Diagnosis of latent tuberculosis infection

Madhukar Pai, MD, PhD
Assistant Professor, Epidemiology
McGill University, Montreal, Canada
madhukar.pai@mcgill.ca

Importance of LTBI

• It is estimated that nearly one-third of the world’s population is infected with *M. tuberculosis*
• In most individuals, *M. tuberculosis* infection is contained initially by host defences, and infection remains latent.
• However, latent TB infection (LTBI) has the potential to develop into active disease at any time.
• Identification and treatment of latent tuberculosis infection can reduce the risk of development of disease by as much as 60 - 90 percent, and so has potential to protect the health of the individuals as well as the public by reducing the number of potential sources of infection
The spectrum of latent tuberculosis: rethinking the biology and intervention strategies

Clinical disease
- Bacterial replication maintained at a subclinical level by the immune system
- Infection controlled with some bacteria persisting in non-replicating form
- Infection eliminated in association with T cell priming
- Infection eliminated without priming antigen-specific T cells

Disease
- Active infection
- Quiescent infection
- Acquired immune response
- Innate immune response

Effect of HIV infection
- Bacterial load

Nat Rev Micro 2009
LTBI vs. TB Disease

**Latent TB Infection**
- TST* or IGRA† positive
- Negative chest radiograph
- No symptoms or physical findings suggestive of TB disease
- Respiratory specimens are not smear or culture positive
- Not infectious to others

**Pulmonary TB Disease**
- TST or IGRA usually positive
- Chest radiograph may be abnormal
- Symptoms may include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens may be smear or culture positive
- Potentially infectious

* tuberculosis skin test
† IGRA = IFN-gamma release assay

Source: US CDC

Indications for LTBI testing

- The goal of testing for LTBI is to identify individuals who are at increased risk for the development of tuberculosis and therefore would benefit from treatment of latent TB infection.
- Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive.
- In general, testing for LTBI is warranted to identify individuals who are at risk of new infection, and to identify individuals at increased risk of reactivation due to associated conditions.
- However, LTBI testing is a challenge
  - There is no definite method to confirm or rule out LTBI
LTBI: a diagnostic challenge [case #1]

My 19 year old son is being worked up for his 2nd kidney transplant and is currently on hemodialysis. He has been through numerous drug reactions (some of them extremely rare) and he is not too keen on the skin test. The TB skin test is a part of the protocol of the Ottawa Hospital as there were two people last year who died of TB post renal transplant.

From the studies I have found on the internet it appears that the TB skin test is not a very accurate method of detection of LTBI in hemodialysis patients.

Is there anyone in Canada who is using this test and would it be possible to bring it to Ottawa? We are told that the Ottawa hospitals have a great concern about TB as they service the Inuit population. That said, I would assume that employing a TB blood test would be of great benefit to our renal patient population.

LTBI: a diagnostic challenge [case #2]

I am a healthcare worker, and have just had a positive TB skin test.

It's only been one year since my last skin test which was negative.

My primary care doctor read my chest x-ray as negative and did not recommend INH, but the Health Dept. here recommends taking INH for 6-9 months.

Doctors and nurses whom I work with say that false positives happen all the time and to not worry about it. I have read about the side effects of this drug, and want to be sure that I actually am a carrier before taking it.

I have been reading about the QFT-G and am wondering if it will help resolve my dilemma about taking INH?
LTBI: a diagnostic challenge [case #3]

We are parents in distress looking for help. Our 18 month old daughter has been diagnosed with TB in virtue of a lung infiltration that appeared in her x-ray taken some 3 months ago. The infiltration is still there according to a new x-ray taken 10 days ago.

We tested her with the "skin test tuberculina" but got a negative result, even though she was vaccinated with the BCG. Our doctor said that was because she was in a state of "anergia" and insists it is TB that she has. Nevertheless, other two specialists –though not our doctor- have manifested contrary opinions to our paediatrician. The issue here is that our doctor wants to commence treatment against active TB and my wife and I are not convinced our paediatrician’s opinion is correct. We learned treatment is long and has secondary effects.

Worst of all, there seems to be no test available in Mexico that can assert if what our paediatrician says is correct.

Through the internet we learned about the new T-Spot.TB but we can’t find it here in Mexico. We are willing to travel to Canada and beyond in order to make sure if our daughter is ill with TB but are not about ready to begin a lengthy and weighty treatment that may not be needed.

We are appalled to find there is such a state of lack of definition regarding TB diagnosis.

Who should be tested?

Who should be tested for latent TB infection?

- Those with increased risk of new TB infection (all patients should be tested regardless of age)
- Close contacts of patients with active pulmonary/respiratory TB
- Casual contacts of patients with highly contagious active TB
- Health care workers and other occupations in which there is risk of exposure to patients with untreated contagious active TB (prison facilities, homeless shelters...)
- Those with increased risk of reactivation
  - High risk (all patients should be tested regardless of age)
  - HIV infection (any stage of disease)
  - Transplant, chemotherapy, or other major immunosuppressing condition
  - Lymphomas, leukemia, head & neck cancer
  - Abnormal chest x-ray with granulomatous changes typical of healed TB (not including granulomas)
  - Sarcoidosis
  - Renal failure (requiring dialysis)
  - Treatment with TNF-alpha inhibitors
  - Moderaterisk (patients under age 65 should be tested)
    - Diabetes mellitus
    - Systemic glucocorticoids (31.5 mg/day for 2.1 month)
  - Highly increased risk (patients under age 65 should be tested)
    - Underweight (20% of ideal body weight)
    - For most individuals this is equivalent to body mass index (BMI) <18.5
    - Opiate smoker (2 pack/cig)
    - Chest x-ray with solitary granuloma

Pat & Menzies. UpToDate 2009
How do we test for LTBI?

- **Tuberculin skin test**
  - Mantoux method, using purified protein derivative (PPD) at the recommend dose of 5 tuberculin units (0.1 mL); in other regions, PPD RT-23 is used at the standard dose of 2 TU

- **Interferon-gamma release assays (IGRAs)**
  - QuantiFERON-TB Gold In Tube
  - T-SPOT.TB

- Both tests are imperfect!
Tuberculin skin test

• TST
  – Measures cell-mediated immune response (CMI)
    • Uses PPD: a crude antigenic mixture
• Limitations of TST:
  – false positives and false negatives are possible
  – technical issues in administration and interpretation
  – difficulty in separating true infection from the effects of BCG and non-tuberculous mycobacteria (NTM)
  – repeated TST boosts the immune response
  – requires a 3-dimensional interpretation

Administering the TST

• Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
• Produce a wheal 6 to 10 mm in diameter

Source: US CDC
Reading the TST (1)

- Measure reaction in 48 to 72 hours
- Measure induration, not erythema
- Record reaction in millimeters, not "negative" or "positive"
- Ensure trained health care professional measures and interprets the TST

Source: US CDC

Reading the TST (2)

- Educate patient and family regarding significance of a positive TST result
- Positive TST reactions can be measured accurately for up to 7 days
- Negative reactions can be read accurately for only 72 hours
- A period of up to 8 weeks after primary TB infection may be required for TST conversion to occur. Individuals with recent close contact to a known infectious case of TB, whose initial TST is negative, should have repeat TST 8 weeks after the end of exposure

Source: US CDC
### TST Interpretation

<table>
<thead>
<tr>
<th>Tuberculin skin test (TST) result (mm)</th>
<th>Interpretation to identify reaction as consistent with infection *</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 mm</td>
<td>Negative result; unlikely infection.</td>
</tr>
<tr>
<td>5-9.9 mm</td>
<td>Indeterminate result; further testing may be needed.</td>
</tr>
<tr>
<td>≥10 mm</td>
<td>Positive result; likely infection.</td>
</tr>
</tbody>
</table>

* The goal of testing for latent tuberculosis infection is to identify individuals who are at increased risk for the development of tuberculosis and therefore would benefit from treatment of latent infection. It is recommended that individuals with risk factors be tested with a skin test to assess the presence of infection at least once in a lifetime (true test).

**Factors That May Cause False-Positive TST Reactions**

- **Nontuberculous mycobacteria**
  - Reactions caused by nontuberculous mycobacteria are usually ≤ 10 mm of induration

- **BCG vaccination**
  - Reactivity in BCG vaccine recipients generally wanes over time; positive TST result is likely due to TB infection if risk factors are present

Source: US CDC
Factors That May Cause False-Negative TST Reactions

<table>
<thead>
<tr>
<th>Potential causes of false negative tuberculin tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technical (potentially correctable)</strong></td>
</tr>
<tr>
<td>Tuberculin material:</td>
</tr>
<tr>
<td>- Improper storage (exposure to light or heat)</td>
</tr>
<tr>
<td>- Contamination, improper dilution, or chemical denaturation</td>
</tr>
<tr>
<td>Administration:</td>
</tr>
<tr>
<td>- Injection of too little tuberculin, or too deeply (should be subcutaneous)</td>
</tr>
<tr>
<td>- Administration more than 20 minutes after drawing up into the syringe</td>
</tr>
<tr>
<td>Reading:</td>
</tr>
<tr>
<td>- Inexperienced or biased reader</td>
</tr>
<tr>
<td>- Error in recording</td>
</tr>
<tr>
<td><strong>Biologic (not correctable)</strong></td>
</tr>
<tr>
<td>Infections:</td>
</tr>
<tr>
<td>- Active TB (especially if advanced)</td>
</tr>
<tr>
<td>- Other bacterial infection (lymphoid fever, brucellosis, typhus, leprosy, pertussis)</td>
</tr>
<tr>
<td>- HIV infection (especially if CD4 count &lt;200)</td>
</tr>
<tr>
<td>- Other viral infection (measles, mumps, varicella)</td>
</tr>
<tr>
<td>- Fungal infection (South American blastomycosis)</td>
</tr>
<tr>
<td>- Live virus vaccination: (measles, mumps, pox)</td>
</tr>
<tr>
<td>- Immunosuppressive drugs: (steroids, TNF inhibitors, and others)</td>
</tr>
<tr>
<td>- Metabolic disease: chronic renal failure, severe malnutrition, stress (surgery, burns)</td>
</tr>
<tr>
<td>- Diseases of lymphoid organ: (lymphoma, chronic lymphocytic leukemia, sarcoidosis)</td>
</tr>
<tr>
<td>Age: infants &lt;6 months, elderly</td>
</tr>
</tbody>
</table>

TST requires a 3-dimensional interpretation

[Diagram showing TST size, PPV, and Risk of disease]

http://meakins.mcgill.ca/wspemp/homeE.htm
When BCG is given after infancy or repeated many times, it can affect TST results

False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

M. Farhat,*1 C. Greenaway,*1 M. Pal,*2 D. Mendes*

* Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Quebec, Canada; †Massachusetts General Hospital, Harvard University, Boston, Massachusetts, USA; ‡Division of Infectious Disease and Microbiology, SMH-Jewish General Hospital, McGill University, Montreal, ††Joint Departments of Epidemiology & Biostatistics and Preventive Health, McGill University, Montreal, Quebec, Canada

| Analysis of 24 studies with N = 240,243 subjects |
| When BCG is given in infancy, false-positive TST results due to BCG occur in 6% of vaccinated subjects |
| When BCG is given after infancy, false-positive TST results due to BCG occur in 40% of vaccinated subjects |
In India, BCG has limited effect on TST

In Uganda, BCG has limited effect on TST
In Japan, BCG has a major effect on TST

In Ukraine, BCG has a major effect on TST
Advances in the development of antigens specific to *M. tuberculosis*

- ESAT-6
- CFP-10

IGRAs

- T-SPOT.TB® [Oxford Immunotec, UK]
- QuantIFERON-TB Gold® In Tube [Cellestis Ltd, Australia]
Quick Summary of Evidence

- TST specificity is high in BCG non-vaccinated; but low and variable in BCG vaccinated
- IGRAs (especially QFT) have very high specificity (>95%)
  - IGRA specificity is higher than TST
  - IGRAs are not affected by BCG vaccination
    - Maybe very helpful in settings that give BCG after infancy or give multiple vaccinations
- Sensitivity of IGRAs and TST is not consistent across tests and populations
  - Overall, IGRAs are ~80% sensitive in culture+ TB patients
    - Sensitivity is lower in high incidence countries
  - QFT is as sensitive as TST (~80%)
    - QFT sensitivity is higher in low incidence than high incidence countries
  - T-SPOT.TB appears to be more sensitive (~90%) than both QuantiFERON tests and TST
    - But this may partly be because of cut-offs used for T-SPOT vs QFT
- In low-incidence settings, IGRAs correlate well with markers of exposure
  

IGRAs in immunocompromised

- Immunocompromised groups are highly variable, and most studies are small:
  - All tests underperform in severely immunocompromised patients
    - Using both TST and IGRA might help increase sensitivity
  - IGRA sens in HIV+ is lower (~60 – 65%) than HIV- (~80 – 90%)
  - About 15% of HIV+ TB patients have indeterminate IGRA results
  - Indeterminate IGRA results increase with level of immunosuppression (i.e. low CD4 counts)
  - Very limited data on predictive value
  - Utility as rule out test for active TB is not well established
    - Unlikely to have a rule out value, given the modest sensitivity
IGRAs for active TB diagnosis

- No role in adults
  - Cannot distinguish between latent and active TB
  - Sensitivity is not high
    - Cannot rule out
  - Specificity will always be low in high TB incidence settings
    - Cannot rule in
  - No evidence that IGRAs offer any added value over conventional microbiological tests

- In children
  - Cannot be used in isolation
  - Cannot replace microbiological investigations
  - Useful as “evidence of infection” which should be interpreted with other information (e.g. contact, symptoms, radiological findings)

Predictive value of IGRAs

<table>
<thead>
<tr>
<th>High Incidence</th>
<th>Low Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublished: S Africa, Senegal, Colombia</td>
<td>Unpublished: Japan</td>
</tr>
</tbody>
</table>

**Unpublished: S Africa, Senegal, Colombia**

**Unpublished: Japan**
### Rates of disease progression by test

<table>
<thead>
<tr>
<th>IGRA = TST</th>
<th>IGRA &gt; TST</th>
<th>IGRA+ &gt; IGRA-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambia (26 cases)</td>
<td>Germany (6 cases)</td>
<td>Ethiopia (7 cases)</td>
</tr>
<tr>
<td>Netherlands (9 cases)</td>
<td></td>
<td>Austria (3 cases)</td>
</tr>
<tr>
<td>South Africa (50 cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey (15 cases)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most TST or IGRA positive individuals will not progress to active TB

### Promising but both tests may have only modest predictive abilities

- A substantial % of TST or IGRA+ persons will not progress to TB disease
- Why is predictive value likely to be only modest?
  - IFN-gamma alone might not be sufficiently predictive of progression (or correlate of protection)
  - A single (cross-sectional) TST or IGRA result cannot tell us about the underlying phenotype of when infection occurred and how the host immune system responded
What are the key unresolved issues?

- What is the predictive value of IGRAs for the development of active TB? Will this vary by high vs. low incidence setting?
- Will treatment of IGRA positive subjects reduce the future probability of active TB?
- What is the interpretation of IGRA conversions and reversions?
- What is the exact role of IGRAs in high incidence countries?
- Can IGRA be used to rule out active TB diagnosis?
- What is the exact role of IGRAs in children and HIV+?

Guidelines on IGRAs:
A global survey

May 30 – June 1, 2009
Dubrovnik, Croatia
## Results*

<table>
<thead>
<tr>
<th>General testing approach</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST may be replaced by IGRA (i.e. only IGRA is used)</td>
<td>Germany (anti-TNF-a), Swiss (anti-TNF-a), Poland (anti-TNF-a), Denmark (anti-TNF-a, BCG-vaccinated contacts/adults)</td>
</tr>
<tr>
<td>Either TST or IGRA may be used</td>
<td>USA (QFT preferred in BCG+), France, Australia(refugees), Japan (QFT preferred in all groups except in children &lt;5 y), Denmark(child contacts)</td>
</tr>
<tr>
<td>Two-step approach: TST first, followed by IGRA (either to improve specificity or sensitivity)</td>
<td>Canada, UK, Italy, Spain, Australia, Slovakia Germany (contacts), Swiss (contacts), Netherlands (contacts, immigrants), Norway, Korea(contacts)</td>
</tr>
</tbody>
</table>

* some guidelines recommend more than one approach, depending on the risk group tested (e.g. contacts, immunocompromised, children, etc)

---

## North American Guidelines

![World map with North American countries highlighted]
CDC recommends that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for healthcare workers).

Given the high risk for progression to active disease in HIV-infected persons, any HIV-infected person with reactivity on any of the current LTBI diagnostic tests should be considered infected with *M. tuberculosis*.
USA: AAP Red Book
2009

At this time, neither an IGRA nor the TST can be considered a "gold standard" for diagnosis of LTBI. Current recommendations for use of IGRA's in children are as follows:

- For immune-competent children 5 years of age and older, IGRA's can be used in place of a TST to confirm cases of tuberculosis or cases of LTBI and likely will yield fewer false-positive test results.
- Children with a positive result from an IGRA should be considered infected with *M. tuberculosis* complex. A negative IGRA result cannot universally be interpreted as absence of infection.
- Because of their higher specificity and lack of cross-reaction with BCG, IGRA's may be useful in children who have received BCG vaccine. IGRA's may be useful to determine whether a BCG-immunized child with a reactive TST more likely has LTBI or has a false-positive TST reaction caused by the BCG.
- IGRA's cannot be recommended routinely for use in children younger than 5 years of age or for immune-compromised children of any age because of a lack of published data about their utility with these groups.
- Indeterminate IGRA results do not exclude *tuberculosis* infection and should not be used to make clinical decisions.

USA: CDC Guidelines
2009: QFT-GIT/TSPOT.TB

*To be released later this year*

At the 2nd Global IGRA Symposium, it was announced that the new guideline will allow for the use of either TST or IGRA.

IGRA will be preferred over TST for BCG vaccinated

TST will be preferred over IGRA in young children <5 years of age
USA: ATS/CDC/IDSA
Revised Diagnostic Standards for TB
2009: QFT-GIT/TSPOT.TB

American Thoracic Society
Diagnostic Standards and Classification of Tuberculosis in Adults and Children
This statement is the official statement of the American Thoracic Society and the Council on Lung Health, Asthma, and Prevention of the American Lung Association, and has been reviewed and approved by the ATS Board of Directors, June 2000. This statement was submitted to the Council of the Infectious Disease Society of America, November 2000.


To be released

Will be broadly consistent with the new CDC 2009 recommendations

Will cover all TB diagnostics, not just LTBI

Canadian IGRA guidelines

Canadian Communicable Disease Report
Revue des maladies transmissibles du Canada

Canadian Tuberculosis Committee
Comité canadien de lutte antituberculeuse

2007

2008
IGRAs for active TB diagnosis

Table 1. Recommendations on Interferon Gamma Release Assays (IGRAs) for specific indications or subgroups

| No | Specific subgroup or clinical indication | Previous ACS recommendation (CCDR 2007) | Updated recommendation | What has changed and why?
|----|----------------------------------------|----------------------------------------|------------------------|-----------------------------------------------
| 1  | Diagnosis of active TB in adults with suspected TB disease | IGRA are not recommended for the diagnosis of active TB. | IGRA are not recommended for the diagnosis of active TB. | The previous recommendation is now subdivided into separate adult and children (<18 years of age) sections. The recommendations for adults remains unchanged. For children, please see below. |
| 2  | Diagnosis of active TB in children (<18 years of age) with suspected TB disease | -- | Evidence of TB infection in children is often used in making a diagnosis of active TB, in addition to symptoms, radiological abnormalities, history of exposure, and microbiological investigations such as microscopy and culture. Whole blood culture specimen for definitive microbiological diagnosis remains paramount. IGRA may be used as a supplementary diagnostic in combination with the TST and other investigations to help support a diagnosis of TB. However, IGRA should not be a substitute for or substitute for the need for an appropriate specimen collection. | The new recommendation shares the use of IGRA as a supplementary diagnostic with in children with suspected TB disease. |

CCDR 2008

IGRAs for contact investigation

Table 1. Recommendations on Interferon Gamma Release Assays (IGRAs) for specific indications or subgroups

| No | Specific subgroup or clinical indication | Previous ACS recommendation (CCDR 2007) | Updated recommendation | What has changed and why?
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adult and childhood contacts of a case of active infectious tuberculosis</td>
<td>IGRA may be used as a confirmatory test for a positive TST in contacts who, on the basis of assessment of the duration and degree of contact with an active infectious case, are felt to have a low positive probability of recently acquired LTBI. IGRA was not recommended as a means of screening LTBI contacts and is not recommended for persons at low risk for contact with active disease.</td>
<td>IGRA may be used as a confirmatory test for a positive TST in contacts of or who, on the basis of assessment of duration and degree of contact with an active infectious case, are felt to have a low positive probability of recently acquired LTBI. IGRA may be recommended for persons at increased risk for progression to active disease.</td>
<td>This recommendation is largely unchanged, but the scope has been expanded to cover adults as well as children. Because of the practical difficulties in drawing blood for IGRA, it is recommended that IGRA be done on or before the day when the TST is read.</td>
</tr>
<tr>
<td>2</td>
<td>Children with positive TST who wish to participate in a trial of LTBI treatment</td>
<td>IGRA may be used as a confirmatory test for a positive TST in contacts of or who, on the basis of assessment of duration and degree of contact with an active infectious case, are felt to have a low positive probability of recently acquired LTBI. IGRA was not recommended as a means of screening LTBI contacts and is not recommended for persons at low risk for contact with active disease.</td>
<td>IGRA may be used as a confirmatory test for a positive TST in contacts of or who, on the basis of assessment of duration and degree of contact with an active infectious case, are felt to have a low positive probability of recently acquired LTBI. IGRA may be recommended for persons at increased risk for progression to active disease.</td>
<td>This recommendation is largely unchanged, but the scope has been expanded to cover adults as well as children. Because of the practical difficulties in drawing blood for IGRA, it is recommended that IGRA be done on or before the day when the TST is read.</td>
</tr>
</tbody>
</table>

CCDR 2008
IGRAs for immunocompromised

1. In an immunocompromised person (adult or child), the TST should be the initial test used to detect LTBI. If the TST is positive, the person should be considered to have LTBI.

2. However, in light of the known problem with false-negative TST results in immunocompromised populations, a clinician should be concerned about the possibility of LTBI in an immunocompromised person with a negative initial TST result. If the IGRA result is positive, the person might be considered to have LTBI. If the IGRA result is indeterminate, the test should be repeated to rule out laboratory error. If the repeat test is also indeterminate, the clinician should suspect anergy and rely on the person's history, clinical features, and any other laboratory results to make a decision as to the likelihood of LTBI. The approach of accepting either test result (TST or IGRA) as positive will improve the sensitivity of detecting LTBI in immunocompromised populations, which would appear to be desirable. However, in a meta-analysis of five randomized trials, all conducted in countries with a high TB incidence and with the use of IGRA, positive IGRA results are of no benefit in TST-negative HIV-infected adults. Thus, the clinician must weigh the potential benefit of detecting more persons with positive test results against the lack of evidence for the benefit of intensified treatment in such persons.

3. This recommendation is largely unchanged, but the table has been expanded to cover adults as well as children. Also, a note has been added that the T-Spot.TB test may be more sensitive and therefore helpful in immunocompromised populations.

CCDR 2008

---

IGRAs for immigrant screening, HCWs, prevalence surveys

CCDR 2008
Ongoing research in Montreal

• CIHR funded studies on:
  – Cost-effectiveness of IGRAs
  – IGRAs in serial testing of healthcare workers
  – IGRAs in household contacts
  – IGRAs in diagnosis and management of TB infection in children
  – IGRAs and other biomarkers for LTBI treatment monitoring