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

McGill TB Research Methods Course
14 July 2014

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Global TB Programme
WHO, Geneva, Switzerland

World Health Organization

GLOBAL TB PROGRAMME

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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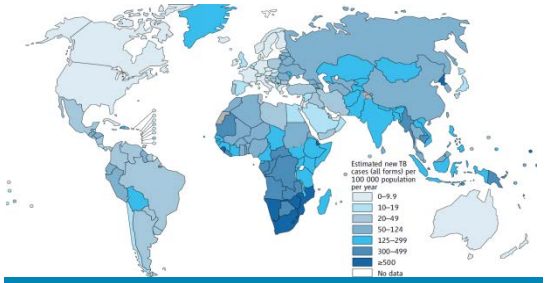
The Global Burden of TB -2012



	Estimated number of cases	Estimated number of deaths
All forms of TB	**8.6** (8.3-9.0) million • 0.5 m in children • 2.9 m in women	**1.3** (1.0-1.6) million* • 74.000 in children • 410.000 in women
HIV-associated TB	**1.1** (1.0-1.2) million (13%)	**320,000** (300k-340k)
Multidrug-resistant TB	**450,000** (300k-600k)	**170,000** (102k-242k)

Source: WHO Global Tuberculosis Report 2013

** Including deaths attributed to HIV/TB*

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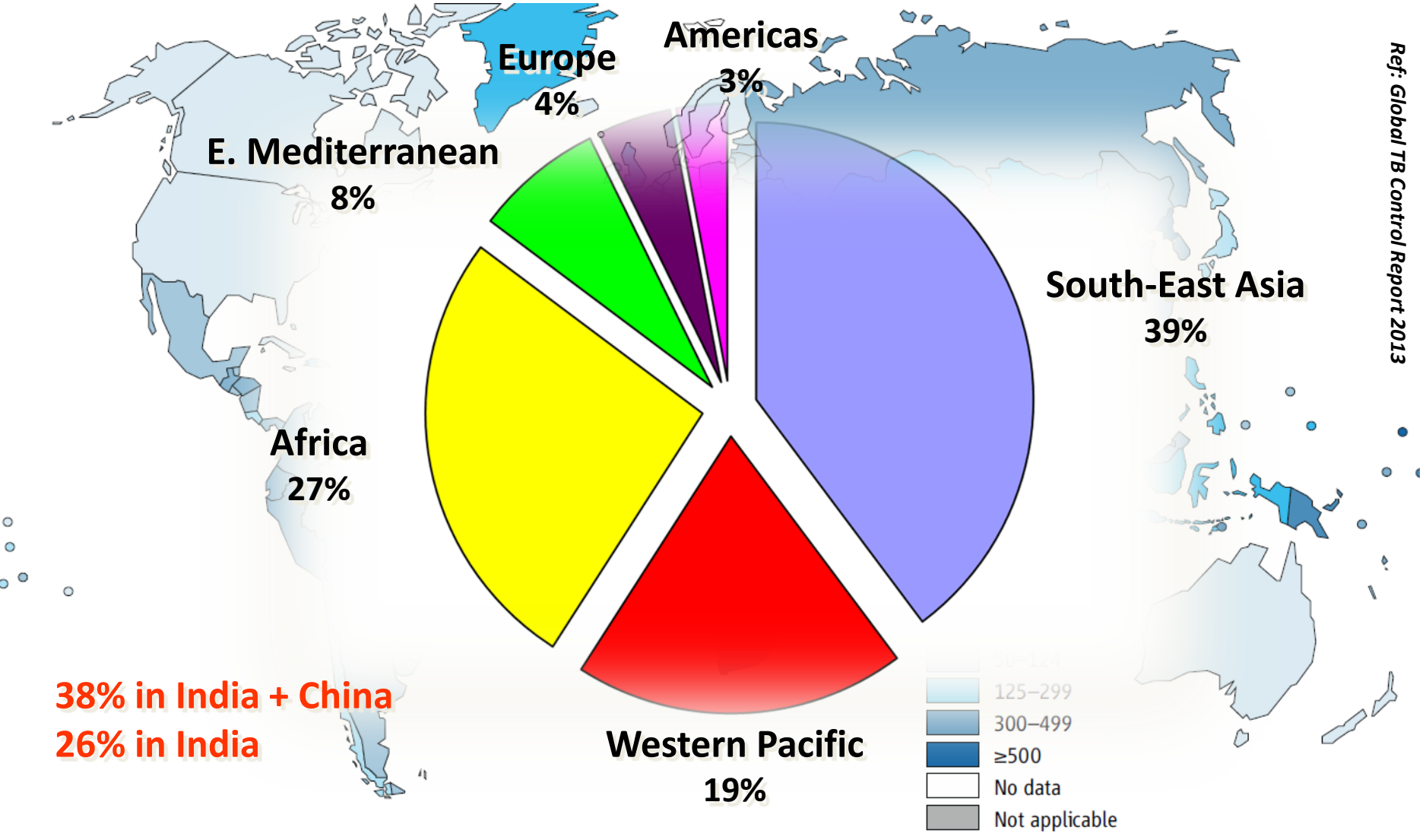
Estimated TB incidence rate, 2012



Ref: Global TB Control Report 2013

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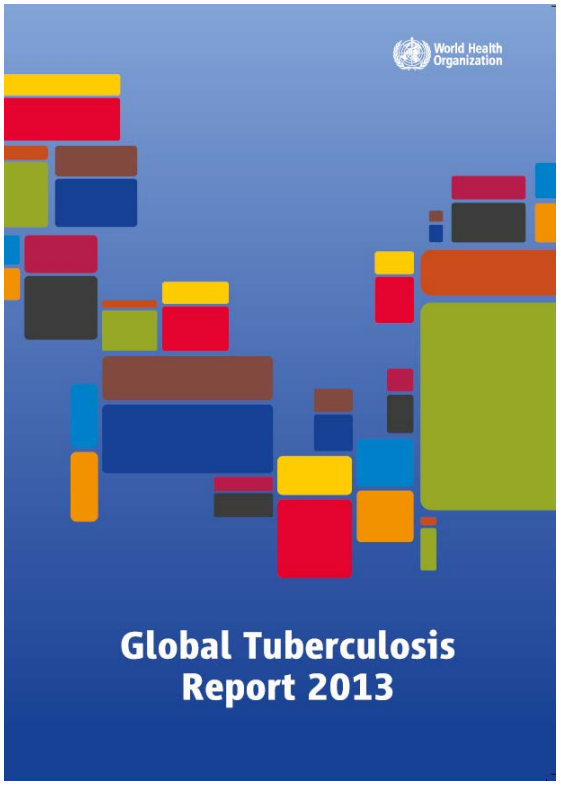
Global Progress on impact - 2012



- ✓ **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

Reaching MDGs and Stop TB Targets by 2015?

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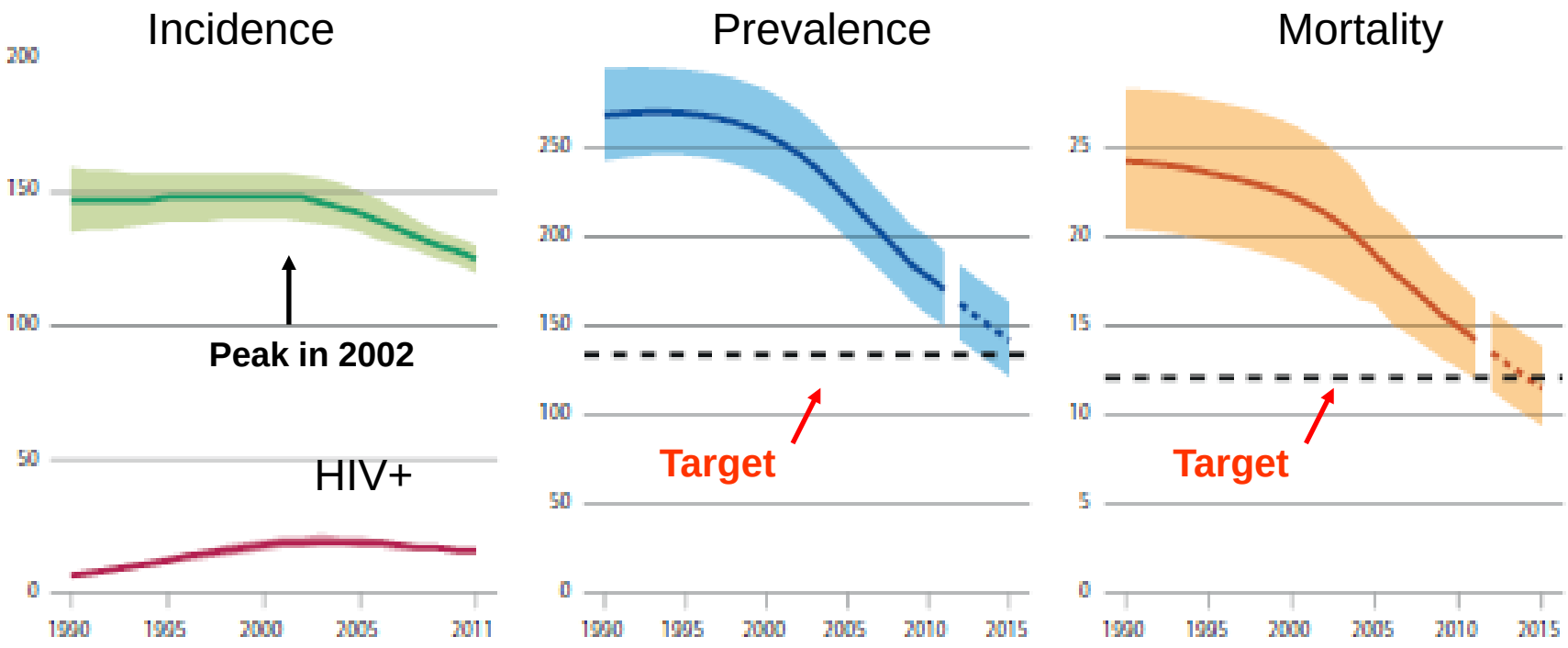
MDG, WHO & Stop TB Goals: falling incidence, halve prevalence and death rates 1990-2015



Target met globally

Target missed by 2015?

Target met by 2015?

WHO Global Tuberculosis Control 2013

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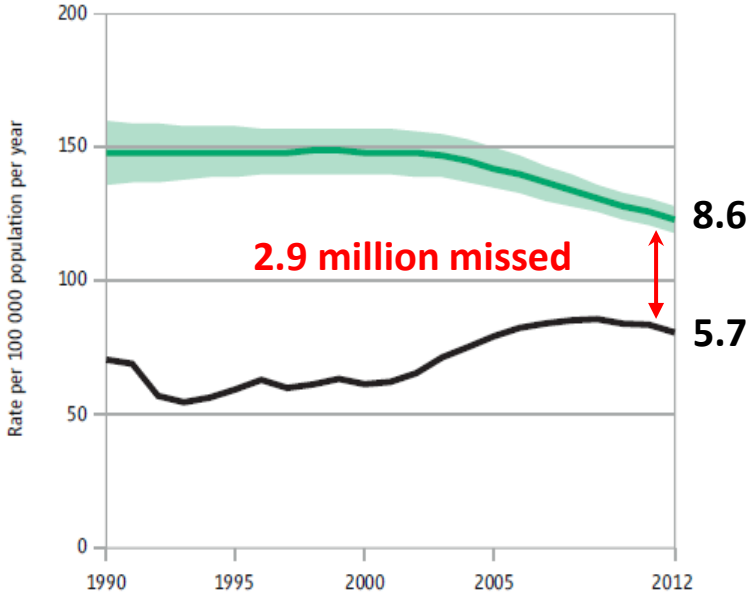
What are the challenges in 2014 if we target "elimination"?

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

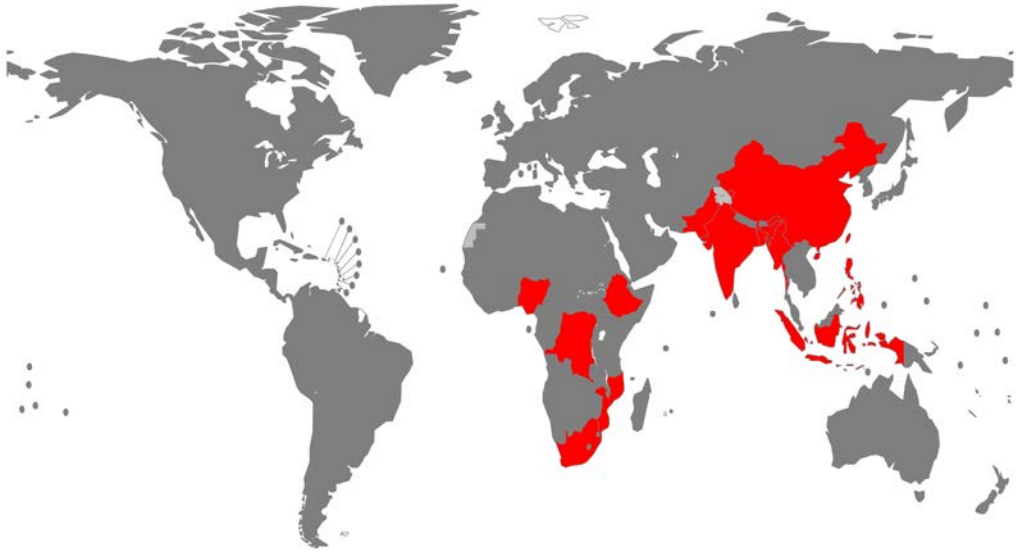
(nearly 3 million not diagnosed or reported)

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



Global notifications
Estimated incidence

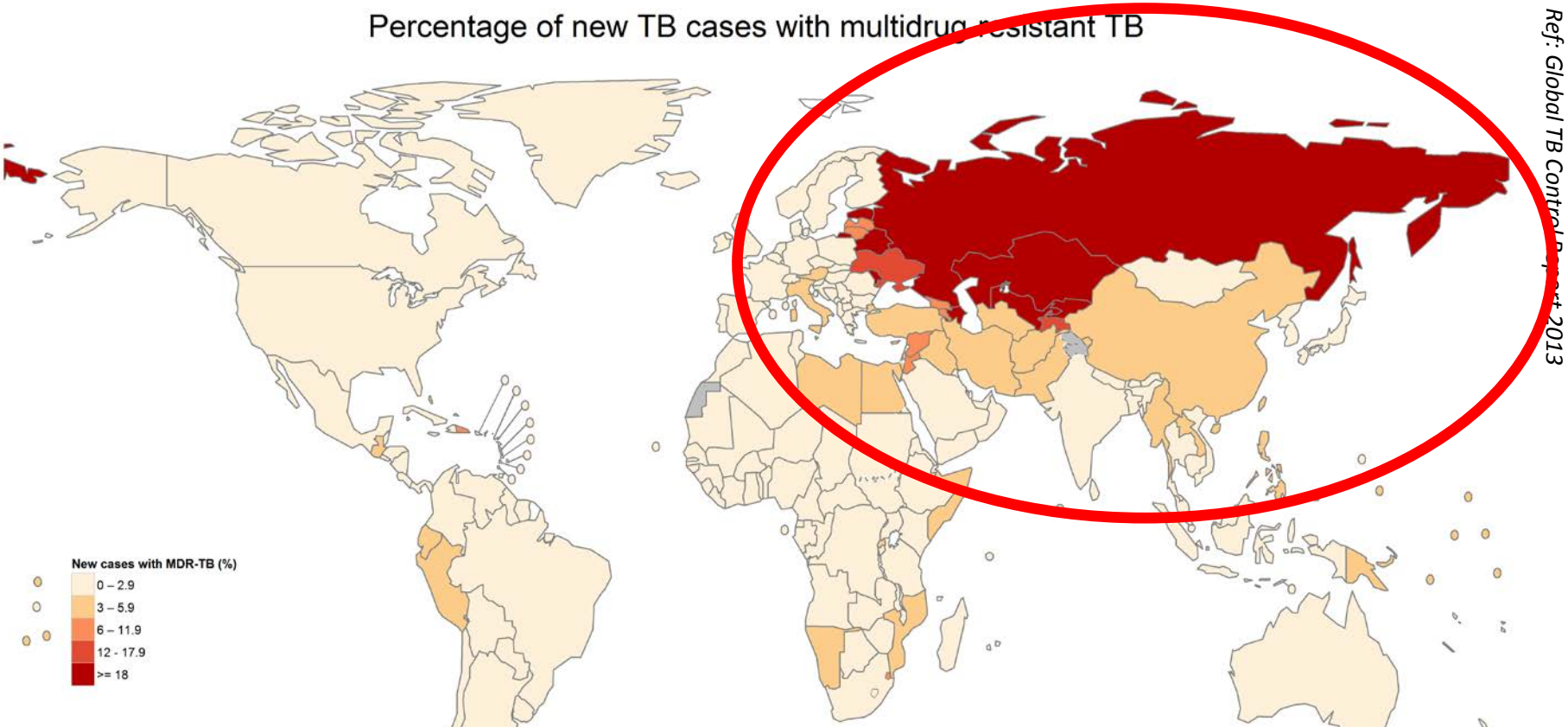
Share of total missed cases



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

Address MDR-TB as a crisis:

Percentage of new TB cases with MDR-TB



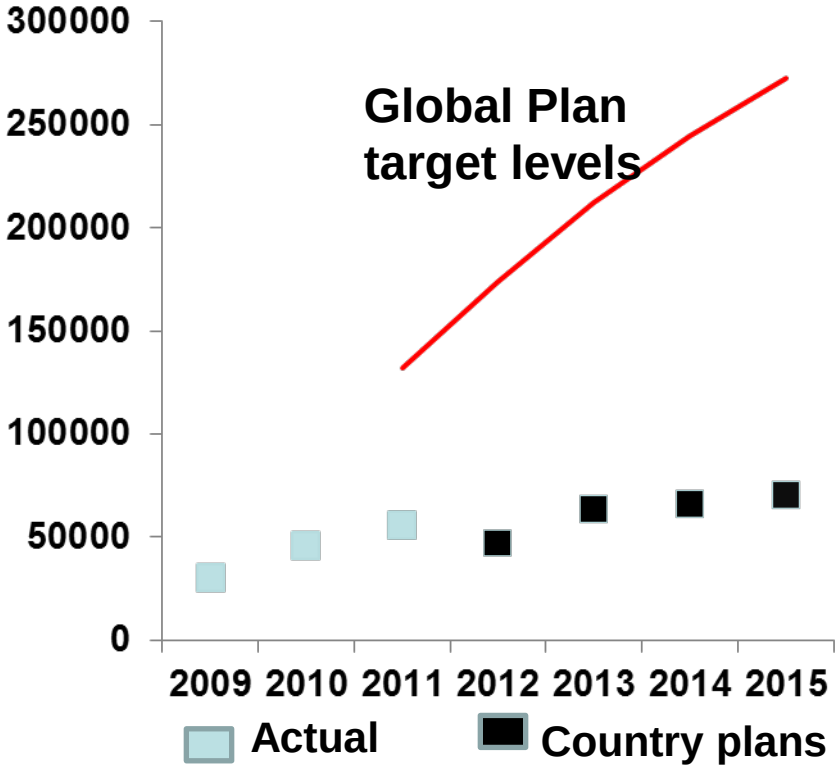
Ref: Global TB Control Report 2013

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

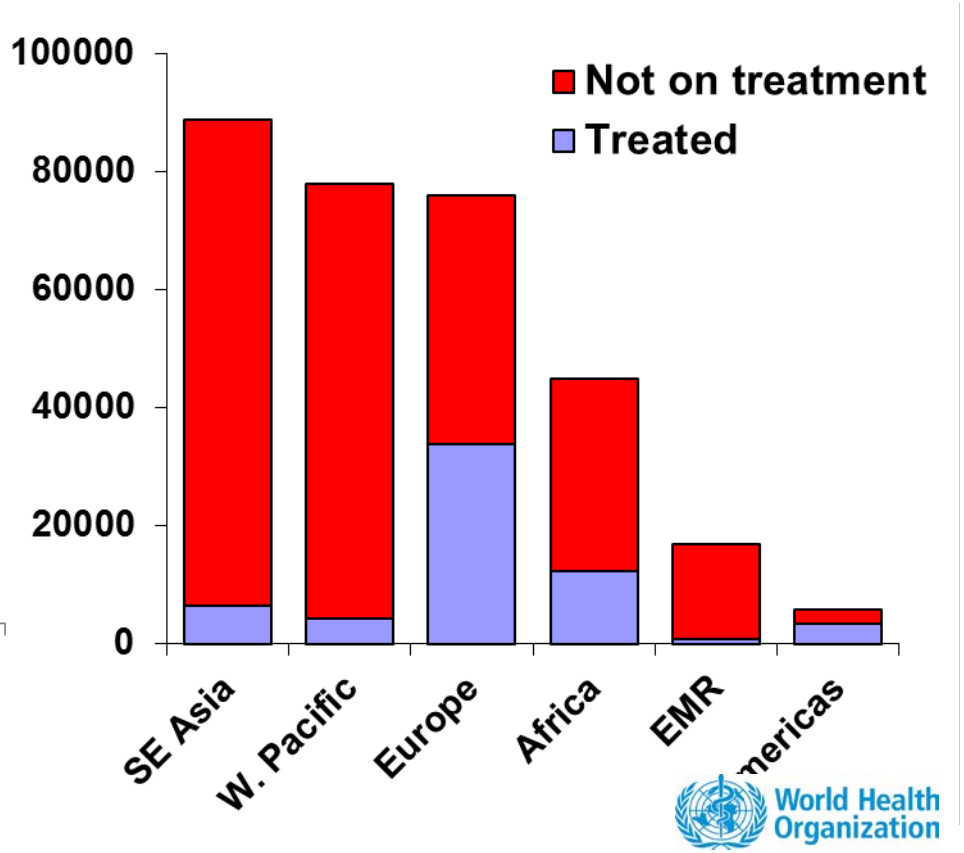
Response to MDR-TB: % DST, detected and treated

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

Enrolments on treatment



Only ~ 1 in 5 MDR-TB cases among notified TB patients detected and treated globally in 2011



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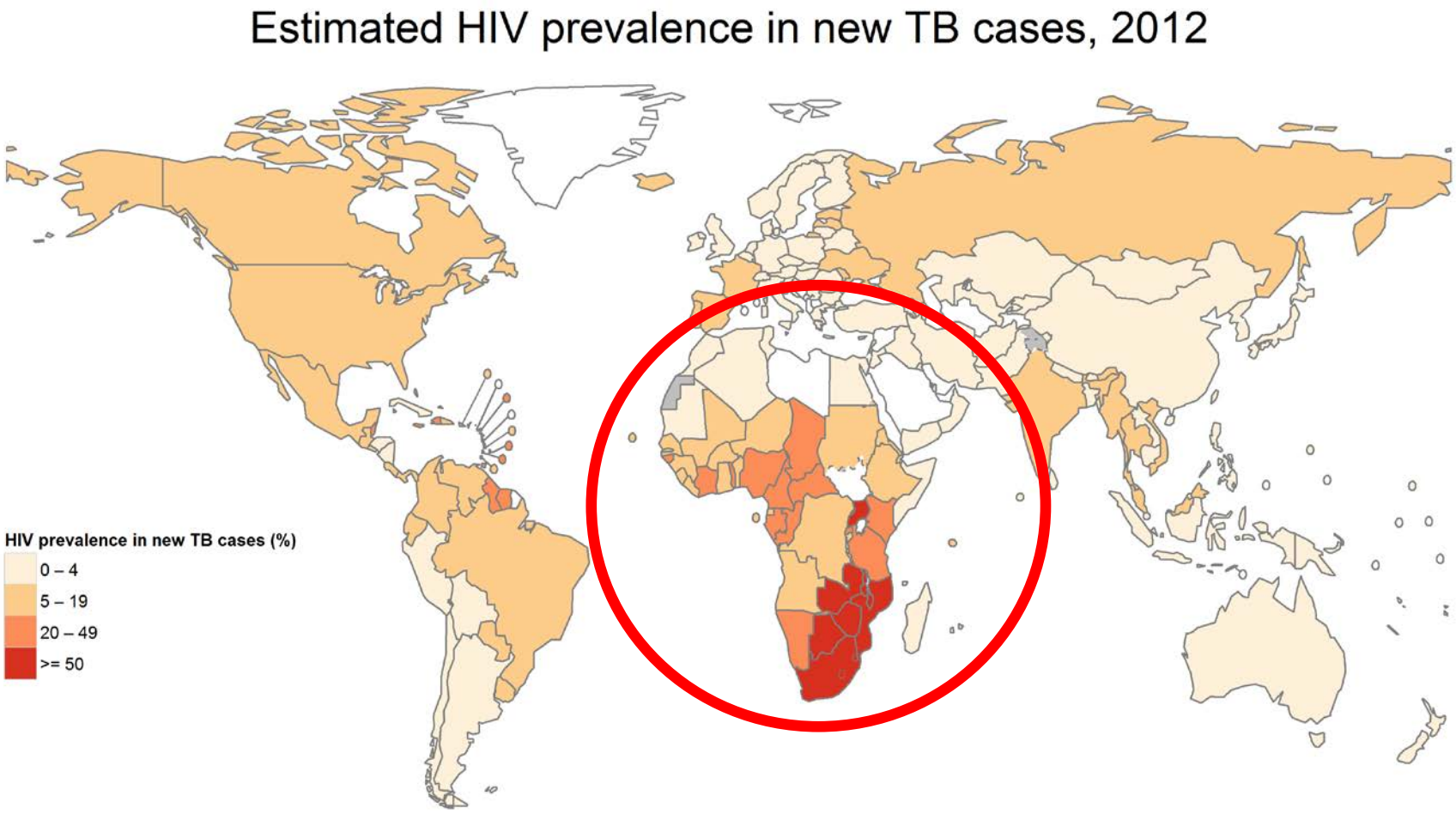
World Health Organization

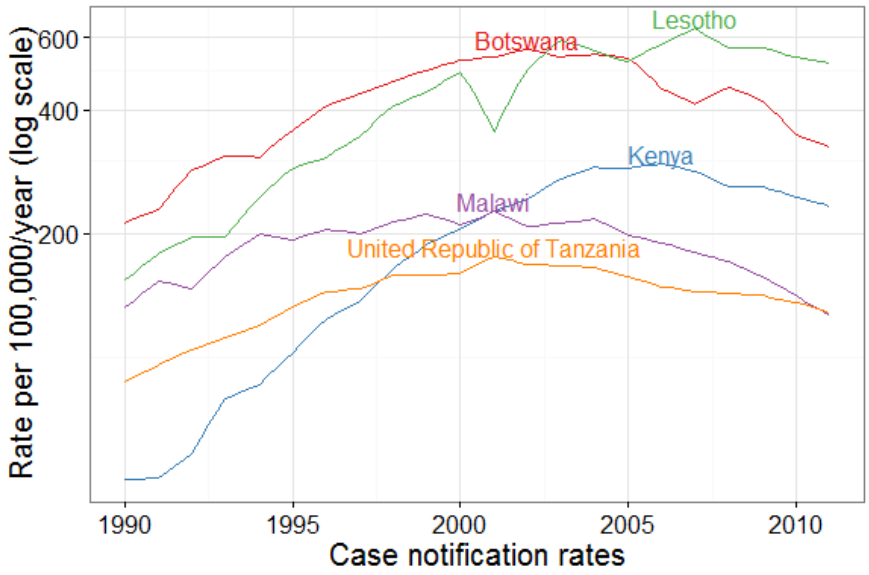
Accelerate response to TB/HIV

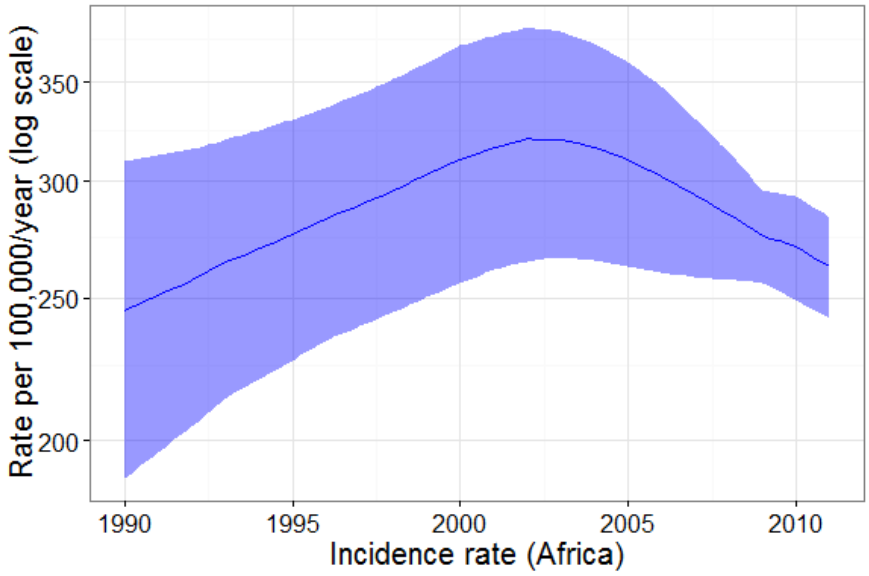


Ref: Global TB Control Report 2013

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





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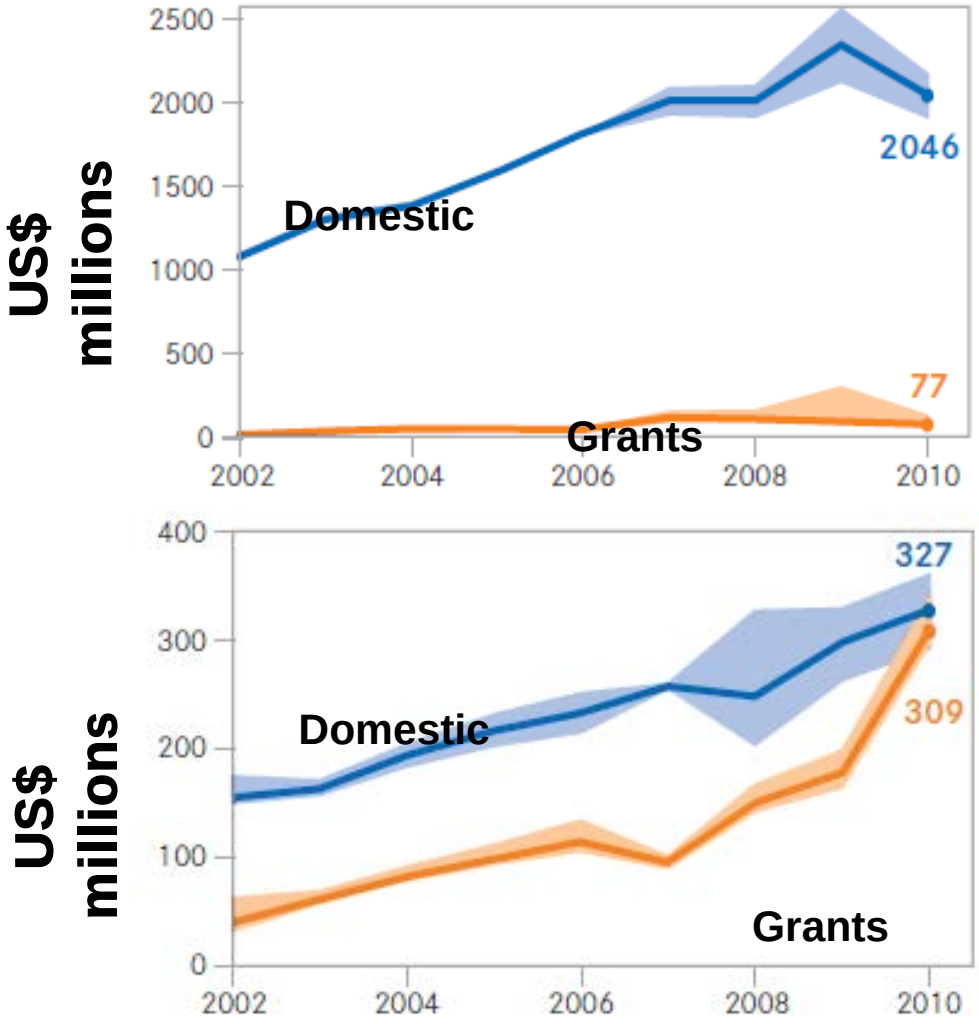
BRICS mostly domestic funding
Other HBCs ~50% is donor funding



BRICS

96% domestic financing

Other 17 high-burden countries

49% donor financing

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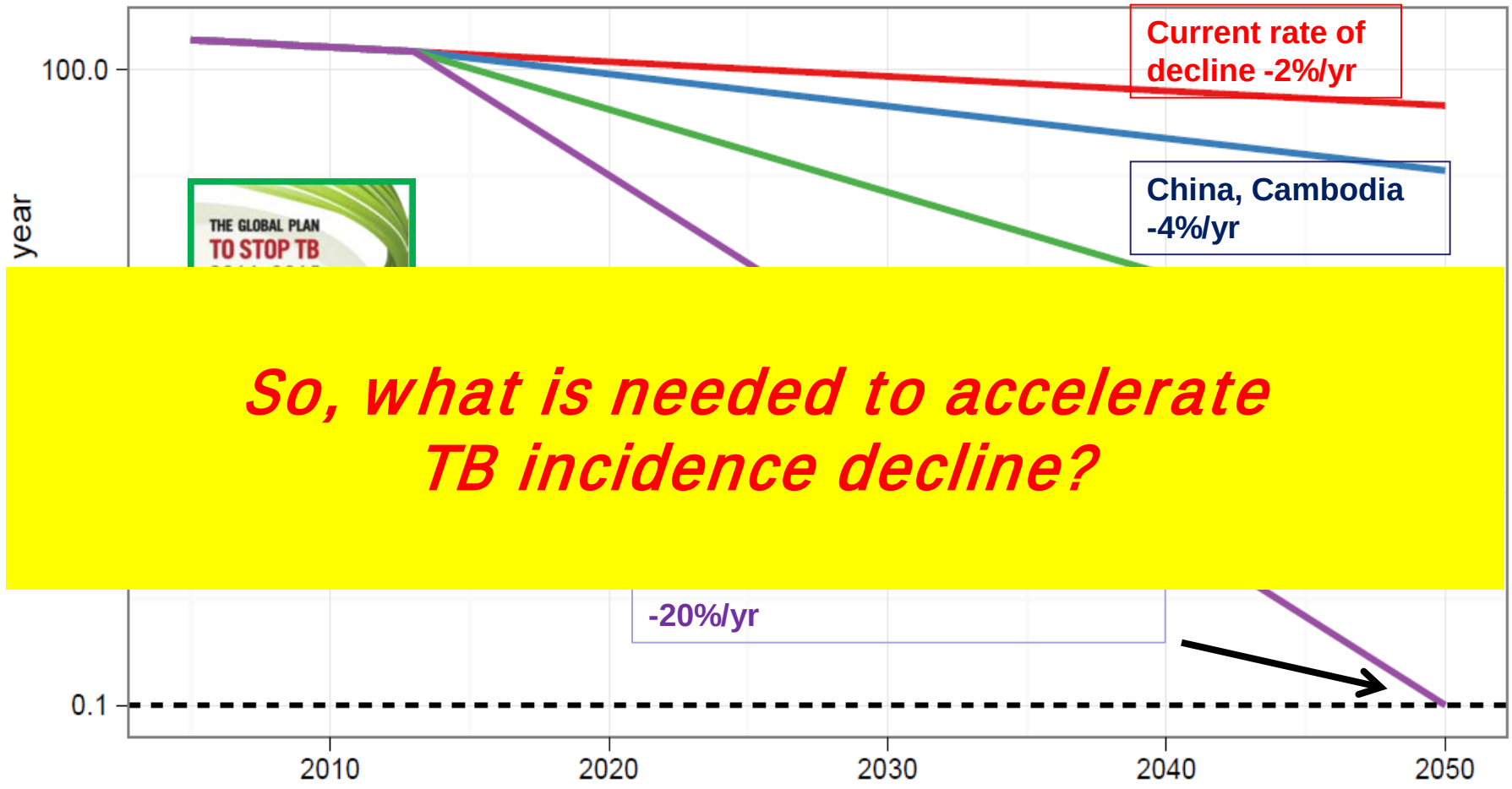
Full implementation of Global Plan: 2015 MDG target reached but TB not eliminated by 2050



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Current decline | Recent best | All-time best | Elimination

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

Current rate of decline -2%/yr

China, Cambodia -4%/yr

W Europe after WWII -10%/yr

Elimination target:<1 / million / yr -20%/yr

Rate per 100,000 / year

100.0
10.0
1.0
0.1

2010
2020
2030
2040
2050

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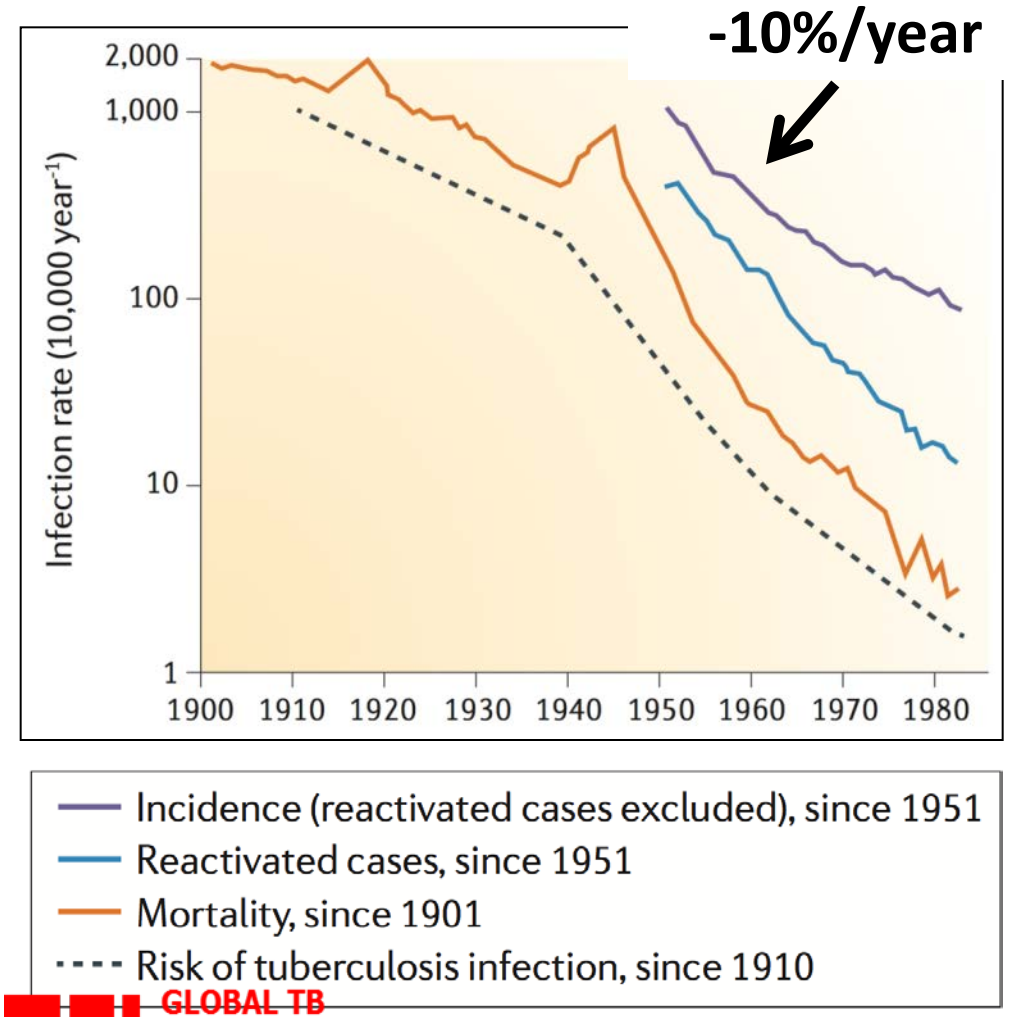
Current decline
Recent best
All-time best
Elimination

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 (?)**

Nat Rev Microbiol 2012; 10: 407–16.

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

Rate per 100,000 / year

100.0
10.0
1.0
0.1

2010
2020
2030
2040
2050

Current rate of decline -2%/yr

China, Cambodia -4%/yr

Eskimos > 10 ; < 20

W Europe after WWII -10%/yr

Elimination target:<1 / million / yr -20%/yr

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Current decline
Recent best
All-time best
Elimination

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

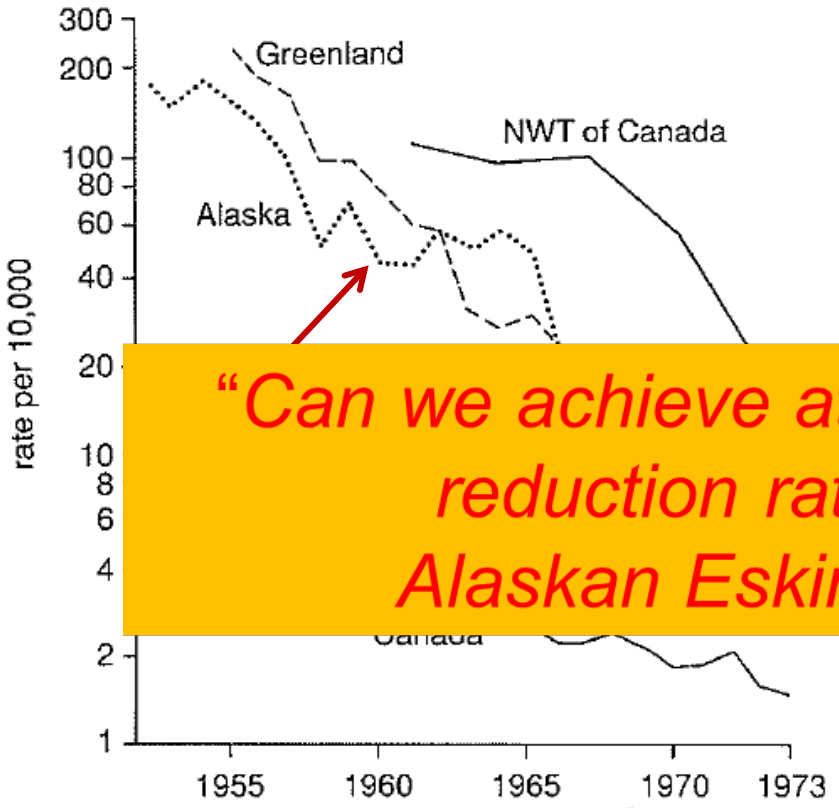


Figure 4 Incidence of new active tuberculosis (rates per 10,000) among the Eskimos of the Arctic: Greenland, Alaska and Northwest Territories of Canada; and total population of Canada, 1952-1973 (38)

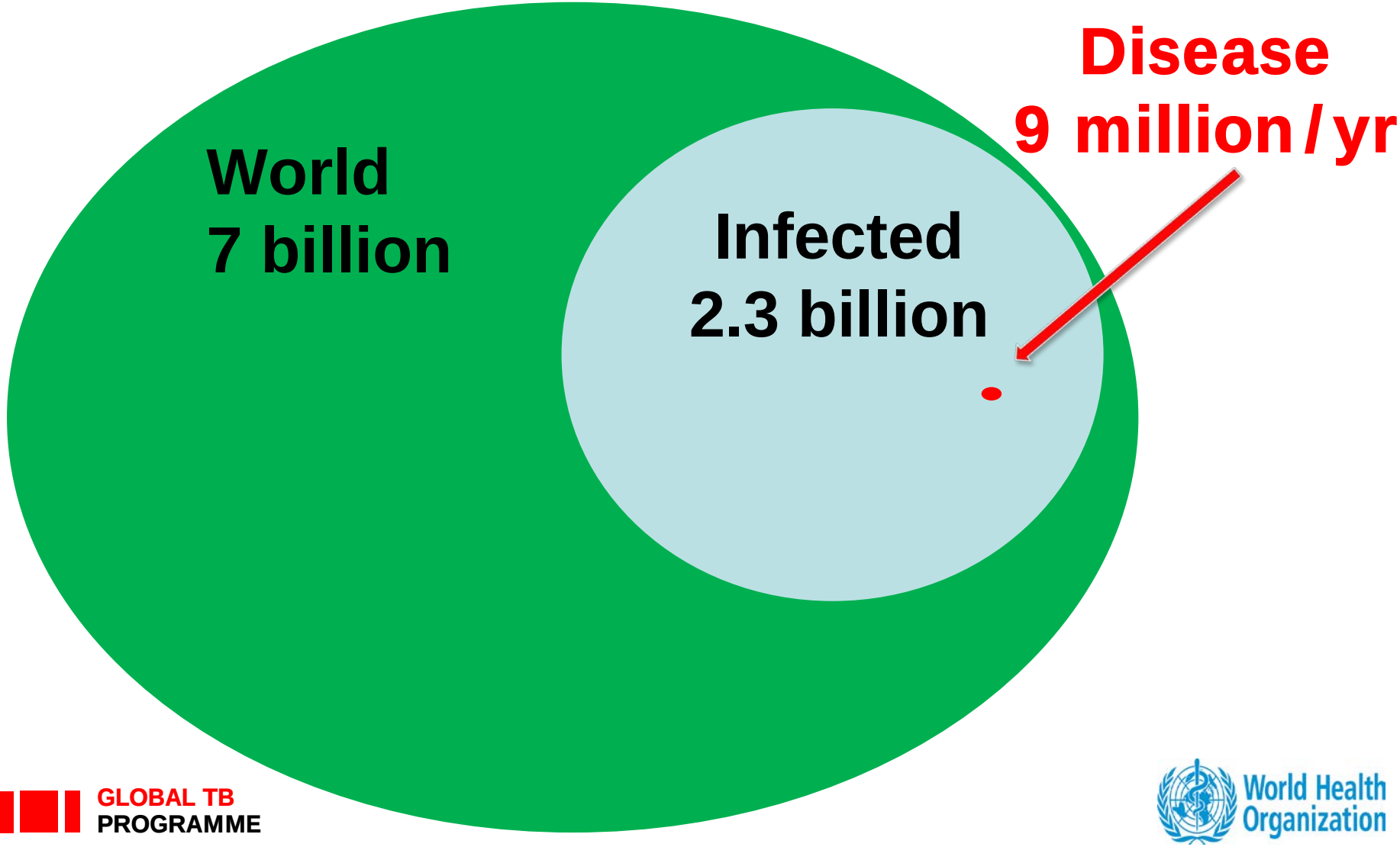
Grzybowski S, Styblo K, Dorken E. Tuberculosis in Eskimos. Tubercle 1976; (suppl.) 57: 1-58

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

Recipe:

- ✓ **Highly focused & high intensity interventions**
- ✓ **BCG vaccination**
- ✓ **Improved health access & social protection**
- ✓ **Economic development (?)**

TB infection and disease worldwide



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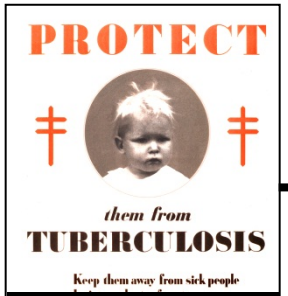
World Health Organization

Life cycle of tuberculosis



Uninfected

Latent

Active

Fast 0.7/yr

Faster (HIV+)

≈ 10%

≈ 90%

Slow
50/100k/yr

Infection

Reinfection

≈10 infections/case

Spontaneous cure 3/10

Death 5/10

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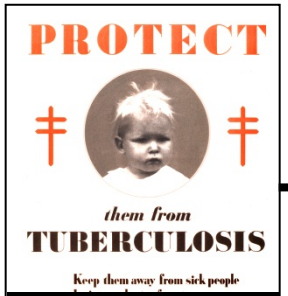
Life cycle of tuberculosis: *where are the roadblocks?*



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Infection

Reinfection

≈10 infections/case

Persistent transmission is the primary problem

Spontaneous cure 3/10

Death 5/10

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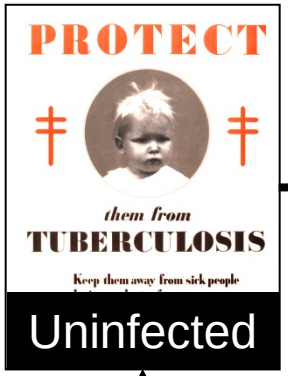
Life cycle of tuberculosis: *where are the roadblocks?*



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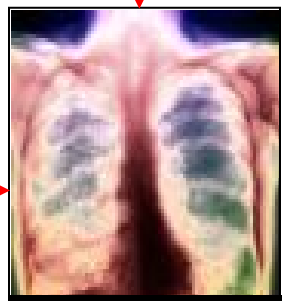

Active

Reinfection

≈10 infections/case

Spontaneous cure 3/10

Death 5/10

Progression to disease is a secondary problem

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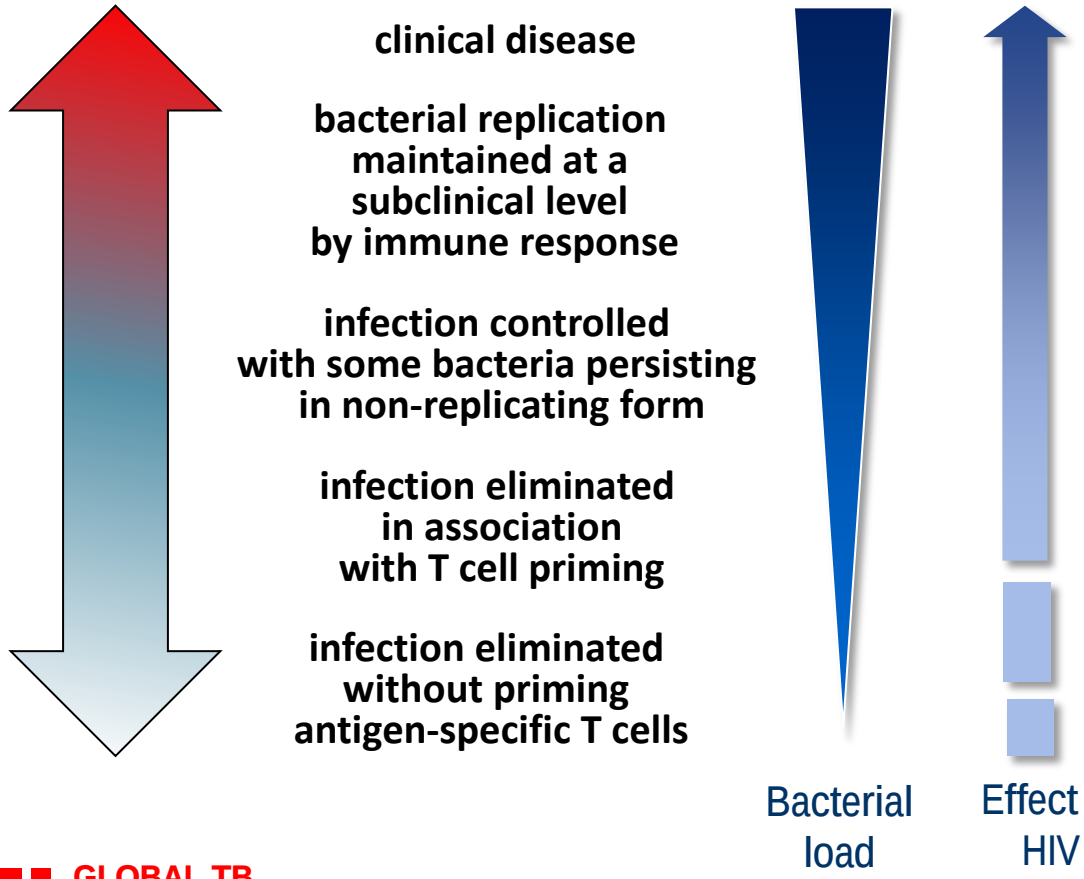
~10 million prevalent cases of active TB

~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



- **whom to treat?**
- **how to treat ?**
- **whom to protect ?**
- **how to protect ?**

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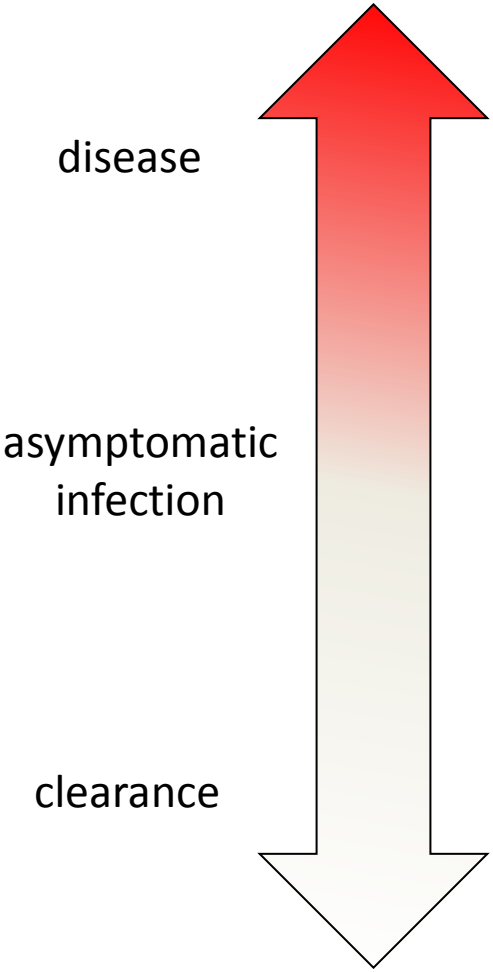
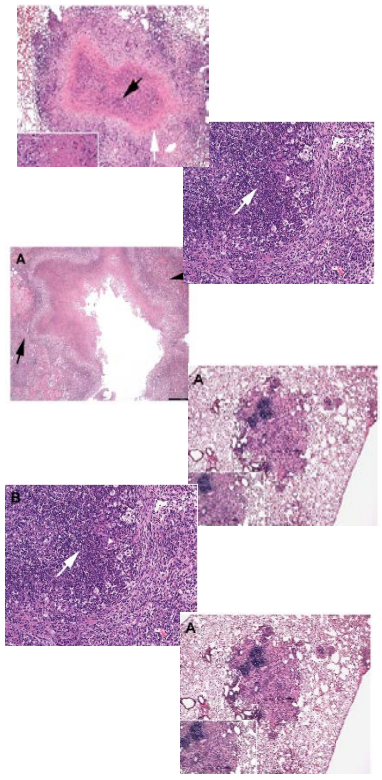
Young *et al* Trends Microbiol 2009, 17:183

World Health Organization

Lesion diversity model



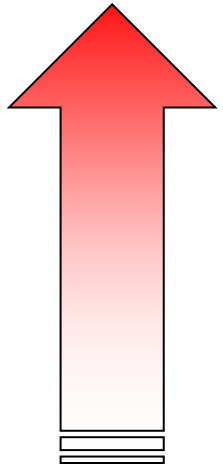


diverse lesions throughout the spectrum

different types of lesion

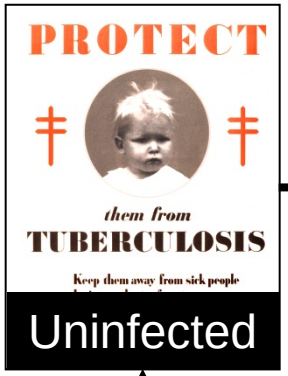
different microenvironments

replicating or non-replicating bacteria



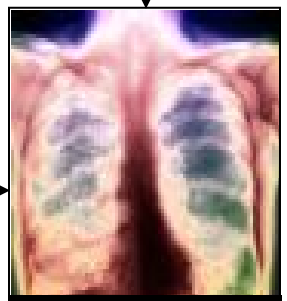
increasing number of “active” lesions

Roadblocks



Uninfected

Latent



Active

Ineffective prevention

Delayed diagnosis

Delayed/insufficient/ inappropriate treatment

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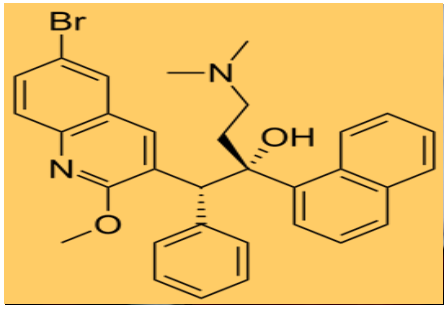
Limitations of today's Diagnostics, Drugs and Vaccine – but…*something moving!*

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

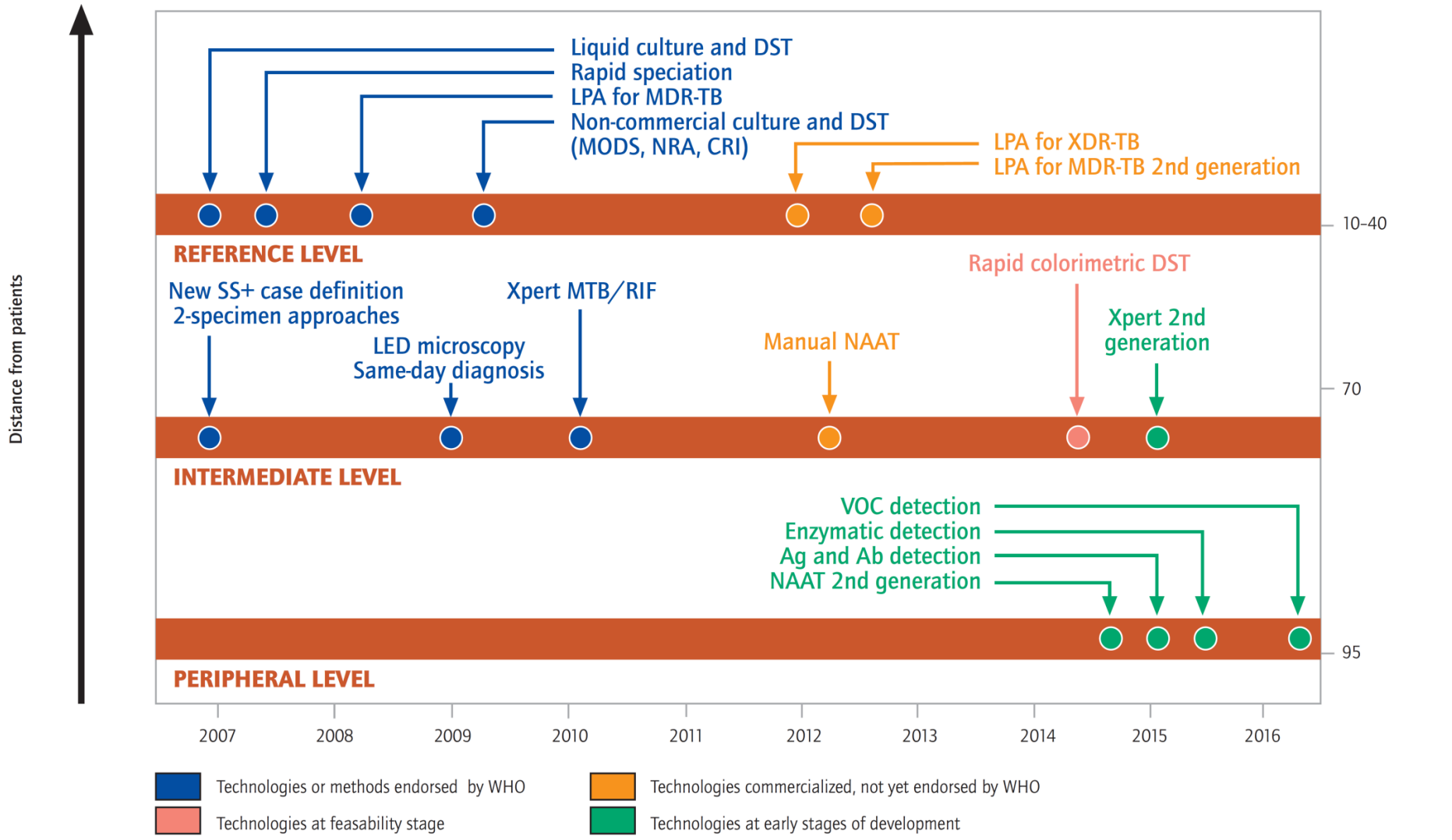
- Four drugs, taken for at least 6 months
- Not compatible with some ARVs
- MDR-TB treatment lengthy, low cure rates, expensive, toxic
- *But…new drugs introduced in 2013/14*



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



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World Health Organization

Introducing Xpert MTB/RIF

WHO endorsement Dec 2010

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

Phased implementation & evaluation 2011

26 countries using it in mid-2011

WHO Policy update – Oct 2013

Scale up 2012 - 2014

2,343 Xperts and 6.3 million Xpert cartridges in the public sector in 104 countries

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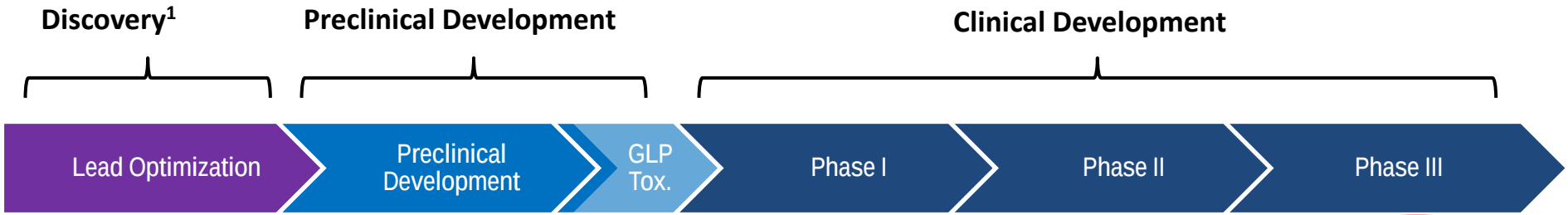
Global TB Drug Pipeline



Discovery[1]

- Diarylquinoline
- DprE Inhibitors
- GyrB inhibitors
- InhA Inhibitors
- LeuRS Inhibitors
- MGyrX1 inhibitors
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Riminophenazines
- Ruthenium (II) complexes
- Spectinamides
- Translocase-1 Inhibitors

Preclinical Development

- CPZEN-45
- DC-159a
- Q201
- SQ609
- SQ641

GLP Tox.

- BTZ043
- TBA-354

But no compound at Phase I level !

4 Repurposed Drugs
6 New Drugs
3 New Classes

Phase II

- AZD5847
- Bedaquiline (TMC-207)
- Linezolid
- Novel Regimens[2]
- PA-824
- Rifapentine
- SQ-109
- Sutezolid (PNU-100480)

Phase III

- 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.

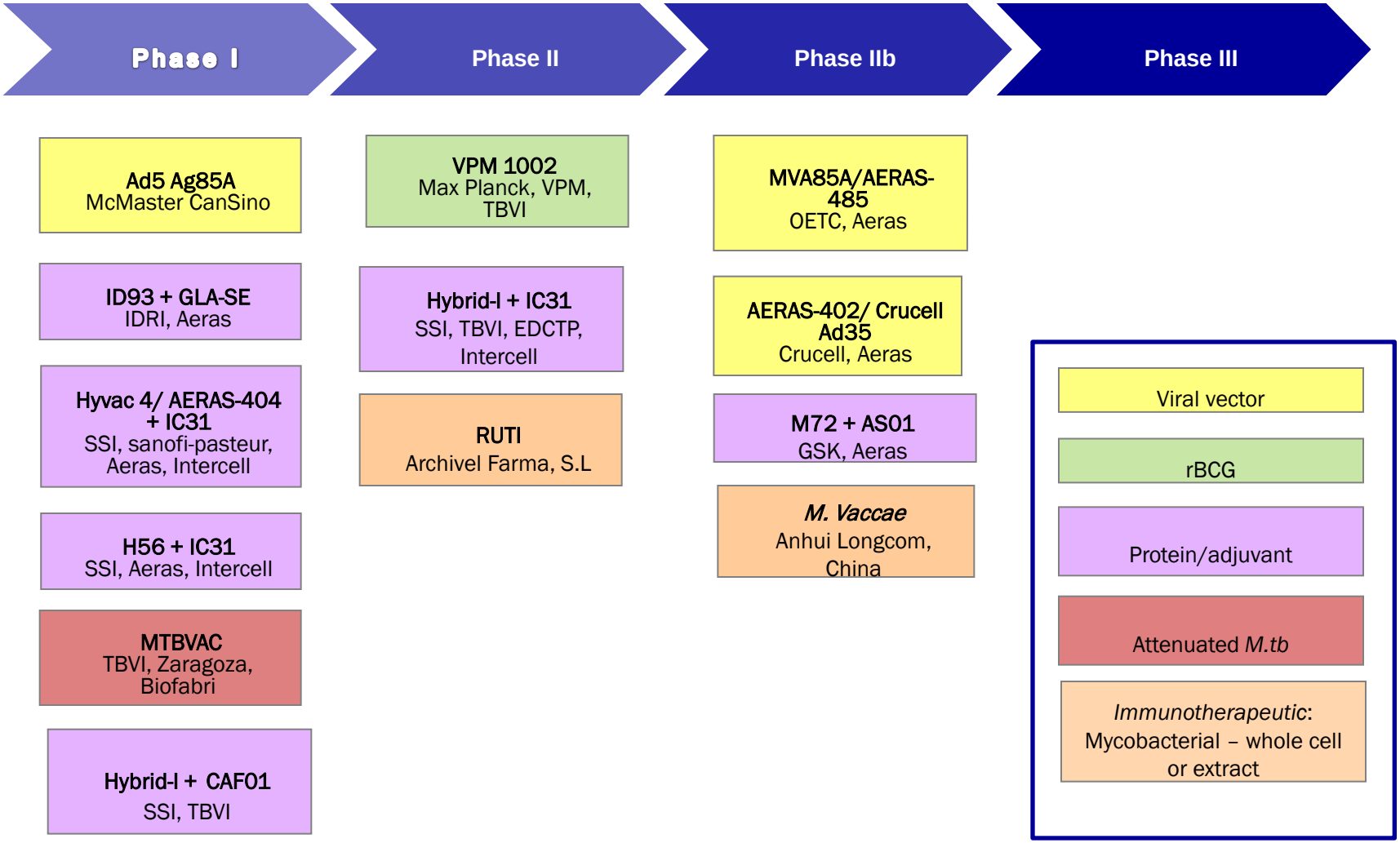
[2] Combination regimens: first clinical trial (NC001) of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide was initiated November 2010 and completed in 2011 with promising results. The second clinical trial (NC002) of this regimen was launched in March 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.

WORKING GROUP ON NEW TB DRUGS

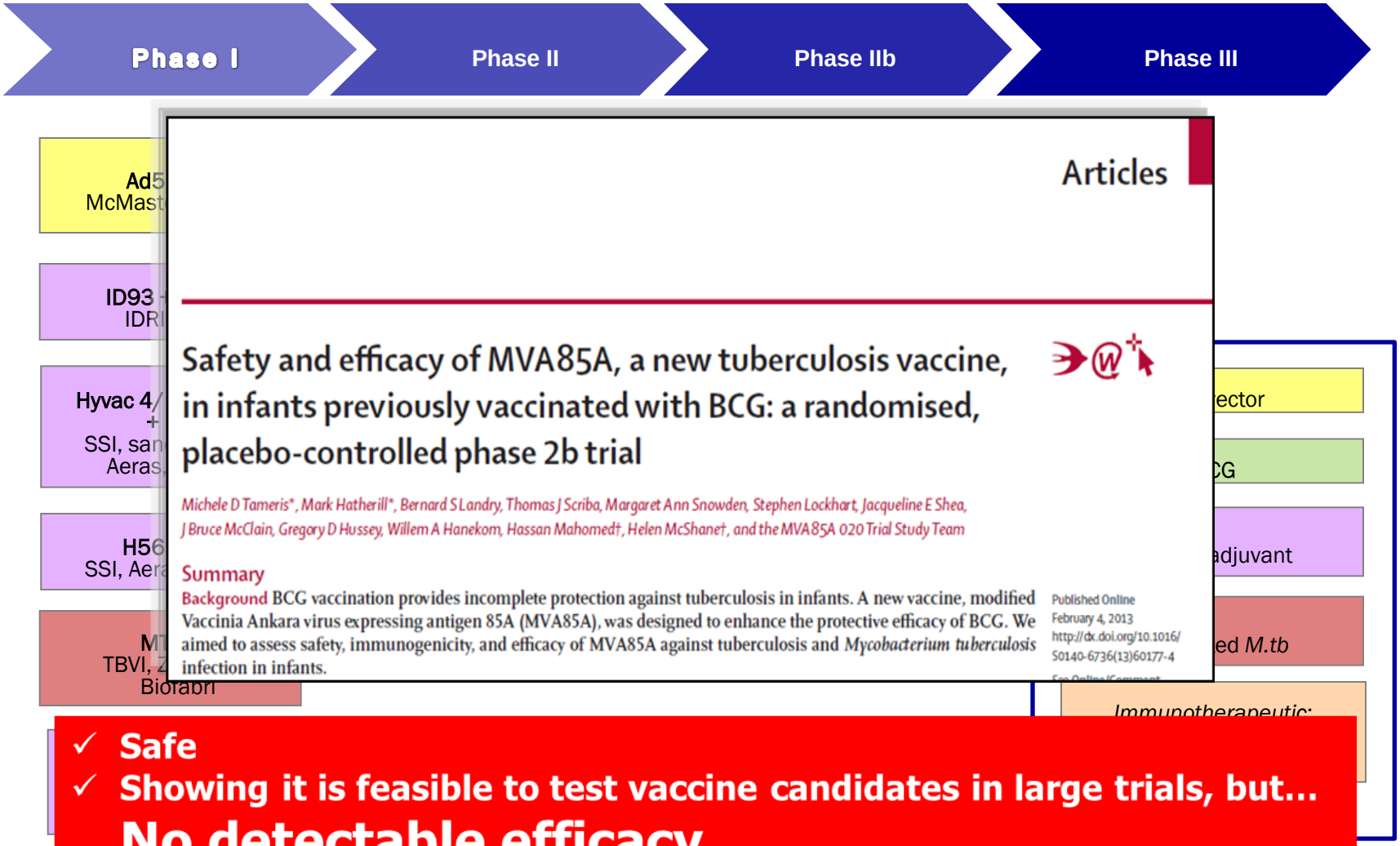
www.newtbdrugs.org

Updated: June 18, 2013

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



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



- ✓ **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

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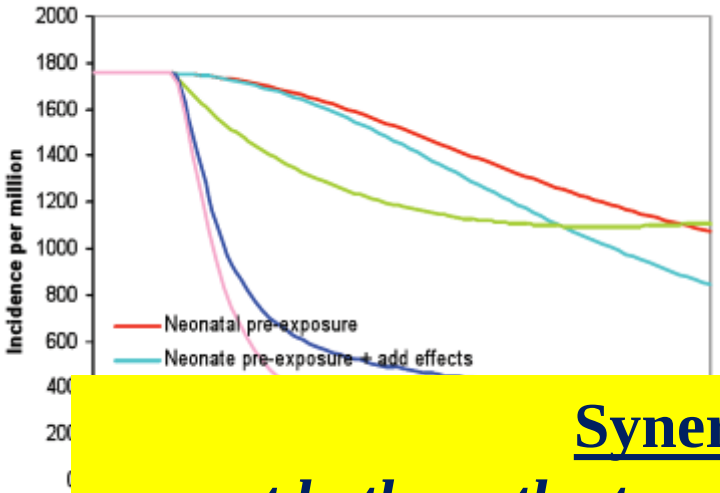
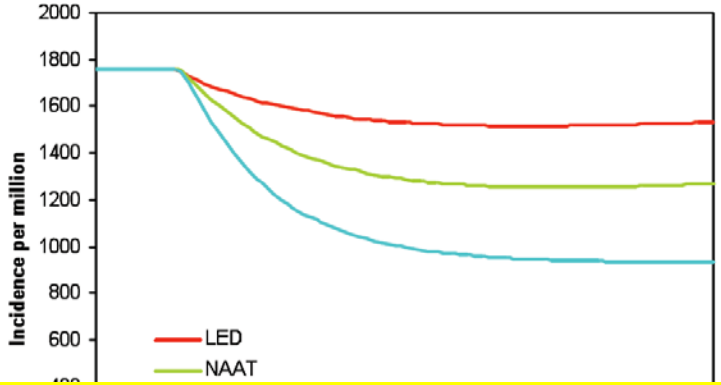


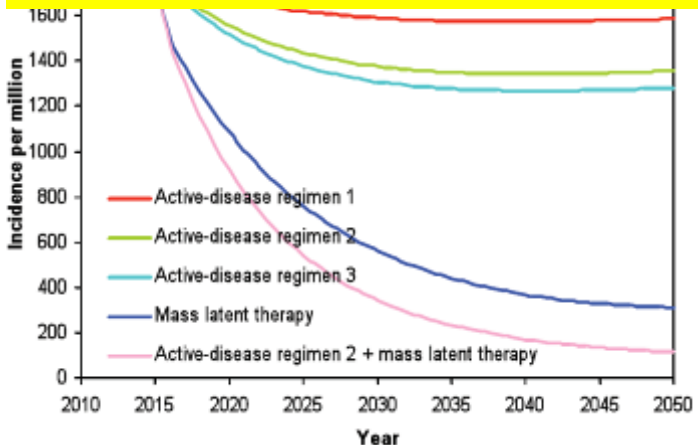


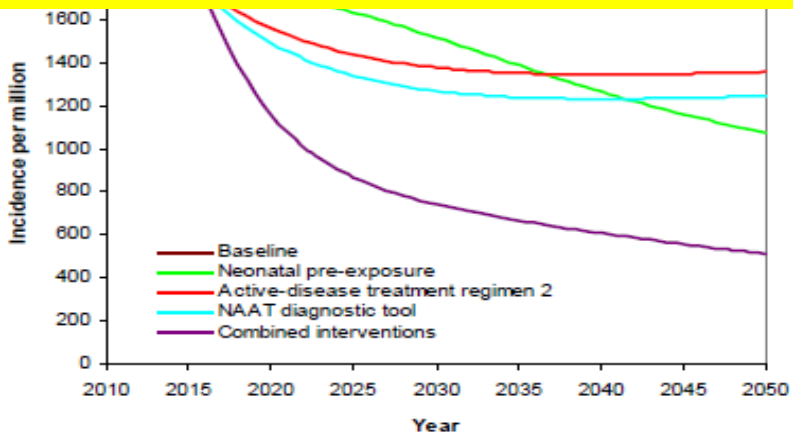
Synergy of interventions

- act both on the transmission and reactivation pathways

- better diagnostics, treatment and prevention

- address the larger health context





Source: L. A

PNAS 2009

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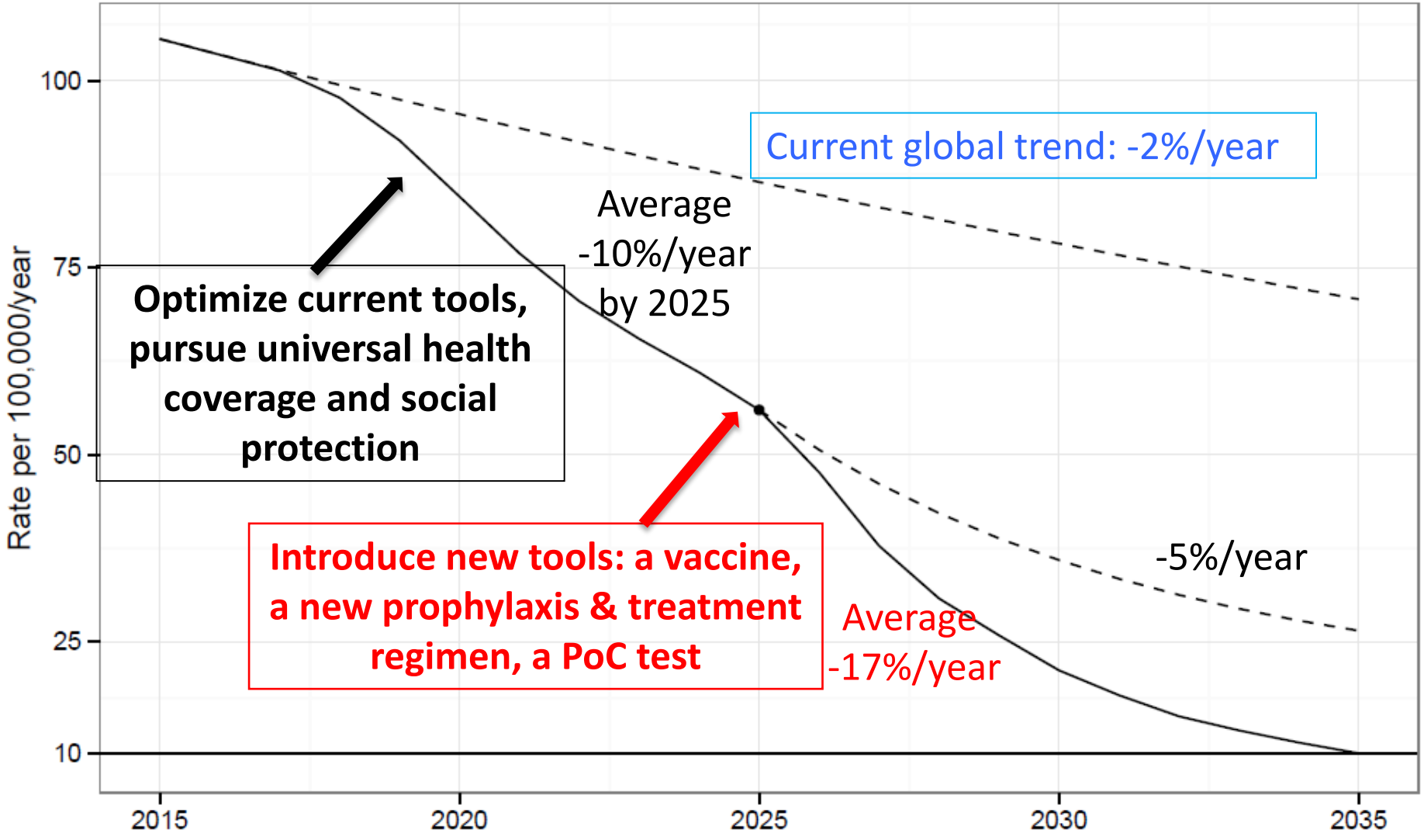
- The WHO post 2015 Global TB Strategy and the importance of research

Projected acceleration of TB incidence decline to target levels



67th World Health Assembly, Geneva, May 2014

SIXTY-SEVENTH WORLD HEALTH ASSEMBLY WHA67.1

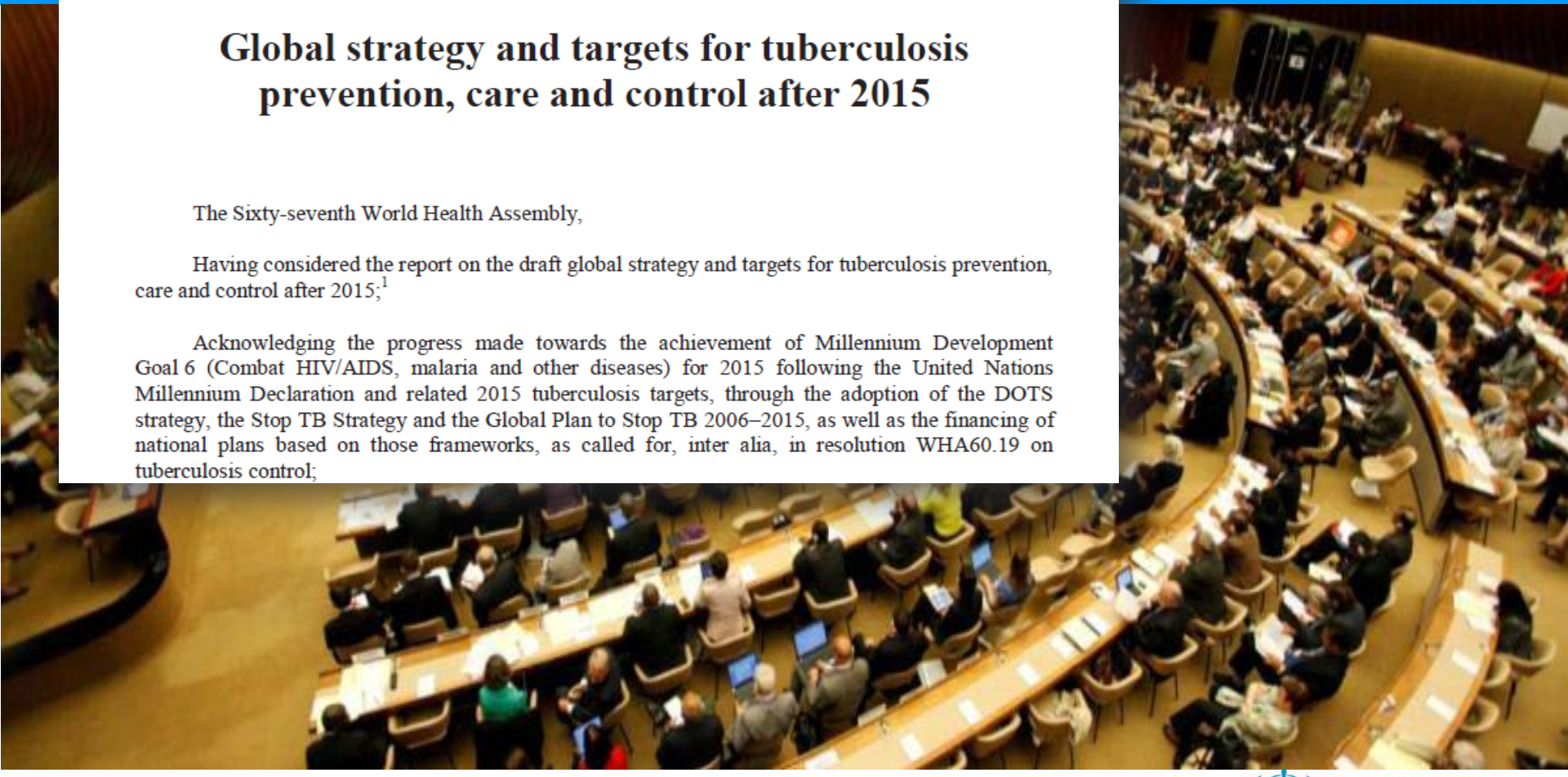
Agenda item 12.1 21 May 2014

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:

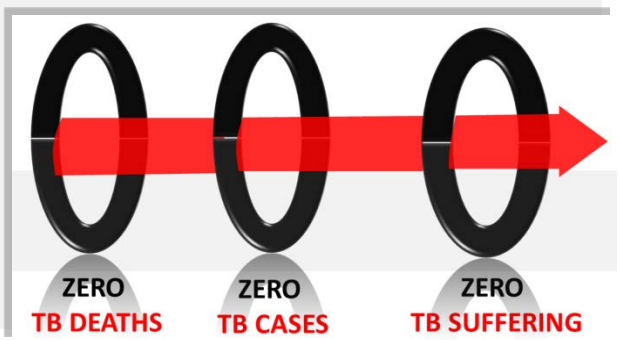
- End the Global TB Epidemic

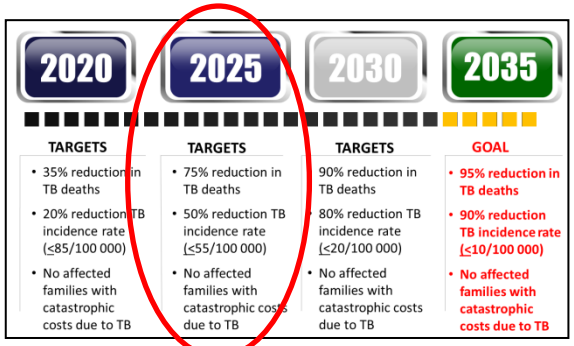
MILESTONES FOR 2025:

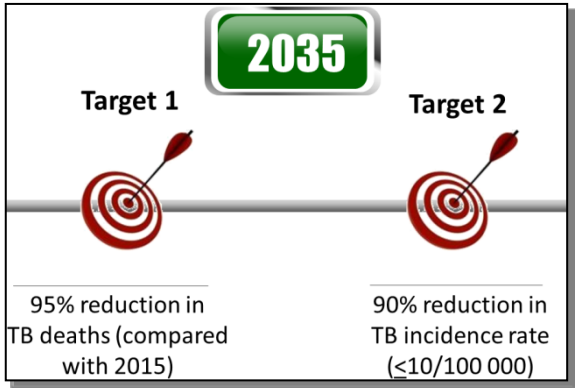
- 75% reduction in TB deaths (compared with 2015)
- 50% reduction in TB incidence rate (< than 55/100,000)
- No affected families face catastrophic costs due to TB

TARGETS FOR 2035:

- 95% reduction in TB deaths (compared with 2015)
- 90% reduction in TB incidence rate (≤10/100,000)





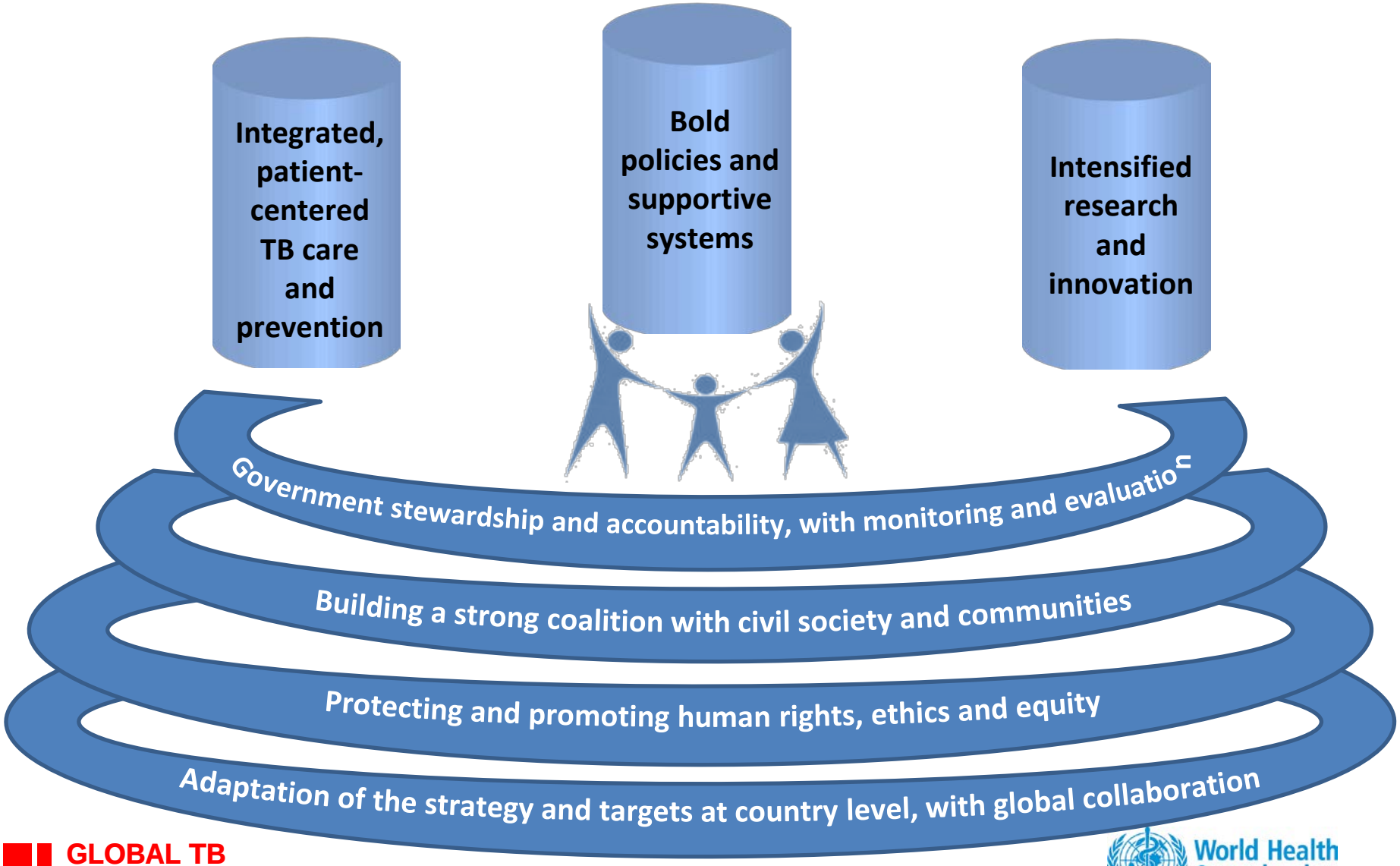


GLOBAL TB PROGRAMME

World Health Organization

Post-2015 Global TB Strategy

Three Pillars and four overarching Principles



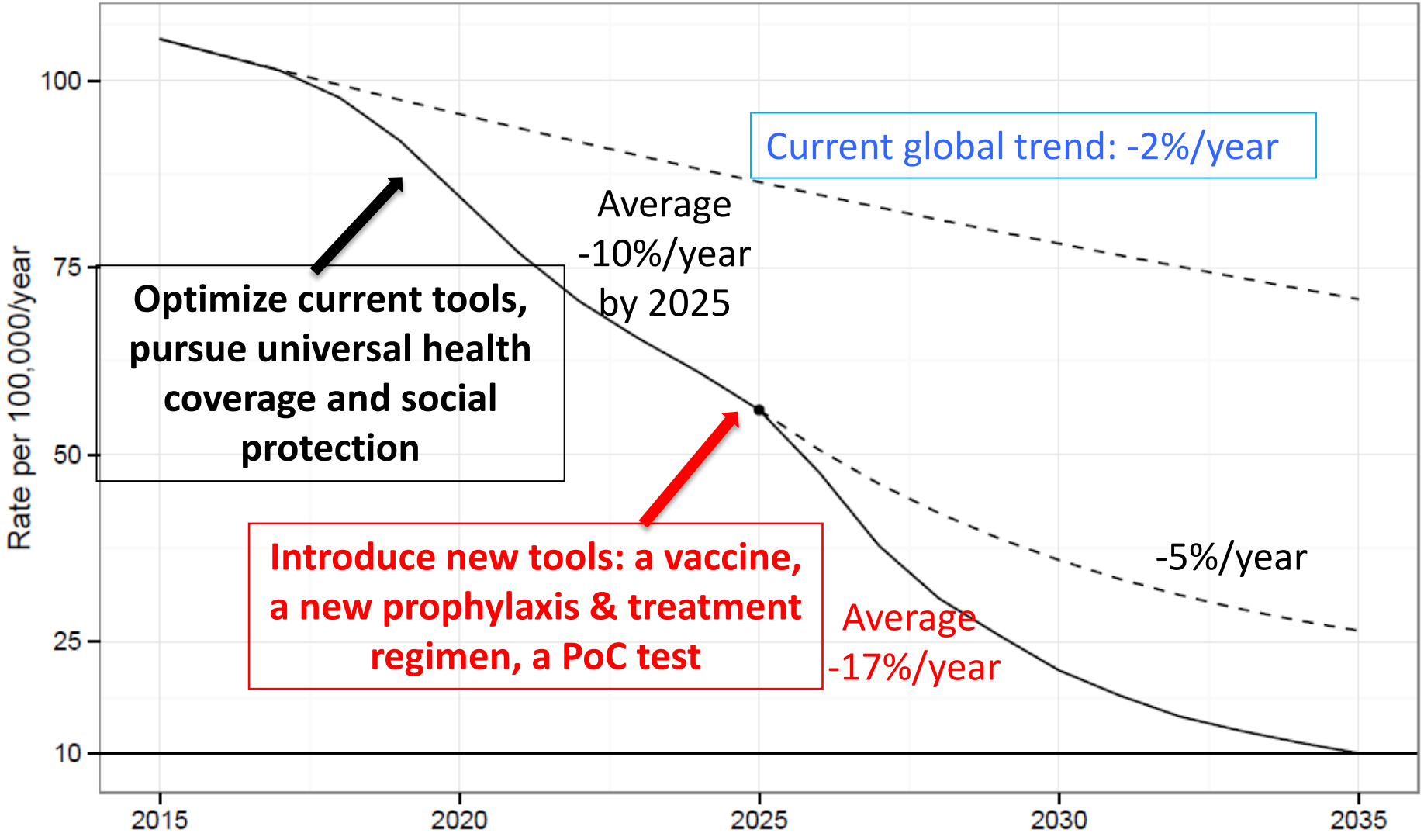
PILLAR III

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



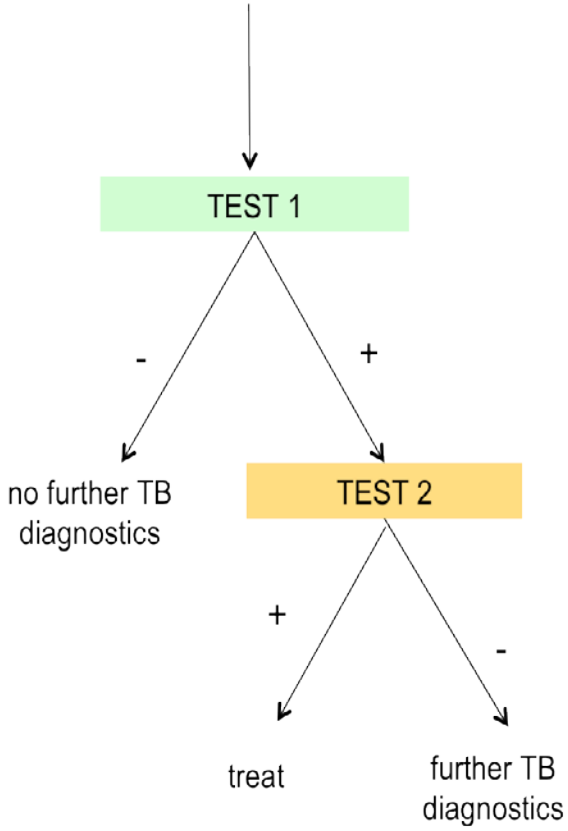
Improving Global TB Control
– what do we need ?

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

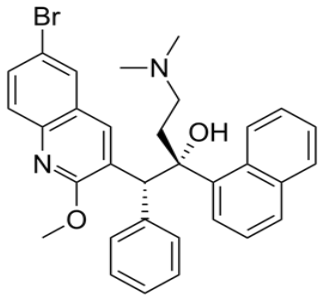
3. *Inform Policy recommendations*
    - provide evidence on what can be expected from new interventions in real-life settings
    - increasingly important for international policy decisions and funding (e.g. GRADE for policy ecommendation)

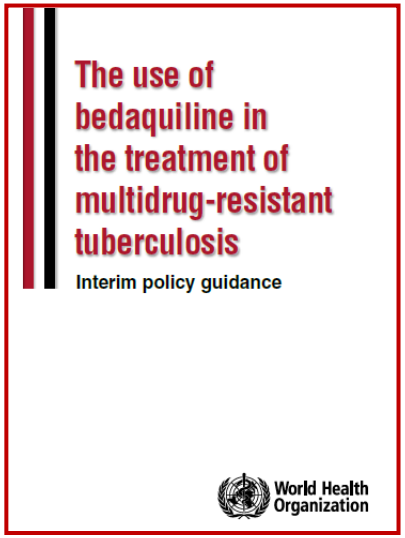
From tools to strategies



From tools to strategies

New drugs/treatments of TB/MDR-TB





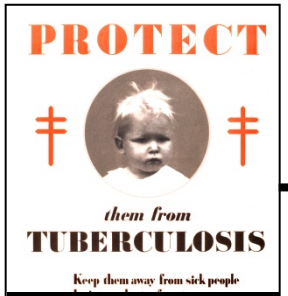
- Evaluation of feasibility, effectiveness and impact

- Further tests of resistance?
- which ones ?
- how ?
- where ?
- for whom ?

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

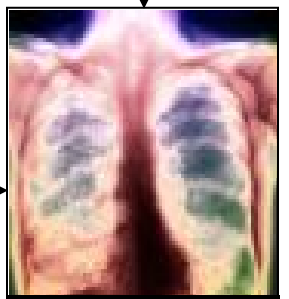
-> pharmacovigilance and monitoring

From focus to context



Uninfected

Latent



Active

Difficulty in accessing health care

Ineffective prevention

Delayed diagnosis

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?

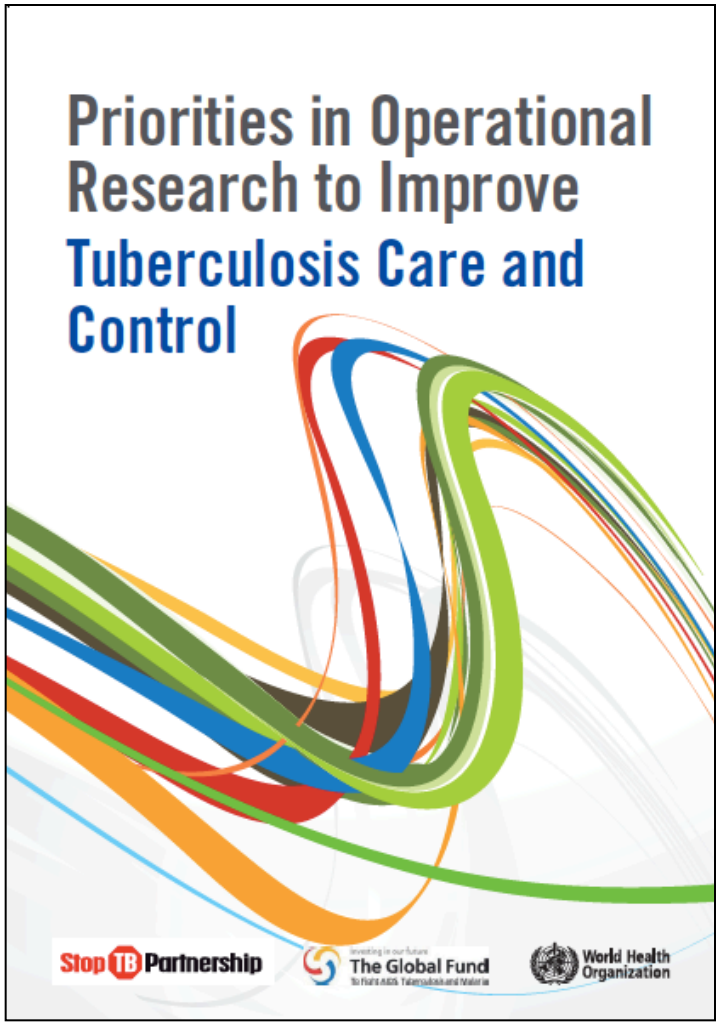
Priorities in Operational Research to Improve Tuberculosis Care & Control

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*



GLOBAL TB PROGRAMME

Launched in Delhi, India, on 29th August 2011

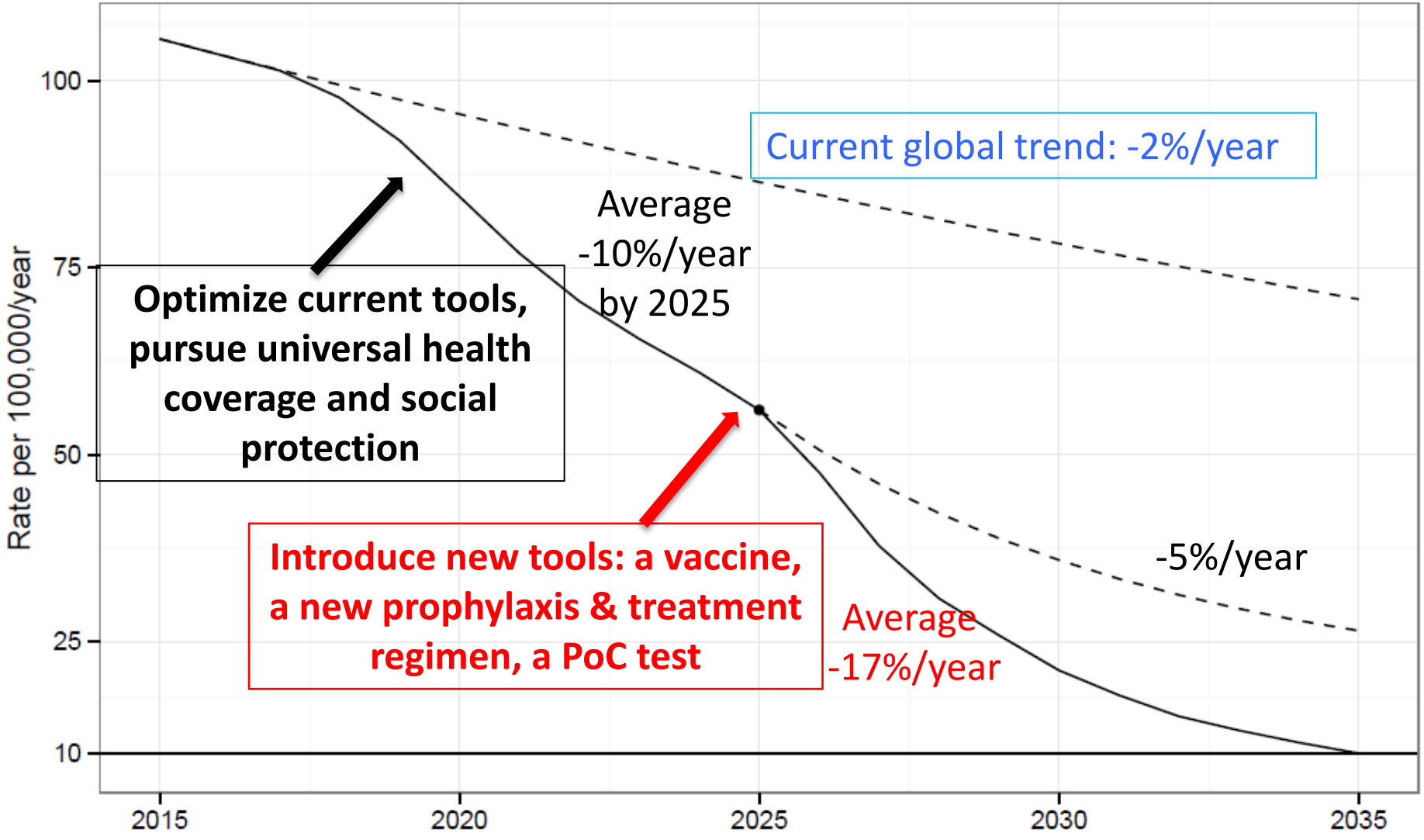
World Health Organization

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



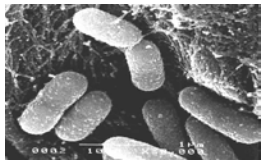
The Continuum of TB Research

Point of Care Diagnostics of TB

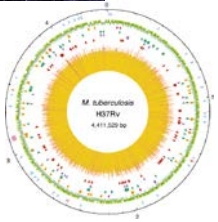
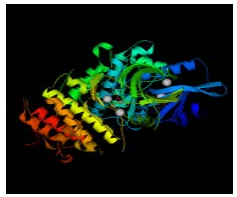
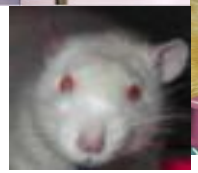
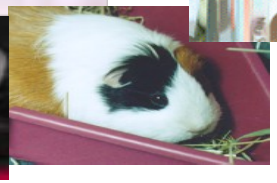
Treat all forms of TB in all populations

Prevent TB in all populations

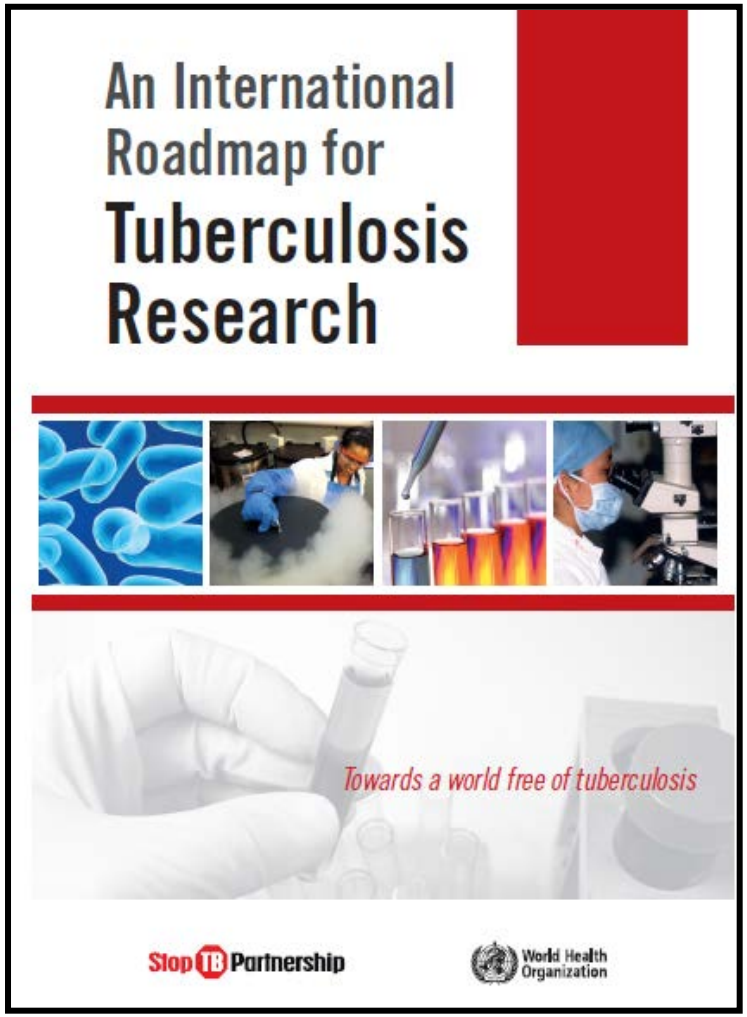
Fundamental Science	Translational Studies	Preclinical Studies	Clinical Studies/Trials	Deployment/ Operational research



The International Roadmap for TB 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

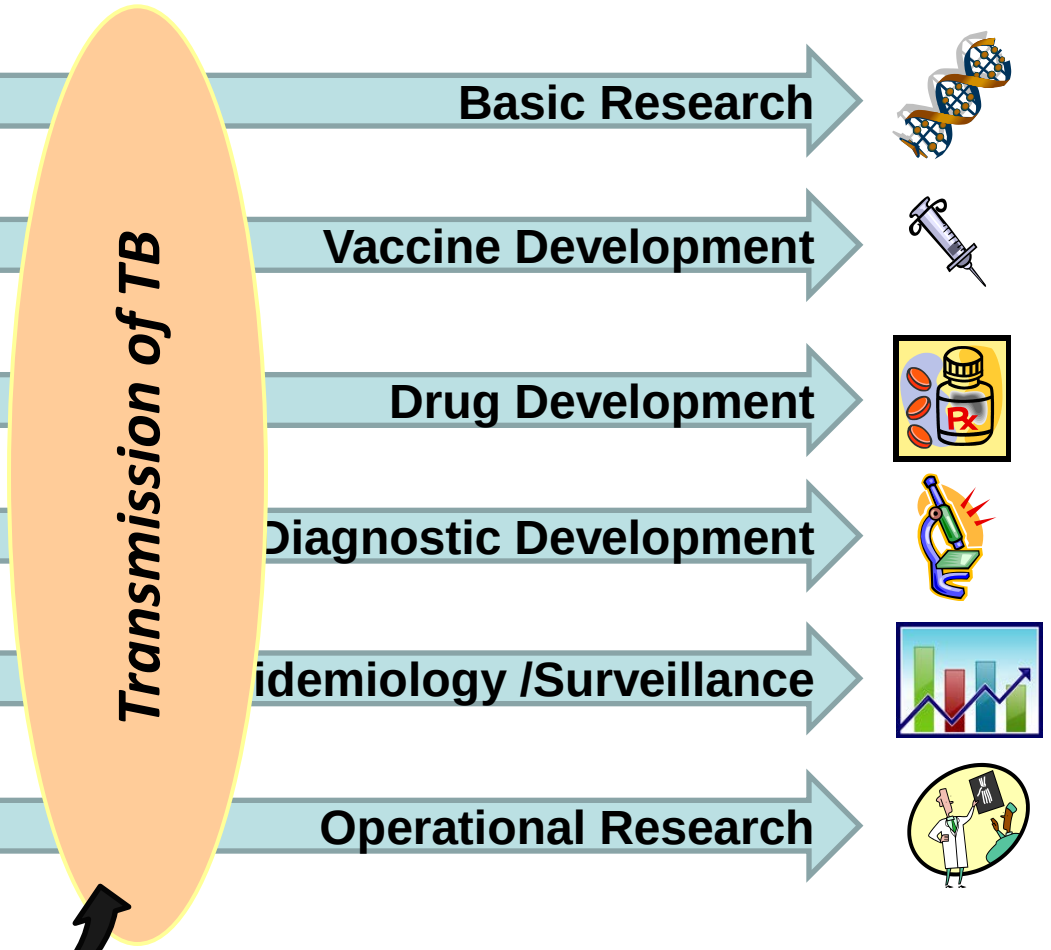
Contributions from a large panel of partners and stakeholders involved in TB research worldwide

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

provides "menu" of key knowledge gaps



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

GLOBAL TB PROGRAMME

Accelerating research
for TB elimination

WHO THE STOP TB DEPARTMENT

Research for Elimination Initiative

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

- 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

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?

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PUBLIC HEALTH SERVICE
From Tubercle, Vol. 43, No. 3, pp. 301-321, September 1962.

OCCASIONAL SURVEY

THE ERADICATION OF TUBERCULOSIS: THEORETICAL PROBLEMS AND PRACTICAL SOLUTIONS*

By GEORGES CANETTI
from the Institut Pasteur, Paris

" 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
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- WGNV: Jennifer Woolley, Uli Fruth
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- 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….

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GLOBAL TB
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World Health Organization

Thank you for your attention !

Photos: Dominic Chavez