WHO Recommendation for IGRA Testing

ARYATI

26 Agustus 2023

INTERFERON GAMMA RELEASE ASSAY (IGRA)

WHAT

- Pemeriksaan in vitro yang mengukur interferon gamma yang dilepaskan limfosit pada darah setelah inkubasi semalam dengan paparan terhadap antigen spesifik *M. tuberculosis* (*ELISA based*) atau jumlah limfosit-T yang memproduksi interferon-gamma (*ELISPOT Based*)
- Merupakan reaksi hipersensitifitas tipe IV/ *delayed hypersensitivity*

WHO

1. Orang dengan peningkatan resiko progresi TB laten → TB aktif
2. Orang dengan peningkatan risiko terpapar TB aktif

WHEN

Active TB case finding → tanpa tanda/gejala dan memiliki faktor risiko

WHO consolidated guidelines on tuberculosis: Module 3: Diagnosis – Tests for tuberculosis infection. Geneva: World Health Organization; 2022.

INTERFERON GAMMA RELEASE ASSAY (IGRA)

WHERE

Fasilitas kesehatan yang memiliki peralatan dan personel untuk pemeriksaan IGRA

WHY

Pemeriksaan IGRA dapat membantu dalam pemberian *Tuberculosis Preventive Treatment* (TPT) yang tepat sasaran

HOW

- QuantiFERON®-TB Gold In-Tube or Gold Plus (QIAGEN GmbH, Hilden, Germany)
- T-SPOT.TB (Oxford Immunotec Ltd, Abingdon, United Kingdom)
- WANTAI TB-IGRA (Beijing Wantai Biological Pharmacy Enterprise Co., Beijing, China)

WHO consolidated guidelines on tuberculosis: Module 3: Diagnosis – Tests for tuberculosis infection. Geneva: World Health Organization; 2022.

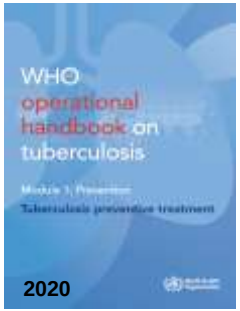
WHO : Use of IGRA in low- and middle- income countries - 2011

1

- IGRA atau TST tidak dapat digunakan untuk diagnosis TB aktif
- IGRA tidak dapat menggantikan TST pada negara pendapatan rendah-menengah

WHO Operational Handbook on Tuberculosis – Modul 1 : Tuberculosis Preventive Treatment- 2020

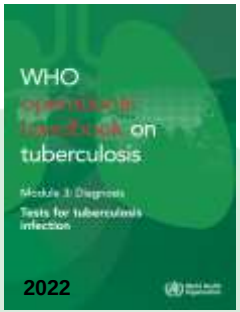
2



- IGRA maupun TST dapat digunakan sebagai pemeriksaan untuk infeksi TB (Laten TB)
- *Highlight* : Program TPT

WHO Operational Handbook on Tuberculosis – Modul 3 : Diagnosis Test for tuberculosis infection- 2022

3



- IGRA maupun TST dapat digunakan sebagai pemeriksaan untuk infeksi TB (Laten TB)
- *Highlight* : Pentingnya pemeriksaan infeksi TB (Laten TB)

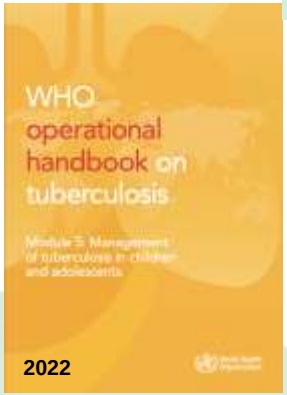
WHO Policy Statement : Use of IGRA for the diagnosis of TB Infection- 2022

4

- Rekomendasi tambahan WHO untuk pemeriksaan IGRA : Beijing Wantai's IGRA dan QIAGEN QuantiFERON TB-Gold Plus

WHO Operational Handbook on Tuberculosis – Modul 5 : Management of tuberculosis in children and adolescent - 2022

5



- IGRA maupun TST dapat digunakan sebagai pemeriksaan untuk infeksi TB (Laten TB)
- TST atau IGRA berguna untuk mendukung diagnosis TB pada **anak-anak** dengan gejala klinis namun hapusan mikroskopis negatif / tidak dapat mengeluarkan sputum

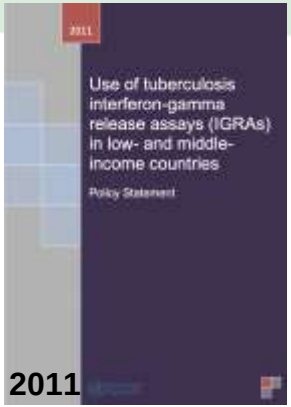
TB Disease vs TB Infection

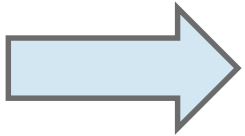
TB Disease (Active TB)

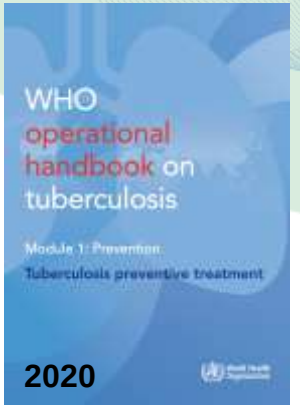
- Disease that occurs in someone infected with M. tuberculosis
- Characterized by signs or symptoms of TB disease or both

TB Infection (Latent Tuberculosis Infection (LTBI))

- State of persistent immune response to stimulation by M. tuberculosis antigens with no evidence of clinically manifest TB disease
- Most infected people have no signs or symptoms but are at risk for TB disease



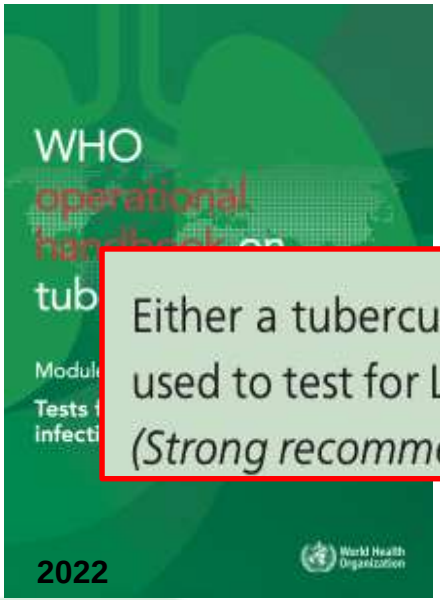




WHO (2020) : Supports IGRA testing globally for at-risk populations – removing its 2011 guidance against interferon-gamma release assays (IGRAs) in low and middle income countries.

(Strong recommendation, low quality of evidence)

Source: Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement. 2011.



Box 1.2. Summary of WHO recommendations on TB infection tests *(14)*

Mycobacterium tuberculosis antigen-based skin tests (TBSTs) may be used to test for TB infection.
(Conditional recommendation for the intervention, very low certainty of the evidence)

Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI.
(Strong recommendation, very low certainty of the evidence)

(including HIV-positive individuals) suspected of active TB in these settings.
(Strong recommendation)

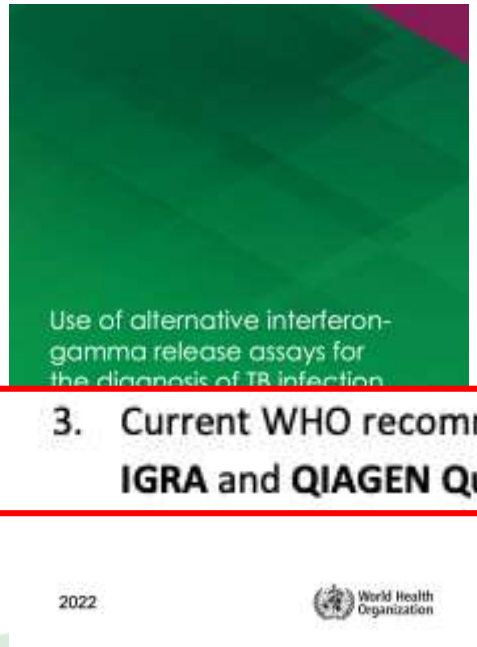
HIV: human immunodeficiency virus; IGRA: interferon-gamma release assay; LTBI: latent tuberculosis infection; TB: tuberculosis; TBST: *Mycobacterium tuberculosis* antigen-based skin test; TST: tuberculin skin test; WHO: World Health Organization.

Summary of methods

A systematic review and a meta-analysis were performed to compare the index tests with the tests currently recommended by WHO. A description of manufacturers' unit costs and practical implementation considerations were also provided.

Research questions

- **Sensitivity**: In people with active TB, what is the sensitivity of the index tests compared with QFT-G, QFT-GIT or T-Spot (hereafter referred to as "reference tests") or TST?
- **Specificity**: In people at very low risk of TB infection, what is the specificity of the index tests relative to the reference tests or TST?
- **Agreement (concordance)**: In patients with active TB, people at very low risk of TB infection or those tested for TB infection, what is the agreement (for both positive and negative results) between the index and reference tests or TST? This is expressed in terms of the Cohen's kappa test, which is a measure of agreement corrected for chance agreement.
- **Reproducibility**: What is the within-person, short-term reproducibility of the index tests in patients tested on repeated occasions (i.e. the same samples, tested at either the same time or different times, or both) in patients without TB disease and at low risk of a new TB infection?



1. Based on available data, **Beijing Wantai's TB-IGRA** and **QIAGEN QuantiFERON-TB Gold Plus** performance *is comparable* to that of WHO-recommended IGRAs for the detection of TB infection.
2. Based on available data, **QIAGEN** QIAreach QuantiFERON-TB, SD Biosensor Standard E TB-Feron ELISA and Oxford Immunotec T-SPOT.TB 8 with T-Cell Select *could not be adequately*

3. Current WHO recommendations for the use of IGRAs are also valid for **Beijing Wantai's TB-IGRA** and **QIAGEN QuantiFERON-TB Gold Plus**.

2022

World Health Organization

IGRA in Children

- TST or IGRA is useful to support a diagnosis of TB in children with suggestive clinical features who are sputum smear-negative / who cannot produce sputum.
- A positive test : prior or current infection with *M. tuberculosis* and can be particularly useful in the absence of known TB exposure (no positive contact history), as it confirms the child has been infected at some point in time

Asymptomatic neonates with mother with TB

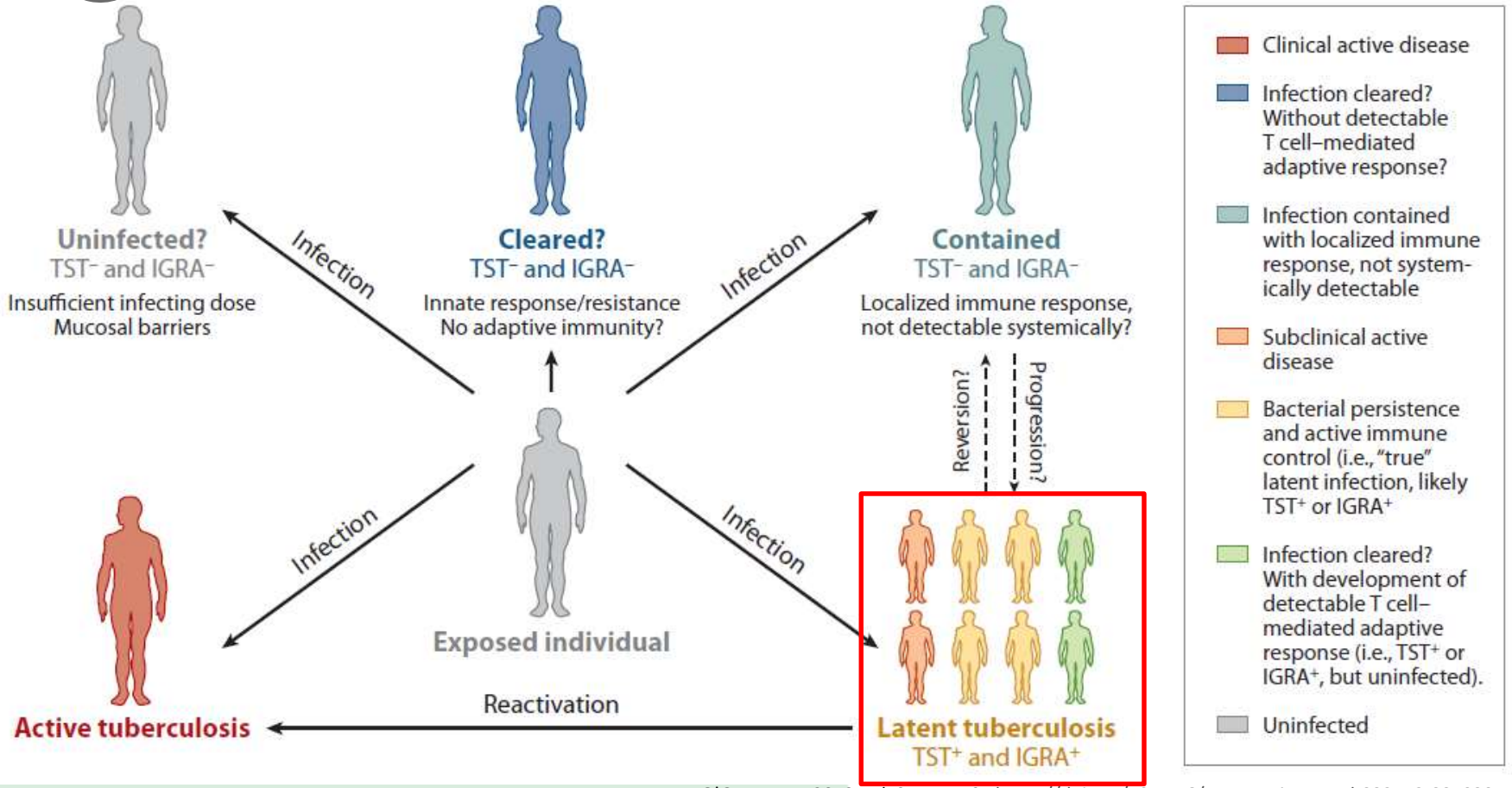
→

- BCG should be postponed
- Should received TPT once TB disease has been excluded
- If remains asymptomatic → performed TST/ IGRA after TPT*→

TST or IGRA negative/ not available → give BCG (unless the baby is HIV positive)

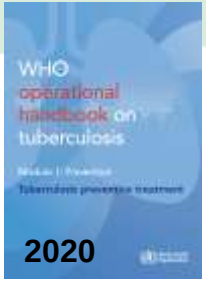
* Preferably 3HR (3 months isoniazid and rifampicin) regimen

Heterogeneity resulting from *M. tuberculosis* infection



O'Garra et a, 2013 Vol. 31:475-527 https://doi.org/10.1146/annurev-immunol-032712-095939

WHO



TB Infection Testing (LTBI) for TPT

WHO recommends two broad groups of at-risk populations that fulfil the above criteria for systematic assessment of eligibility and provision of TPT.

1. **People with elevated risk of progression from infection to TB disease**
   - People living with HIV *
   - Patients suffering from silicosis, patients starting or preparing for anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, and patients preparing for organ or haematologic transplantation.

Tb Laten → Tb disease

2. **People with increased likelihood of exposure to TB disease**
   - Household contacts of people with bacteriologically confirmed TB, usually subdivided into:
     a. Children below five years of age *
     b. Children five years and above, adolescents and adults
   - Persons who live or work in institutional or crowded settings, such as prisoners, health workers, recent immigrants from countries with a high TB burden, homeless people and people who use drugs.

Peningkatan paparan TB

* Testing for TB Infection is not required in PLHIV and child household contacts aged < 5 years

Tuberculosis Preventive Treatment (TPT)

WHEN

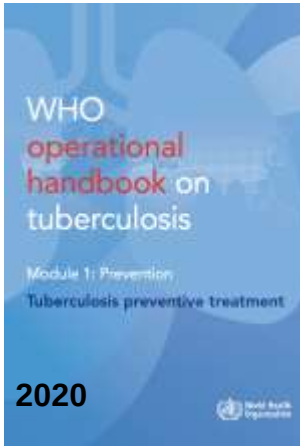
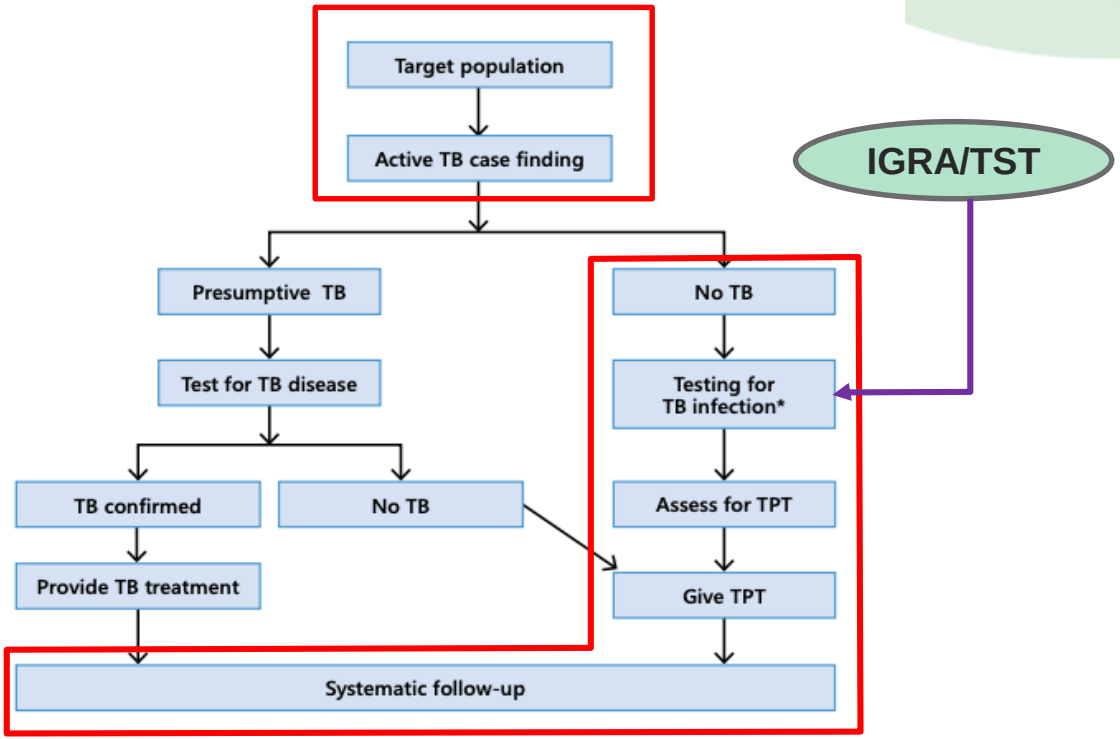


Fig. 1.1: Cascade of TB case finding and preventive treatment



*Not required in PLHIV and child household contacts aged < 5 years

TB Disease must be ruled out before starting TPT

WHERE

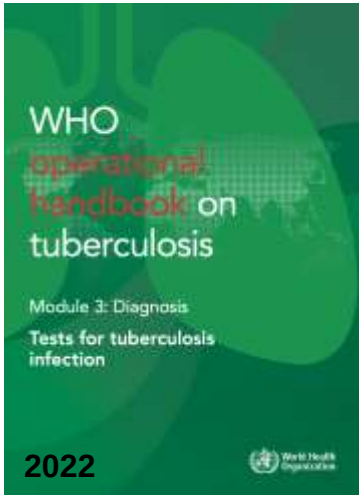


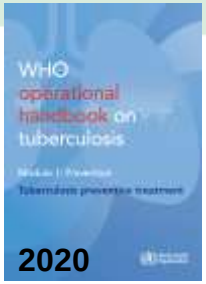
Table 4.1. Equipment and personnel needed for WHO-recommended IGRA tests *(8)*

IGRA Test Rekomendasi WHO

	QFT-GIT	WANTAI TB-IGRA	QFT-Plus	T-SPOT.TB	TB infection skin tests
Equipment					
Fridge for supply storage	☑	☑	☑	☑	☑
Lymphocyte counter	×	×	×	☑	×
Incubator	☑	☑	☑	☑	×
Centrifuge	☑	☑	☑	☑	×
Plate washer and agitator	☑	☑	☑	☑	×
ELISA/ELISPOT reader	☑	☑	☑	☑	×
Personnel					
Phlebotomist	☑	☑	☑	☑	×
Technician for incubation	☑	☑	☑	☑	×
Technician for centrifugation or aspiration	☑	☑	☑	☑	×
Technician for ELISA or ELISPOT	☑	☑	☑	☑	×
Trained health professional for intradermal injection and reading	×	×	×	×	☑

ELISA: enzyme-linked immunosorbent assay; ELISPOT: enzyme-linked immunosorbent spot; IGRA: interferon-gamma release assay; QFT-GIT: QuantiFERON Gold In-Tube; QFT-Plus: QuantiFERON-TB Gold Plus; TB: tuberculosis; WHO: World Health Organization.

WHY



A joint Call to Action to scale up tuberculosis preventive treatment (TPT)

ERS · USAID · Unitaid · World Health Organization · IAS · Stop TB Partnership · The Global Fund · unicef · KNCV · The Union

Testing for TB infection

- Testing for TB infection using tuberculin skin testing (TST) or interferon-gamma release assays (IGRAs) helps direct TPT to people who may benefit most from it and avert unnecessary TPT and related harms. A positive test could also motivate better people to take TPT. However, national programmes currently have limited capacity for testing. Quality-assured TST is in limited supply and IGRAs are more expensive and require blood samples to be taken and transported to well-equipped laboratories.
- Overcoming the infrastructural and supply barriers to the provision of TST/IGRA is desirable and the longer-term goal should be to build the health system capacity needed for this, in terms of human resources, logistics and supply chain and monitoring and evaluation. This will also lay the foundation for the swift roll-out in future of new improved point-of-care tests for TB infection.
- However, in the short term, any unavailability of TST/IGRA should not be a barrier to giving TPT to those groups most at risk of developing TB disease. In children under five years who are in contact with active TB and in PLHIV, TB infection testing is **not** required given the urgency to treat exposure in these sub-populations.
- In addition to testing for TB infection, exclusion of TB disease is important before starting TPT. Chest radiography can play an important role in ruling out TB disease and increase confidence in TPT. Counselling is another important component of people-centred care, to help individuals make an informed choice when offered TPT, based on a clear understanding of the potential benefits and harms of treatment.
- Governments and donors should factor in the human and infrastructural resources necessary to bring testing of TB infection and chest radiography within reach of more people

Testing for TB Infection :
TST or IGRA

↓

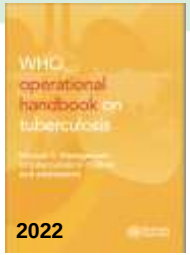
Positive result can motivate people to take TPT

↓

Helps direct TPT, avert unnecessary TPT

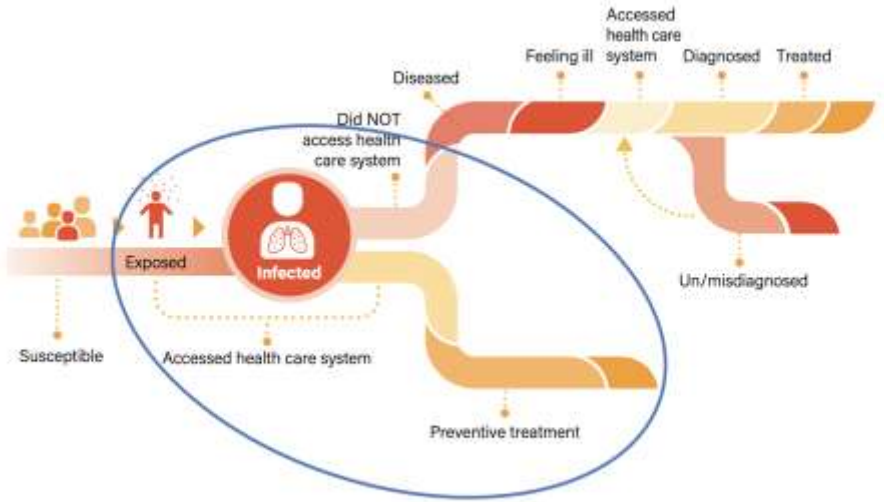
Overcoming the infrastructural and supply barriers for TST/IGRA is desirable

WHY



Confirmation of TB infection by TST or IGRA is desirable before the start of TPT

Figure 3.1. Pathway through exposure, infection and disease covered in Chapter 3



Source: Roadmap towards ending TB in children and adolescents. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/275422).

- TST or IGRA can be used to test for TB infection
- Revaccination is **not recommended** even the TST or IGRA is negative
- Testing for TB infection should not be a requirement for initiating TPT among people living with HIV and child contacts aged < 5 years, particularly in countries with a high TB incidence

HOW

REKOMENDASI PENGGUNAAN IGRA UNTUK DIAGNOSIS INFEKSI TB - WHO

2011	2020	2021-2022
• QIAGEN QuantiFERON-TB Gold* • QIAGEN QuantiFERON-TB Gold In-Tube* • Oxford Immunotec T-SPOT.TB	TST atau IGRA (atau keduanya) dapat digunakan untuk diagnosis infeksi TB	Tambahan: • Beijing Wantai's IGRA • QIAGEN QuantiFERON-TB Gold Plus

* Sudah tidak dikomersialkan

WHO consolidated guidelines on tuberculosis: Module 3: Diagnosis – Tests for tuberculosis infection. Geneva: World Health Organization; 2022. Executive summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK586665/

Evolusi Teknologi IGRA QuantiFERON

WHO Recommendation

First generation
QuantiFERON-TB

2001: FDA approved

- Measured cell-mediated immunity to tuberculin purified protein derivative (PPD)
- **Breakthrough: TST becomes a blood test**

Sudah tidak dikomersialkan

Second generation
QuantiFERON-TB Gold

2004: FDA approved

- Liquid antigen version
- Antigens specific for M.tb with 99% specificity
- **Clinical benchmark: No cross reactivity with BCG**

Sudah tidak dikomersialkan

Third generation
QuantiFERON-TB Gold In-Tube

2007: FDA approved

- Logistical advantage – remote incubation
- **Lab benchmark: Scalable**
- >1500 peer reviewed publications

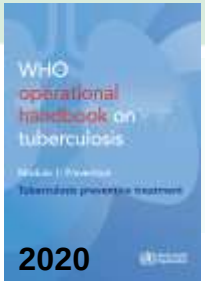
Sudah tidak dikomersialkan

Fourth generation
QuantiFERON-TB Gold Plus

2014: CE-IVD
2017: FDA approved

- **Addition of patented CD8 antigens – potential biomarker of intracellular TB burden**
- Opsi Pengambilan darah yang fleksibel
- >2500 peer reviewed publications

HOW



IGRA Testing Considerations

	IGRA
Test requirements	• IGRAs are in vitro blood tests that detect interferon gamma in blood using ELISA • Requires fresh blood specimens to mix with antigens and controls, to be processed within 8–30 hours after collection while white blood cells are viable • Need an efficient sample transport mechanism • Need different blood collection tubes for different altitudes
Potential inaccuracy	• Delay in transportation of blood specimen • Errors in processing of blood specimen • Wrong interpretation of assay • False-negative results likely in immuno-deficiency conditions, faded immune memory, technical-operational variability, and in children below two years of age

	IGRA
Advantages	• Single visit required to conduct test; however, test result may be shared with the person on the second visit, when like the TST, clinical management decisions are made • Results possible within 24 hours • No booster effect • No false-positive results due to BCG
Challenges	• Higher test cost • Need for phlebotomy • Need sophisticated laboratory equipment, highly skilled laboratory personnel to perform and interpret test results • Potential for delays in sample transportation due to long distances to laboratories that offer IGRA testing • Processing and results take at least one day (often longer), hence the person may need to return to collect results • If the laboratory SOP requires batching of tests to reduce costs there may be delays in reporting results beyond a week
Preferred test	• Persons who have received BCG (either as a vaccine or for cancer therapy), although this is less applicable in adults who received BCG as infants due to waning of effect • Groups that are unlikely or unable to return for TST reading, such as homeless persons and people who use drugs or due to reasons like long distance, job security, or other pressing commitments

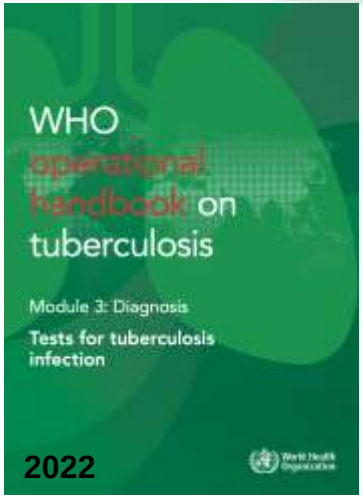


Table A2.1.1. Interpretation of QFT-Plus test results

Nil (IU/mL)	TB1 minus nil (IU/mL)	TB2 minus nil (IU/mL)	Mitogen minus nil (IU/mL)[a]	QFT-Plus result	Report or interpretation
≤8.0	≥0.35 and ≥25% of nil	Any value	Any value	Positive[b]	*M. tuberculosis* infection likely
	Any value	≥0.35 and ≥25% of nil			
	<0.35 or ≥0.35 and <25% of nil	<0.35 or ≥0.35 and <25% of nil	≥0.50	Negative	*M. tuberculosis* infection NOT likely
	<0.35 or ≥0.35 and <25% of nil	<0.35 or ≥0.35 and <25% of nil	<0.50	Indeterminate[c]	Likelihood of *M. tuberculosis* infection

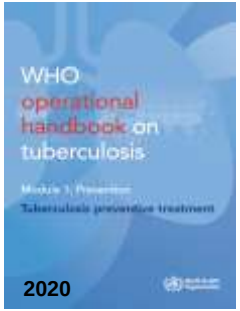
Source: product insert *(1)*.

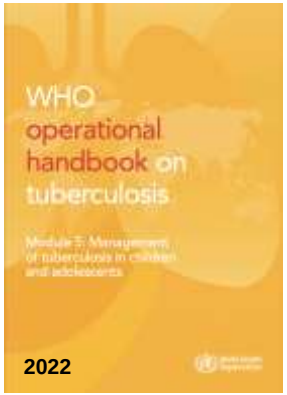
- When presented with an indeterminate result, physicians may choose to redraw a specimen or perform other procedures as appropriate.
- Suggesting possible error in performing test or immune suppresion

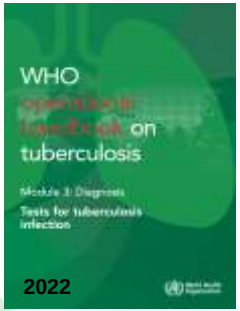
TAKE HOME MESSAGE

- IGRA adalah pemeriksaan yang mengukur interferon gamma yang dilepaskan limfosit sebagai respon imun terhadap antigen *M. tuberculosis*
- IGRA dilakukan pada populasi berisiko dengan tujuan mendeteksi TB laten untuk diberikan TPT secara tepat sasaran
- WHO merekomendasikan IGRA untuk deteksi *TB infection* (TB laten)
- IGRA rekomendasi WHO : QuantiFERON GIT, QuantiFERON-Plus, T-Spot.TB dan Wantai’s TB IGRA

Terima Kasih







WHO

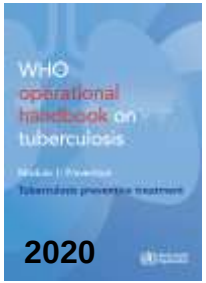
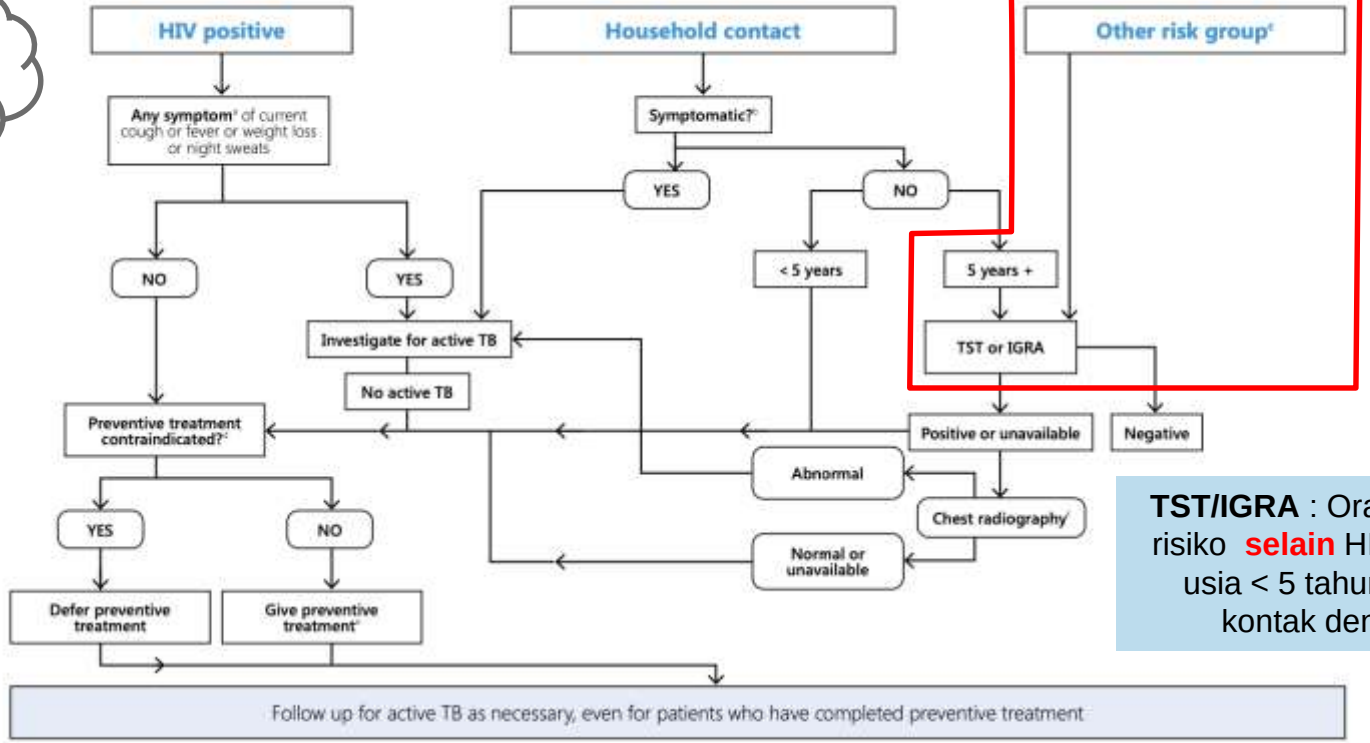


Fig. 4.1: Algorithm for TB screening and TPT



TST/IGRA : Orang dengan faktor risiko **selain** HIV dan anak-anak usia < 5 tahun yang memiliki kontak dengan TB aktif

a. If < 10 years, any one of current cough or fever or history of contact with TB or reported weight loss or confirmed weight loss > 5% since last visit or growth curve flattening or weight for age <-2 Z-scores. Asymptomatic infants < 1 year with HIV are only treated for LTBI if they are household contacts of TB. TST or IGRA may identify PLHIV who will benefit most from preventive treatment. Chest radiography (CXR) may be used in PLHIV on ART, before starting LTBI treatment.

b. Any one of cough or fever or night sweats or haemoptysis or weight loss or chest pain or shortness of breath or fatigue. In children < 5 years, they should also be free of anorexia, failure to thrive, not eating well, decreased activity or playfulness to be considered asymptomatic.

c. Including silicosis, dialysis, anti-TNF agent treatment, preparation for transplantation or other risks in national guidelines. People in this category should also have TB disease ruled out if they have suggestive clinical manifestations.

d. Including acute or chronic hepatitis; peripheral neuropathy (if isoniazid is used); regular and heavy alcohol consumption. Pregnancy or a previous history of TB are not contraindications.

e. Regimen chosen based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity, availability and preferences.

f. Chest radiography may have been carried out earlier or as part of intensified case finding.