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Ministry of Health

រូបមន្តស្តង់ដារព្យាបាលជំងឺរបេង
Tuberculosis Standard Treatment Regimens

មជ្ឈមណ្ឌលជាតិកំចាត់រោគរបេង និងហង់សិន
National Center for Tuberculosis and Leprosy Control

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FOREWORD

Appropriate determination and correct use of anti-tuberculosis drugs with full duration and DOT implementation are of great importance for the cure of tuberculosis.

This standard tuberculosis treatment regimens booklet was prepared and revised based on treatment regimens recommended by WHO (2010 and 2011) and on the NTP booklet published in March 2008. The main revision focuses on the dosages and duration for treatment of childhood TB. This booklet contains three main parts: diagnosis, treatment regimens for adults and that for children.

This booklet is for health care workers who work in tuberculosis control at all levels. It is also useful for other health workforce and others who are involved and interested in tuberculosis control.

Phnom Penh, 03 October, 2011

Director General for Health Services

Dr. Tep Lun

A- TB Diagnosis

Tuberculosis is classified as pulmonary tuberculosis and extra-pulmonary tuberculosis

1. Pulmonary TB:

The major sign of pulmonary TB is prolonged cough of more than two to three weeks, in general productive. Smear microscopic examination should be done as quickly as possible for those who have this symptom. Cough of more than two to three weeks is usually accompanied with other symptoms such as weight loss, fatigue, fever, nocturnal fever, night sweats, chest paint, shortness of breath, loss of appetite and coughing up blood.

a- Smear positive pulmonary TB:

- At least two sputum specimens positive by microscopic examination, or
- One sputum specimen positive by microscopic examination and radiological abnormalities consistent with pulmonary TB, or
- One sputum specimen positive by microscopic examination, which is culture positive for M. tuberculosis.

b- Smear negative pulmonary TB:

- At least six sputum specimens negative by microscopic examination including radiological abnormalities consistent with active pulmonary TB.

2. Extra-pulmonary TB:

Confirmed diagnostic of extra-pulmonary TB is difficult and based on the available diagnostic tool including biopsy and histology.

Various forms of extra-pulmonary TB which have been observed frequently including lymph node TB, Pleural tuberculosis, pericardial tuberculosis, Meningitis tuberculosis, bone tuberculosis, miliary tuberculosis etc

Patients with extra-pulmonary TB also have general symptom similar to pulmonary TB : weight loss, nocturnal fever and night sweats.

Other symptoms occur relating to organs affected for example:

- Enlarge in size, sometime fistula for lymph node TB
- Swollen joint, sometime painful for joint TB
- Headache, fever, stiffness of the neck and somnolence for meningitis TB (especially for children).

If extra-pulmonary TB is suspected you have to refer them to referral hospital for diagnosis work up. For extra-pulmonary TB patient you have to detect pulmonary TB as well especially through sputum and X-ray examination if patient has productive cough.

3. TB in children: based on:

- **History-taking** (history of living close to TB patient and symptoms)

  * Close contact is defined as living in the same household as or in frequent contact with a source case (e.g. the child's caregiver) with sputum smear positive pulmonary TB.
  Symptoms: chronic cough, fever and weight loss or failure to thrive

- **Clinical Examination** (including growth assessment)

  * Physical signs highly suggestive of extra-pulmonary TB:
    - Gibbous deformity of the backbone especially recent onset (resulting from vertebral TB)
    - Non-painful enlarged cervical lymphadenopathy with fistula formation
  * Physical signs requiring investigation to exclude extra-pulmonary TB: TB Meningitis, Pleural effusion, pericardial effusion, abdomen distended ascites, non painful enlarged lymph node without fistula formation, non-painful enlarged joint and signs of tuberculin hypersensivity.

- **Tuberculin Skin Test:**

Tuberculin skin test positive occurs when person is infected with Mycobacterium tuberculosis but it does not necessarily mean that a person has active tuberculosis. Tuberculin skin test can also be used as an adjunct in diagnosing TB in children with signs and symptoms of TB and when used in conjunction with other diagnostic tests.
Tuberculin skin test should be regarded as positive as follow:

* in high-risk children (including HIV infected children and severely malnourished children): ≥5mm diameter of induration
* in all other children (whether they have received a bacille Calmette Guerin (BCG) vaccination or not): ≥10mm diameter of induration

- **Bacteriological confirmation whenever possible**

Appropriate specimens from the suspected sites of involvement (sputum, gastric aspirates, lymph node biosy and any other material that is biopsied) should be obtained for microscopy and where facilities and resources are available, for culture and also histo-pathological examination.

- **Investigations relevant for suspected pulmonary TB and suspected extra-pulmonary TB**

* Suspected pulmonary TB: chest X-ray: opacification, miliary, infiltrates.
* Suspected extra-pulmonary TB:
  - Peripheral lymph node : lymph node biopsy or fine needle aspiration
  - Miliary TB: chest X-ray and lumbar puncher
  - TB menigitis: lumbar puncher and computerized tomography where available)
  - Pleural effusion: chest X-ray, pleural aspiration
  - Abdominal TB: abdominal ultrasound and ascitic tap
  - Osteoarticular : X-ray, joint tap or synovial biopsy
  - Pericardial TB: ultrasound and pericardial tap

- **HIV testing**

All children suspected of having TB is recommended to take HIV testing .

In cases where specimens or examination result is negative of not available, the presence of three or more of the following should strongly suggest a diagnosis of TB in children:

- chronic symptoms suggestive of TB
- Physical signs highly of suggestive of TB
- A positive Tuberculin skin test or close contact with newly diagnosed smear positive case
- Chest X-ray suggestive of TB

B- TB Treatment Regimens for Adults

There are three categories of standard treatment regimens for tuberculosis in adult in the Kingdom of Cambodia. Each category has total duration of 6 to 8 months and consists of two phases, the initial phase (intensive phase) and the continuation phase.

Treatment Category 1: 2RHZE / 4RH

This category 1 of treatment is used for treating:

- New smear-positive pulmonary TB
- Smear-negative pulmonary TB, severe form.
- Extra-pulmonary TB, severe form.
- TB/HIV patients.

Initial Phase: 2 months*

In this phase, TB patients have to take 4 TB drugs every morning for 2 months under direct observation by health staff or trained person (called " DOT ").

The 4 drugs are Rifampycin and Isoniazid (combined tablet), Pyrazinamid and Ethambutol.

** At the end of the second month, if sputum smear examination is still positive then one month more of the initial phase has to be undertaken. In this case, the continuation phase still has 4 months and the total duration of treatment is 7 months.*

Continuation Phase: 4 months

In this phase, TB patients have to take 2 TB drugs every morning for 4 months under direct observation by community member receiving instruction by health worker.

The 2 drugs are Rifampicine and Isoniazid (combined tablet).

Please see table on next page for dosage.

Category 1: 2RHZE / 4RH

Intensive Phase: 2 months		Contiuation Phase: 4 months
Weight Band (kg)	RHZE 150/75/400/275 mg	RH 150/75 mg
30-39 Kg	2 tabs	2 tabs
40-54 Kg	3 tabs	3 tabs
55-70 Kg	4 tabs	4 tabs
> 70 Kg	5 tabs	5 tabs
Dosage/Kg/day	R = 10 mg, H = 5 mg, Z = 25 mg, E = 15 mg	

Notes: RHZE: Rifampicin + Isoniazid + Pyrazinanide + Ethambutol, RH: Rifampicin + Isoniazid

Treatment Category 1:
Treatment regimen for Tuberculous meningitis or Miliary TB:
2RHZS [1] / 4RH

In this regimen, we use Streptomycin instead of Ethambutol because Streptomycin can better diffuse through meninges barriers.

Initial Phase: 2 months:

In this phase, the TB patients have to take tablets or injection 5 TB drugs every morning for 2 months under direct observation by health staff or trained person (called DOT).
The 5 drugs are Rifampycin, Isoniazid, Pyrazinamid and Ethambutol (combined tablet), and Streptomycin.

Continuation Phase: 4 months

In this phase, TB patients have to take 2 TB drugs every morning for 4 months.

The 2 drugs are Rifampicin and Isoniazid (combined tablet).

Please see table on next page for dosage.

[1] *In case there is no combined form RHZ, RHZE can be used with Streptomycin*

Category 1: 2RHZES / 4RH

This treatment regimen for TB meningitis or Miliary TB

Intensive Phase: 2 months			Continuation Phase 4 months
Weight Band (kg)	RHZ* 150/75/400 mg	S 1000 mg	RH 150/75 mg
30-39 Kg	2 tabs	500	2 tabs
40-54 Kg	3 tabs	750	3 tabs
55-70 Kg	4 tabs	1000	4 tabs
> 70 Kg	5 tabs	1000	5 tabs
Dosage/Kg/day	R = 10 mg, H = 5 mg, Z = 25 mg, E = 15 mg, S = 15 mg		

Notes: RHZ: Rifampicin + Isoniazid + Pyrazinanide, RH: Rifampicin + Isoniazid and E: Ethambutol, S: Streptomycin

* *In case there is no RHZ available RHZE can be replaced*

Treatment Category 2: 2RHZES / 1RHZE / 5RHE

This category 2 of treatment is used for treating:

- Relapse cases
- Failure cases
- Return after default cases
- Others.

Initial Phase: 3 months* divided into 2 parts:

The first part of initial phase lasts for 2 months using 5 drugs. Within this period, the TB patients have to take tablets or injection every morning under direct observation by health staff or trained person.
The 5 drugs are Rifampycin, Isoniazid, Pyrazinamid and Ethambutol (combined tablet), and Streptomycin.
The second part of initial phase lasts for 1 months using 4 drugs. Within this period, TB patients must take drugs every morning under direct observation by health staff or trained person.
The 4 drugs are Rifampycin, Isoniazid, Pyrazinamid and Ethambutol (combined tablet).

* *At the end of the third month, if sputum smear examination is still positive then one month more of the initial phase has to be prolonged (the second part). In this case, the continuation phase has only 4 months.*

Continuation Phase: 5 months

In this phase, TB patients have to take 3 TB drugs every morning directly observed by instructed community member.
Drug distribution should be done weekly together with regular advice from health worker.
The 3 drugs are Rifampycin and Isoniazid (combined tablet), and Ethambutol.

Please see table on next page for dosage.

Category 2: 2RHZES / 1RHZE / 5RHE

Intensive Phase: 3 months				Continuation Phase: 5 months	
Month 1 and Month 2			Month 3	Month 4 to Month 8	
Weight Band (kg)	RHZE 150/75/400/275 mg	S 1000 mg	RHZE 150/75/400/275 mg	RH 150/75 mg	E 400 mg
30-39 Kg	2 tabs	500 ម.ក្រ	2 tabs	2 tabs	1.5 tabs
40-54 Kg	3 tabs	750 ម.ក្រ	3 tabs	3 tabs	2 tabs
55-70 Kg	4 tabs	1000 ម.ក្រ	4 tabs	4 tabs	3 tabs
>70 Kg	5 tabs	1000 ម.ក្រ	5 tabs	5 tabs	3.5 tabs
Dosage/Kg/day	R = 10 mg, H = 5 mg, Z = 25 mg, E = 15 mg, S = 15 mg				

Notes: RHZE: Rifampicin + Isoniazid + Pyrazinanide + Ethambutol, RH: Rifampicin + Isoniazid and E: Ethambutol

S: Streptomycin. For Patient > 45 years old, dose of Streptomycin is only 750 mg/day

Streptomycin is prohibited to use for Pregnant woman

Treatment Category 3: 2RHZE / 4RH

This category is used for treating:

- smear-negative pulmonary TB, non-severe form.
- extra-pulmonary TB, non-severe form.

Initial Phase: 2 months

In this phase, TB patients must take 4 TB drugs every morning for 2 months under direct observation by health staff or trained person.
The 4 drugs are Rifampycin and Isoniazid, Pyrazinamid and Ethambutol (combined tablet).

Continuation Phase: 4 months

In this phase, TB patients have to take 2 TB drugs every morning for 4 months.
The 2 drugs are Rifampicin and Isoniazid (combined tablet)

Please see table on next page for dosage.

Category 3: 2RHZE / 4RH

Intensive Phase: 2 months		Contiuation Phase: 4 months
Weight Band (kg)	RHZE 150/75/400/275 mg	RH 150/75 mg
30-39 Kg	2 tabs	2 tabs
40-54 Kg	3 tabs	3 tabs
55-70 Kg	4 tabs	4 tabs
> 70 Kg	5 tabs	5 tabs
Dosage/Kg/day	R = 10 mg, H = 5 mg, Z = 25 mg, E = 15 mg	

Notes: RHZE: Rifampicin + Isoniazid + Pyrazinanide +Ethambutol, RH: Rifampicin + Isoniazid

C- TB Treatment Regimens for Children

The treatment of tuberculosis in children has also two phases the same as adults, the initial and continuation phases.

Treatment Category 1: 2RHZE / 4RH

This category 1 of treatment is used for treating children who has:

- New smear-positive pulmonary TB
- Smear-negative pulmonary TB, severe form.
- Extra-pulmonary TB, severe form.
- TB/HIV patients.

Initial Phase: 2 months*

In this phase, TB patients have to take 4 TB drugs every morning for 2 months under direct observation by health staff or trained person (called " DOT ").

The 4 drugs are Rifampycin, Isoniazid and Pyrazinamid (combined tablet), and Ethambutol.

** At the end of the second month, if sputum smear examination is still positive then one month more of the initial phase has to be undertaken. In this case, the continuation phase still has 4 month and the total duration of treatment is 7 months.*

Continuation Phase: 4 months

In this phase, TB patients have to take 2 TB drugs every morning for 4 months.

The 2 drugs are Rifampicine and Isoniazid (combined tablet).

Please see table 5 on next page for dosage.

Category 1: 2RHZE/ 4RH

for use in children under 15 years

Weight Band (kg)	Intensive Phase: 2 months				Continuation Phase: 4 months	
	RHZ 60/30/150	**RH** 60/30	**H** 100	**E** 100	**RH** 60/30	**H** 100
<=7	1 tab	1 tab		1 tab	2 tabs	
8-10	2 tabs	1 tab		2 tabs	3 tabs	
11-13	3 tabs	1 tabs		2 tabs	4 tabs	
14-15	3 tabs	2 tabs		3 tabs	5 tabs	
16-20	4 tabs	1 tab	1 tab	4 tabs	5 tabs	1 tab
21-25	5 tabs	2 tab	1 tab	5 tabs	7 tabs	1 tab
26-29	6 tabs	3 tab		6 tabs	9 tabs	
Dosage/Kg/day	R=15mg (10-20), H=10mg (10-15) , Z=35mg (30-40), E=20mg (15-25)					

Notes: RHZ: Rifampicin + Isoniazid + Pyrazinanide, RH: Rifampicin + Isoniazid and E: Ethambutol

Treatment regimen for Tuberculous meningitis or osteoarticular TB: 2RHZE / 10 RH

In this regimen, WHO recommended NTP to use a 4 drug-regimen (RHZE) for 2 months, followed by a two-drug regimen (RH) for 10 months; the total duration of treatment being 12 months (RAPID ADVICE).

This regimen of treatment is used for treating children who has:

- TB Meningitis
- Miliary TB
- Osteoarticular TB

Initial Phase: 2 months:

In this phase, the TB patients have to take tablets or injection 4 TB drugs every morning for 2 months under direct observation by health staff or trained person.

The 4 drugs are Rifampycin, Isoniazid and Pyrazinamid (combined tablet), and Ethambutol.

Continuation Phase: 10 months

In this phase, TB patients have to take 2 TB drugs every morning for 4 months.

The 2 drugs are Rifampicine and Isoniazid (combined tablet).

Please see table on next page for dosage.

Category 1: 2RHZE/ 10 RH

for use in children under 15 years

Weight Band (kg)	Intensive Phase: 2 months				Continuation Phase:**10** months	
	RHZ 60/30/150	**RH** 60/30	**H** 100	**E** 100	**RH** 60/30	**H** 100
<=7	1 tab	1 tab		1 tab	2 tabs	
8-10	2 tabs	1 tab		2 tabs	3 tabs	
11-13	3 tabs	1 tabs		2 tabs	4 tabs	
14-15	3 tabs	2 tabs		3 tabs	5 tabs	
16-20	4 tabs	1 tab	1 tab	4 tabs	5 tabs	1 tab
21-25	5 tabs	2 tab	1 tab	5 tabs	7 tabs	1 tab
26-29	6 tabs	3 tab		6 tabs	9 tabs	
Dosage/Kg/day	R=15mg (10-20), H=10mg (10-15) , Z=35mg (30-40), E=20mg (15-25)					

Notes: RHZ: Rifampicin + Isoniazid + Pyrazinanide, RH: Rifampicin + Isoniazid and E: Ethambutol

Treatment Category 2: 2RHZES / 1RHZE / 5RHE

This category 2 of treatment with total duration of 8 months is used for treating:

- Relapse cases
- Failure cases
- Return after default cases
- Others.

Initial Phase: 3 months* divided into 2 parts:

The first part of initial phase lasts for 2 months using 5 drugs. Within this period, the TB patients have to take tablets or injection every morning under direct observation by health staff or trained person.
The 5 drugs are Rifampycin, Isoniazid and Pyrazinamid(combined tablet), Ethambutol and Streptomycin.
The second part of initial phase lasts for 1 months using 4 drugs. Within this period, TB patients must take drugs every morning under direct observation by health staff or trained person.
The 4 drugs are Rifampycin, Isoniazid and Pyrazinamid (combined tablet), and Ethambutol.

* *At the end of the third month, if sputum smear examination is still positive then one month more of the initial phase has to be prolonged. In this case, the continuation phase has only 4 months.*

Continuation Phase: 5 months

In this phase, TB patients have to take 3 TB drugs every morning directly observed by instructed community or family member. Drug distribution should be done weekly together with regular advice from health worker.
The 3 drugs are Rifampycin and Isoniazid (combined tablet), and Ethambutol.

Please see table on next page for dosage

Category 2: 2RHZES/1 RHZE/ 5 RHE
for use in children under 15 years

Weight Band (kg)	Intensive Phase: 3 months									Continuation Phase 5 months		
	Month 1 and Month 2					Month 3						
	RHZ 60/30/150	**RH** 60/30	**H** 100	**E** 100	**S** **1g**	**RHZ** 60/30/150	**RH** 60/30	**H** 100	**E** 100	**RH** 60/30	**H** 100	**E** 100
<=7	1 tab	1 tab		1 tab	100mg	1 tab	1 tab		1 tab	2 tabs		1tab
8-10	2 tabs	1 tab		2 tabs	150mg	2 tabs	1 tab		2 tabs	3 tabs		2tabs
11-13	3 tabs	1 tab		2 tabs	200mg	3 tabs	1 tab		2 tabs	4 tabs		2 tabs
14-15	3 tabs	2 tabs		3 tabs	250mg	3 tabs	2 tabs		3 tabs	5 tabs		3 tabs
16-20	4 tabs	1 tab	1 tab	4 tabs	300mg	4 tabs	1 tab	1 tab	4 tabs	5 tabs	1tab	4 tabs
21-25	5 tabs	2 tabs	1 tab	5 tabs	350mg	5 tabs	2 tabs	1 tab	5 tabs	7 tabs	1 tab	5 tabs
26-29	6 tabs	3 tabs		6 tabs	400mg	6 tabs	3 tabs		6 tabs	9 tabs		6 tabs
Dosage/Kg/day	R=15mg (10-20), H=10mg (10-15) , Z=35mg (30-40), E=20mg (15-25), **S**= 15 mg											

Notes: RHZ: Rifampicin + Isoniazid + Pyrazinanide, RH: Rifampicin + Isoniazid and E: Ethambutol, S: Streptomycin

Treatment Category 3: 2RHZ / 4RH

This category is used for treating:

- smear-negative pulmonary TB, non-severe form.
- extra-pulmonary TB, non-severe form.

Initial Phase: 2 months

In this phase, TB patients must take 3 TB drugs every morning for 2 months under direct observation by health staff or trained person.
The 3 drugs are Rifampycin, Isoniazid and Pyrazinamid (combined tablet).

Continuation Phase: 4 months

In this phase, TB patients have to take 2 TB drugs every morning for 4 months.
The 2 drugs are Rifampicin and Isoniazid (combined tablet)

Please see table on next page for dosage.

Note: Drugs administration should be closely monitored and drugs should be distributed weekly or more frequently.

Category 3: 2RHZ/ 4RH
for use in children under 15 years

Weight Band (kg)	Intensive Phase: 2 months			Continuation Phase: 4 months	
	RHZ 60/30/150	**RH** 60/30	**H** 100	**RH** 60/30	**H** 100
<=7	1 tab	1 tab		2 tabs	
8-10	2 tabs	1 tab		3 tabs	
11-13	3 tabs	1 tab		4 tabs	
14-15	3 tabs	2 tabs		5 tabs	
16-20	4 tabs	1 tab	1 tab	5 tabs	1 tab
21-25	5 tabs	2 tabs	1 tab	7 tabs	1 tab
26-29	6 tabs	3 tabs		9 tabs	
Dosage/Kg/day	R=15mg (10-20), H=10mg (10-15) , Z=35mg (30-40)				

Notes: RHZ: Rifampicin + Isoniazid + Pyrazinanide, RH: Rifampicin + Isoniazid and

D. Definition

Tuberculosis : Tuberculosis is an infectious disease caused by Mycobacterium Tuberculosis.

Classification according to localization and bacteriological status:

- Smear positive pulmonary tuberculosis :

a) Either: a patient with at least two sputum specimens positive by microscopic examination.

b) Or: a patient with one sputum specimen positive by microscopic examination and radiological abnormalities consistent with pulmonary TB, and a decision by a physician.

c) Or: a patient with one sputum specimen positive by microscopic examination, which is culture positive for M. tuberculosis.

- Smear negative pulmonary tuberculosis:

A patient with radiological abnormalities consistent with pulmonary TB. At least six sputum specimens negative by microscopic examination and lack of clinical response despite using a broad spectrum of antibiotics, and a decision by a physician to treat.

- Extra-pulmonary tuberculosis :

Extra-pulmonary tuberculosis is tuberculosis affecting organs other than the lungs such as hilar nodes, pleura, cervical lymph nodes, meninge, bone, joints etc.

Diagnosis is based on culture of biopsy of tissue concerned and clinical signs suggestive of TB, and a decision by a physician to treat.

Category of Diagnosed Patient:

- ***New case :*** A patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than one month.

- ***Relapse :*** A patient previously treated for TB who has been declared cured or treatment completed, and is now diagnosed with bacteriologically positive tuberculosis.

- ***Failure :*** A patient who, while on treatment, has sputum positive at month 5 or later between month 5 and end of treatment.

- ***Return After Default :*** A patient who has been treated for at least one month and return with sputum smear positive after interrupting treatment for more than two months.

- ***Transfer in :*** A patient who has been transferred from the treatment center of another operational district for continuing treatment.

- ***Others:*** All other cases that are not mentioned in the above five categories. These include chronic cases, those who has sputum smear positive at the end of re-treatment regimen.

Note :
Although smear negative pulmonary cases or extra-pulmonary cases may also be treatment failure, relapse or chronic cases, but this is a rare event (supported by pathological or bacteriological evidence).

Definition of Treatment Result:

- ***Cure:*** A patient who is sputum smear negative at the end of month 5 and month 8.

- ***Completed :*** A patient who has completed treatment, but who does not meet the criteria to be classified as a cure or failure.

- ***Treatment failure :*** A patient who is sputum smear positive at the end of month 5 or later during treatment.

- ***Died :*** A patient who dies for any reason during the course of treatment.

- ***Defaulter :*** A patient whose treatment was interrupted for two consecutive months or more.

- ***Transfer out :*** A patient who has been transferred to another treatment facility of another operational district and for whom the treatment result is not known.

- ***Treatment success:*** is the combination of cure and treatment completed.

Note: in countries where culture is current practice; patient can be classified as cure or failure on the basis of culture result.

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