Research in the post-2015 Global TB Strategy: the path to elimination?

McGill TB Research Methods Course
14 July 2014

Christian Lienhardt
Global TB Programme
WHO, Geneva, Switzerland
Overview of the presentation

- The global burden of TB
- The challenges to TB elimination
- The new tools pipelines: expectations, hopes and limitations
- The WHO post 2015 Global TB Strategy and the importance of research
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The Global Burden of TB - 2012

Estimated number of cases

All forms of TB
- 8.6 (8.3-9.0) million cases
  - 0.5 m in children
  - 2.9 m in women

HIV-associated TB
- 1.1 (1.0-1.2) million cases (13%)

Multidrug-resistant TB
- 450,000 (300k-600k)

Estimated number of deaths

All forms of TB
- 1.3 (1.0-1.6) million* deaths
  - 74,000 in children
  - 410,000 in women

HIV-associated TB
- 320,000 (300k-340k) deaths

Multidrug-resistant TB
- 170,000 (102k-242k)

Source: WHO Global Tuberculosis Report 2013

* Including deaths attributed to HIV/TB
Estimated TB incidence rate, 2012

- South-East Asia: 39%
- Western Pacific: 19%
- Africa: 27%
- E. Mediterranean: 8%
- Americas: 3%
- Europe: 4%

38% in India + China
26% in India

Ref: Global TB Control Report 2013
Global Progress on impact - 2012

- 2015 MDG on track and reduction in TB mortality of 45% since 1990
- 56 million patients cured, 1995-2012
- 22 million lives saved since 1995
- BUT, TB incidence declining far too slowly, 1/3 of cases not in the system, MDR-TB challenge not yet properly addressed

Ref: Global TB Control Report 2013
MDG, WHO & Stop TB Goals: falling incidence, halve prevalence and death rates 1990-2015

Incidence

Prevalence

Mortality

Peak in 2002

Target met globally

Target missed by 2015?

Target met by 2015?
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What are the challenges in 2014 if we target "elimination"?

1. Only 2/3 of estimated cases reported or detected
2. Still 1.3 million people died of TB out of the estimated 8.6 million new cases in 2012;
3. Only one in five of the notified patients estimated to have MDR-TB is being currently diagnosed and treated;
4. Insufficient tools to combat the disease and challenging transfer of tools and technologies
5. Weak health policies, systems and services
6. Social and economic determinants maintain TB
7. Funding not secure
Reaching the "missed" cases 
(nearly 3 million not diagnosed or reported)

Global trends in case notification (black) and estimated TB incidence (green) rates, 1990–2012. Case notifications include new and relapse cases (all forms).

Share of total missed cases

2.9 million missed

8.6

5.7

12 countries account for 75% (2.1) million of the estimated "missed" cases globally

Ref: Global TB Control Report 2013
Address MDR-TB as a crisis: 
*Percentage of new TB cases with MDR-TB*

India, China, Russia and South Africa have 65% of all MDR-TB cases

Ref: Global TB Control Report 2013
Response to MDR-TB: % DST, detected and treated

Only 4% of new and 6% of already treated TB patients undergo DST

Global Plan
target levels

Enrolments on treatment

Only ~ 1 in 5 MDR-TB cases among notified TB patients detected and treated globally in 2011
Accelerate response to TB/HIV

Estimated HIV prevalence in new TB cases, 2012
TB/HIV co-infection

- TB leading cause of death in PLHIV
- ¼ of PLHIV worldwide die due to TB.
- PLHIV infected with TB 20-40 times more likely to develop active TB.
- 80% of all TB/HIV cases are in Africa
BRI CS mostly domestic funding
Other HBCs ~50% is donor funding

BRI CS
96% domestic financing

Other 17 high-burden countries
49% donor financing
Full implementation of Global Plan: 2015 MDG target reached but TB not eliminated by 2050

<table>
<thead>
<tr>
<th>Year</th>
<th>Current rate of decline</th>
<th>China, Cambodia</th>
<th>Elimination</th>
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<tbody>
<tr>
<td>2010</td>
<td>-2%/yr</td>
<td>-2%/yr</td>
<td>-20%/yr</td>
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<tr>
<td>2020</td>
<td>-2%/yr</td>
<td>-4%/yr</td>
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<tr>
<td>2030</td>
<td>-2%/yr</td>
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<td>2040</td>
<td>-2%/yr</td>
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<tr>
<td>2050</td>
<td>-2%/yr</td>
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So, what is needed to accelerate TB incidence decline?
Full implementation of Global Plan: 2015 MDG target reached but TB not eliminated by 2050

W Europe after WWII: -10%/yr

Current rate of decline: -2%/yr

China, Cambodia: -4%/yr

Elimination target: <1 / million / yr

-20%/yr
TB incidence declined 10%/year after WWII in Europe (the Netherlands)

Recipe:

- Sustained socio-economic development
- Universal health coverage & social protection
- TB care widely accessible
- BCG vaccination in children
- Screening of high-risk groups (but limited impact)
- Infection control practices (?)

Full implementation of Global Plan: 2015 MDG target reached but TB not eliminated by 2050

Current rate of decline: 
-2% / yr

W Europe after WWII: 
-10% / yr

China, Cambodia: 
-4% / yr

Eskimos: 
> 10 ; < 20

Elimination target: 
<1 / million / yr

-20% / yr
"Best ever" case scenario: 15% /year incidence decline in Eskimos in Alaska, NW Canada and Greenland

Recipe:
- Highly focused & high intensity interventions
- Screening and massive TLTBI
- TB care decentralised
- BCG vaccination
- Improved health access & social protection
- Economic development (?)

“Can we achieve at global level the case reduction rates seen in the Alaskan Eskimo population?”

Figure 4  Incidence of new active tuberculosis (rates per 10,000) among the Eskimos of the Arctic: Greenland, Alaska and Northwest Territories of Canada; and total population of Canada, 1952-1973 [28]

Grzybowski S, Styblo K, Dorken E. Tuberculosis in Eskimos. Tubercle 1976; (suppl.) 57: 1-58
TB infection and disease worldwide

World
7 billion

Infected
2.3 billion

Disease
9 million/yr
Life cycle of tuberculosis

- **Uninfected**
- **Infection**
- **Latent**
  - Fast 0.7/yr
  - Faster (HIV+)
  - Slow 50/100k/yr
- **Active**
  - Spontaneous cure 3/10
  - Death 5/10

- **Reinfection**
- **≈ 10%**
- **≈ 90%**

- **≈10 infections/case**
Life cycle of tuberculosis: *where are the roadblocks?*

- **Uninfected**
- **Latent**
  - Fast 0.7/yr
  - Faster (HIV+)
  - Slow 50/100k/yr
- **Active**
  - Spontaneous cure 3/10
  - Death 5/10

Persistently transmission is the primary problem

- Infection
- Reinfection

≈10 infections/case
Life cycle of tuberculosis: *where are the roadblocks?*

- **Uninfected**
- **Latent**
  - Fast 0.7/yr
  - Faster (HIV+)
  - 10% probability of progression
  - 90% rate of latency
  - 1 infection/case
- **Active**
  - 10 infections/case
  - Progression to disease is a secondary problem
  - Spontaneous cure 3/10
  - Death 5/10

Approximately 10% of infections progress to active disease.
~10 million prevalent cases of active TB
~2 billion people with latent TB*: 5-10% disease risk

* = antigen-specific T cells (evidence of current/prior infection)

Response to infection as a spectrum

- clinical disease
- bacterial replication maintained at a subclinical level by immune response
- 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

• whom to treat?
• how to treat?
• whom to protect?
• how to protect?

Global TB Programme

Young et al. Trends Microbiol 2009, 17:183
Lesion diversity model

- **disease**
- **asymptomatic infection**
- **clearance**

- diverse lesions throughout the spectrum
- different types of lesion
- different microenvironments
- replicating or non-replicating bacteria
- increasing number of “active” lesions

GLOBAL TB PROGRAMME
Roadblocks

- Ineffective prevention
- Delayed diagnosis
- Delayed/insufficient/inappropriate treatment
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Limitations of today’s Diagnostics, Drugs and Vaccine – but... *something moving!*

**Diagnostics - More than 100 years old**
- Detects only half of the cases in patients tested
- Less effective for diagnosing TB in PLHIV
- *But... rapid test for TB and (M)DR strains now available*

**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
- *But... new drugs introduced in 2013/14*

**Vaccine - Nearly 90 years old**
- Unreliable protection against pulmonary TB
- No apparent impact on the TB epidemic
- *But... series of candidate vaccines in human trials*
Pipeline for new TB diagnostics

**GLOBAL TB PROGRAMME**

- **REFERENCE LEVEL**
  - New SS+ case definition
  - 2-specimen approaches
  - Liquid culture and DST
  - Rapid speciation
  - LPA for MDR-TB
  - Non-commercial culture and DST (MODS, NRA, CRI)
  - LPA for XDR-TB
  - LPA for MDR-TB 2nd generation

- **INTERMEDIATE LEVEL**
  - LED microscopy
  - Same-day diagnosis
  - Xpert MTB/RIF
  - Manual NAAT
  - VOC detection
  - Enzymatic detection
  - Ag and Ab detection
  - NAAT 2nd generation

- **PERIPHERAL LEVEL**
  - Technologies or methods endorsed by WHO
  - Technologies commercialized, not yet endorsed by WHO
  - Technologies at feasibility stage
  - Technologies at early stages of development

Distance from patients

Access after 5 years (%)

**World Health Organization**
Introducing Xpert MTB/RIF

Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB (strong recommendation)

WHO endorsement Dec 2010

Phased implementation & evaluation 2011

26 countries using it in mid-2011

WHO Policy update – Oct 2013

Scale up 2012 - 2014

2,343 Xpers and 6.3 million Xpert cartridges in the public sector in 104 countries
Lead Optimization

Preclinical Development

GLP Tox.

Phase I

Phase II

Phase III

Diarylquinoline

DprE Inhibitors

GyrB inhibitors

InhA Inhibitors

LeuRS Inhibitors

MgyrX1 inhibitors

Mycobacterial Gyrase Inhibitors

Pyrazinamide Analogs

Riminophenazines

Ruthenium (II) complexes

Spectinamides

Translocase-1 Inhibitors

But no compound at Phase I level!

4 Repurposed Drugs

6 New Drugs

3 New Classes

AZD5847

Bedaquiline (TMC-207)

Linezolid

Novel Regimens

PA-824

Rifapentine

SQ-109

Sutezolid (PNU-100480)

Delamanid (OPC-67683)

Gatifloxacin

Moxifloxacin

Rifapentine

Drugs currently in the regulatory review process

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

1 Ongoing projects without a lead compound series can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

2 Combination regimens: first clinical trial (NC001) of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide was initiated November 2010 and completed in 2011 with promising results. The second clinical trial (NC002) of this regimen was launched in March 2012 and will test the efficacy of the regimen in drug-sensitive and multidrug-resistant patients. The third clinical trial (NC003) will evaluate PA-824, TMC-207, pyrazinamide and clofazimine in combinations and is scheduled to begin September 2012.
Global TB Vaccine Pipeline 2013: good but needs to keep growing

Phase I

- Ad5 Ag85A
  McMaster CanSino

- ID93 + GLA-SE
  IDRI, Aeras

- Hyvac 4/ AERAS-404 + IC31
  SSI, sanofi-pasteur, Aeras, Intercell

- H56 + IC31
  SSI, Aeras, Intercell

- MTBVAC
  TBVI, Zaragoza, Biofabri

- Hybrid-I + CAF01
  SSI, TBVI

Phase II

- VPM 1002
  Max Planck, VPM, TBVI

- Hybrid-I + IC31
  SSI, TBVI, EDCTP, Intercell

- RUTI
  Archivel Farma, S.L

Phase IIb

- MVA85A/AERAS-485
  OETC, Aeras

- AERAS-402/ Crucell Ad35
  Crucell, Aeras

- M72 + AS01
  GSK, Aeras

- M. Vaccae
  Anhui Longcom, China

Phase III

- Viral vector
- rBCG
- Protein/adjuvant
- Attenuated M.tb
- Immunotherapeutic: Mycobacterial – whole cell or extract

GLOBAL TB PROGRAMME
Global TB Vaccine Pipeline 2013: good but needs to keep growing

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial


Summary

Background BCG vaccination provides incomplete protection against tuberculosis in infants. A new vaccine, modified Vaccinia Ankara virus expressing antigen 85A (MVA85A), was designed to enhance the protective efficacy of BCG. We aimed to assess safety, immunogenicity, and efficacy of MVA85A against tuberculosis and Mycobacterium tuberculosis infection in infants.

Published Online February 4, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60177-4

Safe
Showing it is feasible to test vaccine candidates in large trials, but...
No detectable efficacy
Potential impact of new TB vaccines, diagnostics and drugs in SE Asia

Synergy of interventions
- act both on the transmission and reactivation pathways
- better diagnostics, treatment and prevention
- address the larger health context
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- The new tools pipelines: expectations, hopes and limitations
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Projected acceleration of TB incidence decline to target levels

- Optimize current tools, pursue universal health coverage and social protection by 2025
- Introduce new tools: a vaccine, a new prophylaxis & treatment regimen, a PoC test

Current global trend: -2%/year

Average -10%/year by 2025

Average -5%/year

Average -17%/year
Global strategy and targets for tuberculosis prevention, care and control after 2015

The Sixty-seventh World Health Assembly,

Having considered the report on the draft global strategy and targets for tuberculosis prevention, care and control after 2015;¹

Acknowledging the progress made towards the achievement of Millennium Development Goal 6 (Combat HIV/AIDS, malaria and other diseases) for 2015 following the United Nations Millennium Declaration and related 2015 tuberculosis targets, through the adoption of the DOTS strategy, the Stop TB Strategy and the Global Plan to Stop TB 2006–2015, as well as the financing of national plans based on those frameworks, as called for, inter alia, in resolution WHA60.19 on tuberculosis control;
Post-2015 Global TB Strategy at a glance

VISION:
- A WORLD FREE OF TB
- Zero deaths, disease and suffering due to TB

GOAL:
- End the Global TB Epidemic

MILESTONES FOR 2025:
- 75% reduction in TB deaths (compared with 2015)
- 50% reduction in TB incidence rate (< than 55/100,000)
- No affected families face catastrophic costs due to TB

TARGETS FOR 2035:
- 95% reduction in TB deaths (compared with 2015)
- 90% reduction in TB incidence rate (<10/100,000)
Post-2015 Global TB Strategy
Three Pillars and four overarching Principles

1. Integrated, patient-centered TB care and prevention
2. Bold policies and supportive systems
3. Intensified research and innovation

Government stewardship and accountability, with monitoring and evaluation
Building a strong coalition with civil society and communities
Protecting and promoting human rights, ethics and equity
Adaptation of the strategy and targets at country level, with global collaboration
Intensified Research and Innovation

A. Discovery, development and rapid uptake of new tools, interventions, and strategies

B. Research to optimize implementation and impact, promote innovations
Projected acceleration of TB incidence decline to target levels

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Improving Global TB Control
– what do we need ?

1. Better functioning TB programmes:
   • identify causes of deficiencies that are amenable to improvement by technical or managerial intervention

2. New interventions to improve TB control:
   • effective and efficient use of new tools & strategies
   • determination of the conditions/requirements under which they can be effectively implemented

3. Inform Policy recommendations
   • provide evidence on what can be expected from new interventions in real-life settings
   • increasingly important for international policy decisions and funding (e.g. GRADE for policy recommendation)
From tools to strategies

GLOBAL TB PROGRAMME

TEST 1
- no further TB diagnostics
+ TEST 2

- treat
+ further TB diagnostics
From tools to strategies

New drugs/treatments of TB/MDR-TB

- Evaluation of feasibility, effectiveness and impact
- Further tests of resistance?
  - which ones?
  - how?
  - where?
  - for whom?

-> various strategies regarding
- eligible patient population
- single- or multistep DST

-> pharmacovigilance and monitoring
From focus to context

- **Difficulty in accessing health care**
- **Ineffective prevention**
- **Late diagnosis**
- **Uninfected** → **Latent** → **Active**
- **Differences in economic factors**
- **Changing risk factors for TB**
- **Delayed/insufficient/inappropriate treatment**
From focus to context

Access to care:

• The Health system environment
  - Availability and quality of services
  - Reimbursements of costs
  - Insurance schemes
  - Social protection

• Patients costs
  - Health seeking behaviour
  - Adherence
  - Incentives, enablers
Evidence for scale-up of new interventions

1. Is it scalable?
   Retain **effectiveness** when brought to scale?
   - Real-life conditions
   - Adverse consequences?

2. Is it worth scaling up?
   **Cost-effectiveness** and **affordability** when applied at scale?
   - Monetary, non-monetary costs
   - Compare various ways of scale-up (e.g. algorithms)

3. How should it be scaled-up?
   - What are its key **delivery** aspects?
   - Operational bottlenecks? Access?
Priorities in Operational Research to Improve Tuberculosis Care & Control

Objective:

to assist countries/NTPs in conducting OR to improve TB care and control and applying for grants for OR

Contents:

- Description of *five priority OR areas* and rationale for research questions
- Determination of *research cycles* describing a logical timeline of successive research projects
- For each research question, development of a *standard research template*

Launched in Delhi, India, on 29th August 2011
Priorities in Operational Research to Improve Tuberculosis Care & Control

5 main areas:

1. Improving access, screening and diagnosis of TB
2. Developing sustainable collaboration with all care providers for TB care and control
3. Prevention of TB in HIV-infected patients and joint treatment of TB and HIV
4. Treatment of Drug-susceptible and M/XDR-TB: optimal access, delivery and community participation
5. Capacity Building for Operational Research
Projected acceleration of TB incidence decline to target levels

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The Continuum of TB Research

- Point of Care Diagnostics of TB
- Treat all forms of TB in all populations
- Prevent TB in all populations

Fundamental Science
Translational Studies
Preclinical Studies
Clinical Studies/Trials
Deployment/Operational research

Prevent TB in all populations

Point of Care Diagnostics of TB

Treat all forms of TB in all populations
An International Roadmap for Tuberculosis Research

**Overall goal:**
To identify knowledge gaps and priority areas in TB research towards elimination of TB by 2050

**Objectives:**
- to identify the essential research questions for better TB control towards the elimination of TB
- to strengthen the role of every aspect of TB research along the continuum
- to mobilize and focus resources into TB research areas of importance

*Contributions from a large panel of partners and stakeholders involved in TB research worldwide*

Launched at the 42nd Lung Health Conference, Lille, 29th October 2011
Cross Disciplinary Teams to Contribute to Public Health Outcome-Oriented Science

International TB Research Roadmap

Transmission of TB

provides “menu” of key knowledge gaps

Opportunities for cross-disciplinary interactions to transform how strategic questions in TB are addressed –
Accelerating research for TB elimination

Research for Elimination Initiative

- Context-specific Strategy for Elimination
- Optimal implementation of all TB interventions
- Translational and cross cutting research for novel interventions

Global TB elimination Champions and Role Models

Pathfinder to Global TB elimination

Countries in the pre-elimination + selected countries in the concentrated epidemic phase
Future prospects

- Need a *multi-sectorial/multi disciplinary approach*, from fundamental science to synergistic implementation of combined strategies

- Integrate biomedical research as a critical component of the Global TB Strategy to modernize TB care and control

- Create *connections between disciplines of science* that historically have not intersected (biomedical /epidemiology/operational research)

- Research to optimize implementation and adopt innovations at country level

- Promote the development of *national research agendas* on TB linked with the global health research agenda
Elimination 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."
Acknowledgements

• WHO Global TB Programme: Monica Dias, Philippe Glaziou, Knut Lonnroth, Mario Raviglione, Mukund Uplekar, Diana Weil
• Chris Dye
• WGND: Cherise Scott, Melvin Spigelman, Barbara Laughon
• WGNV: Jennifer Woolley, Uli Fruth
• NDWG: Alessandra Vargas, Daniela Cirillo
• All colleagues/partners who participated in the TB Research Roadmap, particularly: Michael Brennan, Henry Boom, Martina Casenghi, Dick Chaisson, Jeremiah Chakaya, Frank Cobelens, Willem Hanekom, Anthony Harries, Mark Harrington, Stefan Kaufmann, Gilla Kaplan, Afranio Kritski, Hannu Laang, Dermot Maher, Nguyen Viet Nhung, Madhukar Pai, Andrew Ramsay, Eric Rubin, Giorgio Roscigno, Christine Sizemore, Peter Small, Bertie Squire, Soumya Swaminathan, Tido von Schoen Angerer, Andrew Vernon, Gerhard Walzl, Douglas Young, Rony Zachariah, and many others….
Thank you for your attention!

Photos: Dominic Chavez