MONASH South Africa

Global Burden and Response to Tuberculosis

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Seminar: Hons Bachelor of Public Health

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In this seminar

1. Tuberculosis – the basics and history

2. Global burden of TB

3. Drug resistant TB

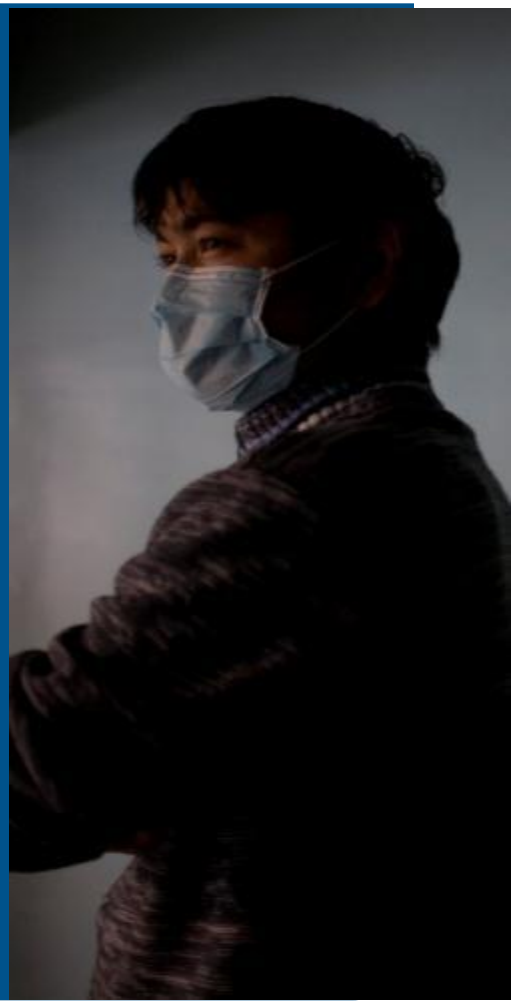
4. Global response and TB control

   - Strategies, Targets & Tools for elimination of TB
   - Challenges and roadblocks for eradication of TB

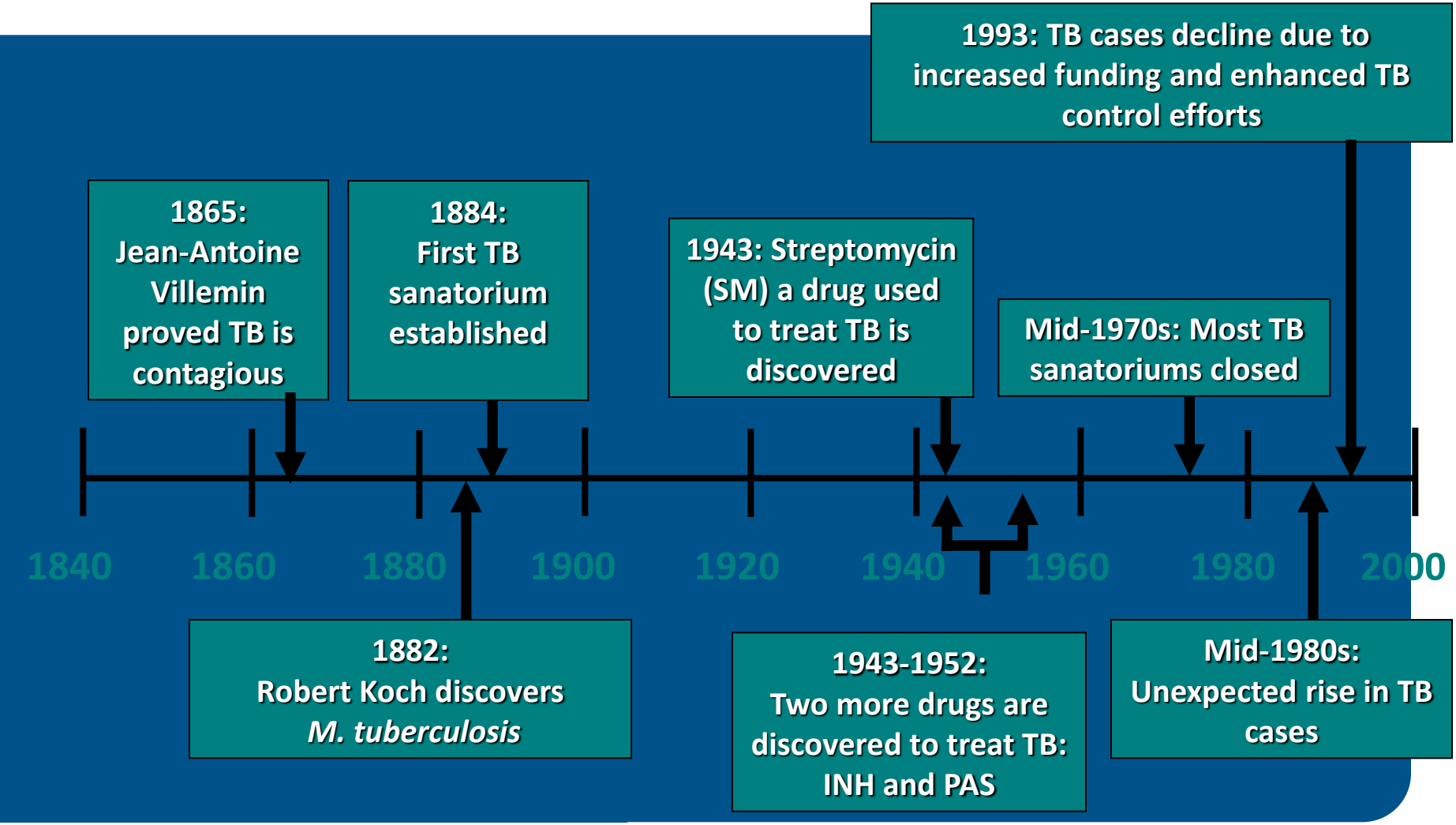
5. Conclusions and call to action

Tuberculosis: basics

- Tuberculosis (TB) is one of the oldest diseases of humans
- TB is a major cause of death worldwide, it competes with HIV/AIDS as the greatest killer globally due to a single infectious agent
- TB is also one of the top killers of women worldwide, half a million women died from TB in 2011
- TB is caused by the bacterium *Mycobacterium tuberculosis*
- TB usually affects the lungs, although other organs are involved in 15-30% of cases
- If properly treated, TB caused by drug-susceptible strains is curable in virtually all cases
- If untreated, TB may be fatal within 5 years in 2/3 of cases
- One third of world has latent TB infection



TB History Timeline

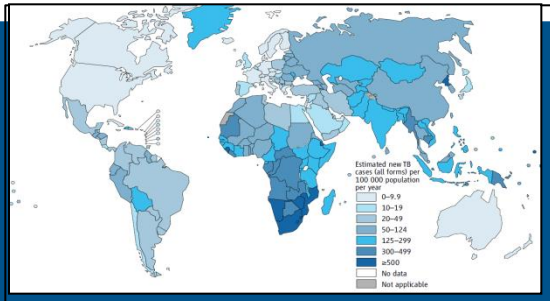


TB Resurgence

- **Increase in TB in mid 1980s**
- **Contributing factors:**
  - Inadequate funding for TB control programs
  - HIV epidemic
  - Increased immigration from countries where TB is common
  - Spread in homeless shelters and correctional facilities
  - Increase and spread of multidrug-resistant TB

March 16, 1992 Newsweek Magazine Cover

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)

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Source: WHO Global Tuberculosis Report 2013

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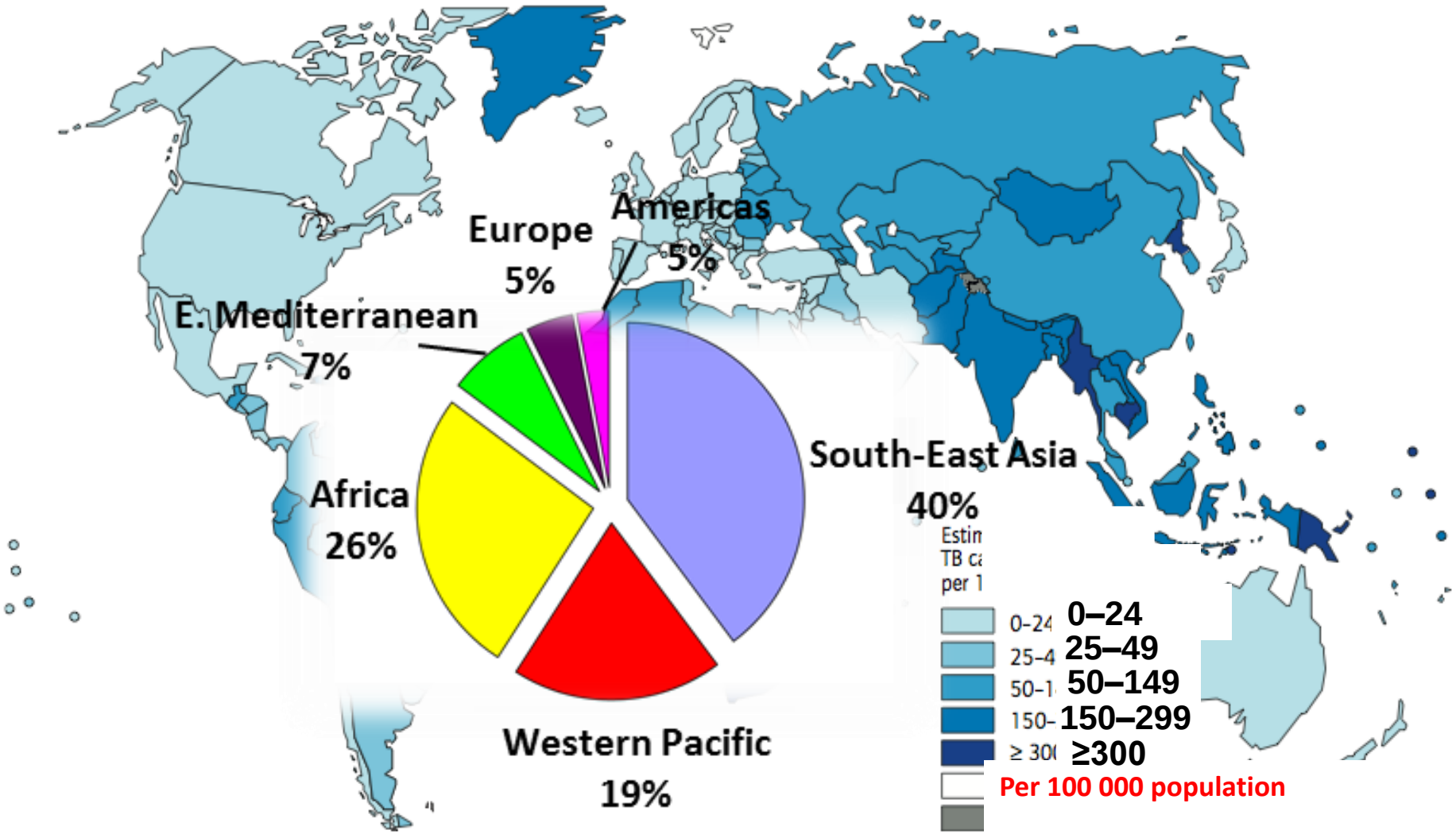
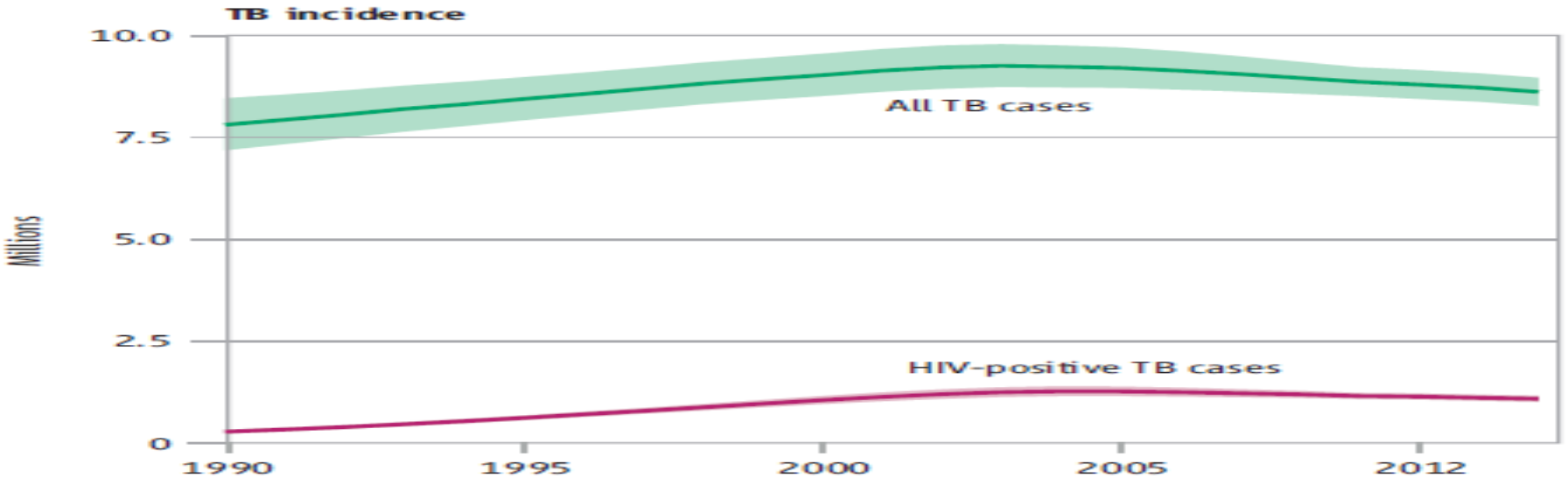
** Including deaths attributed to HIV/TB*

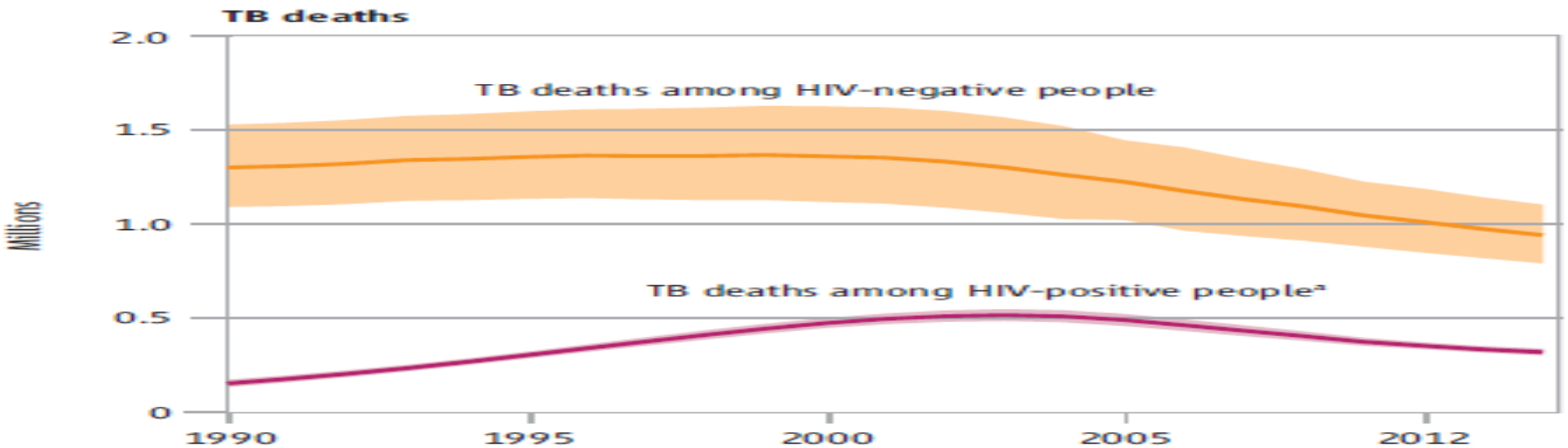
Incidence rates, 2011



Highest rates in Africa, linked to high rates of HIV infection
~80% of HIV+ TB cases in Africa

Trends in TB incidence and TB deaths, 1990-2012



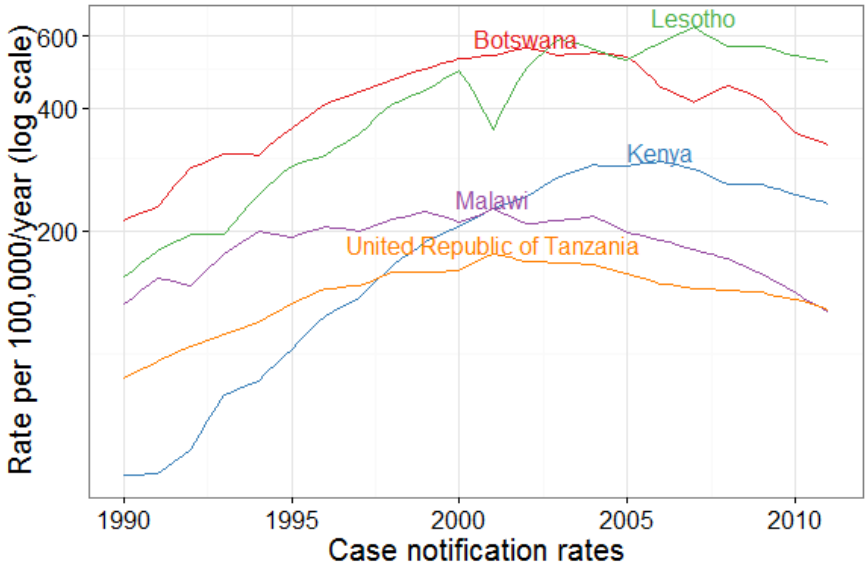


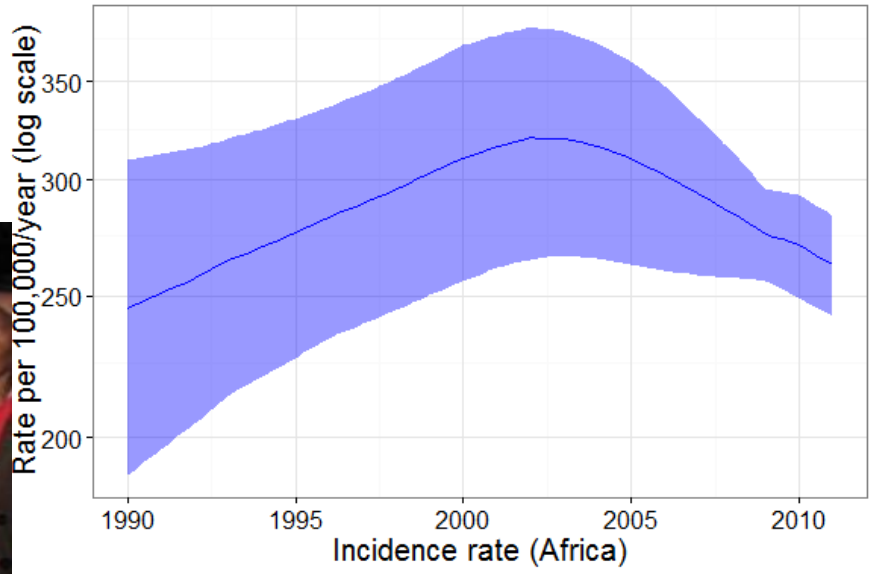
[a] HIV-associated TB deaths are classified as HIV deaths according to ICD-10.

Source: WHO Global Tuberculosis Report 2013

TB/HIV co-infection: 80% of burden in Africa

- ✓ 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.
- ✓ Untreated, TB in PLHIV leads to death in weeks
- ✓ 80% of all TB/HIV cases are in Africa





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Drug-Resistant TB

- Caused by *M. tuberculosis* organisms resistant to at least one TB treatment drug
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)

- Resistant means drugs can no longer kill the bacteria

Drug-Resistant TB

Primary Resistance	**Caused by person-to-person transmission of drug-resistant organisms**
Secondary Resistance	**Develops during TB treatment:** • **Patient was not given appropriate treatment regimen** **OR** • **Patient did not follow treatment regimen as prescribed**

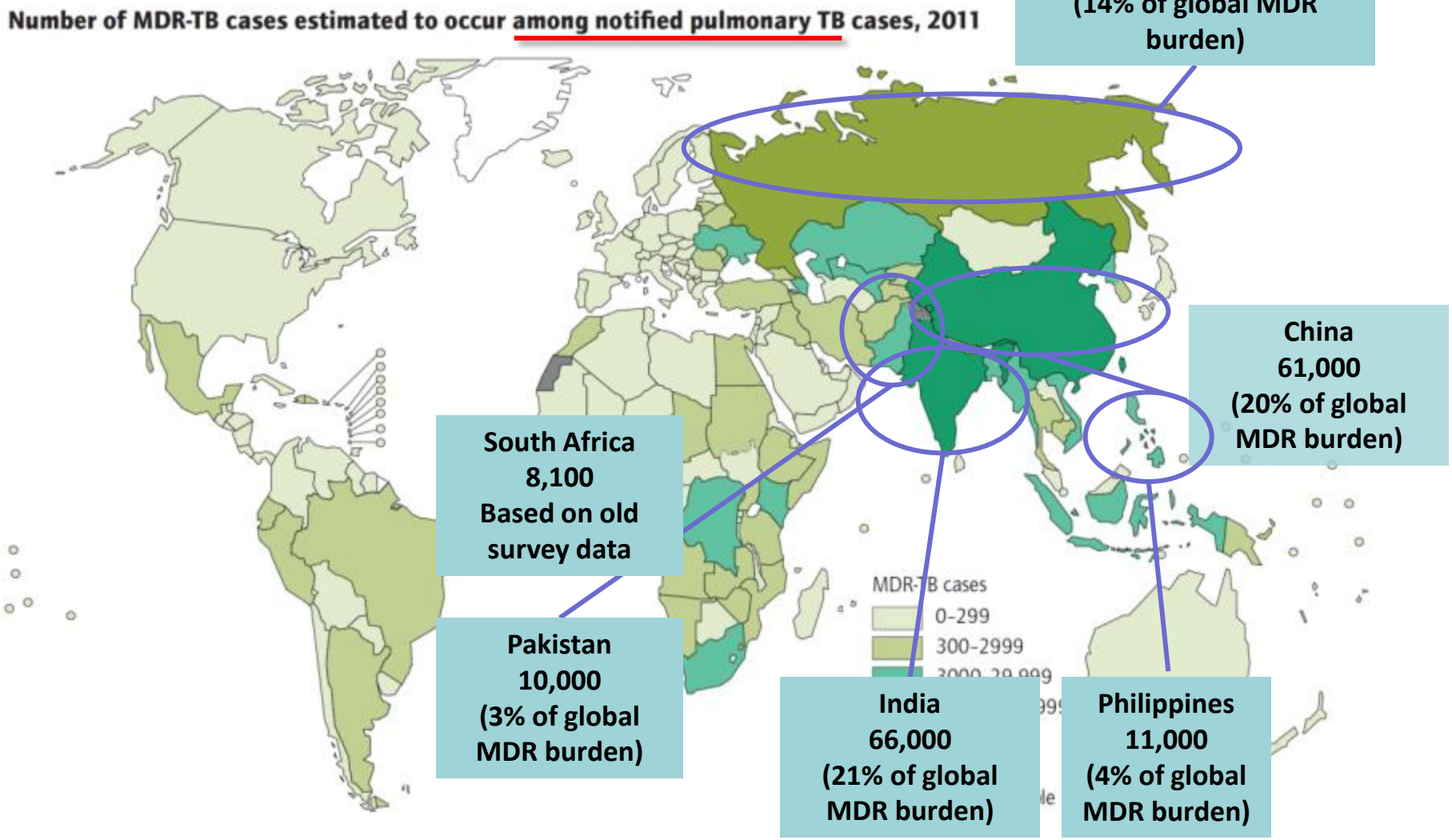
Drug-Resistant TB

Mono-resistant	Resistant to any one TB treatment drug
Poly-resistant	Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)
Multidrug resistant (MDR TB)	Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs
Extensively drug resistant (XDR TB)	Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin, kanamycin, or capreomycin)

Drug resistant TB: Major challenge

- Multi-drug resistant TB (MDR-TB)
  - Second-line drugs, toxic, costly, lengthy
- Extensively drug resistant TB (XDR-TB)
  - Almost incurable, fatal
- Drug resistant TB results from inadequate TB care and irrational use of dru
- New York epidemic in early 90's – Cost of response: US$ 1 billion

Estimated number of MDR-TB Cases, 2011
>60% of all cases are in 6 countries



To date, 84 countries have reported at least one XDR-TB case

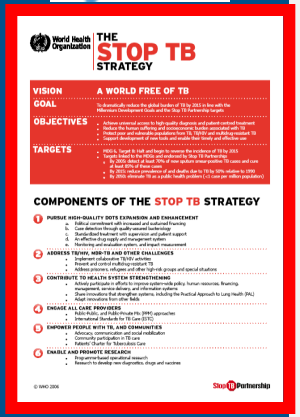
About 9% of MDR-TB cases are XDR

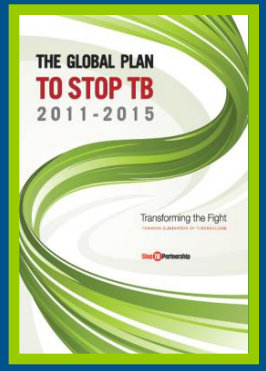
The global response:
Targets, Global Plan, and Stop TB Strategy

UN Millennium Development Goals

World Health Organization

Goal 6: to have halted by 2015 and begun to reverse the incidence…



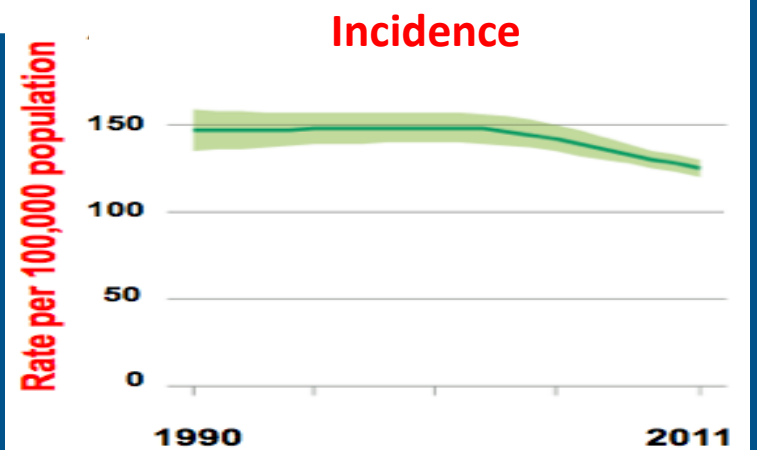


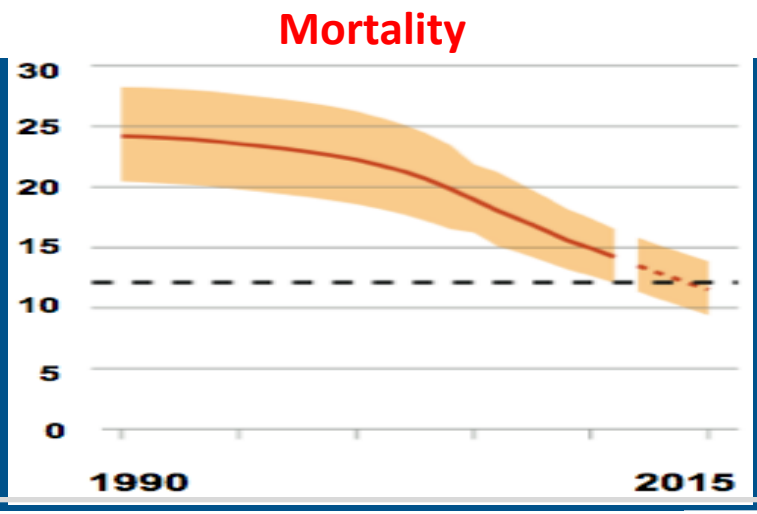
2015: 50% reduction in TB prevalence and deaths compared to 1990

2050: elimination (<1 case per million population)

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

Global Progress on impact - 2012

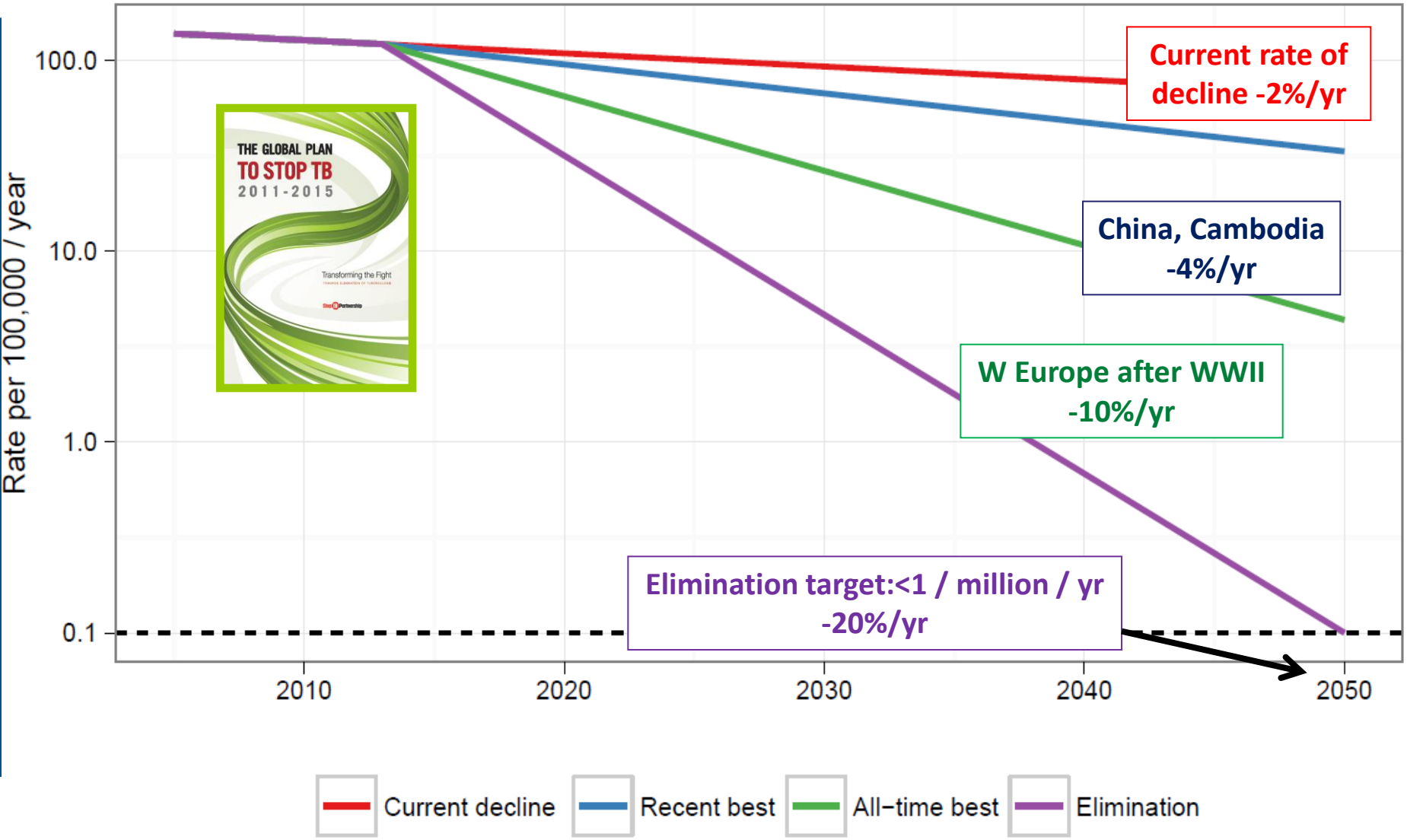




- ✓ 2015 MDG on track and reduction in TB mortality of 45% since 1990
- ✓ 56 million patients cured, 1995-2012
- ✓ 22 million lives saved since 1995
- ✓ <u>BUT</u>, TB incidence declining too slowly, 1/3 of cases not in the system, MDR-TB challenge not yet properly addressed

Source: WHO Global Tuberculosis Report 2013

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



Source: WHO Global Tuberculosis Report 2013

What is needed to accelerate incidence decline and target "elimination"?

- ✓ Economic development: better nutrition & housing
- ✓ Universal health coverage & social protection
- ✓ TB care widely accessible to all and of high-standards
- ✓ Focused, high-intensity interventions, including BCG in children
- ✓ Screening of high-risk groups and mass TLTBI
- ✓ Infection control practices

<u>However</u>… while incidence decline can accelerate, "elimination" is another story, as it requires major reduction of:

(i) transmission rate, and
(ii) reactivation of latent infection among the already infected

In turn, this requires…new tools and increased financing

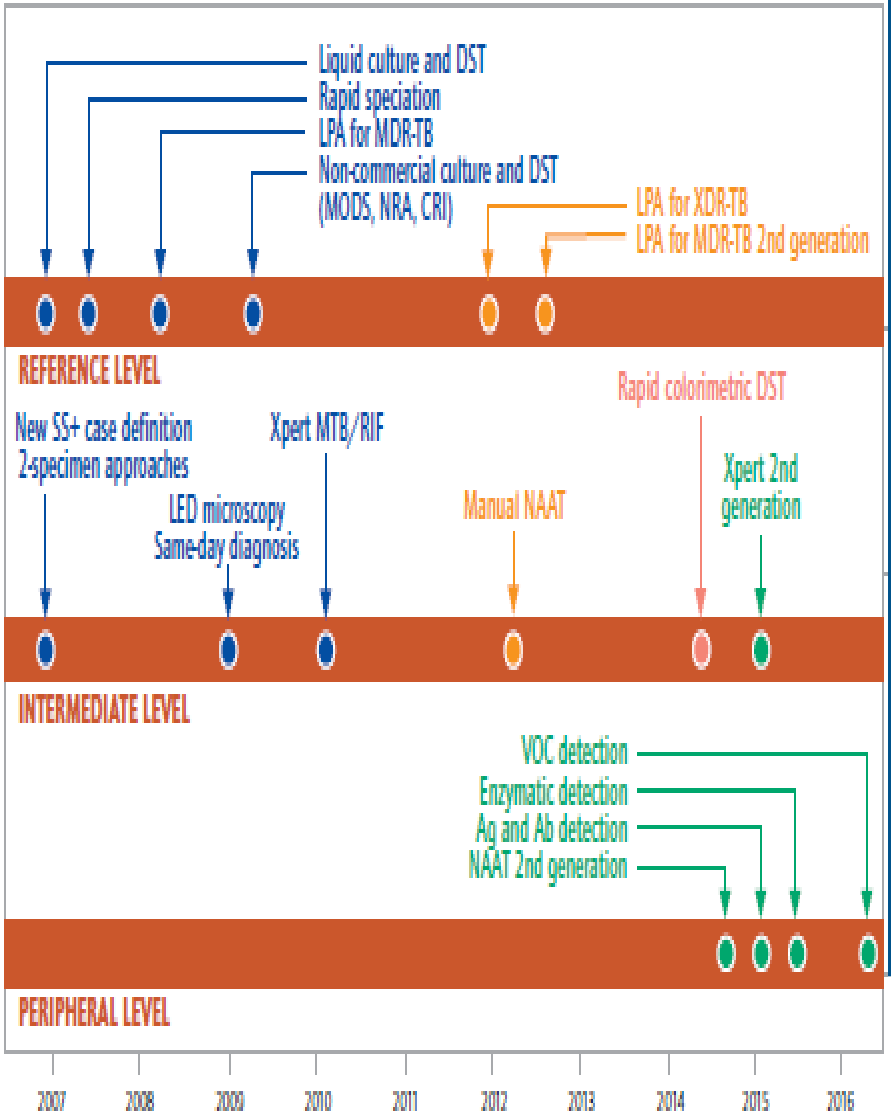
What is in the pipelines for new diagnostics in 2013?

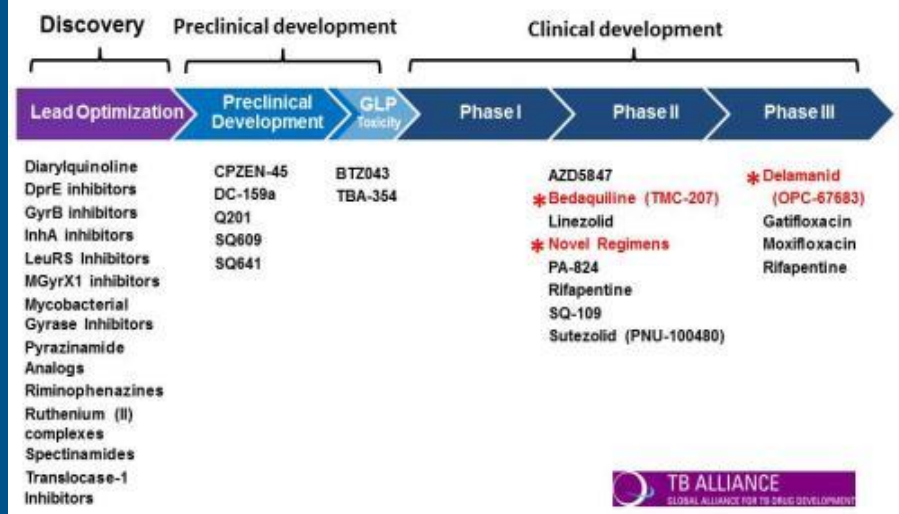
Diagnostics:
- 7 new diagnostics or diagnostic methods endorsed by WHO since 2007;
- 6 in development;
- yet no PoC test envisaged

Drugs:
- 1 new drug approved in late 2012, but probably little impact on epidemiology;
- 1 expected to be approved in 2013;
- a regimen and other 2-3 drugs likely to be introduced in the next 4-7 years

Vaccines:
- 11 vaccines in advanced phases of
- development;
- 1 just reported with no detectable efficacy

What is in the pipelines for new drugs and vaccines in 2013?





Phase I	Phase II	Phase IIb	Phase III
AdAg85A	M72+AS01	MVA85A/ AERAS-485	Mw [M. indicus pranii (MIP)]
Hybrid-I+CAF01	VPM 1002	AERAS-402/ Crucell Ad35	
H56+IC31	Hybrid-1+IC31		
Hyvac 4/ AERAS-404+IC31	RUTI		
ID93			

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11 vaccines for TB prevention in Phase 1 or Phase II trials

What do we need to eliminate TB?

To eliminate TB:
1. Very short potent regimen for all forms, and
2. Simple regimen for mass chemoprophylaxis

<u>Synergy of interventions !</u>
Action on both transmission and reactivation pathways

Or:
Mass pre- and post-exposure vaccine

Tools required for eradication in our lifetime (drugs):

Do we have potent regimen for treatment and prevention?

- ✓ **Ideally, we need *as short a regimen* as possible active against all types of TB, transforming TB into a common infectious disease. However, we only have "short-course chemotherapy"**

- ✓ **Ideally, we need *mass chemoprophylaxis (TLTBI)*, as TLTBI prevents reactivation with up to 70% efficacy. However:**

  - ✓ **Safety issue on a mass scale: fatal hepatitis**
    - **4.13 (95% CI 0.5-34) Risk Ratio (vs placebo) *(Cochrane Review, 2010);***
    - **4-7/100,000 incidence *(Millard PS et al. West J Med. 1996;164:486-91.)***

  - ✓ **Single dose treatment not available: no existing drug kills intracellular bacteria (such as *M. tuberculosis)* in a non-replicative state**

  - ✓ **Screening of truly infected or at real risk not available: no "IGRA-plus"**

Reality check about treatment and chemoprophylaxis

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 5-10 years

2. Today we do have a **treatment for latent TB infection** that is 70% efficacious, but difficult to scale-up to whole population (? 2 billion infected) or even to high-risk groups

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

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

Reality check about vaccines

1. Today we do not have a potent pre- and post-exposure vaccine, we have BCG

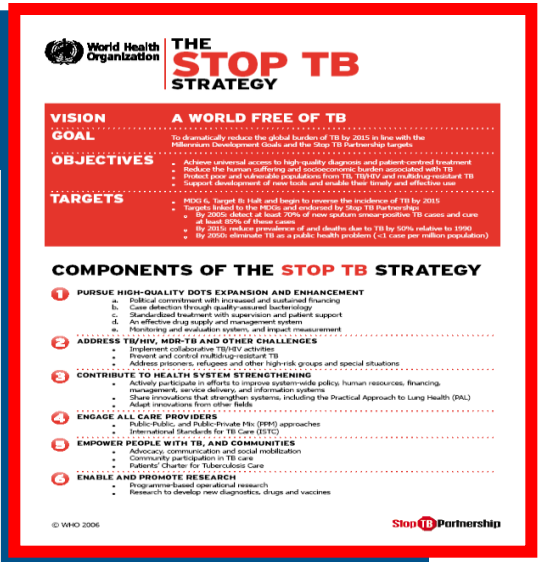
2. Today we do not have yet clarity about correlates of immunity and bio-markers

3. Today, we do not fully understand pathogenesis and immunity

What can be done?

1. **Enhance** strategy and approach to TB care, control and research

2. **Mobilize** resources for research



World Health Organization

THE STOP TB STRATEGY

VISION A WORLD FREE OF TB

GOAL To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets

OBJECTIVES
- Achieve universal access to high-quality diagnosis and patient-centred treatment
- Reduce the human suffering and socioeconomic burden associated with TB
- Protect poor and vulnerable populations from TB, TB/HIV and multidrug-resistant TB
- Support development of new tools and enable their timely and effective use

TARGETS
- MDG 6, Target 8: Halt and begin to reverse the incidence of TB by 2015
- Targets linked to the MDGs and endorsed by Stop TB Partnership:
  - By 2005: detect at least 70% of new sputum smear-positive TB cases and cure at least 85% of these cases
  - By 2015: reduce prevalence of and deaths due to TB by 50% relative to 1990
  - By 2050: eliminate TB as a public health problem (<1 case per million population)

COMPONENTS OF THE STOP TB STRATEGY

1. **PURSUE HIGH-QUALITY DOTS EXPANSION AND ENHANCEMENT**
   - a. Political commitment with increased and sustained financing
   - b. Case detection through quality-assured bacteriology
   - c. Standardised treatment with supervision and patient support
   - d. An effective drug supply and management system
   - e. Monitoring and evaluation system, and impact measurement
2. **ADDRESS TB/HIV, MDR-TB AND OTHER CHALLENGES**
   - Implement collaborative TB/HIV activities
   - Prevent and control multidrug-resistant TB
   - Address prisoners, refugees and other high-risk groups and special situations
3. **CONTRIBUTE TO HEALTH SYSTEM STRENGTHENING**
   - Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery, and information systems
   - Share innovations that strengthen systems, including the Practical Approach to Lung Health (PAL)
   - Adapt innovations from other fields
4. **ENGAGE ALL CARE PROVIDERS**
   - Public-Public, and Public-Private Mix (PPM) approaches
   - International Standards for TB Care (ISTC)
5. **EMPOWER PEOPLE WITH TB, AND COMMUNITIES**
   - Advocacy, communication and social mobilization
   - Community participation in TB care
   - Patients' Charter for Tuberculosis Care
6. **ENABLE AND PROMOTE RESEARCH**
   - Programme-based operational research
   - Research to develop new diagnostics, drugs and vaccines

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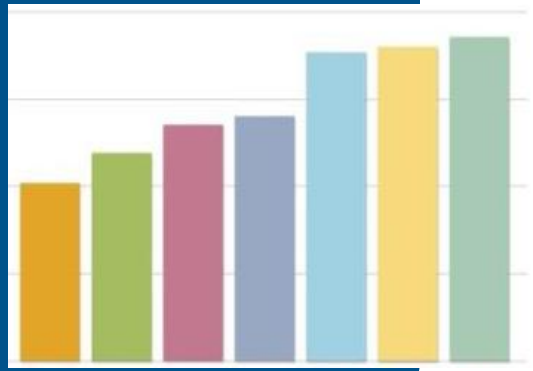
Stop TB Partnership



DRAFT Post-2015 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**

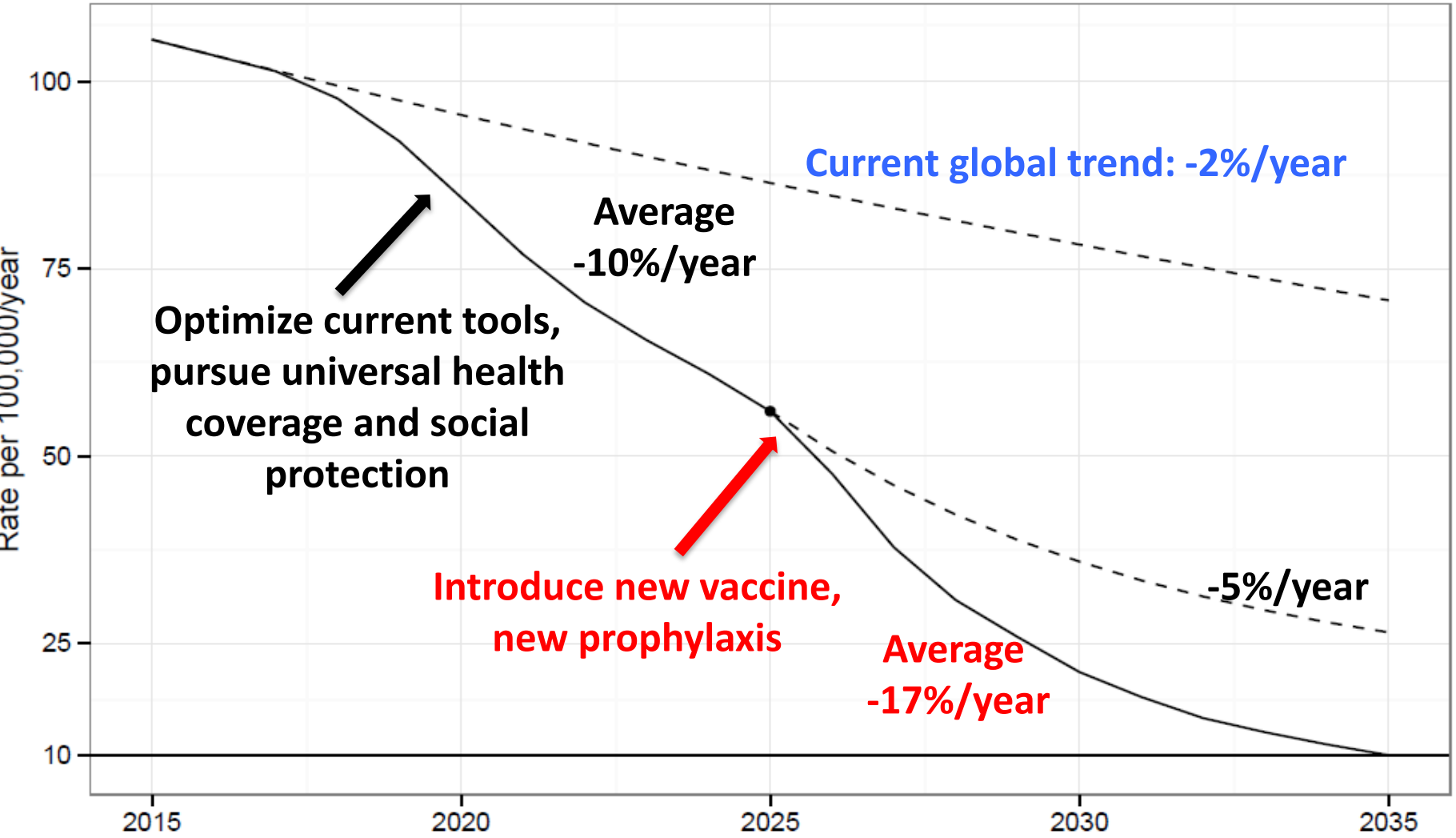
TARGETS FOR 2035:

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

MILESTONES FOR 2025:

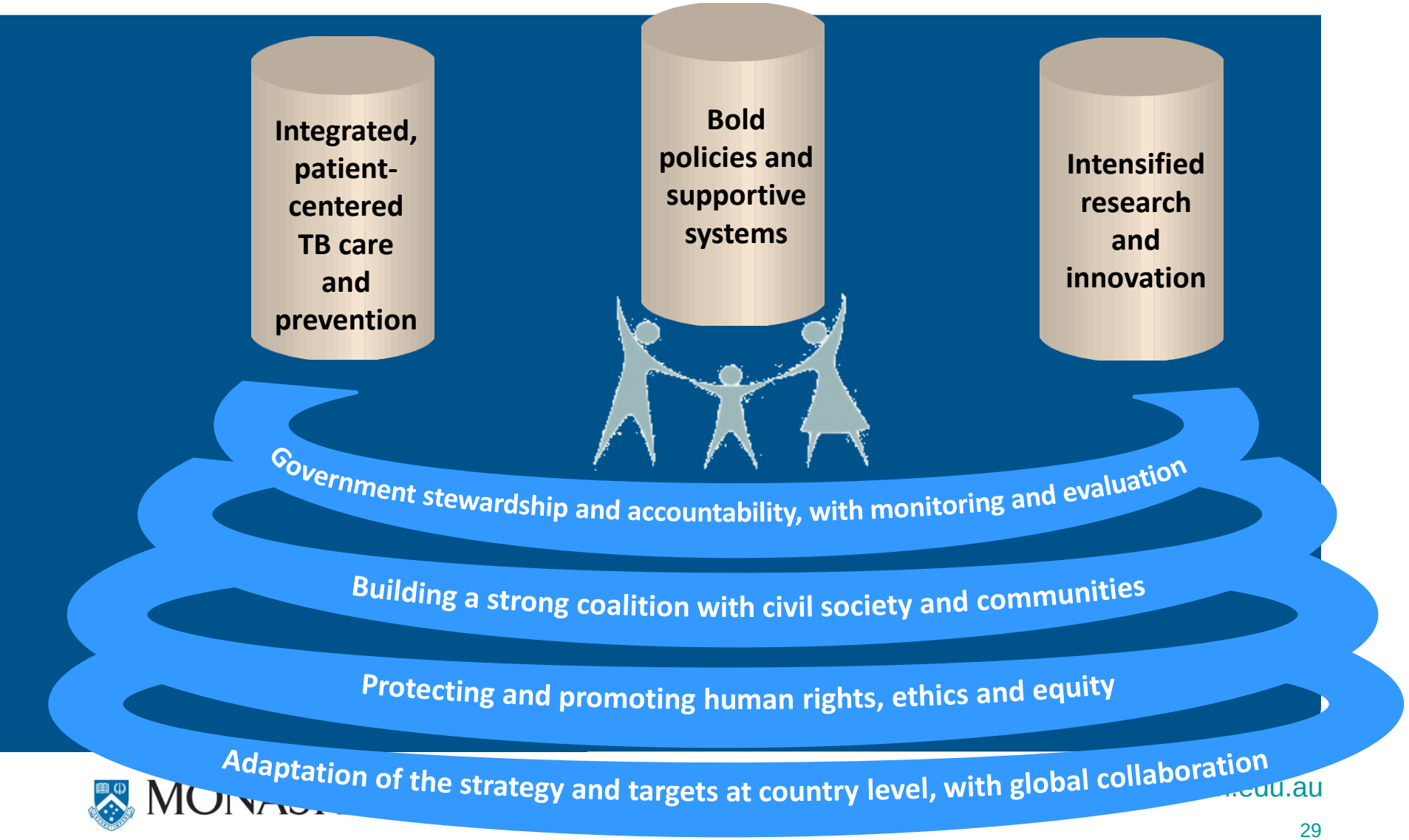
- **75% reduction in TB deaths (compared with 2015)**
- **50% reduction in TB incidence rate (< than 55/100,000)**
- **No affected families face catastrophic costs due to TB**

Projected acceleration of TB incidence decline to target levels



Post-2015 Global TB Strategy

Proposed Pillars and Principles



Post-2015 Global TB Strategy
Proposed Pillars

Targets: 95% reduction in deaths and 90% reduction in incidence (≤ 10 cases / 100,000 population) by 2035

Integrated, patient-centered TB Care and Prevention

- Early diagnosis of TB including universal drug-susceptibility testing ; systematic screening of contacts and high-risk groups
- Treatment of all forms of TB including drug -resistant TB with patient support
- Collaborative TB/HIV activities and management of co-morbidities
- Preventive treatment for high-risk groups and vaccination of children

Bold policies and supportive systems

- Government stewardship , commitment, and adequate resources for TB care and control with monitoring and evaluation
- Engagement of communities , civil society organizations, and all public and private care providers
- Universal health coverage policy; and regulatory framework for case notification, vital registration, drug quality and rational use, and infection control
- Social protection, poverty alleviation, and actions on other determinants of TB

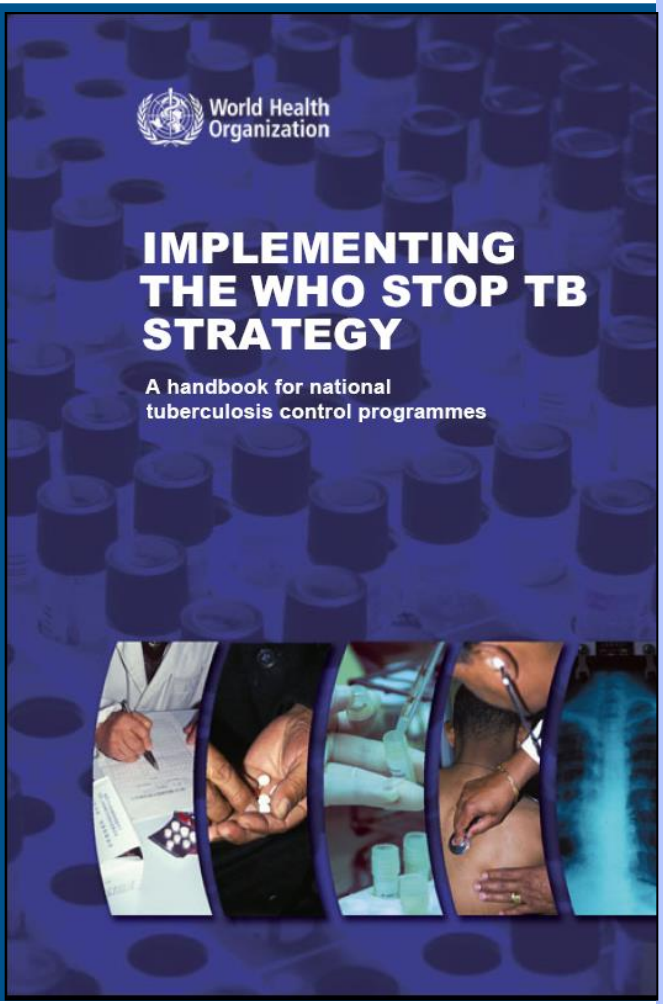
Intensified Research and Innovation

- Discovery, development and rapid uptake of new tools, interventions and strategies
- Operational research to optimize implementation and impact, and promote innovations

Targets for 2025/2030

Target 1	Target 2	Target 3
75%/80% reduction in deaths due to TB (compared with 2015)	40%/60% reduction in TB incidence rate (compared with 2015)	No catastrophic expenditures for families affected by TB

Tools required for eradication in our lifetime:
a potent regimen for prevention/ treatment of latent infection?



1. IPT prevents TB with around 70% efficacy, individual benefits clear, population level less clear (40% reported).

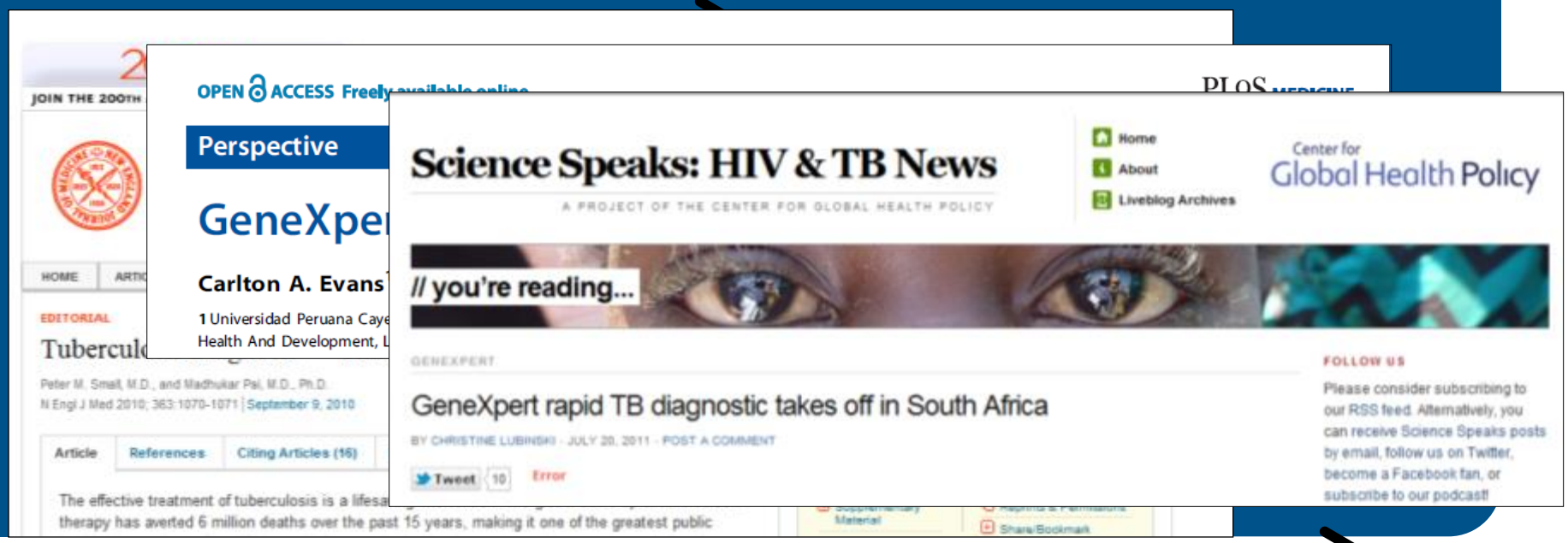
2. WHO recommends treatment of LTBI for:
   - People living with HIV (PLHIV)
   - Children <5 contacts of a TB case
   - Recent TST converters
3. Isoniazid 5 mg/kg daily (max 300 mg) for at least 6 months, but shorter regimens also efficacious (12wHP, 3HR)

4. Fatal hepatitis: 2010 Cochrane review 4.3 RR (0.5-34); incidence 4-7/100,000 *(Millard 1996)*

5. Modelling shows potential, but feasibility and scale-up remain an issue. No predictive test

Innovating with GeneXpert

WHO endorsement December 2010



Nearly 83 countries using it in March 2013

Tools required for eradication in our lifetime (2: Vaccines): Perspectives for a potent vaccine

Mass vaccination with a potent vaccine:

- ***pre-exposure*:**

  would prevent infection to occur, and therefore disease, but impact would take a long time to appear

- ***post-exposure:***

  would prevent "reactivation", and would have impact on transmission as new cases will not emerge any longer out of the pool of already infected. However, it would not prevent new infection

CHALLENGES TO "ELIMINATION"?

1. Funding not secure; catastrophic expenditure for the poor
2. Only 2/3 of estimated cases reported or detected (late)
3. TB/HIV major impact in Africa
4. MDR-TB, with high burden in former USSR and China
5. Un-engaged non-state practitioners and communities, and the private sector
6. Weak health policies, systems and services
7. Social and economic determinants maintain TB
8. Research awakening: old diagnostics, drugs and vaccines

ROADBLOCKS: Today, most used tools for TB control are old and not conducive to elimination

DIAGNOSTIC

Sputum smear microscopy
Discovered 1882

VACCINE

BCG
Developed 1920s

TREATMENT

1st-line TB drugs
Discovered 1943-1970

Roadblock: Taking on the Pharmaceutical Industry

- Lobbying, promotion, economic incentives and infiltration
- Quality differentiation based on level of regulation
- Counterfeit medicines
- Drug resistance
- BUT, we need them on our side!

Conclusions and call to action

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

2. Three pillars will be the basis to accelerate incidence decline: (i) universal access to quality TB care and control, (ii) bold health system policies, and (iii) intensified research efforts

3. For elimination one would need potent short treatments, mass TLTBI and potent pre- and post-exposure vaccines. None is available today

4. Basic research is fundamental to gain further knowledge and R&D pipelines must be expanded , nurtured and well-financed.

5. Increased financial resources for TB Vaccine development: we need a new global TB vaccine "partnership" of all engaged developers, investors, donors so that efforts are synergised and synchronised. This is not a job for one agency only!