# LTBI management -experience in Japan-

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## 1. History of treatment for latent tuberculosis infection (LTBI)

At first, target for LTBI treatment under government policy was young child contact and TST convertor detected on BCG vaccination. Afterwards, it was extended to adolescent and young adult. While LTBI treatment for medical risk group was given under clinical decision. In 2007, both targets were integrated in the government policy. The academia published technical guidelines for contact investigation and LTBI treatment.

| Public health- under government policy | clinical Practice and academia |
|---|---|
| 1957【0-3 year old 】: TST positive without BCG (under mass TST testing before BCG and contact investigation)<br>1974【0-14 year old 】: TST strong positive (under mass TST testing)<br>1989【0-14 year old 】: contact of sputum smear positive with strong TST positivity and【15-29 year old 】contact under outbreak investigation | Until 2005, LTBI treatment was given to medical risk groups (HIV positive and hemodialysis and RA) under clinical decision |
| 2007 LTBI target is expanded to medical risk group (other than contact ), and as for contact with no age limitation on the contact investigation | 2005, Japan tuberculosis society and Japan college of Rheumatology recommended to expand LTBI treatment to medical high risk groups such as RA |
| ※Guide for contact investigation ( prepared by research group) suggested to limit LTBI treatment to age group less than 50 years old in 2007 but is extended to older group from 2010) | 2013, Japan tuberculosis society published Guidelines for LTBI treatment. |

Fig.1 Historical perspective of LTBI treatment

## 2. National policy on LTBI

1)The Guidelines for specific infectious disease on tuberculosis by MHLW revised in May 2011 mentioned:
- Strengthening LTBI treatment
- Strengthen contact investigation with active use of IGRA

2) LTBI is mandatory notification by Infectious Disease Law #12
Revised notification criteria in 2007 include LTBI patient who need treatment.

3) Medical cost for LTBI treatment is covered:
by health insurance (70%) and public subsidy (25%), → patient pay 5% of the medical cost

4) LTBI patients is support by public health center according to Japanese DOTS Strategy

## 3. Target of LTBI treatment

Target for LTBI treatment should be selected considering 6 points below:

1) Risk of infection and developing active TB
- Consider LTBI treatment proactively: RR>4
  HIV/AIDS, organ transplant (immunosuppressant), silicosis, hemodialysis, recent infection (within 2 years) ≒those who are detected through contact investigation and child who showed Koch's phenomenon after BCG, old TB lesion on chest X-ray (untreated) and use of biologics
- Consider LTBI treatment when risk factor overlap: RR<4
  Use of corticosteroid (oral/ inhalation) , DMARDs and other immunosuppressant, poorly controlled DM, low body weight, smoking, gastrectomy

2) Diagnosis of TB infection: IGRA should be used except for BCG unvaccinated person

3) Image diagnosis using chest X-ray
- Purposes are to exclude active TB and to identify old TB

※ CT would be applied to IGRA positive with high risk of having active disease

4) Negative effect when person developing disease
- Those who could be source of secondary infection to many people (such as teacher, HCW etc.)
- Those who may cause serious problem when developing the disease (such as organ transplant)

5) Possibility of side effect by the drug; especially in the elderly

6) Possibility of treatment completion
- Those who is going to a country where no program for LTBI is available

## 4. Contact investigation

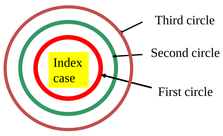
1) Legal framework : Infectious Disease Law

Article 15: proactive epidemiological survey
- Prefectural governor has authority to investigate status, trend and cause of infectious disease, which is delegated to director of public health center.
- The subject must cooperate to the investigation
- It is out of the privacy protection law to Inform the patient's privacy to health center

Article 17: Health check up
- Prefectural governor has authority to recommend (to force, if not followed) taking health examination to a person who have rational reason to suspect being infected with contagious disease.

2) purpose
① detect the infected to give LTBI treatment
②detect active case
③Identify source of infection

3) Principle
"stone in pond" procedure
expand the target by risk of infection




4)contact examination
- Needs for contact examinations should be decided considering Infectiousness and site of disease.
- Excluding NTM is important

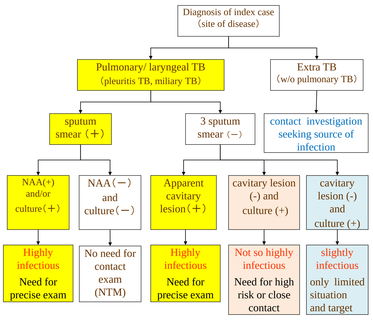



Fig. 2 decision on needs of contact examination

5) Priority group for the examination
- Depend of closeness to the index case, immunological status etc.

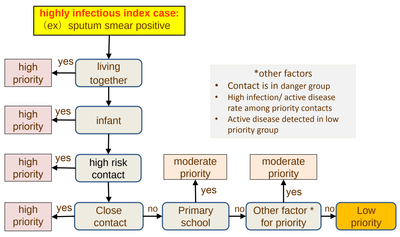



Fig. 3 Priority group for the examination

6) Algorithm for contact investigation:

Adult
- IGRA is primary tool

Child under school age
- TST first for BCG unvaccinated
- IGRA and TST should be done at same time for BCG vaccinated child
- TST first is an option in health center taking blood from child is difficult

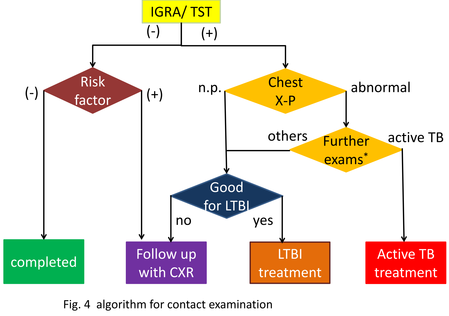



Fig. 4 algorithm for contact examination

## 5. Treatment Regimen

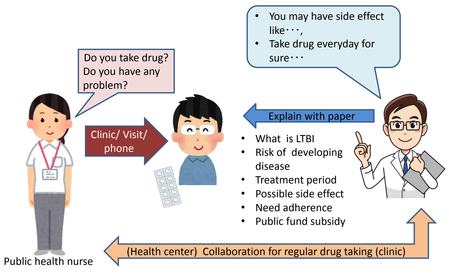
Current recommendatin
- INH: 6 or 9 months
- RIP: 4 or 6 months, in case of INH resistant or side effect
- Dose for children
  INH：10mg/kg（twice of adult dose ）, max: 300mg
  RIP：10-20mg/kg（same to twice of adult dose）, max: 600mg

In case both INH and RFP in not applicable
- Japanese Society for Tuberculosis do not suggest recommendation
  - ➢ Careful follow up without treatment is an option (If disease development are detected, proper treatment as MDR should be immediately given ) , because failure of LTBI treatment may cause further resistant disease.
  - ➢ LTBI treatment for such case should be given by the experienced physician for MDR TB treatment.

Future consideration
- INH+RIP: 3 months ,
- INH+ RPT: weekly 3 month (RPT is not available in Japan)

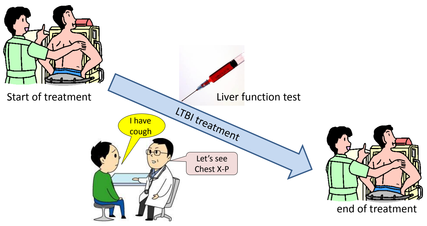
## 6. Health education & patient support

- Health center provide patient support based on Japanese DOTS strategy




## 7. Monitoring for active TB and side effect

- Chest X-ray: at start and end of treatment
- Careful observation for TB symptom is required. If symptom and /or sign are noticed, physical examination , chest X-P etc. should be done.
- Liver function test every 1 to 2 months is recommended: : patients with history of liver dysfunction, pregnant woman, HIV (+) , alcoholism etc.




## 8. Current situation on LTBI treatment

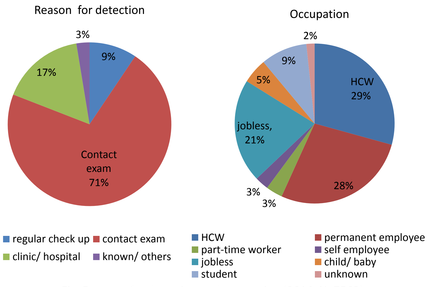



Fig. 5 reason for detection and occupation (2014, N=7562)
70% of LTBI was detected through contact survey. Health care worker comprise 29%

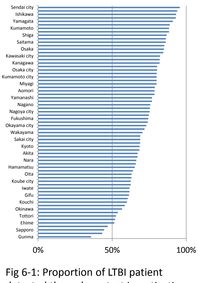



Fig 6-1: Proportion of LTBI patient detected through contact investigation

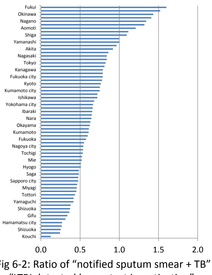



Fig 6-2: Ratio of "notified sputum smear + TB" to "LTBI detected by contact investigation"

Fig. 6 reason for detection and occupation (2014, N=7562)
70% of LTBI was detected through contact survey. Health care worker comprise 29%

## 9. Issue & challenge

1) Notification coverage: How many cases are missing? Especially patients LTBI treated
2) Diagnostic value of IGRA for patient with immunological problems, aged population, migrant form high incidence country etc.
3) Treatment regimen: application of shorter course regimen (under discussion)
4) Relevancy of LTBI treatment for aged population, immigrant from high incidence country, inmates etc.
   - Risk of side effect, default etc.
5) DOTS implementation rate for LTBI (Proportion of LTBI patients with full evaluation of the risk of default and full support for regular intake of drugs among LTBI patients with registration) : 76% in 2014 ,(target is 85%)
6) Larger difference of outcome by health center→developing indicators for implementation of contact investigation( The study is on-going)
   Candidate indicators:
   (1) Contact to case ratio
   (2) % of contacts clinically evaluated
   (3) % of IGRA positive among contacts
   (4) % of LTBI and (5) TB among contacts
   (6) % of LTBI and (7) TB who started treatment
   (8) % of LTBI and (9) TB whose treatment result was confirmed
   (10) % of LTBI and (11) TB who completed treatment
7) Monitoring after LTBI treatment (under controversy)
   - It was reported that 3.8% of IGRA positive and LTBI treatment completed group among the contact developed active disease
   - Developing active TB after LTBI treatment is thought to be not so frequent, maybe because usual LTBI treated group must be a mixture of high and low risk population
   - Risk for developing disease after treatment depend on accuracy of diagnosis, individual risk of developing disease , adherence to treatment etc.→It may be better to follow up very high risk person such as contacts of large scale outbreak case, close contact to highly infectious index case etc.