Eliminating TB by 2050

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3rd Global Symposium on IGRAs
Waikoloa, Hawaii, 15 January 2012

Overview of this presentation

• Current TB burden
• Progress towards international targets
• Challenges at the end of 2011
• Is elimination possible with current tools?
• If not, what do we need?
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The Global Burden of TB -2010

- **Estimated number of cases**
  - All forms of TB: 8.8 million (range: 8.5-9.2 million)
  - HIV-associated TB: 1.1 million (13%) (range: 1.0-1.2 million)
  - Multidrug-resistant TB (MDR-TB): 440,000 (range: 390,000-510,000)

- **Estimated number of deaths**
  - All forms of TB: 1.45 million (range: 1.2-1.6 million)
  - HIV-associated TB: 350,000 (range: 320,000-390,000)
  - Multidrug-resistant TB (MDR-TB): about 150,000
TB Incidence Rates - 2010

• Highest burden in Asia (59% of 8.8 million cases)
• Highest rates in Africa, due to high HIV infection rate
  ~80% of HIV+ TB cases in Africa

13 top settings with highest % of MDR-TB among new cases, 2001-2009

<table>
<thead>
<tr>
<th>Setting</th>
<th>MDR-TB %</th>
</tr>
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<tbody>
<tr>
<td><strong>Minsk, Belarus (2010)</strong></td>
<td>35.3</td>
</tr>
<tr>
<td>Pakov Oblast, Russian Federation (2006)</td>
<td>27.3</td>
</tr>
<tr>
<td>Arkhangelsk Oblast, Russian Federation (2008)</td>
<td>23.8</td>
</tr>
<tr>
<td>Baku city, Azerbaijan (2007)</td>
<td>22.3</td>
</tr>
<tr>
<td>Ivanovo Oblast, Russian Federation (2006)</td>
<td>20.0</td>
</tr>
<tr>
<td>Republic of Moldova (2006)</td>
<td>19.4</td>
</tr>
<tr>
<td>Belgorod Oblast, Russian Federation (2006)</td>
<td>19.2</td>
</tr>
<tr>
<td>Dushanbe city and Rudaki district, Tajikistan (2006)</td>
<td>16.5</td>
</tr>
<tr>
<td>Mary El Republic, Russian Federation (2006)</td>
<td>16.1</td>
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<tr>
<td>Donetsk Oblast, Ukraine (2006)</td>
<td>16.0</td>
</tr>
<tr>
<td>Estonia (2006)</td>
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<td>Tashkent, Uzbekistan (2005)</td>
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The Global TB Control Targets

2015: Goal 6: Combat HIV/ AIDS, malaria and other diseases
   Target 6c: to have halted by 2015 and begun to reverse the incidence...

   *Indicator 6.9: incidence, prevalence and mortality associated with TB
   *Indicator 6.10: proportion of TB cases detected and cured under DOTS

2015: 50% reduction in TB prevalence and deaths by 2015
2050: elimination (<1 case per million population)
The global response so far: Stop TB Strategy & Global Plan

1. Pursue high-quality DOTS expansion

2. Address TB-HIV, MDR-TB, and needs of the poor and vulnerable

3. Contribute to health system strengthening

4. Engage all care providers

5. Empower people with TB and communities

6. Enable and promote research

To save lives, prevent suffering, protect the vulnerable, & promote human rights

Achievements thus far, 2011

- 46 million patients cured, 1995-2010
- 7 million deaths averted compared to 1995 care standards
- Mortality reduced by 40% since 1990 and 50% mortality targets on track globally
- Cure rates 87%, care for TB/HIV improving
- But…. TB incidence declining too slowly, case detection stagnating, and MDR-TB care only now starting scale-up
Incidence, prevalence and mortality rates: global estimates

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What are the challenges in 2012 if we target "elimination"?

1. Funding far from secure with current financial crisis
2. One third of cases not in the “system”, likely late detection and continued transmission
3. TB/HIV, with major impact in Africa, and MDR-TB, with high burden in former USSR and China
4. Weak health policies, systems and services
5. Un-engaged non-state practitioners and un-aware, un-involved communities
6. Insufficient tools, R&D underfunded, and challenging transfer of tools/technology

Underfunding for TB control persists
**Funding gap for TB R&D**

Conclusion: “In 2010, 71 funders invested $617 million on TB R&D, a 73% increase over 2005 levels but no growth since 2009”.

NB: The Global Plan estimates a need of about 2 billion US$ per year.

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Innovative action needed in 4 areas

- Early & increased case detection: new tools
- Scale-up TB/HIV and MDR-TB interventions
- M&E and impact measurement
- Engage all care providers

Active screening among at-risk populations

TB care and control

Health systems and policies
- Free services, labs, quality drugs, regulated private care, better M&E

Development agenda
- Socio-economic factors: living conditions, food insecurity, awareness, risk behaviour, access to care

Research sensu lato
- New tools
- Operational research
- Transfer of technology
Today, most used tools for TB control are old and not conducive to elimination

**DIAGNOSTIC**
- **Sputum smear microscopy**
  - Discovered: 1882
  - Detects only half of the cases in patients tested
  - Less effective for diagnosing TB in PLHIV
  - Rapid tests for TB and MDR-TB (not yet PoC) finally available
  - No potential to facilitate elimination at the moment

**VACCINE**
- **BCG**
  - Developed: 1920s
  - Discovered: 1882

**TREATMENT**
- **1st-line TB drugs**
  - Discovered: 1943-1970

Limitations of today’s Diagnostics, Drugs and Vaccine – Elimination possible?

**Diagnostics - More than 100 years old**
- Detects only half of the cases in patients tested
- Less effective for diagnosing TB in PLHIV
- Rapid tests for TB and MDR-TB (not yet PoC) finally available
- No potential to facilitate elimination at the moment

**Drugs - Last drug 40 years old**
- Four drugs, taken for at least 6 months
- Not compatible with some ARVs
- MDR-TB treatment lengthy, low cure rates, expensive, toxic
- New drugs possibly being introduced starting in 2012/13
- No potential to facilitate elimination at the moment

**Vaccine - Nearly 90 years old**
- Unreliable protection against pulmonary TB
- No apparent impact on the TB epidemic
- A dozen candidates in clinical trial
- No potential to facilitate elimination at the moment
All good, but what do we really need to eliminate TB?

1. Mathematical modelling suggests that TB can be eliminated by 2050 (<1 case per 1 million population) through a revolutionary treatment regimen for disease and latent infection a/o a vaccine

2. An ideal treatment regimen should be highly effective, no more than 2-month long and active against M/XDR-TB

3. Mass latent preventive therapy has great theoretical potential, but remains ill-defined in terms of feasibility and scale-up

4. Mass pre-exposure and post-exposure vaccine will be conducive to elimination

5. Synergy of interventions is necessary: action on both the transmission and the reactivation pathways required
Potential impact of new TB diagnostics, drugs and vaccines in SE Asia

- L. Abu Raddad et al., PNAS 2009

Led & NAAT at microscopy lab level
- Dipstick at point of care
- Regimen 1 = 4-month, no effect on DR
- Regimen 2 = 2-month, 90% effective in M/XDR
- Regimen 3 = 10-day, 90% effective in M/XDR

Source: L. Abu Raddad et al., PNAS 2009

Effects = effects also on latency and infectiousness of cases in vaccinated

Elimination of TB by 2050 requires synergistic interventions

- Not by preventing infection & treating active TB (both act on cutting transmission)

- But by treating latent infection and active TB or by preventing and treating latent infection (cutting transmission and reactivation)
1. Today we do not have a potent treatment regimen that lasts <2 months and treats TB and M/XDR-TB. It will probably not be available for at least 5 years.

2. Today we do not have a potent pre- and post-exposure vaccine. It will probably not be available for a decade.

3. Today we do have a treatment for latent TB infection that is >60% efficacious, but difficult to scale-up to whole population (2 billion infected) or even to high-risk groups.

4. Today we do not have a test capable of identifying who will progress to active TB among the 2 billion infected.

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**Treatment of latent TB infection**
**WHO recommendations**

1. Efficacy to prevent TB well known

2. Isoniazid 5 mg/kg daily (max 300 mg) for at least 6 months (ideally 9 months). Other shorter regimens not yet recommended.

3. Individual benefits clear, population level less clear (40% reported); modelling shows huge potential, but feasibility and scale-up remain an issue.

4. WHO recommends treatment of LTBI for:
   - People living with HIV (PLHIV)
   - Children <5 contacts of a TB case
   - Recent TST converters
Isoniazid preventive therapy in people living with HIV

- People living with HIV and:
  - with unknown or positive TST status, and
  - unlikely to have active TB should receive IPT for at least 6 months
    (strong recommendation)

- In settings with high TB transmission, IPT could be given for 36 months
  (conditional recommendation)

Implementation of IPT on a large scale is a challenge even in PLHIV

- Number of PLHIV on IPT increased in the past 4 years

- But...only 178,144 started on IPT out of 1,464,579 people enrolled on HIV care in 2010 (12%, or 24% of potentially eligible)

- Completion rate in various studies varies 47-94%

- Concerns by providers over side effects (real) and creation of drug resistance (not substantiated)
Any role for IGRAs to facilitate implementation of treatment of LTBI?

WHO has recently reviewed the entire literature on the use of IGRAs in low- and middle-income countries through a long and rigorous process.

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

WHO TB diagnostics policy formulation process

- **Identifying the need for policy change**
  - WHO strategic monitoring of country needs
  - Partners (researchers, industry, etc)
  - Body of evidence available

- **Reviewing the evidence**
  - Commissioning of systematic reviews
  - QUADAS or other diagnostic accuracy tool
  - Meta-analyses (where feasible)

- **Convening an Expert Group**
  - Experts, methodologists, end-users
  - Guidelines Review Committee
  - GRADE process for evidence synthesis

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

- **Formulating and disseminating policy**
  - Guidelines Review Committee
  - Dissemination to Member States
  - Promotion with stakeholders & funders
  - Phased implementation & scale-up plan
IGRAs in Low/ Middle income Countries
WHO policy statement, 2011

- There are insufficient data and low quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high TB and HIV burden.

- IGRAs (IRR 3.24, CI 0.62-5.85) and the TST (IRR 2.28, CI 0.83-7.63) cannot accurately predict the risk of infected individuals to develop active TB disease.

- IGRAs and TST are designed to detect latent TB infection. Neither one should be used for the diagnosis of active TB disease.

- IGRAs are more costly and technically complex than TST. Given comparable performance but increased cost, replacing TST by IGRAs as a public health intervention in resource-constrained settings is not recommended.

Are new developments changing substantially chances of elimination?

1. Xpert MTB/RIF, with high NPV, may facilitate the ruling-out of active TB in a candidate for treatment of LTBI.

2. TST and IGRAs can detect latent infection, but cannot predict who will progress to active disease.

3. The new HP3 regimen can be more easily administered, but still requires 3 months of weekly treatment, and must be tested in PLHIV.

4. We need more to have an impact:
   - An easy test, an “IGRA-PLUS” that can predict high-risk progressors.
   - A PoC test that can reliably exclude active TB.
   - An easy to administer, short, and effective regimen for all, including PLHIV.
   - The capacity to scale programmatically, with focus on high-risk groups.
   - The money and the commitment.
Conclusions

1. The world is on track to achieve the un-ambitious 2015 target of (slow) incidence reduction, and current measures can reduce deaths and cure patients. They cannot eliminate TB.

2. Actions in 4 areas are necessary to target elimination: universal access to quality TB care and control, bold health system policies, alleviation of social and economic determinants and risk factors, and intensified research investments

3. Mathematical models suggest that potent short treatments, mass TLTBI and potent pre- and post-exposure vaccines can eliminate TB

4. The only tool available today is TLTBI. However, its mass scale-up and feasibility remain a challenge, even in focused high-risk groups

5. New advances may allow some progress, but “elimination tools” are not yet available in 2012

Eradication of tuberculosis: Will it be feasible?

"The possibility of eradicating tuberculosis in a country is essentially a function of its economic level...

...There are three major weapons which can be used in a policy of eradication: chemotherapy, vaccination, and chemoprophylaxis.

...In realising this objective, the developed countries can give developing ones considerable help"
Many thanks to all

Use of TB IGRA* 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 supercede 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%).

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.

Two 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.

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 study.
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.

**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).

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.

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).