Global Applications of IGRAs

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Disclosure

I have no personal financial conflicts of interest to report. However, my employer, FIND, has had a contractual relationship with Cellestis that called on FIND to support evaluation studies of the QFTG-IT assay in low-income settings. In turn, Cellestis was to provide the test at favorable prices to the public sector in developing countries.
Outline of Presentation

• IGRA research agenda for low-income settings
• WHO Process for issuing guidance on new TB control tools
• WHO recommendations on the use of IGRA in low-income settings
• Global applications of IGRA: the way ahead

Use of IGRA in Developing Countries: Needs and Potential Uses (1)

• Identification of LTBI in HIV+ persons and contacts (especially children) for treatment
  – Predictive value vs TST not established
  – Current LTBI treatment guidelines not followed even though TST not required
  – Practice could change if test result highly predictive of development of active TB
Use of IGRAs in Developing Countries: Needs and Potential Uses (2)

• Substitution for TST in infection (ARI) surveys
  – Value of single visit test offset by requirements for blood draw and technical requirements of test assays
  – If TST and IGRAs measure different aspects of immune response, IRGAs may not be easily applied substitute for TST

Use of IGRAs in Developing Countries: Needs and Potential Uses (3)

• Aid in diagnosis of pediatric and extrapulmonary tuberculosis
  – Definite need for improved diagnosis
  – Perhaps as a rule-out test
• Monitoring response to treatment of active TB
IRGA Research Needs
Summary of STB WG Meeting
in Geneva, March 2006

- Basic science and assay development
- Test performance in high risk populations and poorly studied groups
- Risk prediction and modeling
- Reproducibility and serial testing
- Issues relating to treatment
- Epidemiology
- Health systems and economic issues

Basic science and assay development

- Identify and validate novel antigens that can increase sensitivity of T cell based assays without compromising their high specificity
- Identify and validate novel antigens that can distinguish between LTBI and active disease
- What is the association between bacterial burden and IFN-g response?
- What type of T cell responses are detected by short incubation IGRAs - effector or memory T cell responses?
- Validation of IGRA cut-points
- Simplification of tests for resource limited settings
Test performance in high risk populations

- Immunocompromised
  - HIV
  - Others (immunosuppressive meds, cancer, diabetes, renal failure, transplantation, etc.)
- Children
- Close contacts
- Healthcare workers

Risk prediction

- What is the predictive value of a positive IGRA test for development of active disease, relative to a positive TST?
  - Among IGRA positive individuals, are individuals with higher levels of IFN-g responses more or less likely to progress to active disease?
- What is the accuracy and role of IGRAs as a “rule out” test for active TB?
Reproducibility and serial testing

- What is the test-related variability in the T cell responses? (i.e. operators, labs, sample processing, incubation times, antigens (proteins vs peptides), formats (ELISA vs ELISPOT), etc.)
- What is the within-subject, biological variability of IFN-g responses over time, including day to day, week to week, and month to month variability of IFN-g levels?
- What is an IGRA conversion?
  - Which IFN-g threshold is optimal for distinguishing between true infection and non-specific, random variation?
  - Are those with dramatic increases in IFN-g more likely to develop active disease? Is the dramatic increase more likely to be seen in those with recent exposure?
- What is an IGRA reversion?
  - Which thresholds should be used for reversion, frequency of reversions, clinical/epidemiological significance of reversions, and factors associated with reversions (e.g. treatment, baseline IFN-g levels, variability around cut-points, etc).

Issues relating to treatment

- How do T cell responses change during and after treatment for latent TB infection?
  - What factors, including host, disease, and assay characteristics, influence variability in responses after treatment?
- How do T cell responses change during and after treatment for active TB?
  - What factors, including host, disease, and assay characteristics, influence variability in responses after treatment?
- Can T cell based assays play a useful role in monitoring response to latent and active TB treatment?
  - What is the ability of IGRA to detect reinfection after treatment for both LTBI and TB disease?
  - What is the ability of IGRA to predict treatment failures?
Epidemiology

• Can IGRAs be used in community surveys to estimate annual risk of TB infection, LTBI prevalence, etc?
  – Use IGRAs to re-appraise traditional estimates used in TB modeling and impact assessment; e.g. Styblo rule, 10% risk of progression from LTBI to active TB, one-third of the world’s population infected, etc.

• What is the accuracy and utility of screening strategies that use combinations of TST and IGRAs; e.g. first screen with TST, and confirmation of positive results by IGRAs?

• How does IGRA performance vary between high and low TB incidence settings?
  – In high burden settings, what is the impact of immune modulators on IGRA performance: BCG, NTM, HIV, leprosy, malnutrition, parasitic infections (e.g. helminths), etc.
  – In high burden settings, which population subgroups are most likely to benefit from IGRAs?

Health systems & economics

• Economic and decision analyses comparing TST with IGRAs for various screening programs (e.g. immigrant screening, contact investigations, serial testing of HCWs, etc.)

• What is the impact of switching from TST to IGRA on laboratory/clinic work load, staff work load, program costs, patient convenience, compliance with testing and follow-up, etc.?

• What resources are needed to increase lab capacity in developing countries to enable implementation of new tools such as IGRAs?

• What is the expected impact of introduction of new LTBI tools on global TB burden?
Use of IGRAs in Developing Countries: Research Needs

- Longitudinal studies of HIV-infected persons
- Longitudinal studies of contacts of TB cases, especially children and HIV+ persons
- Incorporation of IGRAs in ARTI surveys
- Evaluation of IRGAs as diagnostic aid for active TB
- Simplified test formats

WHO TB diagnostics policy formulation process

- Identifying the need for policy change
- Reviewing the evidence
- Convening an Expert Group
- Assessing policy proposal and recommendations
- Formulating and disseminating policy

- WHO monitoring of country needs
- Partners (researchers, industry, etc)
  - Body of evidence available

- Commissioning of systematic reviews
  - QUADAS/other diagnostic accuracy tool
  - Meta-analyses (where feasible)

- Experts, methodologists, end-users
  - Guidelines Review Committee
  - GRADE process for evidence synthesis

- Strategic and Technical Advisory Group
  - Endorsement/revision/addition
  - Advise to WHO to proceed/not with policy

- Guidelines Review Committee
  - Dissemination to Member States
  - Promotion with stakeholders & funders
  - Phased implementation & scale-up plan
GRADE* evaluation

Clear separation:

1) **Recommendation:** 2 grades –
   strong or conditional/optional/weak (for or against an intervention)
   - Balance of benefits and downsides, values and preferences, impact, resource use,
   - ...

2) **Quality of evidence:** 4 categories –
   - ⊕⊕⊕⊕ (High), ⊕⊕⊕ (Moderate), ⊕⊕ (Low), ⊕ (Very low)
   - Methodological quality of evidence
   - Likelihood of bias
   - By outcome and across outcomes

*Grades of Recommendation Assessment, Development and Evaluation

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WHO Policy Statement on the Use of IGRAs in Low and Middle Income Settings

WHO Expert Group Meeting, 20-21 July 2010

Policy Statement, 24 October 2011

WHO Expert Group Meeting on IGRAs, July 2010
Committee Members, Reviewers and Observers

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*Significant COI

TB IGRAs in Low-and Middle income countries

• There is insufficient data and low quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high TB and/or HIV burden;

• IGRAs and the TST cannot accurately predict the risk of infected individuals developing active TB disease;

• Neither IGRAs nor the TST should be used for the diagnosis of active TB disease;

• IGRAs are more costly and technically complex to do than the TST. Given comparable performance but increased cost, replacing the TST by IGRAs as a public health intervention in resource-constrained settings is not recommended.
Use of TB IGRAs* in Low-and Middle income countries

Diagnosis of active TB
Children (LTBI and active TB disease)
Diagnosis of LTBI in HIV-infected individuals
Health care worker (HCW) screening
Contact screening and outbreak investigations
Predicting development of TB

This policy statement is not intended to apply to high-income countries or to supersede their national guidelines

QuantiFERON-TB Gold (QFT-G) and QuantiFERON-TB Gold In-Tube (QFT-GIT), Cellestis, Australia
ELISPOT-based T.SPOT.TB (Oxford Immunotec, UK)

IGRAs in diagnosing active TB disease

• There was no consistent evidence that either IGRA was more sensitive than the TST for diagnosis of active TB diagnosis.

• Two studies that evaluated the incremental value of IGRAs to conventional microbiological tests found no meaningful contribution of IGRAs to the diagnosis of active TB

• IGRAs were considered inadequate as rule-out or rule-in tests for active TB, especially in the context of HIV infection

19 studies simultaneously estimating sensitivity and specificity among 2,067 TB suspects showed a pooled sensitivity of 83% (95% CI 70% - 91%) and pooled specificity of 58% (95% CI 42% - 73%) for T-SPOT (8 studies), and a pooled sensitivity of 73% (95% CI 61% - 82%) and pooled specificity of 49% (95% CI 40% - 58%) for QFT-GIT (11 studies).

Among HIV-infected patients, pooled sensitivity was between 60% (QFT-GIT) and 76% (T.SPOT). Pooled specificity was low for both IGRA platforms (T.SPOT, 61%; QFT-GIT, 52%) and among HIV-infected persons (T.SPOT 61%; QFT-GIT 50%).
IGRAs in diagnosing active TB disease

WHO POLICY RECOMMENDATION

IGRAs (and the TST) should not be used in low- and middle-income countries for the diagnosis of pulmonary or extrapulmonary TB, nor for the diagnostic work-up of adults (including HIV-positive individuals) suspected of active TB in these settings (strong recommendation).

This recommendation places a high value on avoiding the consequences of unnecessary treatment (high false-positives) given the low specificity of IGRAs (and the TST) in these settings.

IGRAs in children

IGRAs and the TST showed similar sensitivity in detecting TB infection or disease, with reduced sensitivity in young or HIV-infected children.

Collecting blood for IGRA testing in young children was a specific challenge

2 small studies prospectively measure incident TB in children tested with IGRAs (QFT) and reported conflicting results.

Association of test response with exposure (categorised dichotomously or as a gradient) was similar for TST, QFT and T-SPOT, although differences in study methodology limited the comparability of results.
IGRAs in children –
WHO POLICY RECOMMENDATION

IGRAs should not replace the TST in low- and middle-income countries for the diagnosis of latent TB infection in children, nor for the diagnostic work-up of children (irrespective of HIV status) suspected of active TB in these settings (strong recommendation).

It should also be noted that there may be additional harms associated with blood collection in children and that issues such as acceptability and cost had not been adequately addressed in any studies.

IGRAs in Health Care Worker Screening

Data on serial testing data and reproducibility of IGRAs as well as evidence on the predictive value of IGRAs in health care workers (HCWs), are still absent for high-incidence settings.

There is no data to suggest that IGRAs are better or worse than the TST for identifying new TB infections after exposure in HCWs, but IGRA serial testing is compounded by a lack of optimum cut-offs and unclear interpretation of IGRA conversions and reversions.

Two cross-sectional studies compared IGRA and TST performance in HCWs.

IGRA and TST positivity rates were high in HCWs, ranging from 40% to 66%.

IGRA positivity was slightly lower than TST positivity but no consistent difference in the prevalence of positive tests was evident.
IGRAs in Health Care Worker Screening

WHO POLICY RECOMMENDATION

IGRAs should not be used in health care worker screening programmes in low- and middle-income countries (strong recommendation).

IGRAs in People Living with HIV

IGRAs seemed to perform similarly to the TST in identifying HIV-infected individuals with latent TB infection and both tests were adversely affected by low CD4+ counts.

The benefit of IPT is greatest in individuals with a positive TST, although routine TST screening is not considered mandatory in HIV-infected persons. There is no evidence to support the efficacy of IPT in TST-negative but IGRA positive individuals.

37 studies involving 5,736 HIV-infected individuals were evaluated. 5 studies compared head-to-head sensitivity of IGRAs and TST with variable results.

In three longitudinal studies, the risk of active TB was higher in HIV-infected individuals with positive versus negative IGRA results; however, the difference was not significant in the two studies that reported IGRA results according to manufacturer-recommended criteria.

In patients with active TB (as a surrogate reference standard for LTBI), pooled sensitivity estimates were heterogeneous but higher for TSPOT (72%, 95% CI 62% - 81%, 8 studies) than for QFT-GIT (61%, 95% CI 41% -75%, 8 studies).
IGRAs in People Living with HIV

WHO POLICY RECOMMENDATION

IGRAs should not replace the TST in low- and middle-income countries for the diagnosis of latent TB infection in individuals living with HIV infection (strong recommendation).

This recommendation also applies to HIV-positive children based on the generalisation of data from adults.

IGRAs in Contact Screening and Outbreak Investigations

The majority of studies showed comparable latent TB infection prevalence by TST or IGRA and variable associations with levels of exposure.

Wide discordance between TST and IGRA results was evident, mostly of the TST-positive/IGRA-negative type.

16 studies evaluated IGRAs in contact screening and outbreak investigations. Data could not be pooled due to significant heterogeneity in study design and outcomes assessed.

Most studies showed comparable prevalence by TST or IGRA in contacts.
IGRAs in Contact Screening and Outbreak Investigations –

WHO POLICY RECOMMENDATION

IGRAs should not replace the TST in low- and middle-income countries for the screening of latent TB infection in adult and paediatric contacts, or in outbreak investigations (strong recommendation).

Global Application of IGRAs: The Way Ahead

- WHO policy recommendation on LTBI testing for
  - high-risk groups, e.g., HIV-infected persons, young household contacts
  - contact investigations
- Simplified test format, e.g., LF assay
- Dramatically lowered cost
- Improved predictive value for active TB
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