Asia
South America
Africa

Excluded studies:

- drugs/alcohol disorders
- LTBI without reactivation
- CNS TB
- TB-HIV

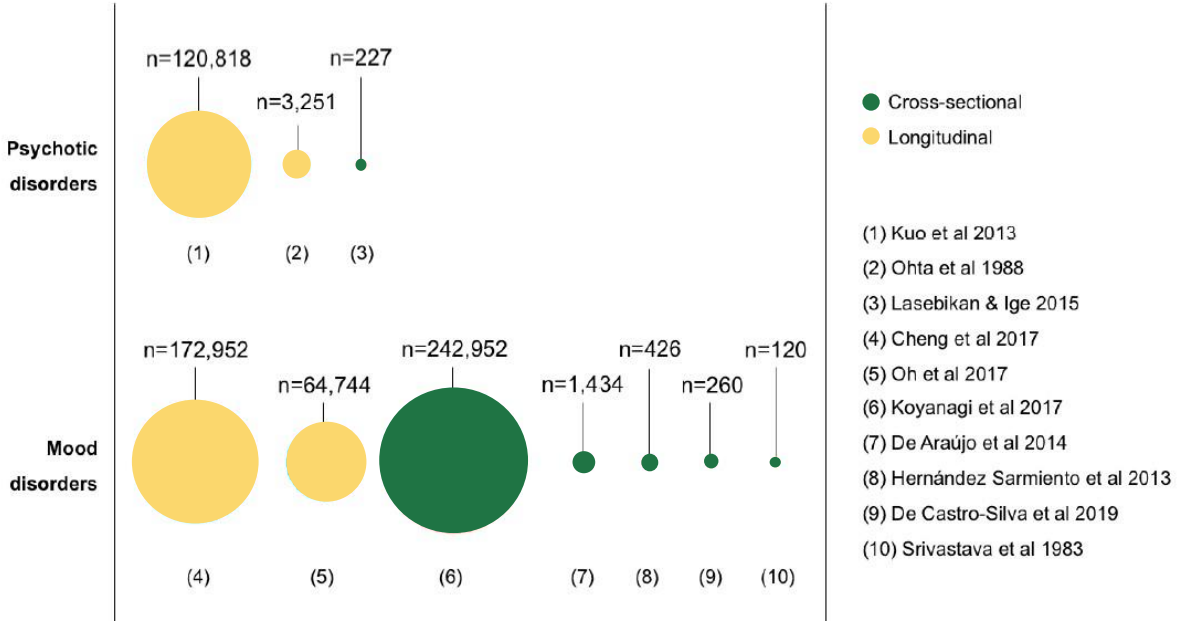
BMJ Open The relationship between mental health and risk of active tuberculosis: a systematic review

4 retrospective cohort studies
n=361 765 (59.6%)

High statistical value

5 cross-sectional studies

1 case-control studies



RESULTS – MOOD DISORDERS

longitudinal

	Primary outcome		Secondary outcomes		Statistical method	Adjustment
	Effect measure	Results	Effect measure	Results		
Oh *et al*[36]	Adjusted HR for TB incidence in depressed vs controls	2.63 (95% CI 1.74 to 3.96, p<0.001)	Adjusted HRs stratified by mild and severe depression	For mild depression=1.99 (95% CI 1.21 to 3.28, p=0.007), for severe depression=3.08 (95% CI 2.00 to 4.73 p<0.0001); linear dose-response	Cox proportional hazards model	Age, sex, income level, DM, COPD, alcoholism
Cheng *et al*[37]	Adjusted HR for pulmonary TB incidence in depressed vs controls	1.15 (95% CI 1.03 to 1.28)	–	–	Cox proportional hazards model	Age, sex, alcohol-related disease, CKD, chronic liver disease, COPD, DM, HIV infection, gastrectomy and pneumoconiosis

cross-sectional

Koyanagi *et al*[45]	Adjusted OR for depressive episode in those with pulmonary TB vs those without	3.68 (95% CI 3.01 to 4.50, p<0.0001)	Adjusted ORs for brief depressive episode and for subsyndromal depression	For brief depressive episode=1.75 (95% CI 1.26 to 2.42, p=0.0008), for subsyndromal depression=1.98 (95% CI 1.47 to 2.67, p<0.0001)	Logistic regression	Age, sex, education, wealth, household size, setting, current smoking, alcohol consumption, BMI, diabetes, country
Castro-Silva *et al*[41]	Prevalence of depression in pulmonary TB patients; crude OR	Screening tool: 60.2% vs 62.1% in controls (OR=0.92, 95% CI 0.55 to 1.54, p=0.79) Diagnostic tool: 59.5% vs 50.9% in controls (OR=1.42, 95% CI 0.63 to 3.19, p=0.42)	–	–	Logistic regression	–
de Araújo *et al*[42]	Adjusted OR for pulmonary TB in those with a CMD vs those without	1.34 (95% CI 1.05 to 1.70)	–	–	Logistic regression	Diabetes, alcohol abuse, ethnicity, drug use, number of household goods, level of education, history of contact and crowding
Hernández Sarmiento *et al*[43]	Crude and adjusted ORs for pulmonary TB in those with mental disorders	Dysthymia (adjusted)=2.54 (95% CI 1.10 to 5.86, p=0.028), dysthymia (crude)=2.66 (95% CI 1.19 to 5.19, p=0.013), previous history of major depression (crude)=2.22 (95% CI 1.07 to 4.6, p=0.028)	–	–	Logistic regression	Age, gender, time living on the streets, education level, marital status, interaction with other homeless people, income sources
Srivastava *et al*[38]	Prevalence of psychiatric illness in pulmonary TB patients vs controls	41.6% vs 13.3% in controls (p<0.001)	Prevalence of at least one psychiatric symptom in pulmonary TB patients	86.6% vs 70.0% in controls	χ^2 test	–

RESULTS – PSYCHOTIC DISORDERS

longitudinal

	Primary outcome		Secondary outcomes		Statistical method	Adjustment
	Effect measure	Results	Effect measure	Results		
Kuo *et al*[39]	Adjusted HR for TB incidence in those with schizophrenia vs controls	1.52 (95% CI 1.29 to 1.79, p<0.001)	–	–	Cox proportional hazards model	Age, sex, Charlson's score, COPD, DM, rheumatoid disease, peptic ulcer disease, liver disease, hypertension, arrhythmia, dyslipidaemia, drug or substance abuse, CKD, cancer, heart failure, peripheral vascular disease, myocardial infarction, hemiplegia/ paraplegia, AIDS
Ohta *et al* [40]	RR for TB incidence observed in those with schizophrenia vs expected based on general population rates	3.04 (p<0.005)	–	–	Observed vs expected relative risk	Age, sex

cross-sectional

Lasebikan and Ige [44]	Prevalence of psychosis and schizophrenia in patients with MDR-TB vs controls	Psychosis: 33.0% (18.3% excluding medication-induced psychotic disorders*) vs 2.7% in controls Schizophrenia: 8.7% vs 0.9% in controls (χ^2=5.9, p=0.02)	Prevalence of psychiatric morbidity in patients with MDR-TB vs controls	81.7% vs 51.7% in controls (χ^2=21.7, p<0.001)	χ^2 test	–

BMJ Open The relationship between mental health and risk of active tuberculosis: a systematic review

Mental disorders (depression and schizophrenia) increase risk of TB disease

Further research is needed to elucidated the pathways by which poor mental health may increase TB incidence

- direct influence on immune system?
- association with other factors for TB?

CONCLUSION

Potential benefit of LTBI screening and treatment for people with mental disorders

Interventions that tackle mental illnesses and their **underlying drivers** to reduce TB incidence

Integrated approach
TB-mental health

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TB-mental health

WHO recommendations update in 2023

Inclusion of new at-risk groups?

TUBERCULOSIS in children

1 million

TB cases per year

20%

Mortality

Few clinical efficacy trial in children (paucibacillary disease, difficulties in obtaining samples)

Most of the treatment recommendations for children are extrapolated from trials involving adults

Standard treatment
HRZE 6 months

WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents

2021-2022

WHO and CDC endorsement of a shortened **4 month** regimen

2 months

RPT
MOX
INH
PZA

+

2 months

RPT
MOX
INH

- age ≥ 12 years
- body weight ≥ 40 Kg
- drug-susceptible pulmonary TB
- NO extra-pulmonary involvement

World Health Organization. WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. https://www.who.int/publications/i/item/9789240046764

Carr W, Kurbatova E, Starks A, et al. Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis - United States, 2022. MMWR Morb Mortal Wkly Rep 2022; 71:285.

2021-2022

WHO and CDC endorsement of a shortened **4 month** regimen

2 months

RPT
MOX
INH
PZA

+

2 months

RPT
MOX
INH

- age ≥ 12 years
- body weight ≥ 40 Kg
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INH

- age ≥ 12 years
- body weight ≥ 40 Kg
- drug-susceptible pulmonary TB
- NO extra-pulmonary involvement

Rispetto agli adulti, nei **bambini** più frequenti forme **non gravi** con **espettorato negativo**

World Health Organization. WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. https://www.who.int/publications/i/item/9789240046764

Carr W, Kurbatova E, Starks A, et al. Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis - United States, 2022. MMWR Morb Mortal Wkly Rep 2022; 71:285.

Shorter
treatment
in **children**?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

Turkova A, Wills GH, Wobudeya E, et al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. N Engl J Med 2022; 386:911.
Chabala C, Turkova A, Thomason MJ, et al. Shorter treatment for minimal tuberculosis (TB) in children (SHINE): a study protocol for a randomised controlled trial. Trials 2018; 19:237.

RANDOMIZED CONTROLLED TRIAL

1204 children
age **< 16 years**
median age 3.4

South Africa
Uganda
Zambia
India

NON-SEVERE TB DISEASE

confined to one lobe, non-cavitary, non miliary; peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion

SMEAR NEGATIVE

at least two respiratory samples (gastric aspirate, expectorated sputum, or induced sputum)

DRUG SUSCEPTIBLE

confirmed
or
presumed

Turkova A, Wills GH, Wobudeya E, et al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. N Engl J Med 2022; 386:911.
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NON INFERIORITY TRIAL

4 months 2 HRZ(E) + 2 HR

vs

6 months 2 HRZ(E) + 4 HR

WHO-reccomended pediatric doses

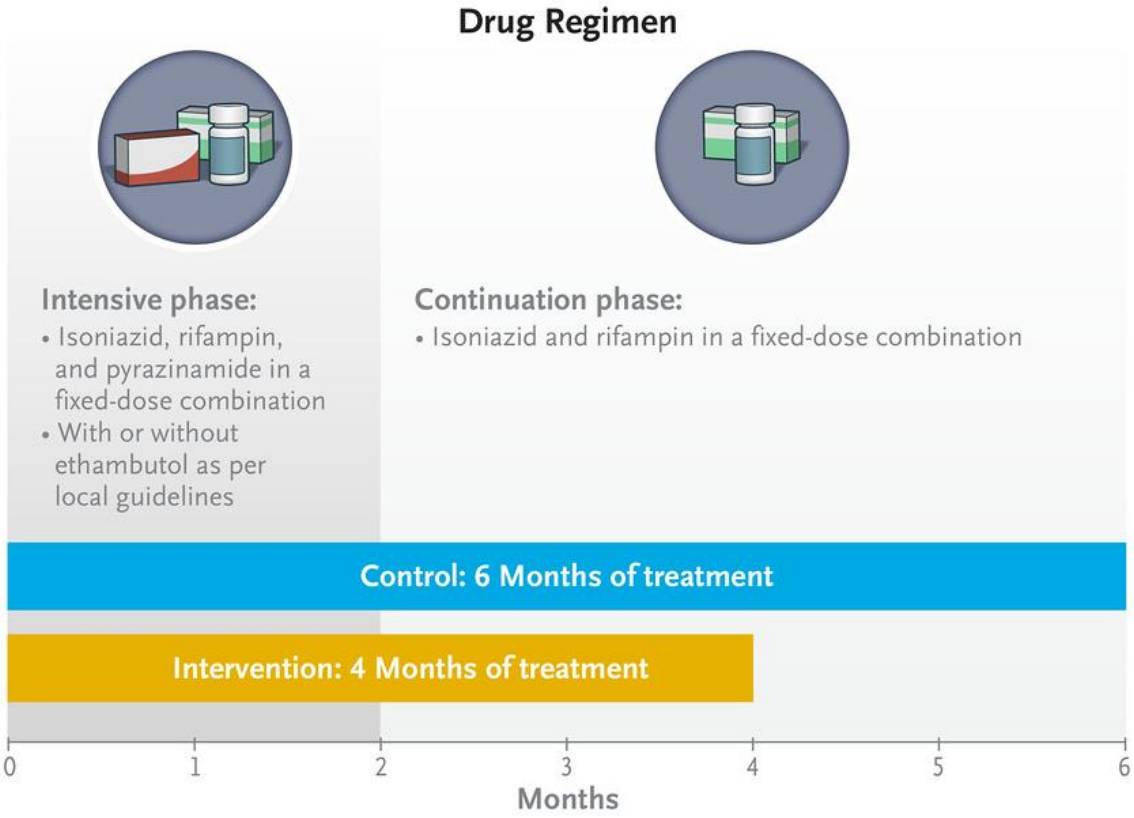
Primary efficacy outcome

Unfavorable status by 72 weeks:

- treatment failure
- loss to follow up
- death

Primary safety outcome

Adverse event of grade 3 or higher during treatment and up to 40 days after treatment



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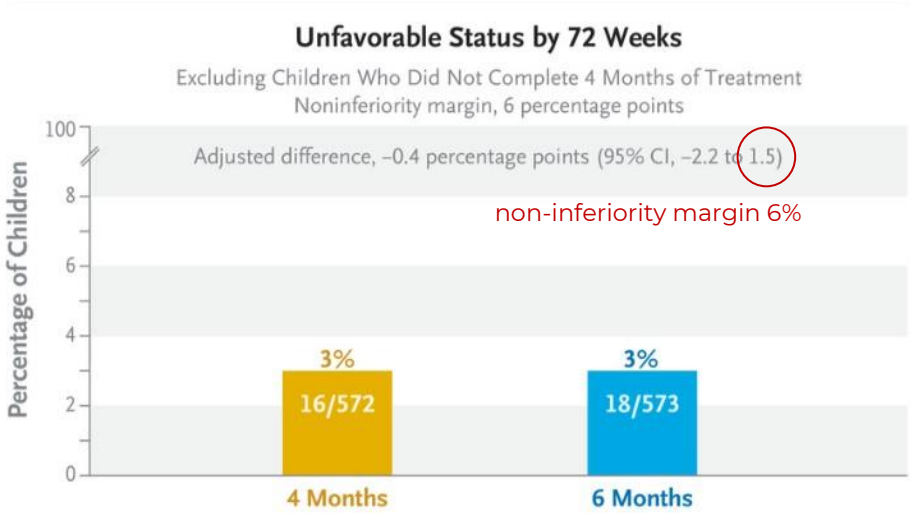
RESULTS
non inferiority

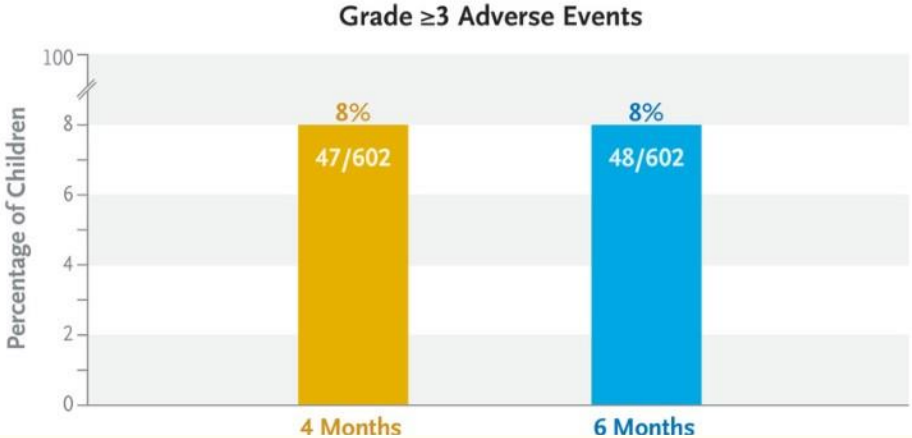
RESULTS

Efficacy: The percentage of children with an unfavorable status by week 72 did not differ significantly between the groups, showing noninferiority of the shorter regimen.

Safety: The percentage of children with an adverse event of grade 3 or higher during treatment or in the 30 days after treatment did not differ significantly between the groups. Pneumonia or other chest infections were the most common such events.

Cost effectiveness analysis
health care costs **-17,34 $** per child
(95% CI, 3.77 to 30.91)





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WHO

2022 new recommendations

Box 5.2 Recommendations on treatment regimens for children and adolescents

In children and adolescents aged between 3 months and 16 years with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used *(new: strong recommendation, moderate certainty of evidence)*.

- Age 3 months to 16 years
- Non-severe TB
- Non MDR/RR-TB

2 HRZ(E)
+
2 HR

WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents
WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-susceptible tuberculosis treatment

CONCLUSIONS

Future studies to explore treatment shortening regardless of smear result

Shortened regimen with the affordable, child friendly, fixed-dose combinations that are already available

Cost effectiveness » global **End TB Strategy**

Turkova A, Wills GH, Wobudeya E, et al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. N Engl J Med 2022; 386:911.

GRAZIE PER L'ATTENZIONE

Box 5.2 Recommendations on treatment regimens for children and adolescents

In children and adolescents aged between 3 months and 16 years with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used *(new: strong recommendation, moderate certainty of evidence)*.

Remarks:

- Non-severe TB is defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern.
- Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (2HRZE/4HR) or recommended treatment regimens for severe forms of extrapulmonary TB.
- The use of ethambutol in the first 2 months of treatment is recommended in settings with a high prevalence of HIV or of isoniazid resistance.

Children and adolescents with severe pulmonary TB disease should be treated with a four-medicine regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at standard dosages *(strong recommendation, moderate certainty of evidence)*.

Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB *(strong recommendation, low certainty of evidence)*.

Table 5.1. Pulmonary TB treatment regimens by age group, disease severity and local epidemiology

Age and severity of TB	Duration and composition of treatment regimen[a]	
	Intensive phase	Continuation phase
Infants aged <3 months or weighing <3 kg		
PTB of any severity	2HRZ or 2HRZE [b]	4HR
Children and adolescents aged 3 months to <12 years		
Non-severe PTB	2HRZ or 2HRZE [b]	2HR [c]
Severe PTB	2HRZE [c]	4HR
Adolescents aged 12–<16 years		
Non-severe PTB	2HRZ or 2HRZE [b]	2HR
Severe PTB	2HRZE [d]	4HR
PTB of any severity	2HPZM	2HPM
Adolescents aged 16–<20 years		
PTB of any severity	2HRZE [e]	4HR
PTB of any severity	2HPZM [f]	2HPM

[a] The standard code for TB treatment regimens uses an abbreviation for each medicine: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), rifapentine (P) and moxifloxacin (M). A regimen consists of two phases – the intensive and continuation phases. The number at the front of each phase represents the duration of that phase in months. For example, 2HRZE consists of treatment with isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months.

[b] In settings with a high HIV prevalence and/or a high isoniazid resistance prevalence, ethambutol should be added to the intensive phase of treatment. High HIV prevalence settings are defined as HIV prevalence ≥1% among adult pregnant women or ≥5% among people with TB. Thresholds for low, moderate or high levels of isoniazid resistance prevalence are established by country NTPs.

[c] The SHINE trial was a non-inferiority trial that compared a 4-month regimen (2HRZ(E)/2HR) with a 6-month regimen (2HRZ(E)/4HR). The 4-month regimen was shown to be non-inferior. Therefore, the 6-month regimen may also be used for children with non-severe PTB if the 4-month regimen has not been adopted.

[d] This regimen applies regardless of HIV prevalence and prevalence of isoniazid resistance.

[e] This regimen applies to older adolescents regardless of disease severity, HIV prevalence and prevalence of isoniazid resistance.

[f] This regimen applies to older adolescents regardless of disease severity, HIV prevalence and prevalence of isoniazid resistance, except for people weighing less than 40 kg and adolescents living with HIV with a CD4 count below 100 cells/mm^3.

In the SHINE trial, ethambutol was included in the first 2 months of treatment, depending on the local policy in place at the recruitment site for both the 4-month regimen and the comparator 6-month regimen. All children living with HIV in the SHINE trial received ethambutol in the first 2 months of treatment (regardless of the regimen they received).

It is preferred that children living with HIV who receive the 4-month regimen receive ethambutol for the first 2 months of treatment, irrespective of the background prevalence of HIV. In addition, it is strongly recommended that ethambutol be added to the 4-month regimen for the first 2 months in settings with a high background prevalence of isoniazid resistance or HIV infection.

Box 5.3 Eligibility criteria for the 4-month regimen (2HRZ(E)/2HR) in children and adolescents aged between 3 months and 16 years with non-severe pulmonary or peripheral lymph node TB in various settings

In children and adolescents who have undergone bacteriological testing and CXR, a 4-month treatment regimen should be started in children and adolescents meeting all of the following three criteria:

- CXR findings consistent with non-severe TB (CXR should ideally be done at baseline, but it can be performed at any point during the treatment course):
  - intrathoracic lymph node TB without significant airway obstruction; or
  - PTB confined to one lobe with no cavities and no miliary pattern; or
  - uncomplicated pleural effusion (without pneumothorax or empyema);
- TB that is negative, trace, very low or low using Xpert MTB/RIF or Ultra, or sputum smear-negative (if Xpert MTB/RIF or Ultra not available);
- the child or adolescent has mild TB symptoms that do not require hospitalization. [a]

In settings without access to CXR, a 4-month treatment regimen should be implemented in children and adolescents meeting all of the following three criteria:

- TB that is negative, trace, very low or low by Xpert MTB/RIF or Ultra, or smear-negative;
- the child or adolescent has mild TB symptoms that do not require hospitalization; [a]
- TB symptoms resolved completely within 1 month of treatment initiation and the child is completely well, including a normal nutritional status, at 4 months of treatment.

WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents
WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-susceptible tuberculosis treatment

In the absence of bacteriological testing and CXR, a 4-month treatment regimen may also be started in children and adolescents meeting any of the following two criteria:

- isolated extrathoracic (peripheral) lymph node TB, without involvement of other extrapulmonary sites of disease;
- the child or adolescent has mild TB symptoms that do not require hospitalization. [a]

[a] Mild symptoms that do not require hospitalization means:

- none of the danger or high-priority signs listed in Table 4.5;
- no asymmetrical and persistent wheezing;
- no signs of EPTB other than peripheral lymph node TB;
- none of the following: SAM, respiratory distress, high fever (over 39 °C), severe pallor, restlessness, irritability or lethargy.

Table 4.5. Danger and priority signs of severe illness or health problems in children aged under 10 years

Aged <5 years	Aged 5–9 years	All children aged <10 years
Danger signs (IMCI)	**Danger signs (ETAT)**	**Priority signs**
Gastrointestinal/circulatory: • Unable to eat or drink • Vomiting up everything • Signs of severe dehydration (sunken eyes, skin pinch returns very slowly) • Severe palmar pallor	Gastrointestinal/circulatory: • Diarrhoea with any two signs of severe dehydration (lethargy, unconsciousness, sunken eyes, very slow return of skin after pinching) • Signs of shock (cold extremities with capillary refill time >3 seconds, weak and fast pulse)	• Any sick child aged <2 months • High fever (>39° C) • Severe pallor • Respiratory distress • Restless, continuously irritable, lethargic • SAM
Respiratory: • Stridor • Oxygen saturation <90%	Respiratory: • Obstructed or absent breathing • Severe respiratory distress • Central cyanosis	
Neurological: • Seizures • Profoundly lethargic, unconscious • Neck stiffness or bulging fontanelle	Neurological: • Coma (or seriously reduced level of consciousness) • Seizures	

5.2.7.2. Dosage tables and formulations for treatment of drug-susceptible TB in children and adolescents

The use of FDC child-friendly tablets is recommended instead of separate formulations in the treatment of children with drug-susceptible TB *(100)*. FDC tablets have advantages over single medicines as they reduce the pill burden and the likelihood of prescription errors. By reducing selective non-adherence, FDC tablets can reduce the risk of development of drug resistance.

Box 5.6 WHO recommendation on use of fixed-dose combination tablets

The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB *(conditional recommendation, low certainty in the evidence)*.

Source: WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 *(3)*.

Dispersible child-friendly FDC formulations for first-line TB medicines have been available since 2015. They can be dispersed in water to achieve an appropriate dose offering the opportunity to simplify and improve treatment *(88, 100, 101)*. Child-friendly FDCs are WHO-prequalified. They are not new medicines but are improved formulations of medicines recommended and used for first-line treatment of TB.

Box 5.7 Currently available water-dispersible formulations for treatment of drug-susceptible TB

For the intensive phase of TB treatment:

- ➔ isoniazid 50 mg + rifampicin 75 mg + pyrazinamide 150 mg (HRZ 50/75/150 mg);
- ➔ a dispersible formulation of ethambutol (E 100 mg) is also available.

For the continuation phase of TB treatment:

- ➔ isoniazid 50 mg + rifampicin 75 mg (HR 50/75 mg). [a]

[a] This formulation is also used for the 3RH TPT regimen (see Chapter 3).

Table 5.3. Recommended dosages of first-line TB medicines for use in children and young adolescents aged 0–14 years (excluding TB meningitis treated with alternative short intensive regimen)

Medicine	Dose (mg/kg body weight)	Range (mg/kg body weight)
Isoniazid (H)	10	7–15 [a]
Rifampicin (R)	15	10-20
Pyrazinamide (Z)	35	30–40
Ethambutol (E)	20	15–25

[a] The higher end of the range for isoniazid applies to younger children. With older children, the lower end of the dosing range becomes more appropriate.