

The role of Fundamental Research in Global TB Control: outcome of the Transformation Research Workshop, Bethesda, March 2010

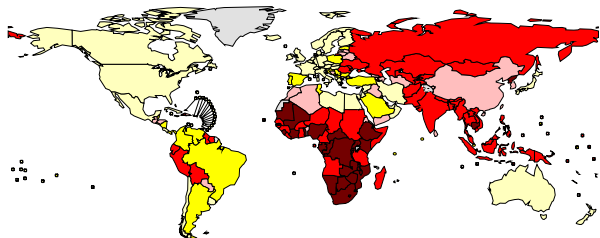


**TB Vaccines – a second
Global Forum
Tallinn, Estonia September
21-24, 2010**



Christian Lienhardt
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Stop TB Partnership
WHO, Geneva*

The global burden of TB in 2008



**Estimated
number of
cases**

**Estimated
number of
deaths**

All forms of TB

9.4 million
(range 8.9–9.9 million)

1.9 million
(range 1.6–2.3 million)

HIV-associated TB

1.4 million (15%)
(1.3–1.6 million)

520,000
(0.45–0.62 million)

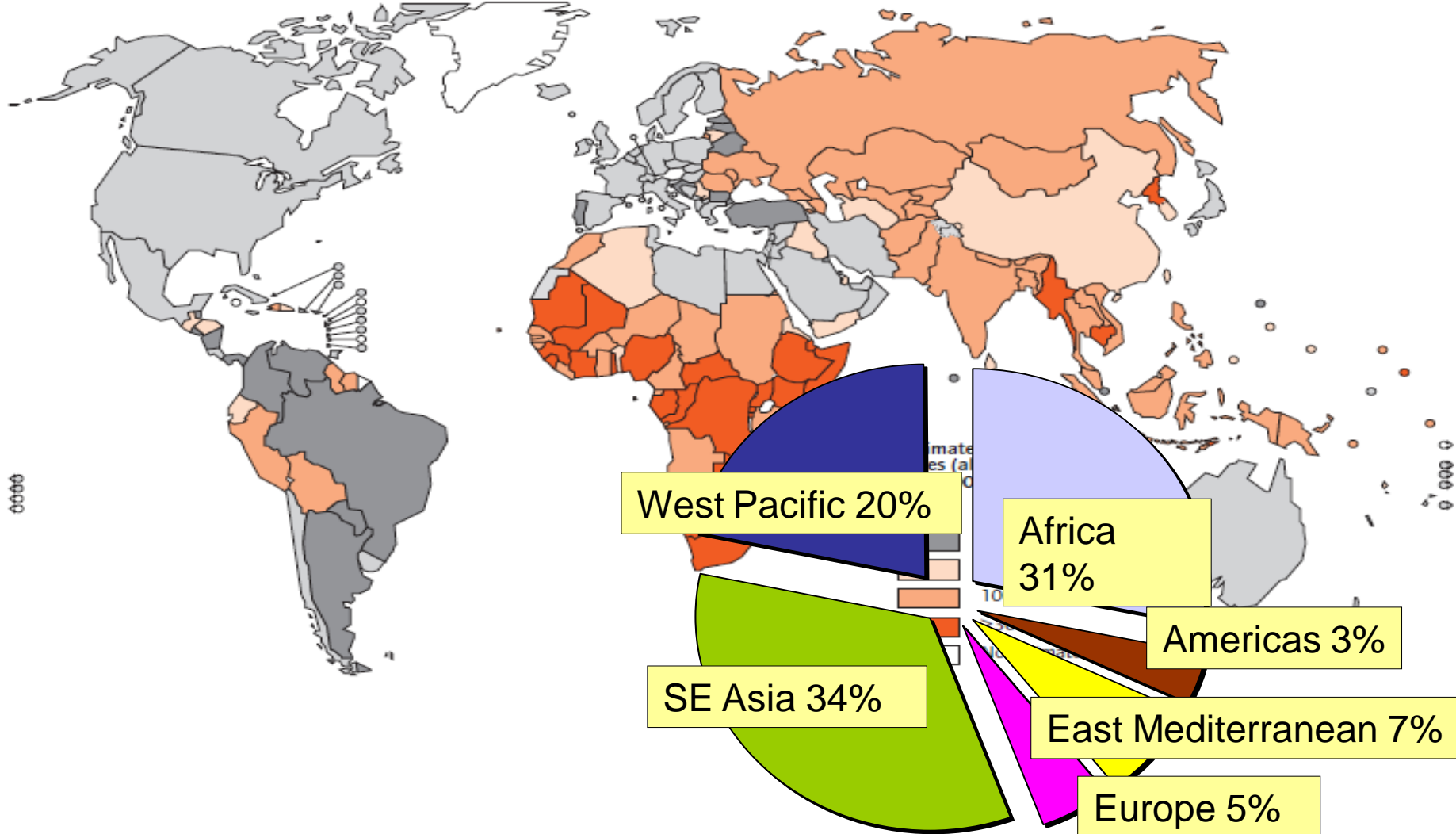
**Multidrug-resistant
TB (MDR-TB)**

440,000
(0.39–0.51 million)

150,000
(0.05–0.27 million)

Estimated TB Incidence rates, 2008

Estimated TB incidence rates, by country, 2008



TB Control Global Targets



2015: Goal 6: Combat HIV/AIDS, malaria and other diseases

Target 8: to have halted by 2015 and begun to reverse the incidence...

Indicator 23: incidence, prevalence and deaths associated with TB

Indicator 24: proportion of TB cases detected and cured under DOTS



2015: 50% reduction in TB prevalence and deaths relative to 1990 levels

2050: elimination (<1 case per million population)

The Global Plan 2006-15 proposed achievements



THE GLOBAL PLAN
TO STOP TB
2006-2015

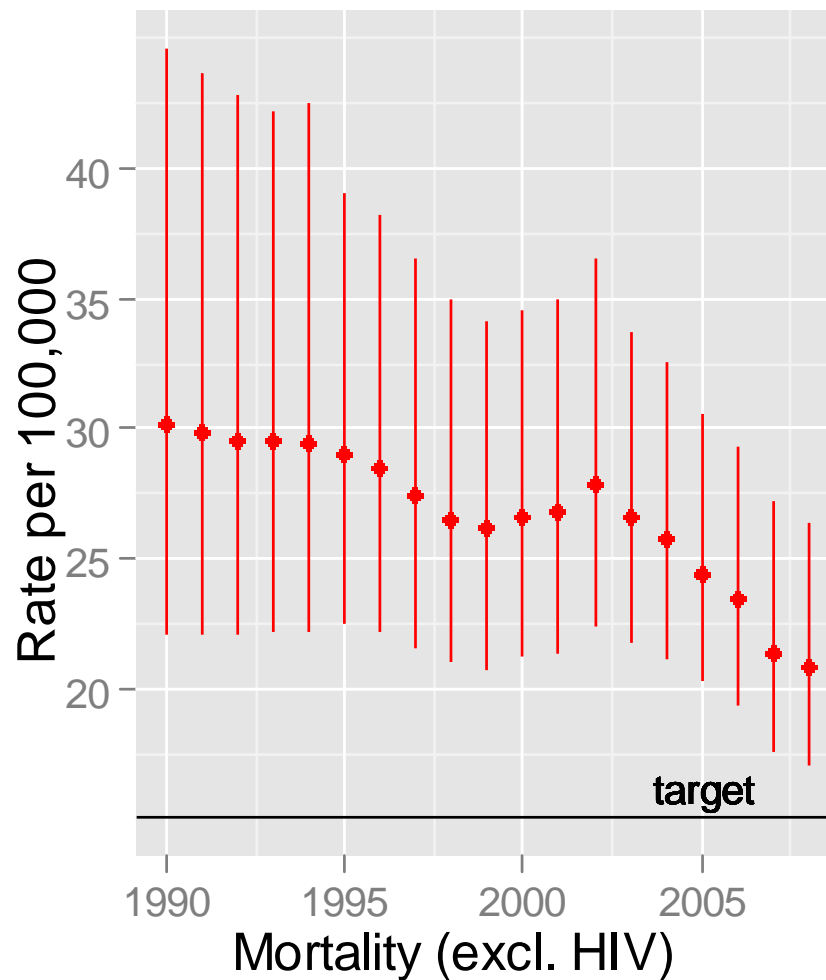
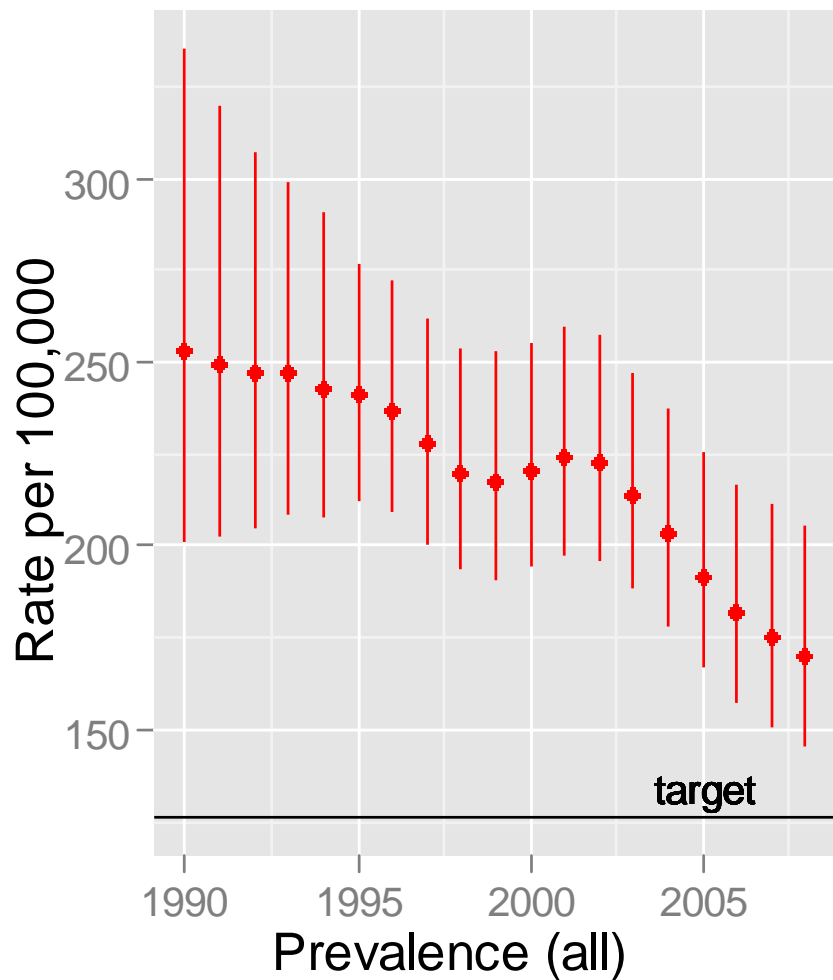
***US\$ 56 billion
needed to control TB in
endemic countries***

***US\$11 billion needed
to develop new tools***

Stop TB Partnership

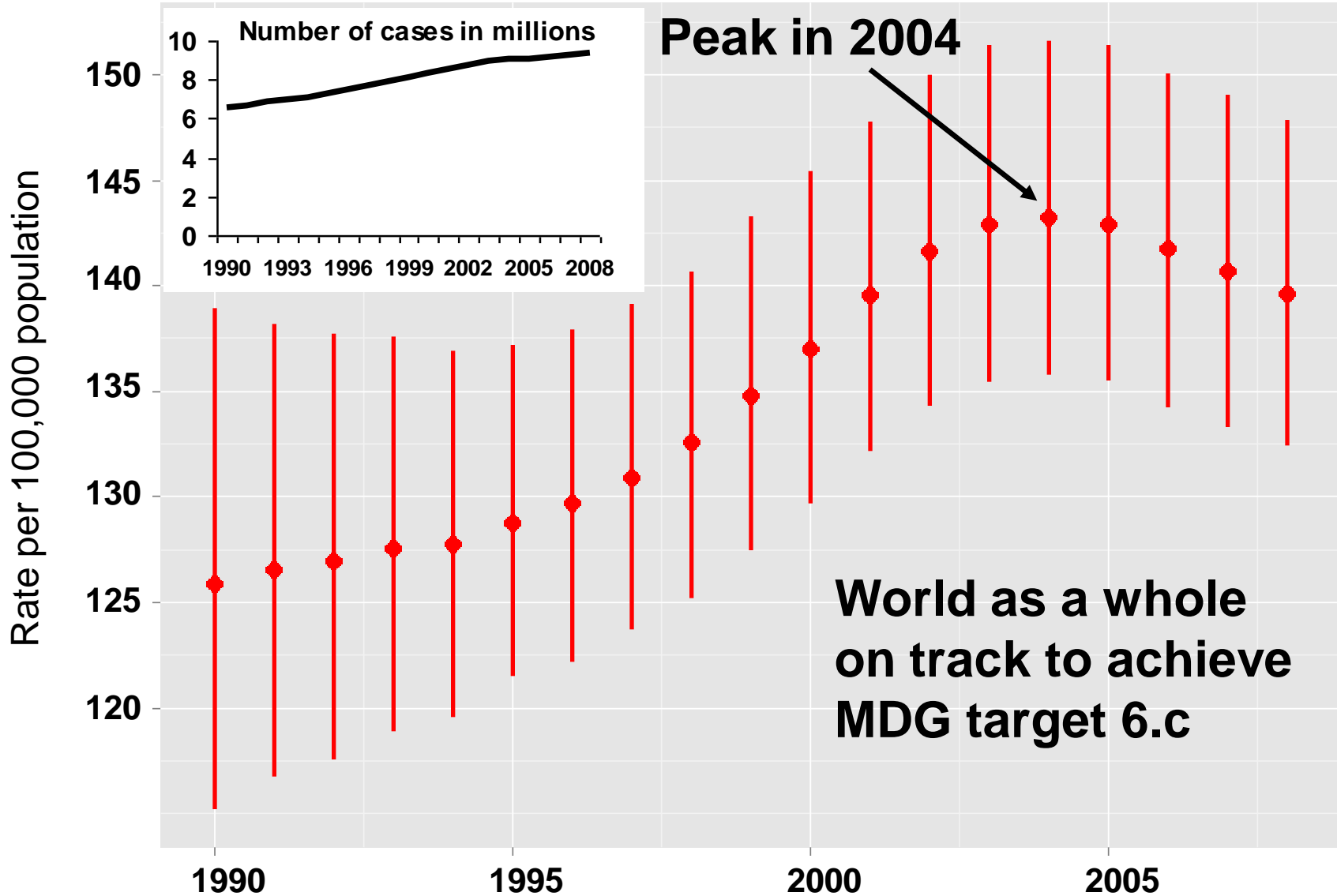
1. MDGs for TB and the Partnership's 2015 targets to halve prevalence and death rates globally
2. Treatment of 50 million people with TB, 3 million TB/HIV co-infected patients on ARV, and 1.6 million with MDR
3. Saving of 14 million lives from 2006-2015
4. The first new TB drug introduced by 2010
5. The "point of care" diagnostics introduced by 2010
6. Develop a new vaccine by 2015

TB prevalence and mortality



On track everywhere except for Africa

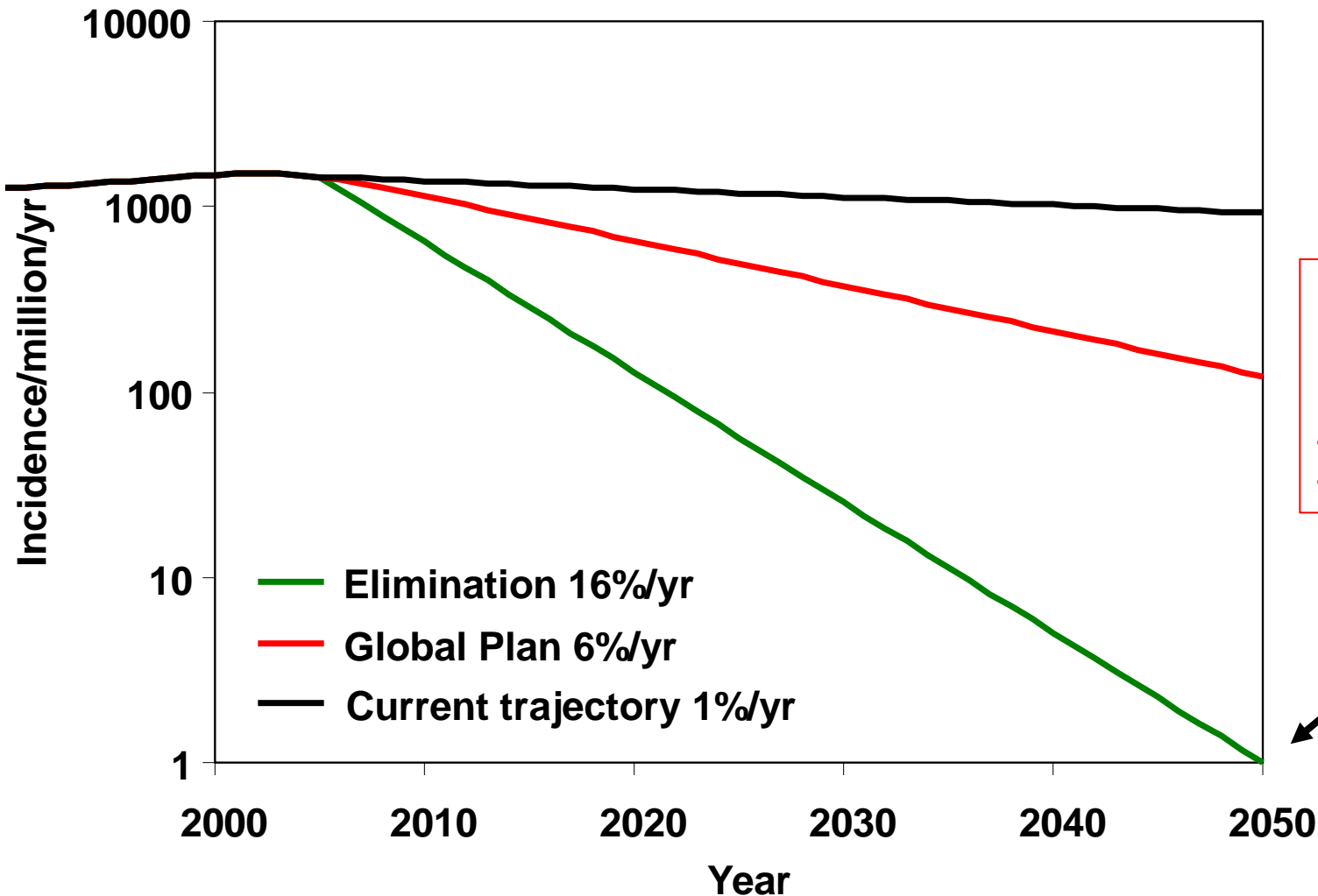
Incidence rates falling globally after peak in 2004



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



THE
STOP TB
DEPARTMENT

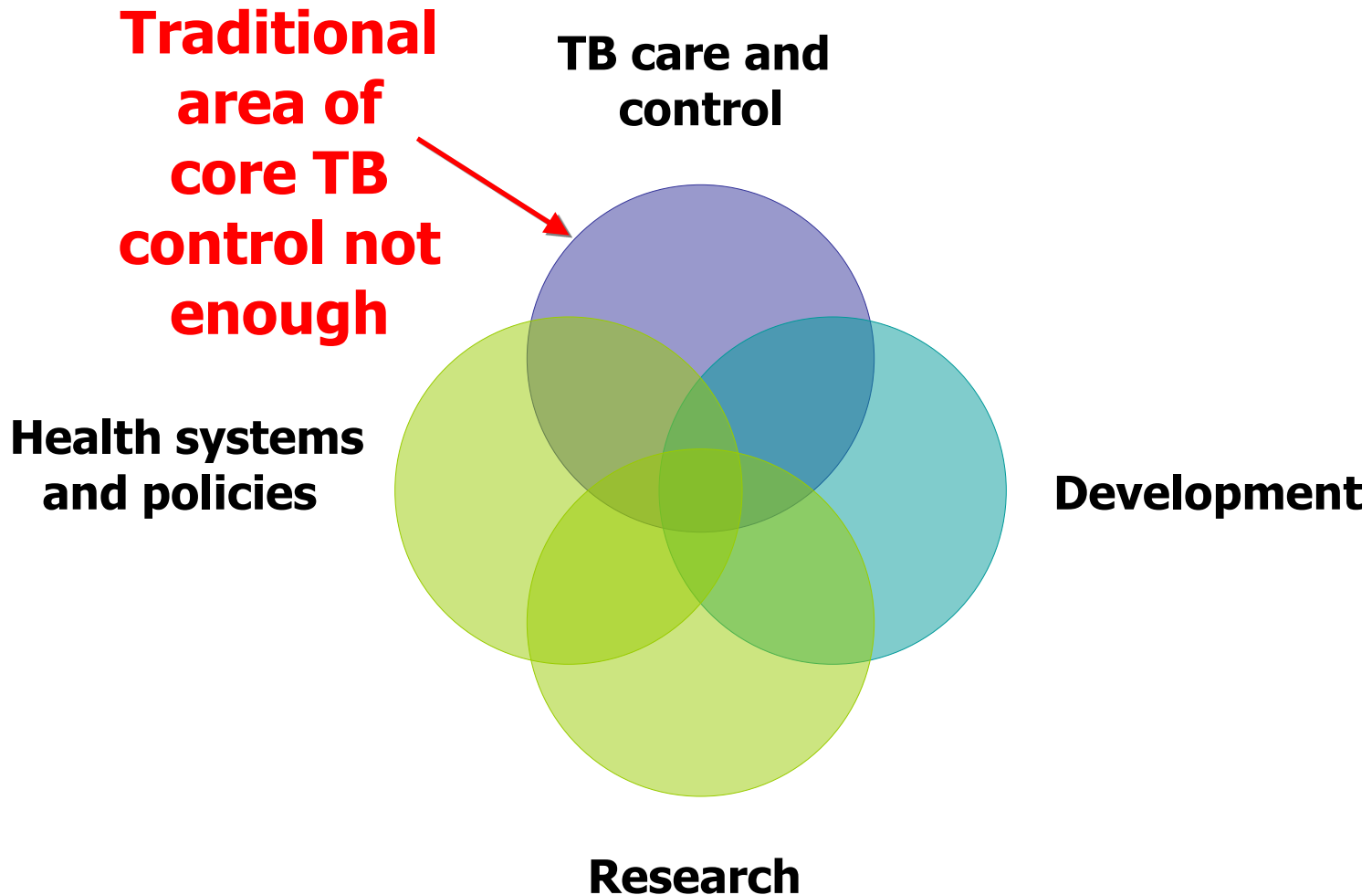


Projected incidence 10x lower than today, but 100x bigger than elimination target in 2050

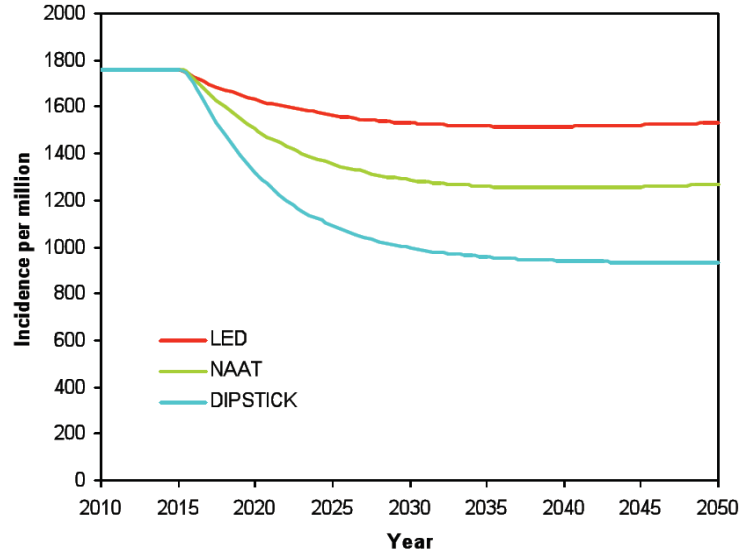
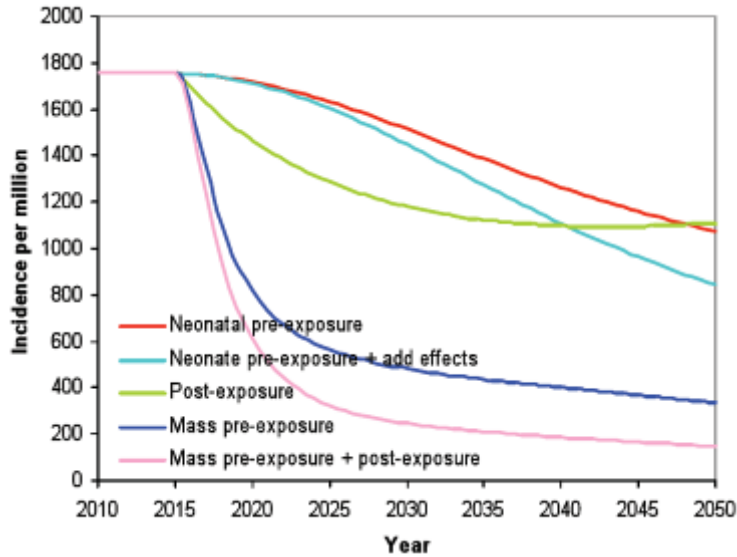
Elimination target: 1 / million / year by 2050

Innovative action needed in 4 spheres

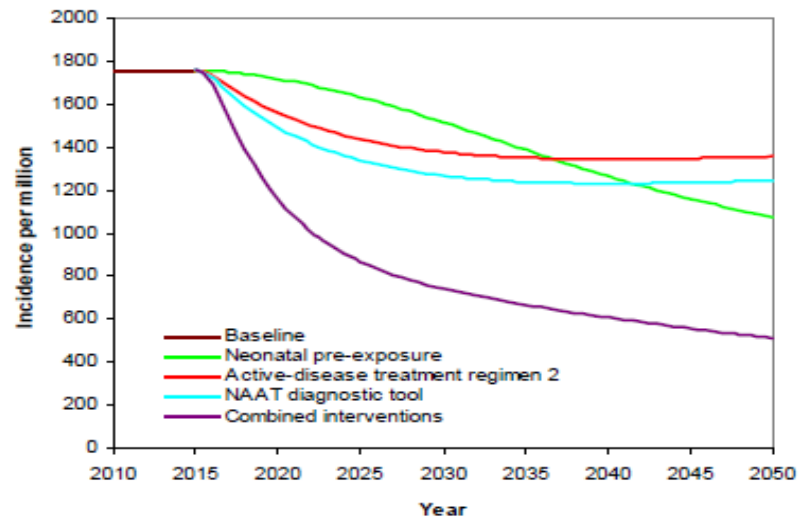
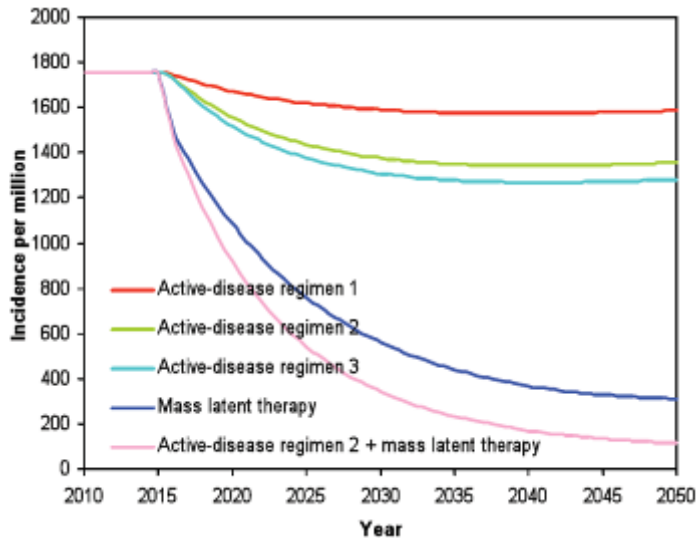
"Moving beyond the TB box"



Potential impact of new TB vaccines, diagnostics and drugs in SE Asia

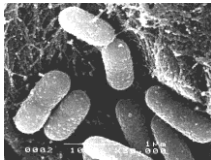


G Combined Interventions and Incidence of TB (all types)

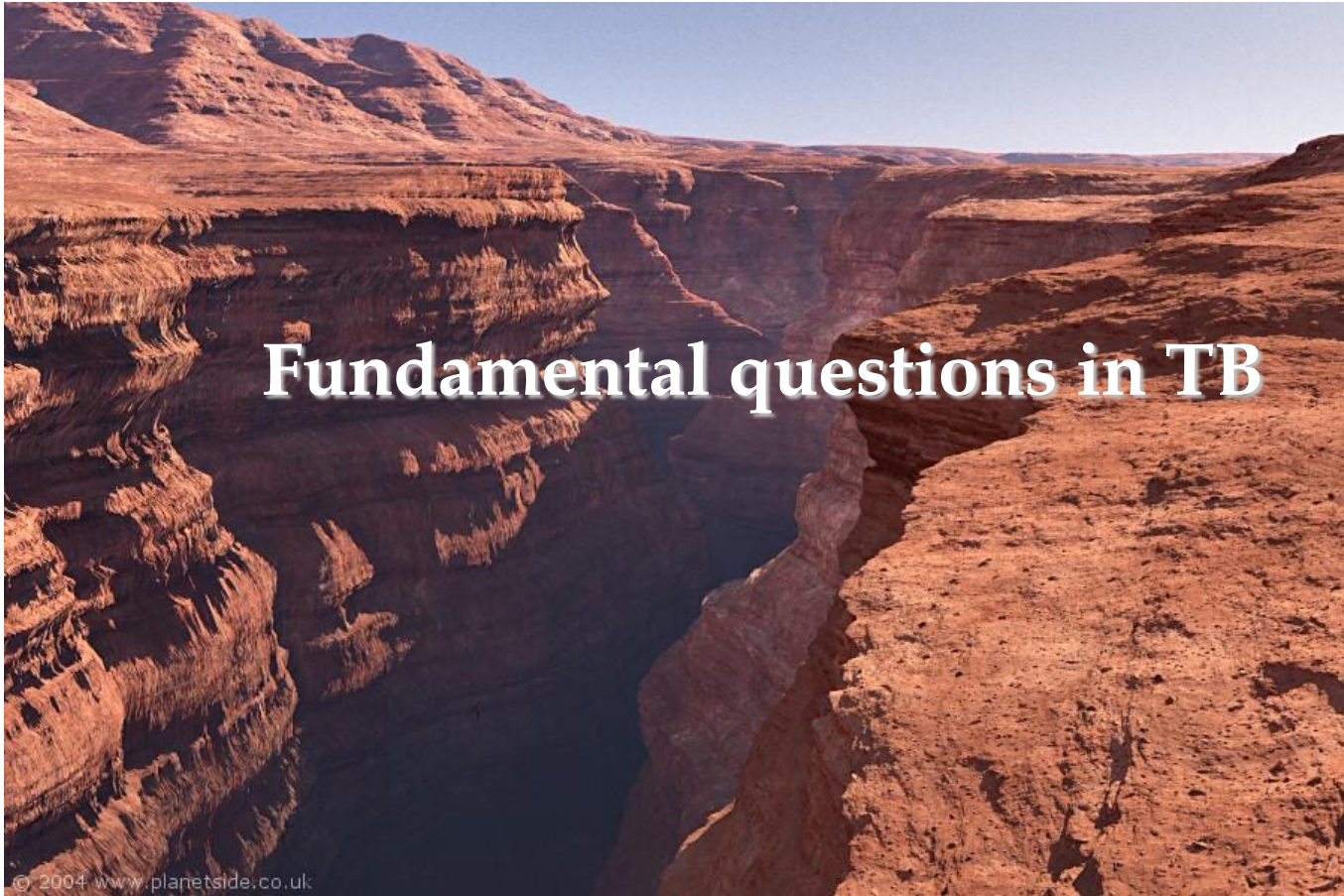


Source: L. Abu Raddad et al, PNAS 2009

Improve Human Health

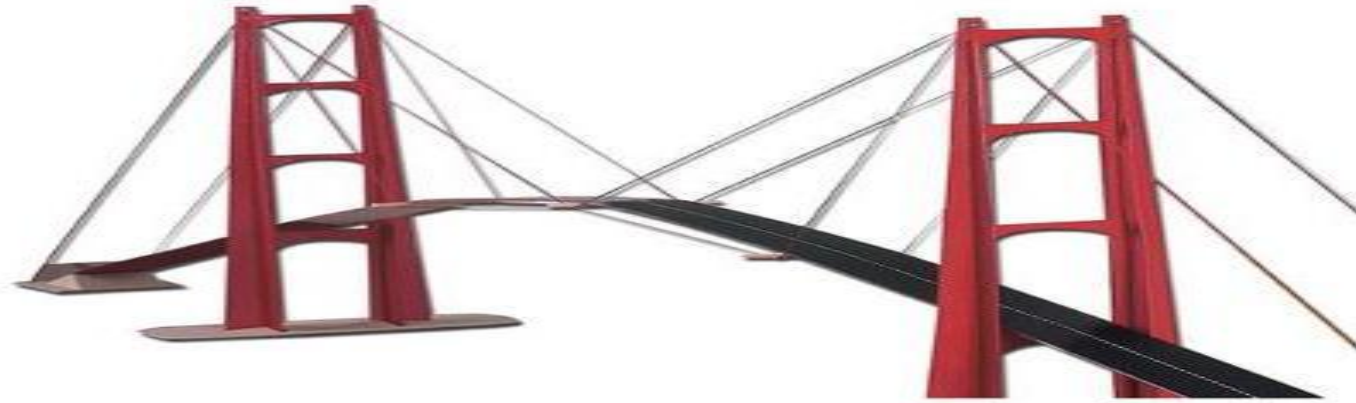


- **Knowledge gaps**



- **Resources gaps**

Fundamental Questions in TB

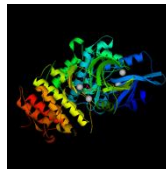
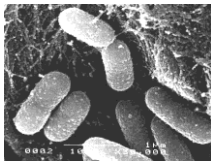


**Basic
Science**

**Translational
Studies**

**Preclinical
Studies**

**Clinical
Studies/Trials**



Improve Human Health

Develop
Point of Care
Diagnostics

Transform the
Field of
Therapeutics

Develop a
Safe and
Effective
Vaccine



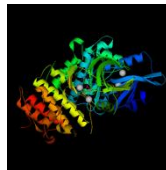
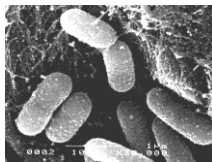
Fundamental questions in TB

Basic
Science

Translational
Studies

Preclinical
Studies

Clinical
Studies/Trials



- Fundamental science is an integral part of an *aggressive, transformational* research response to the continuing global TB epidemic and is crucial to addressing questions that underpin development of new diagnostics, drugs and vaccines and the creation of improved control strategies to meet the goal of elimination of TB by 2050

Workshop in Bethesda – March 2010



- *First meeting organised by the Stop TB Partnership to discuss and integrate fundamental research activities into the Global Plan to Stop TB.*
- The **overall goal** was to define the key fundamental questions that underpin the development of new tools (biomarkers, drugs, diagnostics, vaccines) for TB control.

Major objective 1: How best to characterise human TB?

- How to define the *spectrum of TB* in humans and identify suitable markers of clinically relevant stages of the disease ? (transition between the key stages of human TB, kinetics and role of granuloma formation)
- What are the key microbiological characteristics that correlate with disease outcomes ? (mycobacterial genotype influence, size of the inoculum, location of bacteria during various phases, fitness costs)
- What are the key epidemiological characteristics of TB in various settings ? (variety of dynamics of TB in endemic settings, effect of environment on Mtb transmission)

Major objective 2: what are the key features in molecular host/pathogen interactions ?

- To define the contribution of the *pathogen* to the dynamic nature of TB (bacterial subpopulations, persisters, bacterial genetic and functional diversity, strains types)
- To define the contribution of the *host* to the dynamic nature of TB (how the immune system perceives the pathogen, relationship between host genetics and disease outcome)
- To define the *host-pathogen* interaction in the dynamic nature of TB (Mtb interaction with the immune system during various phases of progression from infection to disease, mechanism of natural killing of Mtb by the host immune system, how Mtb evades killing?)

Major Objective 3: How to prepare the host immune system against Mtb infection and disease ?

- What components of the host immune system are critical for the elimination of Mtb?
- Why prior infection and disease do not protect against recurrent TB?
- What antigens, in addition to those presented by Mtb during natural course of infection, need to be added to vaccines to provide protection?
- Should vaccination strategies be designed to modulate networks involved in T cell regulation and memory rather than simply on effector mechanisms?

Examples of proposed cross-cutting activities



- Conduct large-scale, multi-site longitudinal studies in high exposure settings in populations with a high risk for disease progression (children ≤ 5 , household TB contacts, HIV infected persons).
- Collect specimens at various stages of infection and disease for microbial and host biomarker studies.
- Conduct large, comprehensive, observational longitudinal cohort studies in various settings that include the full spectrum of TB from exposure to disease, as well as various ages affected by TB.
- Develop relevant clinical and microbiological/immunological assays to be used during the follow-up period after treatment completion.

Conclusions

- No one prominent fundamental research question can be addressed in the absence of multi-disciplinary, collaborative clinical studies linking basic and translational studies in carefully planned and detailed large-scale, multi-site, epidemiological studies of populations in high exposure settings, with a high risk for disease progression
- Such studies should lead to the development of high quality sample repositories of well characterized microbial and human samples for coordinated, collaborative development of biomarkers.

Conclusions

- Consensus-driven *Roadmap for International Research to eliminate TB*
- TB Research Movement promotes the need for harmonized and complementary funding of TB research to target revolutionary discoveries that will foster better care and control for the elimination of TB.

www.stoptb.org/researchmovement/

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*Thank you for
your attention !*

