

# Tuberculosis Update

Dean Tsukayama

# Tuberculosis Concerns

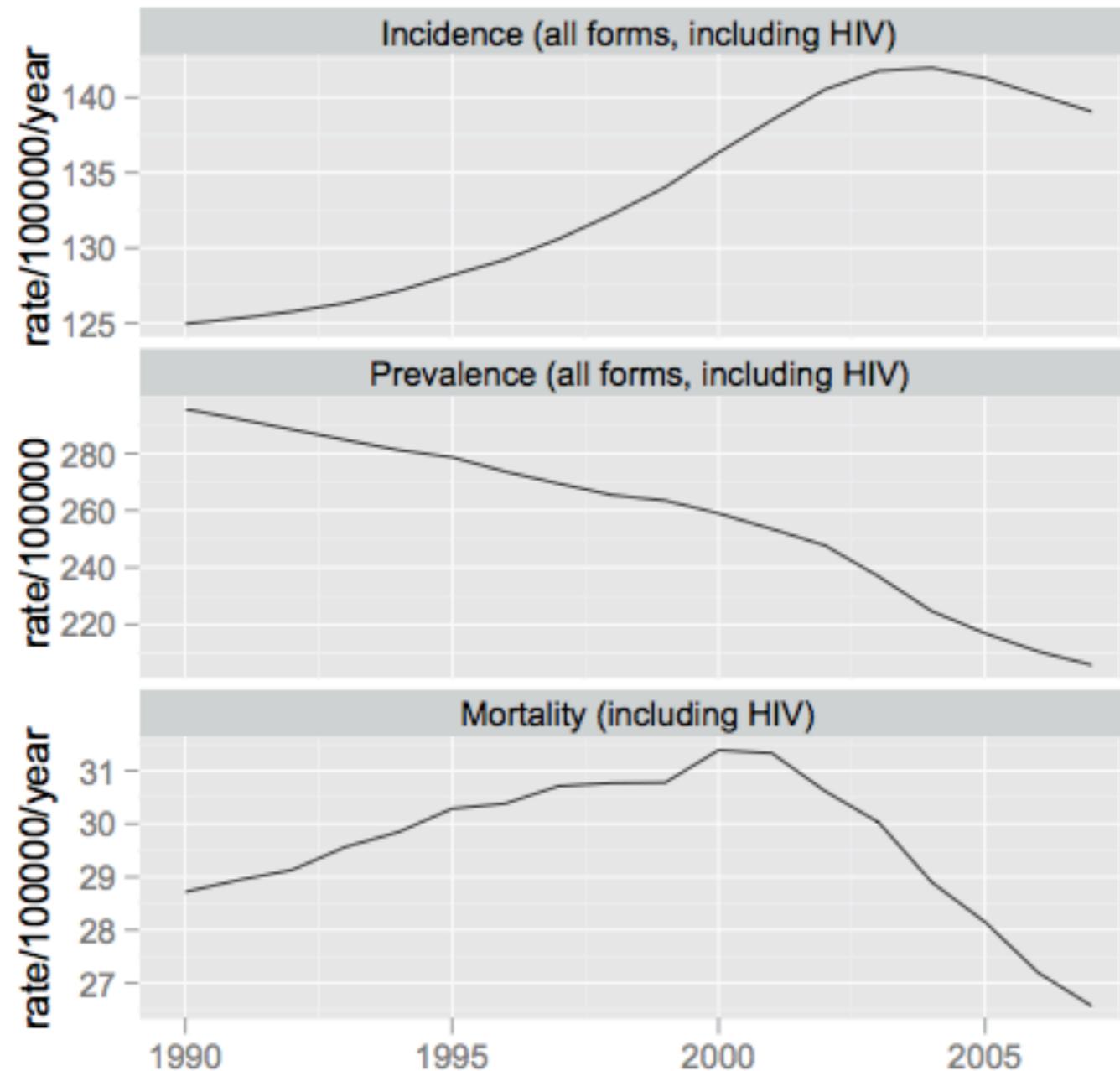
- HIV co-infection
- Increasing incidence of TB in some areas
- Increasing drug-resistant tuberculosis
- Extensively drug resistant tuberculosis

# Epidemiology of Tuberculosis

- People infected: 2 billion
- Annual incidence of disease: 9-10 million
- Annual deaths: 1.8 million

# Incidence of TB

Glaziou et al



**Fig. 3.** Global rates of TB incidence, prevalence and mortality, including people with HIV, 1990 to 2007. (Adapted from WHO. Global tuberculosis control 2009: surveillance, planning, financing. Geneva: World Health Organization; 2009; with permission.)

## TB incidence 2005 - Top 30 Countries

Country	Incidence
Swaziland	1198
South Africa	948
Djibouti	813
Zimbabwe	782
Namibia	767
Lesotho	637
Sierra Leone	574
Zambia	506
Botswana	495
Cambodia	495
Mozambique	431
Togo	429
Cote d'Ivoire	420
Gabon	406
Congo	403
Rwanda	397
Democratic Republic of Congo	392
Ethiopia	378
Burundi	367
Kiribati	365
Kenya	353
Malawi	346
Central African Republic	345
North Korea	344
Uganda	330
Timor-Leste	322
Mali	319
Mauritania	318
Nigeria	311
Haiti	306

## Global - 136/100,000

Other countries of interest	
China	100
El Salvador	51
India	168
Iraq	168
Laos	155
Liberia	301
Korea	96
Mexico	23
Pakistan	181
Philippines	291
Russia	119
Thailand	142
Somalia	224
USA	5
Vietnam	175

# The white plague returns to London—with a vengeance



In 1660, John Bunyan (1628–88), an English Christian writer and preacher, described tuberculosis as “The Captain among these men of death” when tuberculosis case rates in London had reached a phenomenal 1000 per 100 000 population per year,<sup>1</sup> far more than current rates of 340 per 100 000 in sub-Saharan African countries.<sup>2</sup> During the 19th century, the white plague, as tuberculosis was named in Victorian Britain (due to the loss of skin colour seen in London tuberculosis patients), continued to ravage Britain, and up to 25% of deaths in Europe were caused by this disease. The death toll from tuberculosis began to fall in London at the start of the 20th century, as living standards (better housing, nutrition, and economic status) improved; subsequent tuberculosis control was achieved by the introduction in the early 1960s of antituberculosis drugs, improved health services, and BCG vaccination. By the early 1980s, tuberculosis was considered to be conquered in the UK and National Health Service (NHS) tuberculosis services were scaled down considerably.

is spreading, with 172 isoniazid-resistant cases reported in London in 2009.<sup>6</sup> Ominously, there were a further 58 cases of multidrug-resistant tuberculosis in 2009.<sup>7</sup>

The increase in the number of tuberculosis cases in the UK has largely been in non-UK born groups; in 2009, these were black African (28%), Indian (27%), and white (10%).<sup>3</sup> Interestingly many of these cases were not in new migrants; 85% of individuals born overseas had lived in the UK for 2 or more years, and tuberculosis was common in London boroughs that are relatively deprived.<sup>3</sup> Poor housing, inadequate ventilation, and overcrowding—conditions prevalent in Victorian Britain—are causes of the higher tuberculosis incidence rates in certain London boroughs. In all European countries, the disease is mainly concentrated in high-risk groups, such as migrants, refugees, homeless people, drug users, prisoners, and HIV-infected groups.<sup>6,8</sup>

Prisons provide ideal breeding grounds for tuberculosis and development of drug resistance. The spread of tuberculosis in prisons to prisoners and staff, and

Tuberculosis has returned to London in force with an increase in the number of cases by nearly 50% since 1999, from 2309 in 1999 to 3450 in 2009,<sup>3</sup> accounting for almost 40% of all tuberculosis cases in the UK.<sup>3,4</sup> Because the current gold standard for

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# Tackling tuberculosis in London's homeless population

London, UK, has one of the highest rates of tuberculosis in western Europe, and the city's homeless population are most at risk and the hardest to treat. Talha Burki reports.

2009 saw 9040 cases of tuberculosis in the UK: 15 cases per 100 000 individuals. But the disease is concentrated in certain demographics within certain areas. London has a rate of 44 cases per 100 000. In the country's homeless population, the rate is 300 cases per 100 000, an inequality that bears out WHO's assertion that "in many industrialised countries, tuberculosis rates among the homeless can be up to twenty times higher than the general population".

Lancet 376:2055, 2010



## TB lawsuit will cost Ramsey County millions

Article by: , Star Tribune

Updated: May 11, 2010 - 5:48 AM

Ramsey County and a group of former workhouse inmates who contracted or were exposed to tuberculosis while in custody have reached a tentative settlement that could reach \$10 million.

Both sides are seeking approval from U.S. District Judge Richard Kyle to have the settlement be a class action because there could be 100 or more people in line to receive compensation that includes medical care and cash.

The inmates sued in October 2008, claiming the county didn't properly test an infected inmate, and intense negotiations have gone on since. Attorneys for both sides called the proposed deal a major compromise.

"I think we've achieved a positive result and outcome for inmates who, through no fault of their own, contracted a terrible disease,"

said Robert Bennett, lead attorney for the plaintiffs.

A second related federal lawsuit filed by the original infected inmate is pending. It seeks \$14 million in damages.

If the class-action agreement is approved, the county would admit no fault. "By settling the case, the county is able to focus on looking forward rather than backward," said Cliff Greene, whose firm, Greene Espel, worked on the case for the county.

It's difficult to pinpoint exactly how much money will be spent, but it will come from the county's self-insurance fund. Taxpayer money is budgeted to fill that fund every year.

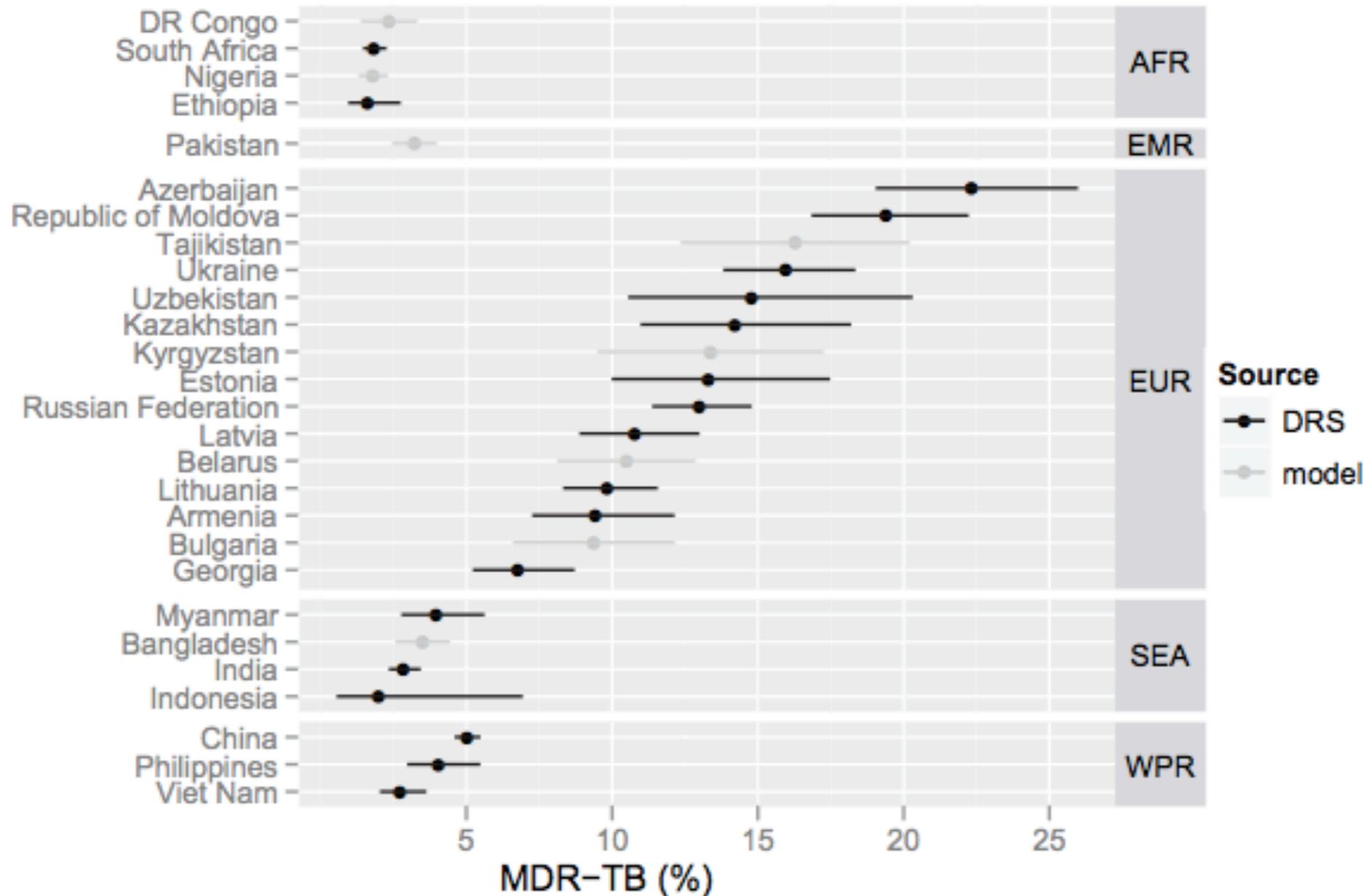
Under the proposed settlement, the county would pay for claims as they come in, not cut one big check that would be divided among the eligible people. That means the costs could be spread over a few budgets.

"The driving force behind this settlement was public health," said Victoria Reinhardt, chairwoman of the Ramsey County Board.

Since the TB was discovered, the county has been taking steps to make sure the infection

The settlement would cover inmates who were at the workhouse between April 17, 2008, and June 9, 2008. After the infected inmates came forward, the county sought out people who were there during that time and offered to test them for the disease. About 170 former inmates tested negative, while **93 tested positive for latent infection** and **seven tested positive for active TB**. Nearly 200 more people need to be tested.

# Drug-resistant TB



**Fig. 7.** Levels of MDR-TB in 27 priority countries for MDR-TB control, expressed as a percentage of new TB cases with no history of previous antituberculosis treatment (or <4 weeks of previous treatment). Estimates were measured directly from DRS (*black dots*) or indirectly using statistical modeling (*light gray dots*).

# KwaZulu Natal

Gandhi et al. Lancet 368:1575, 2006

- 53 cases of extensively drug-resistant tuberculosis reported from a hospital in South Africa
- Represented 6% of all patients with culture-confirmed tuberculosis
- All 44 patients tested for HIV were positive
- 52 patients died
- The mean time to death was 16 days from the time of diagnosis
- 55% had no prior TB treatment
- 67% had a recent hospital admission

# Tuberculosis and HIV Co-infection

- Co-infected: 11 million
- In some countries the prevalence of HIV in newly diagnosed TB is 80%
- TB is the most common cause of death among HIV patients
- People living with HIV are 20X more likely to develop active TB
- 26% of all HIV-related deaths caused by TB
- Between 1990-2005, the incidence of TB increased by 7% per year in countries where the prevalence of HIV among adults is greater than 5%.

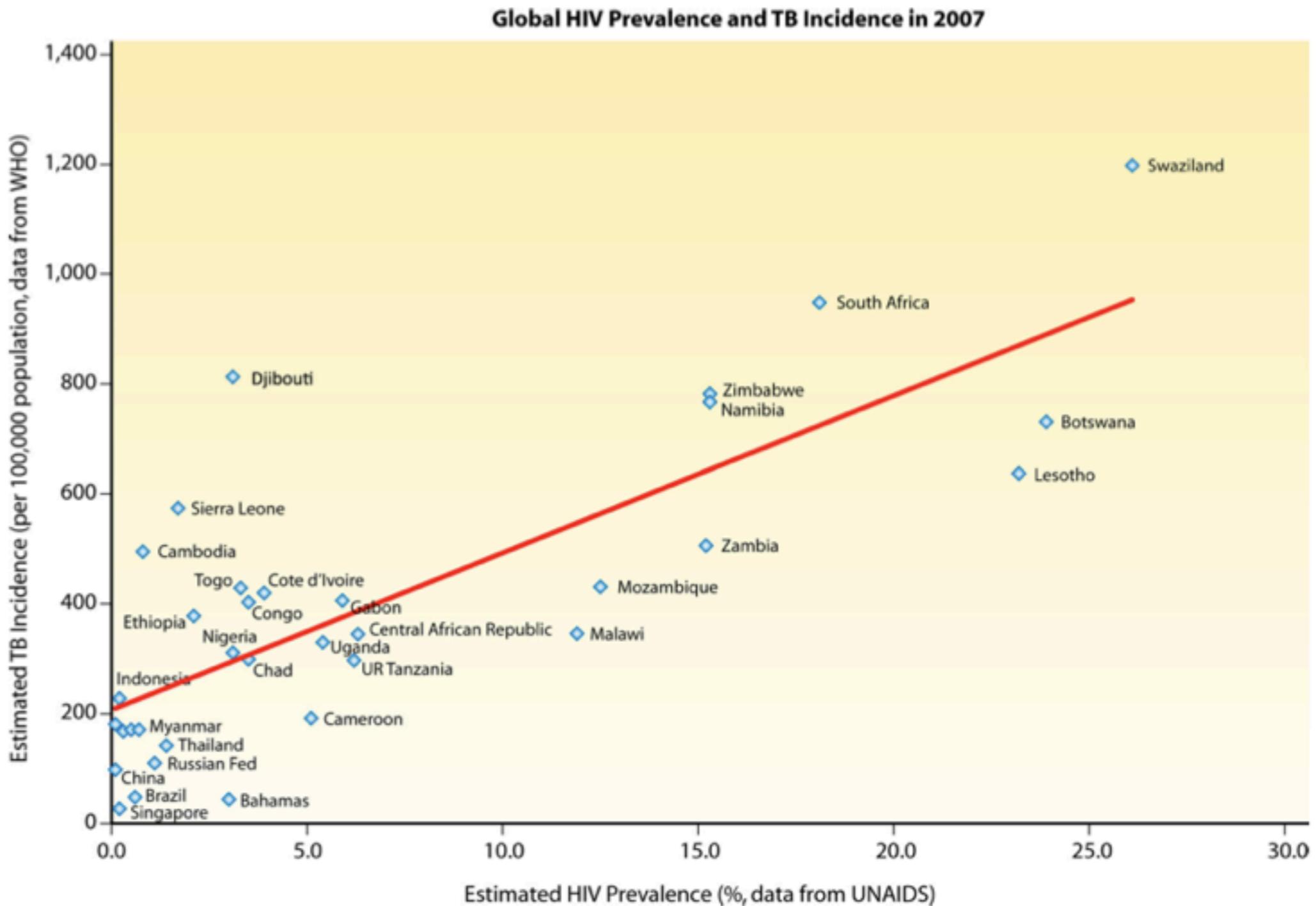
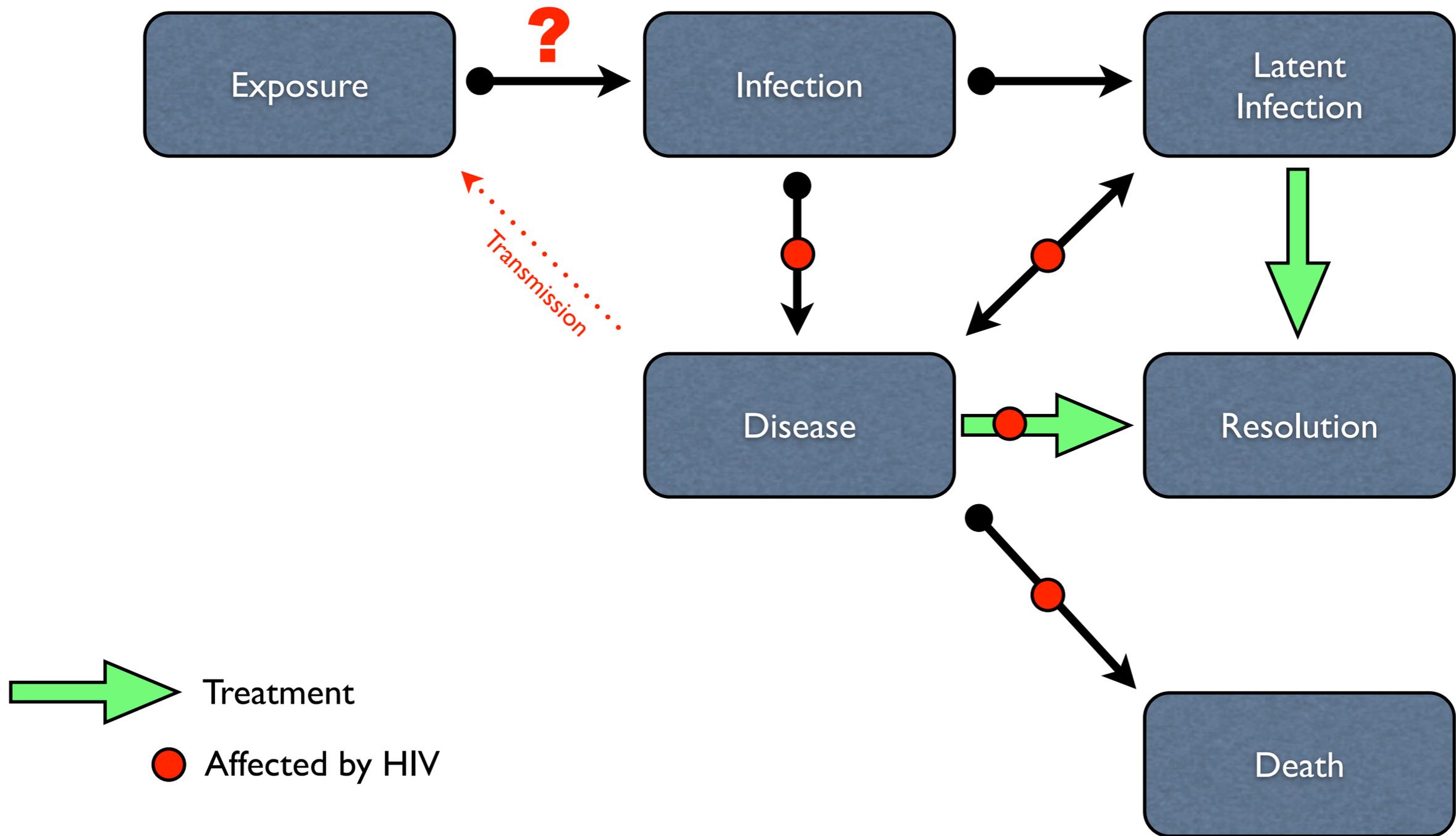


FIG. 1. Higher HIV prevalence rates are associated with higher TB incidence rates. We used data from 132 countries from the UNAIDS/WHO 2008 report on the global AIDS epidemic for HIV prevalence (250) and from the WHO 2009 report on global tuberculosis control for TB incidence (263) and generated a scatter plot showing a positive linear correlation. The Pearson correlation coefficient ( $r$ ) was 0.799, with a (two-tailed)  $P$  value of  $<0.01$  using SPSS statistical software.

# Effect of HIV on TB



# Change in Clinical Presentation

- Lack of cavitation on chest radiograph
- More disease with smear-negative sputum
- Mediastinal adenopathy common
- CNS TB with increase in mass lesions
- Overall increased extrapulmonary disease

# Immune Reconstitution Inflammatory Syndrome (IRIS)

- Initial presentation or worsening of opportunistic infections associated with starting anti-retroviral therapy (ART)
- Can occur within days to months after starting ART
- Most episodes are mild, but IRIS can be life-threatening
- Patients with lowest CD4 counts at highest risk

# CASE

## Initial Presentation

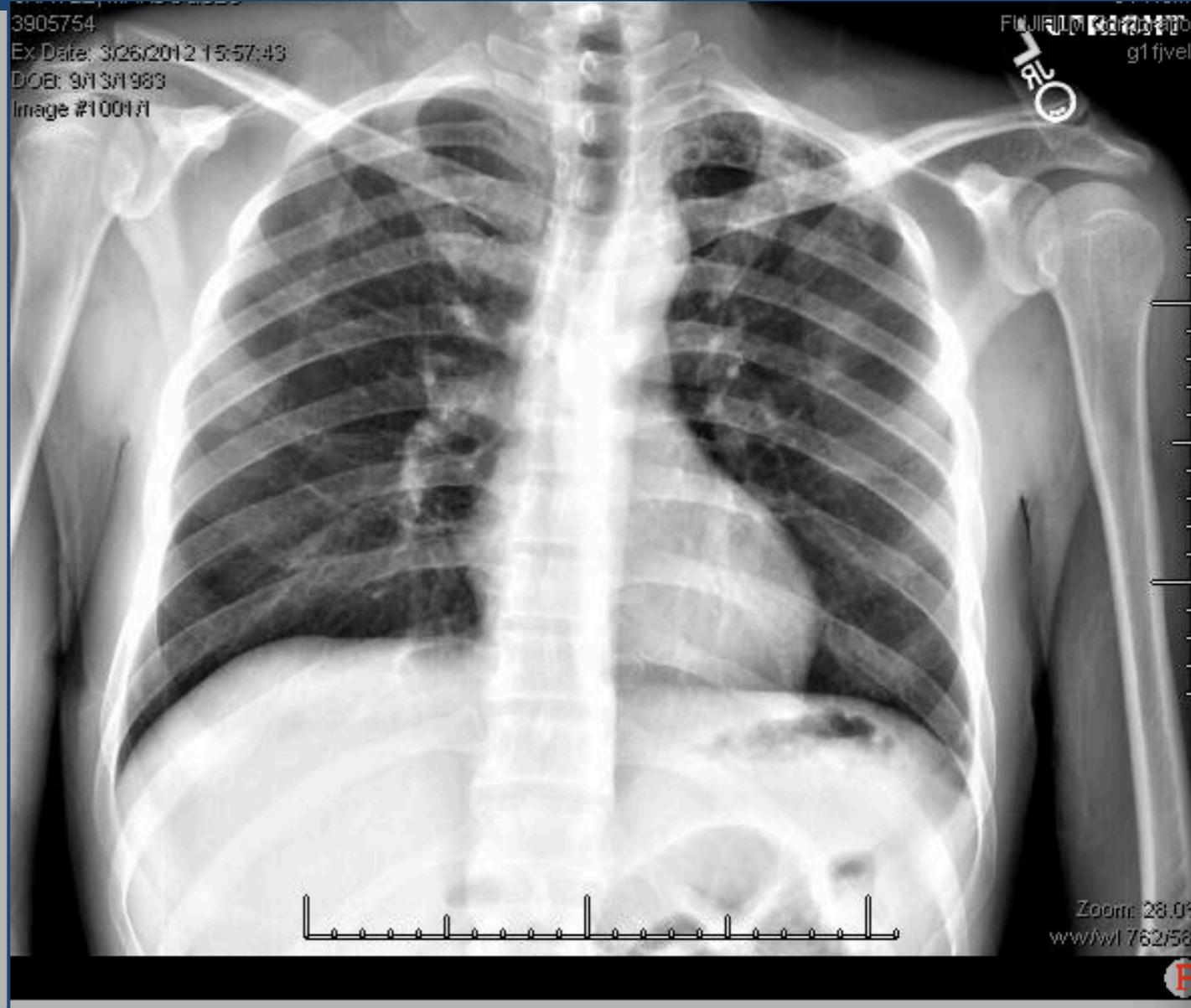
- 28 yo man admitted for anorexia, weight loss, neck mass, epigastric pain. Has intermittent dry cough
- Thrush, right cervical, supraclavicular, and axillary tender lymph nodes, right abdominal tenderness.
- Born in Central America, in the US for 2 years, in MN for 5 months, exposure to horses
- Mother has diabetes
- CXR- miliary nodules, LUL infiltrate
- AFB sputum- smear positive (1/3), RNA probe-positive, culture positive.
- AFB lymph node- culture positive
- TSPOT- positive
- HIV antibody- positive
- CD4-25, Viral load- 41,000
- CT- adenopathy of neck, abdomen



# CASE

## Clinical Course

- Started on 4-drug tuberculosis rx
- Discharged one week after admission. Was feeling better, regained appetite, decreased lymph node swelling
- HIV medication (ART), Atripla plus efavirenz started 2 weeks after TB meds
- 12 days after starting ART, had increasing LAD, headache, nausea and vomiting, readmitted to hospital. Diagnosed with IRIS, had head CT scan, started on prednisone, discharged from hospital
- 2 weeks later hospitalized for the 3rd time with severe abdominal pain, nausea/vomiting, had partial small bowel obstruction, CD4- 257, CXR showing LUL cavities
- Abdominal pain improving, diagnosed with H. pylori infection, continuing on TB and HIV therapy.



# New CDC Analysis Reveals Strong Link Between Poverty and HIV Infection

## *New Study in Low-Income Heterosexuals in America's Inner Cities Reveals High HIV Rates*

VIENNA – The Centers for Disease Control and Prevention today released a first-of-its-kind analysis showing that 2.1 percent of heterosexuals living in high-poverty urban areas in the United States are infected with HIV. This analysis suggests that many low-income cities across the United States now have generalized HIV epidemics as defined by the United Nations Joint Program on HIV/AIDS (UNAIDS).

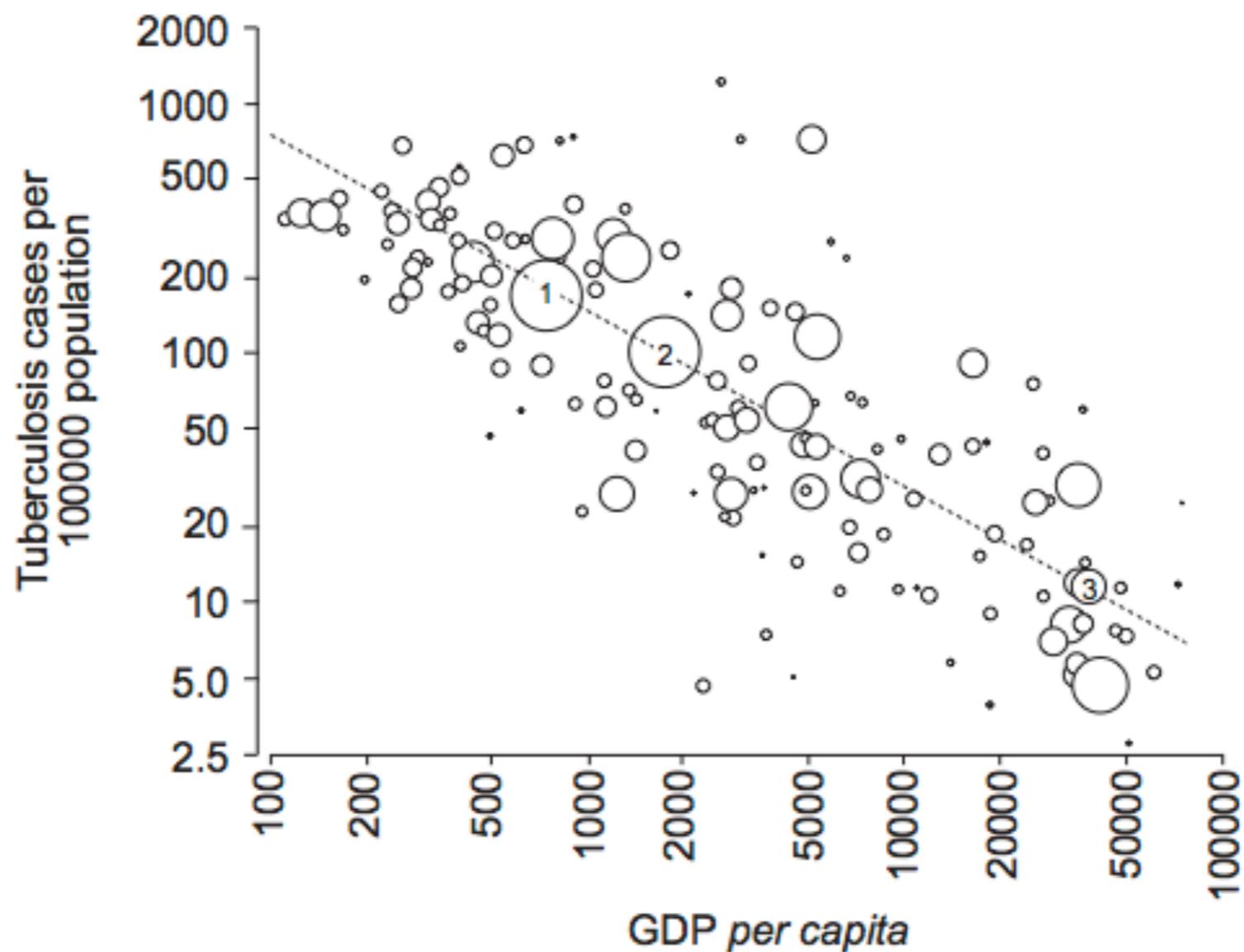
UNAIDS defines a generalized epidemic as one that is firmly established in the general population, with an overall HIV prevalence in the general population of more than 1 percent. While subpopulations with higher risk (such as men who have sex with men and injection drug users) may still contribute disproportionately to the spread of HIV in these areas, heterosexual transmission is also sufficient to sustain an epidemic independent of those groups.

The analysis also shows that poverty is the single most important demographic factor associated with HIV infection among inner-city heterosexuals. Contrary to severe racial disparities that characterize the overall U.S. epidemic, researchers found no differences in HIV prevalence by race/ethnicity in this population. The analysis will be presented at the XVIII International AIDS Conference in Vienna, Austria.

"This study reveals a powerful link between poverty and HIV risk, and a widespread HIV epidemic in America's inner cities," said Kevin Fenton, M.D., Ph.D., director of CDC's National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. "In this country, HIV clearly strikes the economically disadvantaged in a devastating way."

The analysis, led by Paul Denning, M.D., a medical epidemiologist in CDC's Division of HIV/AIDS Prevention, included more than 9,000 heterosexual adults (aged 18-50) in high-poverty areas of 23 cities who participated in the 2006-2007 heterosexual cycle of the CDC's National HIV Behavioral Surveillance System. This system monitors HIV risk behaviors, HIV testing patterns, and use of HIV prevention services among U.S. populations at risk.

High-poverty areas were defined according to the U.S. Census Bureau, and included areas in which at least 20 percent of residents have household incomes below the poverty line.



**FIGURE 1.** Relationship between *per capita* gross domestic product (GDP; World Bank data, 2005) and incidence of tuberculosis per 100,000 population. For graphical presentation, the third root of the population (millions) divided by 10 was used to determine the size of the symbols. This arbitrary choice provides a visual appreciation that large sized populations do not bear an excessive weight at the extremes of the axes, but are rather distributed across the entire scale. Both abscissa and ordinate were drawn logarithmically. 1; India; 2: China; 3: UK.

TB anywhere is TB  
everywhere

# Tuberculosis: Current Management

- Diagnosis

- TST
- Interferon gamma release assay
- AFB smear and culture
- Biopsy with histology

- Treatment

- Active disease
- Latent infection
- Drug susceptibility testing
- 1st and 2nd line medication
- Directly observed therapy

- Prevention

- Screening for latent infection
- Treatment of latent infection
- Contact investigation
- Genotyping of TB isolates
- Respiratory isolation

# Current TB Diagnosis

Tuberculin Skin Test

two to three days

Sputum AFB smear

one day

Sputum AFB culture

up to 6 weeks

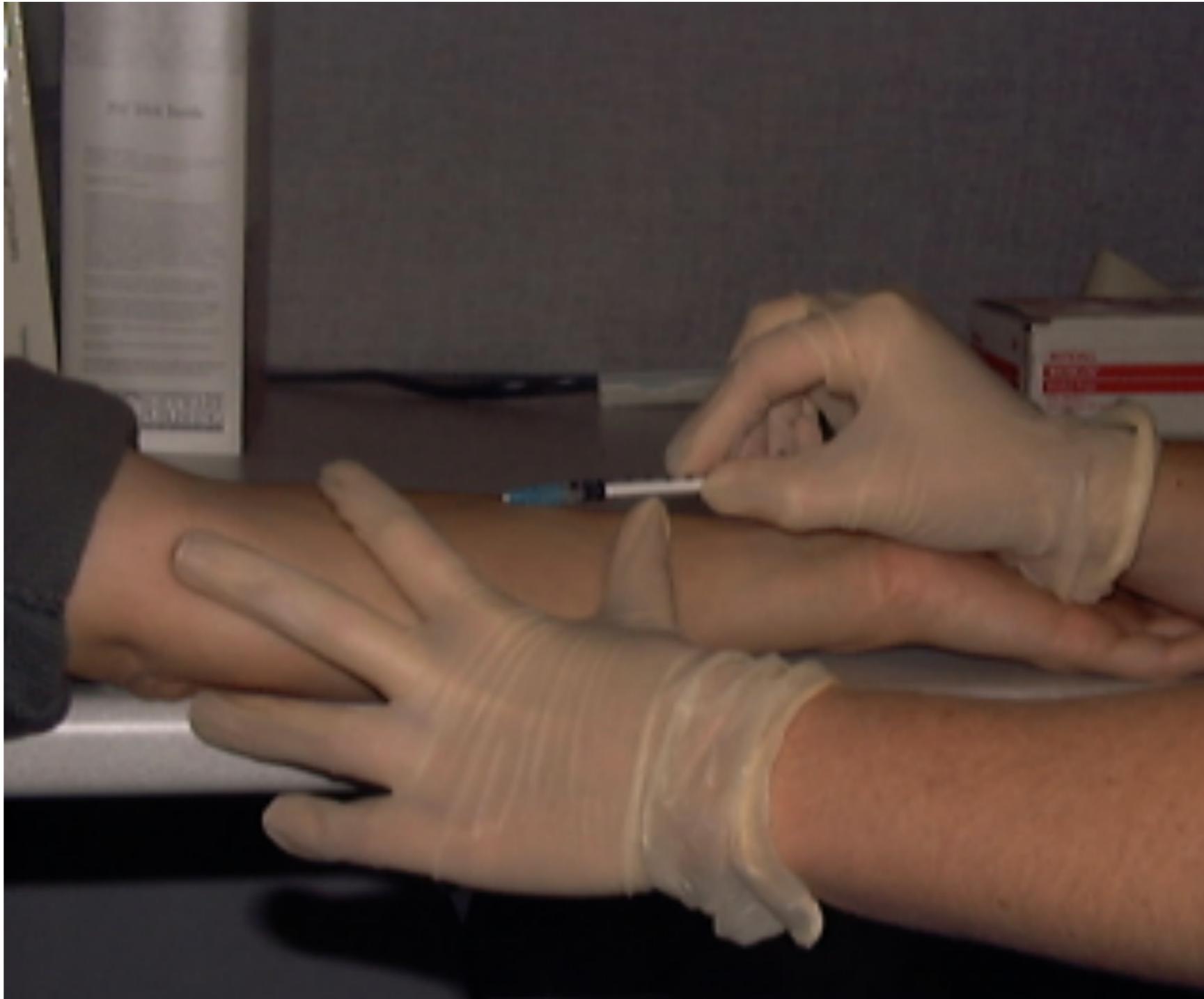
Drug Susceptibility Testing

up to 8 or more weeks

# Problems with current diagnostic tests

- Delay in making diagnosis
- Lack of sensitivity and specificity of TST and sputum smears
- Lack of availability of sputum cultures and drug susceptibility testing in many regions of the world

# 100 years and counting



**Tuberculin Skin Test**

# Tuberculin Skin Test

## False-positive

- Non-tuberculous mycobacteria
- BCG
- Improper reading

## False-negative

- Active tuberculosis
  - Cell-mediated immunosuppression by
    - disease
    - medication
    - extremes of age
  - Some chronic diseases (A)
  - Severe or febrile illness (B)
  - <1 month after
    - live virus vaccine (C)
    - some illnesses (D)
  - Improper placement or reading
- A. Chronic renal failure, cirrhosis, malnutrition, sarcoidosis
- B. Includes tuberculosis
- C. MMR, Polio, Yellow Fever
- D. Measles, mumps, rubella, varicella, mononucleosis, typhoid, brucellosis, influenza

# New TB Diagnostic Tests

Tuberculin Skin Test

**Interferon gamma release assay**

Sputum AFB smear

**Nucleic acid amplification test**

Sputum AFB culture

**Gene sequencing**

Drug Susceptibility Testing

**Molecular probe for drug susceptibility**

# Interferon gamma release assays

- Measures release of interferon gamma by lymphocytes to stimulation by specific MTB antigens- ESAT-6, CFP-10, *TB7.7(QFT only)*
- Test has positive and negative controls
- No cross-reactivity with BCG or *Mycobacterium avium-intracellulare*
- Single blood test
- Two approved tests- Quantiferon and T-Spot

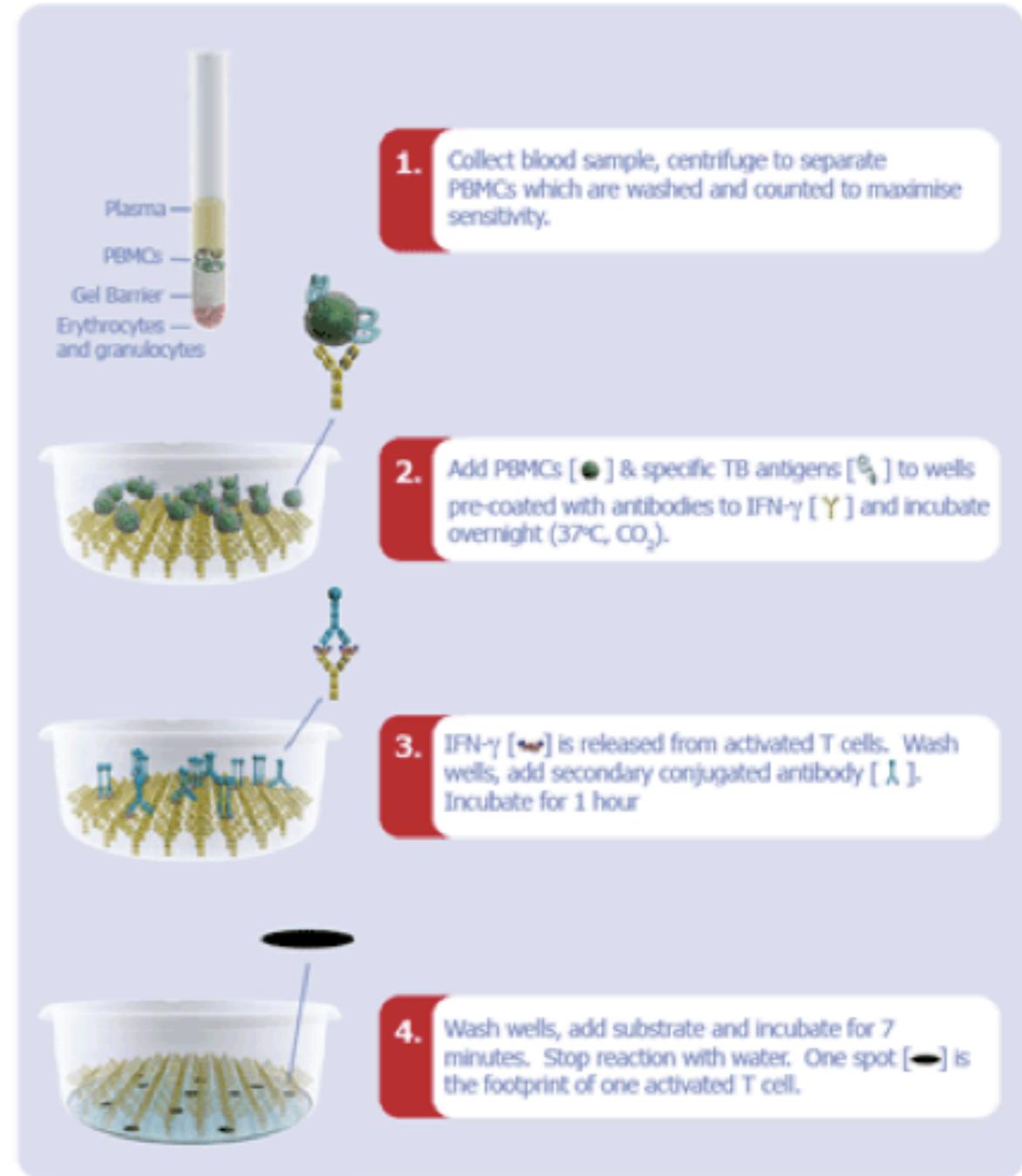
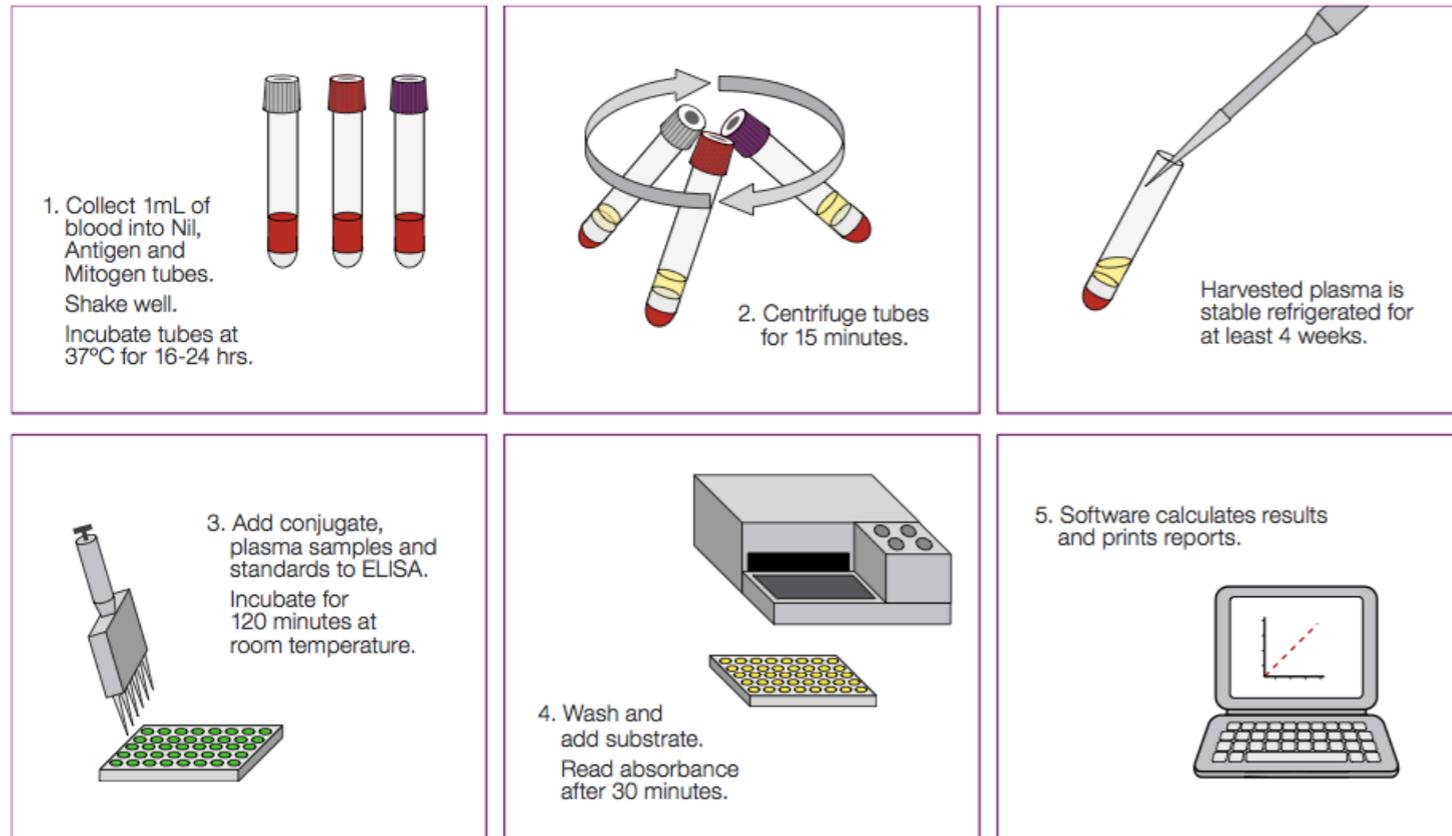
# Interferon gamma release assays

## T-SPOT

### Principles of the T-SPOT® Assay System

## Quantiferon

### 5 easy steps of QFT™ In-Tube



# Latent Tuberculosis

NO  
**GOLD STANDARD**  
FOR DIAGNOSIS

# Test Sensitivity

(%)

Active TB Disease

TST	QFT	T-Spot
70	81 84*	88 89*

\*in developed countries

Diel et al. Chest 137:952, 2010

Meta-analysis of commercial IGRAs

Sensitivity based on detection of active disease

# Test Specificity

(%)

TST	QFT	T-Spot
-	99	86

Diel et al. Chest 137:952, 2010

# Test Specificity

(%)

	TST	QFT	T-Spot
Korea 2006	79	92	85
Germany 2007	58	100	98
Japan 2008	51	93 (81)	-

**Diel et al. Chest 137:952, 2010**

From primary references in article

# Indeterminate Tests

(%)

	QFT	T-Spot
Overall	2.1	3.8
Immunosuppressed	4.4	6.1

Diel et al. Chest 137:952, 2010

# **CDC Guidelines for IGRA Use 2010**

QFT-G may be used in place of (but not in addition to) a TST in all situations in which CDC recommends TST as an aid in diagnosing MTB infections...

# CDC Guidelines for IGRA Use (2005)

## Cautions and Limitations

- Certain limitations of QFT-G are similar to those of the TST, but these limitations have not been studied extensively for QFT-G.
- Sensitivity for particular groups of TB patients (e.g., **young children and immunocompromised patients**) has not been determined.
- QFT -G sensitivity for LTBI might be less than that of the TST, although the lack of a confirmatory test makes this difficult to assess.
- QFT-G, as with the TST, cannot differentiate infection associated with TB disease from LTBI.
- As with a negative TST result, negative QFT-G results should not be used alone to exclude *M. tuberculosis* infection in persons with symptoms or signs suggestive of TB disease.
- The performance of QFT-G, in particular its sensitivity and its rate of indeterminate results, has not been determined in persons who, because of impaired immune function, are at increased risk for *M. tuberculosis* infection progressing to TB disease.

# Impaired Immune Function Likely to affect TST and IGRA

- HIV/AIDS
- Current treatment with immunosuppressive drugs including high-dose corticosteroids, TNF-alpha antagonists, drugs used for managing organ transplantation, malignancies, rheumatologic disorders
- Selected hematologic disorders such as myeloproliferative disorders, leukemias, and lymphomas
- Carcinoma of the head, neck, or lung
- Diabetes
- Silicosis
- Chronic renal failure

# Possible Uses for IGRA

- Routine testing
- Evaluation of infections in person with history of BCG
- Increasing sensitivity for detection of infection
- Single blood draw is preferable

# AFB Smear

- False-positive result from nontuberculous mycobacteria
- False negative in up to 50% of culture-positive cases
- Only test available for diagnosing TB in many parts of the world

<http://www.google.com/imgres?imgurl=http://www.cosmosbiomedical...HWDQ&esq=4&page=4&ndsp=14&ved=1t:429,r:1,s:43>

# Nucleic acid amplification

- identifies unique sequence for MTB from ribosomal RNA/DNA by sequencing or probe
- M. tuberculosis can be identified in one day
- More sensitive on smear-positive specimens
- Also available for avium-intracellulare, kansasii, gordonae

# Traditional Drug Susceptibility Testing

- Liquid and solid media
- 1% proportional growth is considered resistance
- Requires growth of bacteria
- Significant technical expertise, infrastructure required

# Microscopic Observation Drug Susceptibility



**Figure 8. Microscopic observation drug-susceptibility assay.** Characteristic tangling appearance of cords of *Mycobacterium tuberculosis* as visualized at  $\times 20$  magnification under an inverted light microscope. Image courtesy of David AJ Moore and Luz Caviedes and reproduced with permission.

- Sputum sample is directly inoculated into liquid medium
- Growth is recognized by characteristic cord formation
- Can inoculate into medium with antibiotic to test for drug resistance.
- Excellent sensitivity and specificity

# Molecular Detection of MTB

- Extract MTB DNA/RNA from clinical specimens or from culture
- Increase amount of DNA/RNA by nucleic acid amplification
- Identify MTB by:
  - Sequencing DNA
  - Hybridization to specific probes

# Genetic mutations account for drug resistance

- Rifampin- 95% (*rpoB*)
- Isoniazid- 80% (*katG* and *inhA*)
- Pyrazinamide- 70% (*pncA*)
- Ethambutol- 70% (*embB*)
- Streptomycin- 70% (16rRNA and *rpsL*)

# Rifampin resistance

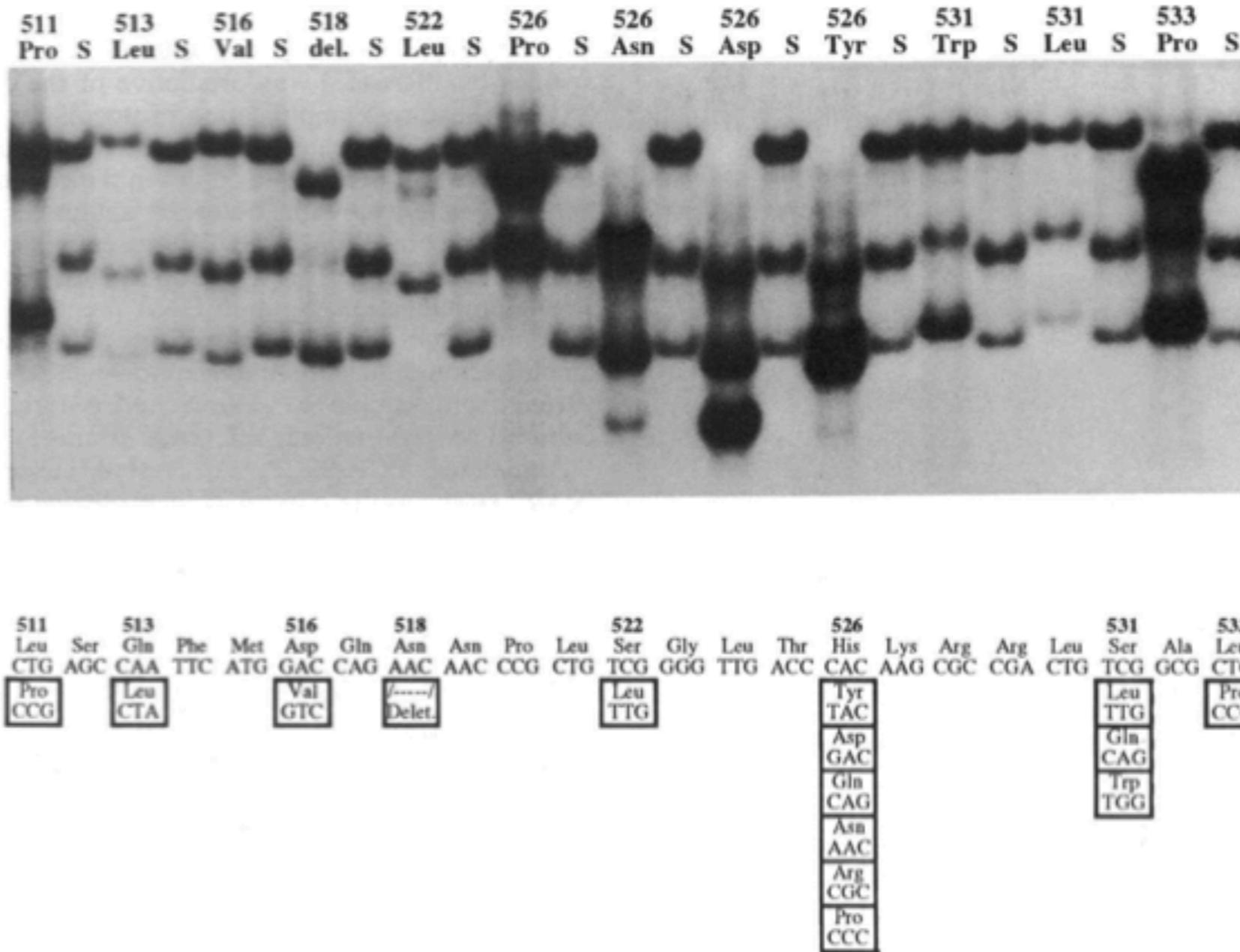
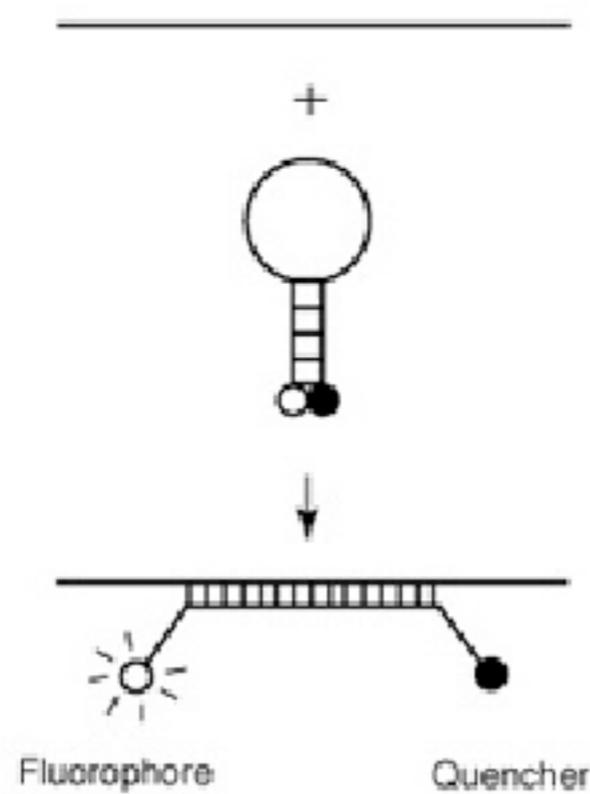
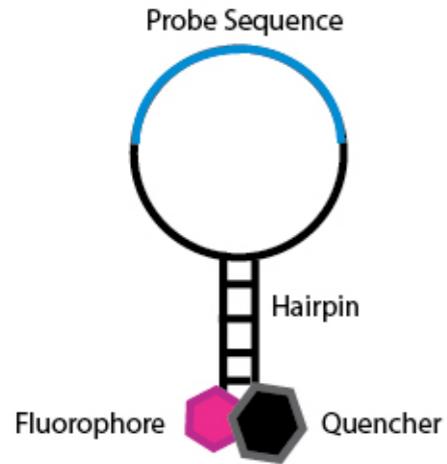


FIG. 1. PCR-SSCP patterns (upper panel) of previously reported *rpoB* mutations (boxed sequences in lower panel) leading to rifampin resistance in *M. tuberculosis* (12). Two recently encountered mutations, Tyr-516 (a pattern like Val-516) and Tyr-531 (a new pattern) are not shown. Rifampin-susceptible strains (S) were run as references between each resistant isolate. The finding of a three-band pattern after manual SSCP may reflect the presence of two possible conformations for one of the DNA strands or a reannealing band. The numbers correspond to the *E. coli* RNA polymerase amino acid positions (6).

# Molecular Beacon



Target

amplified DNA from specimen

Molecular Beacon

Probe for wild-type sequence

Hybrid

No mutation leads to fluorescence

# Line Probe Assay

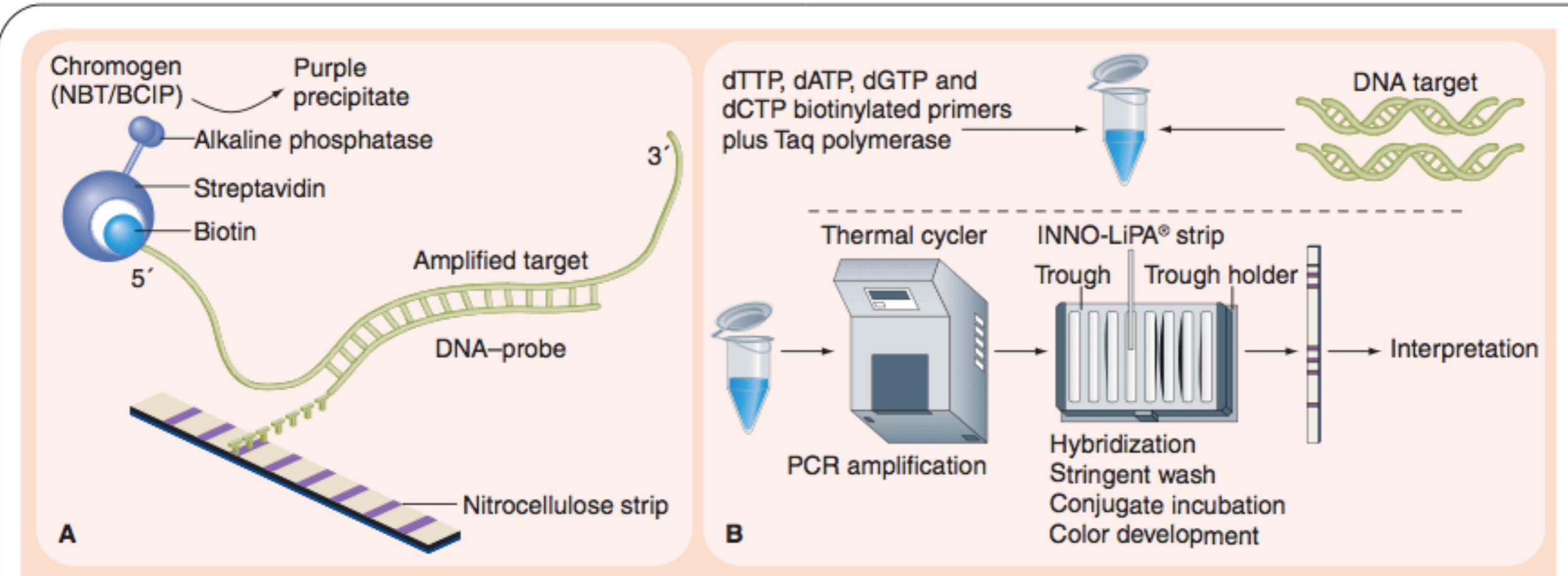


Figure 4. Line-probe assays for detection of drug resistance. (A) Principle of reverse hybridization. (B) INNO-LiPA® assay. The INNO-LiPA test contains ten oligonucleotide probes (one specific for the *Mycobacterium tuberculosis* complex, five overlapping wild-type S probes, and four R probes for detecting specific mutations) that are immobilized on nitrocellulose strips. LiPA is performed by extracting DNA and amplifying the rifampicin resistance-determining region of the *rpoB* gene using PCR. The PCR products are then hybridized with the immobilized probes, and results are determined by colorimetric development. Image adapted from Innogenetics NV (Gent, Belgium) © 2006 Innogenetics Group.



## Media centre

### WHO endorses new rapid tuberculosis test

A major milestone for global TB diagnosis and care

News release

8 DECEMBER 2010 | LONDON | GENEVA - Today, WHO endorsed a new and novel rapid test for tuberculosis (TB), especially relevant in countries most affected by the disease. The test could revolutionize TB care and control by providing an accurate diagnosis for many patients in about 100 minutes, compared to current tests that can take up to three months to have results.

#### A major milestone

"This new test represents a major milestone for global TB diagnosis and care. It also represents new hope for the millions of people who are at the highest risk of TB and drug-resistant disease." said Dr Mario Raviglione, Director of WHO's Stop TB Department. "We have the scientific evidence, we have defined the policy, and now we aim to support implementation for impact in countries."

WHO's endorsement of the rapid test, which is a fully automated NAAT (nucleic acid amplification test) follows 18 months of rigorous assessment of its field effectiveness in the early diagnosis of TB, as well as multidrug-resistant TB (MDR-TB) and TB complicated by HIV infection, which are more difficult to diagnose.

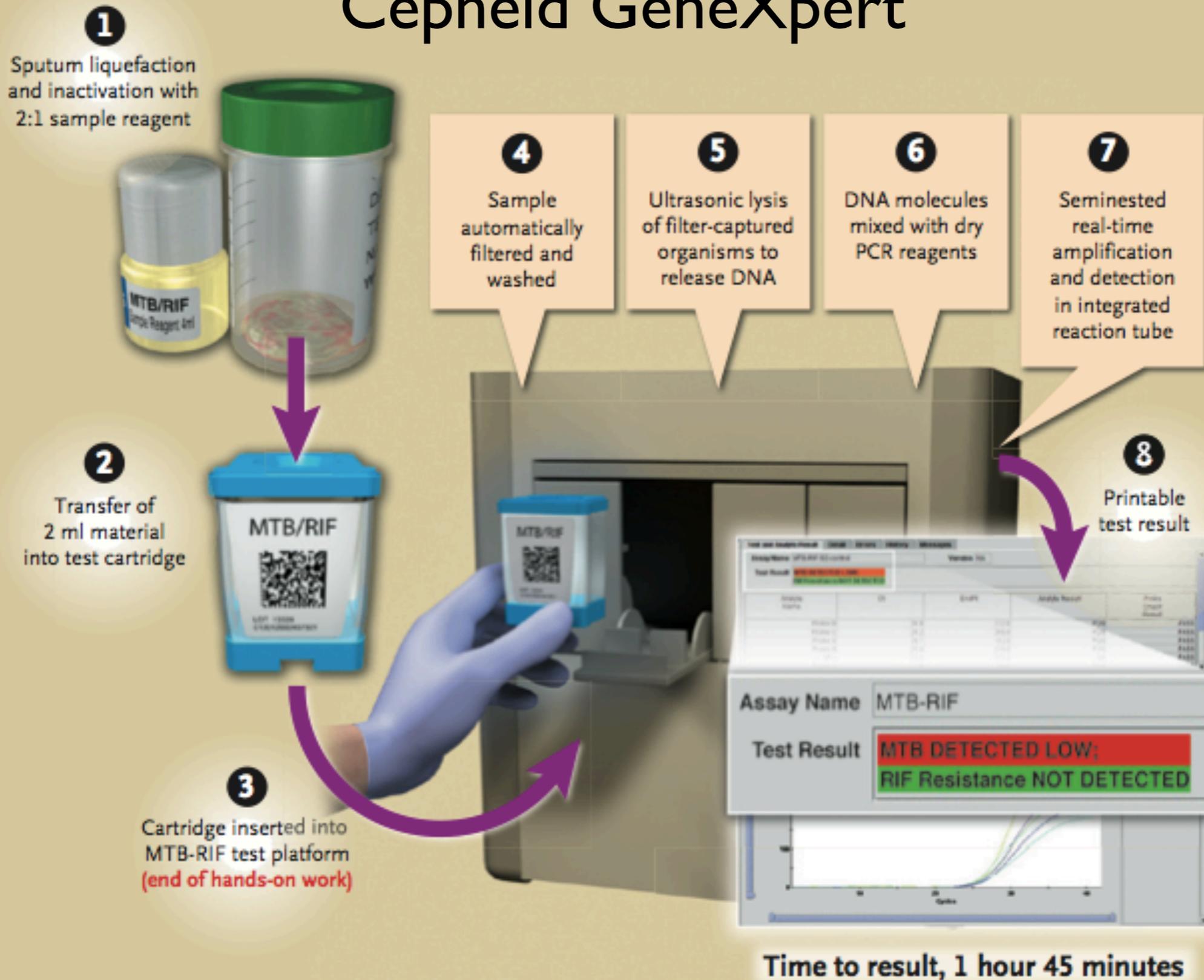
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#### Related links

[New rapid test for tuberculosis](#)

[More on tuberculosis](#)

# Cepheid GeneXpert



Boehme et al. NEJM 363:1005, 2010

**Figure 2. Assay Procedure for the MTB/RIF Test.**

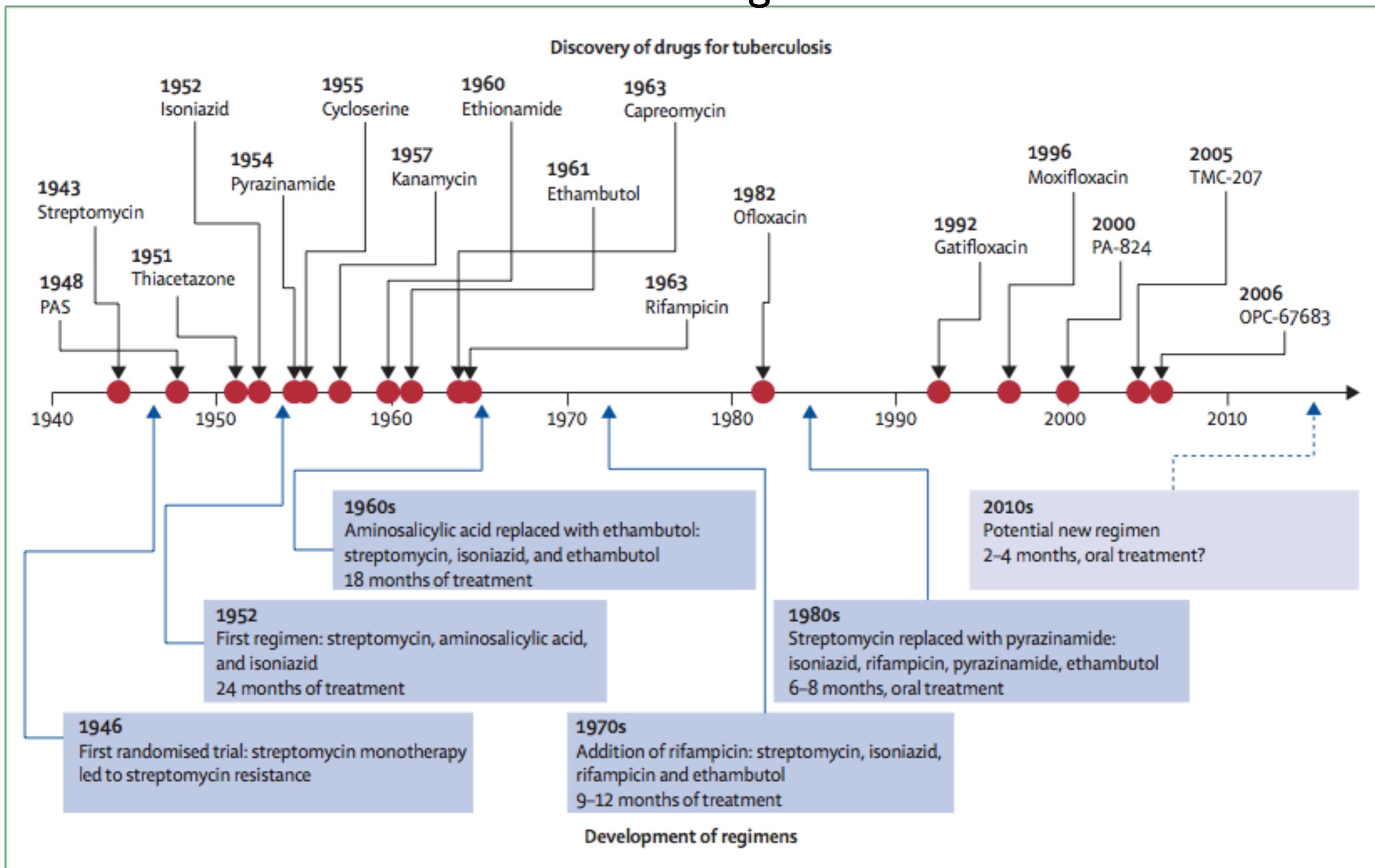
Two volumes of sample treatment reagent are added to each volume of sputum. The mixture is shaken, incubated at room temperature for 15 minutes, and shaken again. Next, a sample of 2 to 3 ml is transferred to the test cartridge, which is then loaded into the instrument. All subsequent steps occur automatically. The user is provided with a printable test result, such as "MTB detected; RIF resistance not detected." PCR denotes polymerase chain reaction.

# Limitations of molecular diagnosis

- Insufficient DNA or contamination
- Mixed susceptible and resistant populations
- Neutral polymorphisms
- Silent mutations (falsely interpreted as resistant)
- Not all mutations associated with resistance are known

# Treatment of Tuberculosis

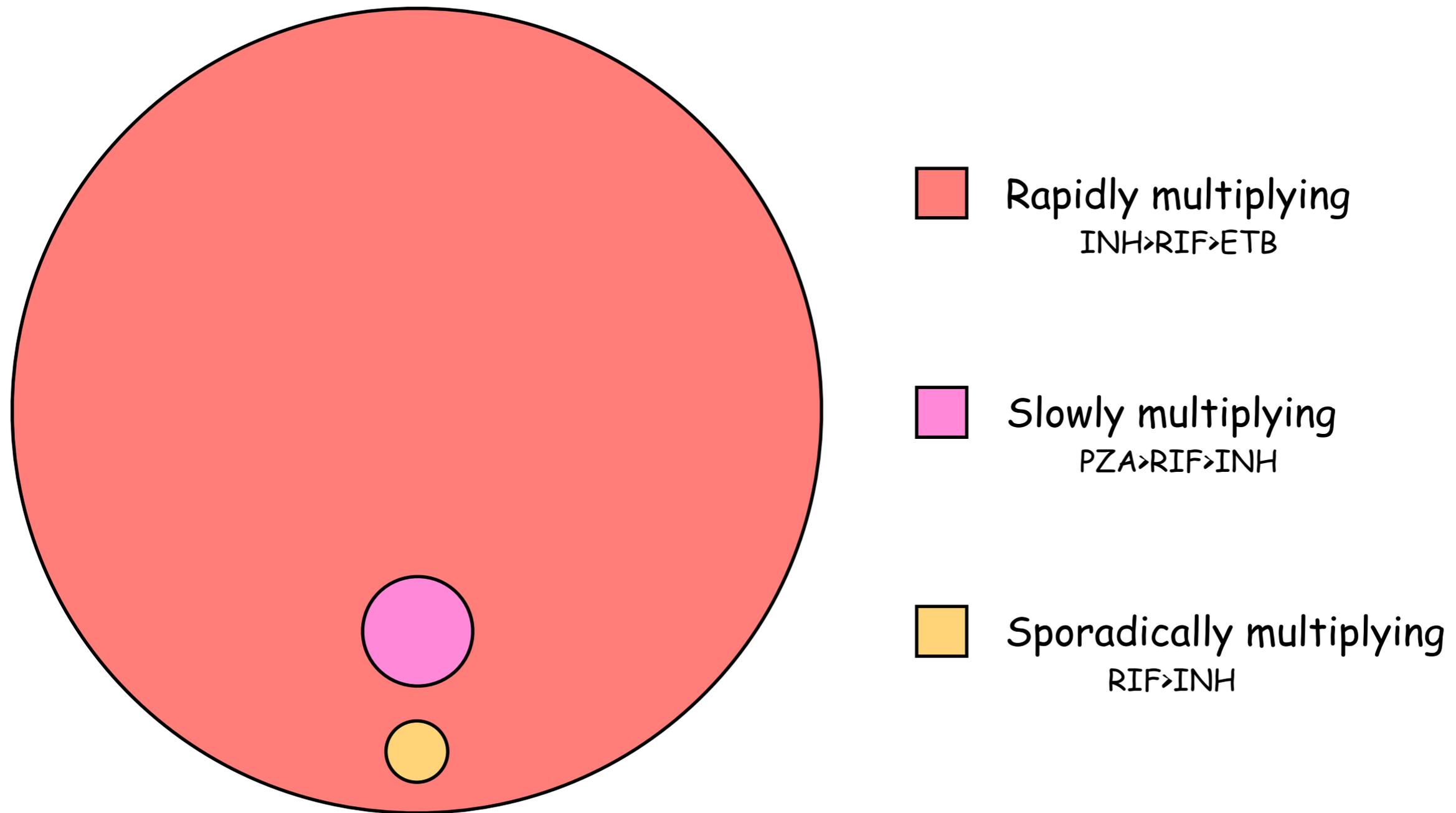
# TB Drugs



**Figure 2: History of drug discovery and development of treatment regimens for tuberculosis**

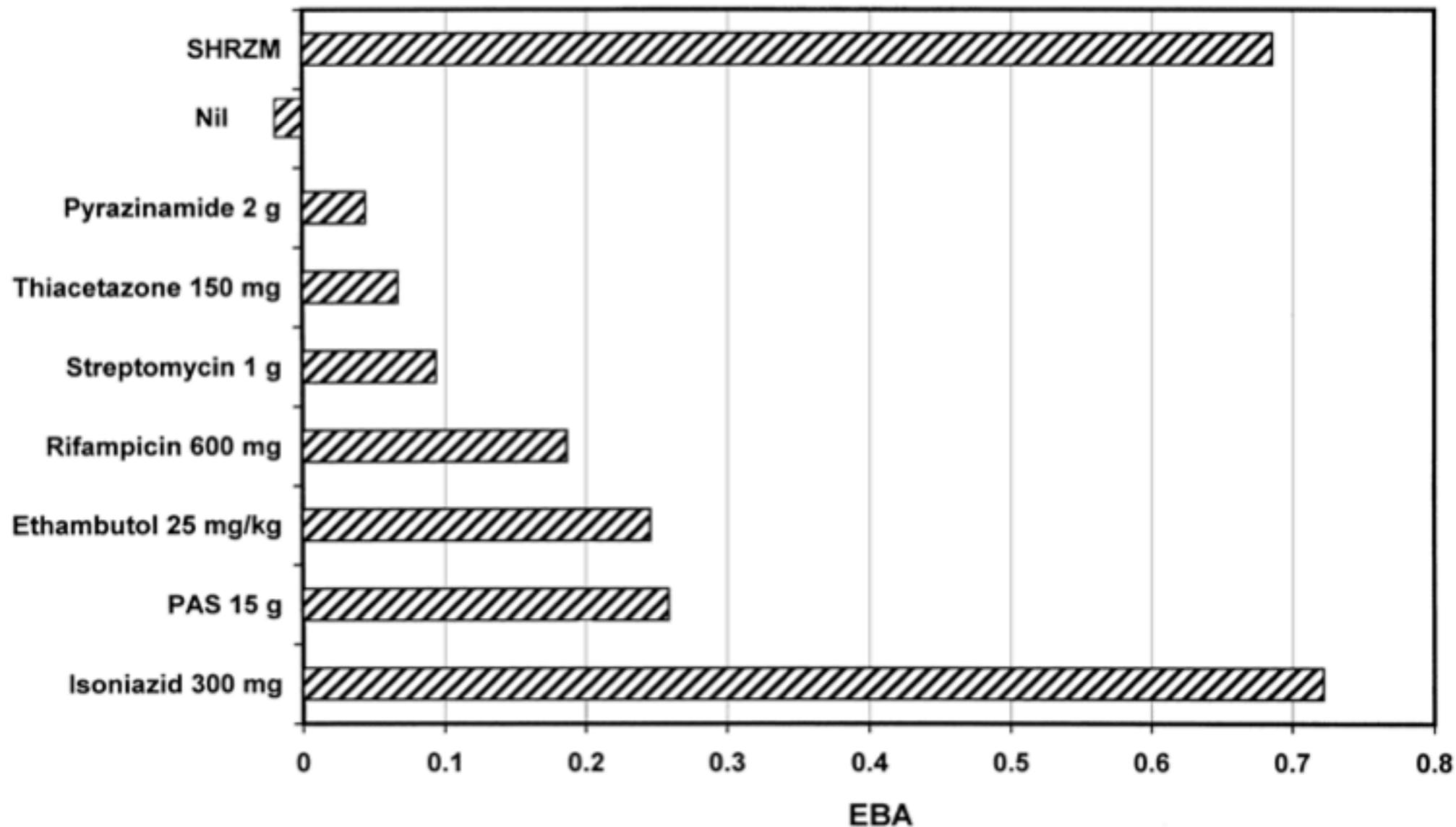
Compounds that are in the early-stage of development, but for which there are no human proof-of-concept data, are not shown. Arrow with dashed line represents future regimen. Red dots represent when the drugs were first reported.

# Treatment of Tuberculosis



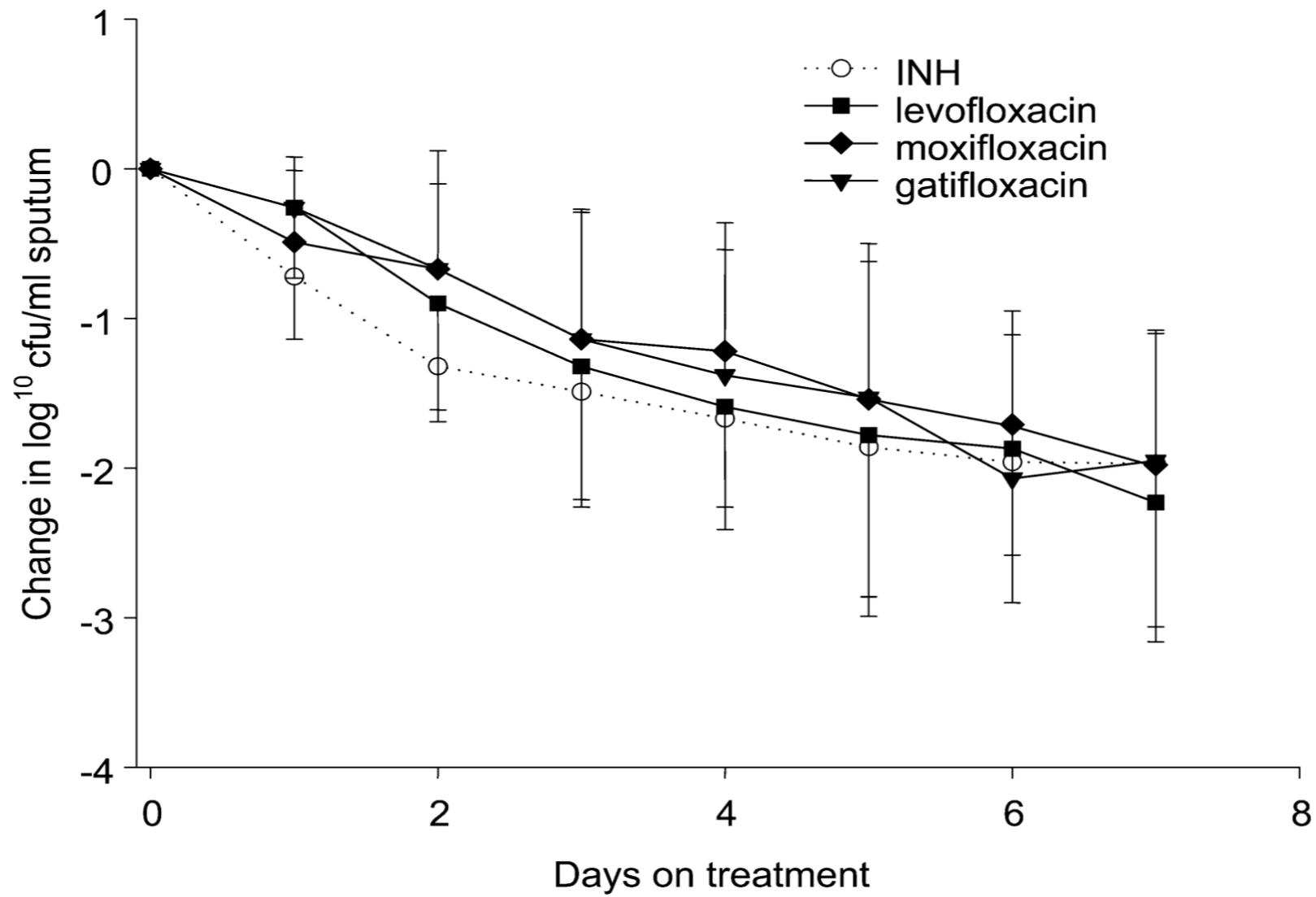
**Populations of MTB**

# Early Bactericidal activity



**Figure 1** The early bactericidal activity (EBA) of various antituberculosis drugs given alone for the first 2 days of treatment. Data from Jindani et al.<sup>12</sup> PAS = *p*-amino salicylic acid.

# EBA of quinolones



# Quinolones

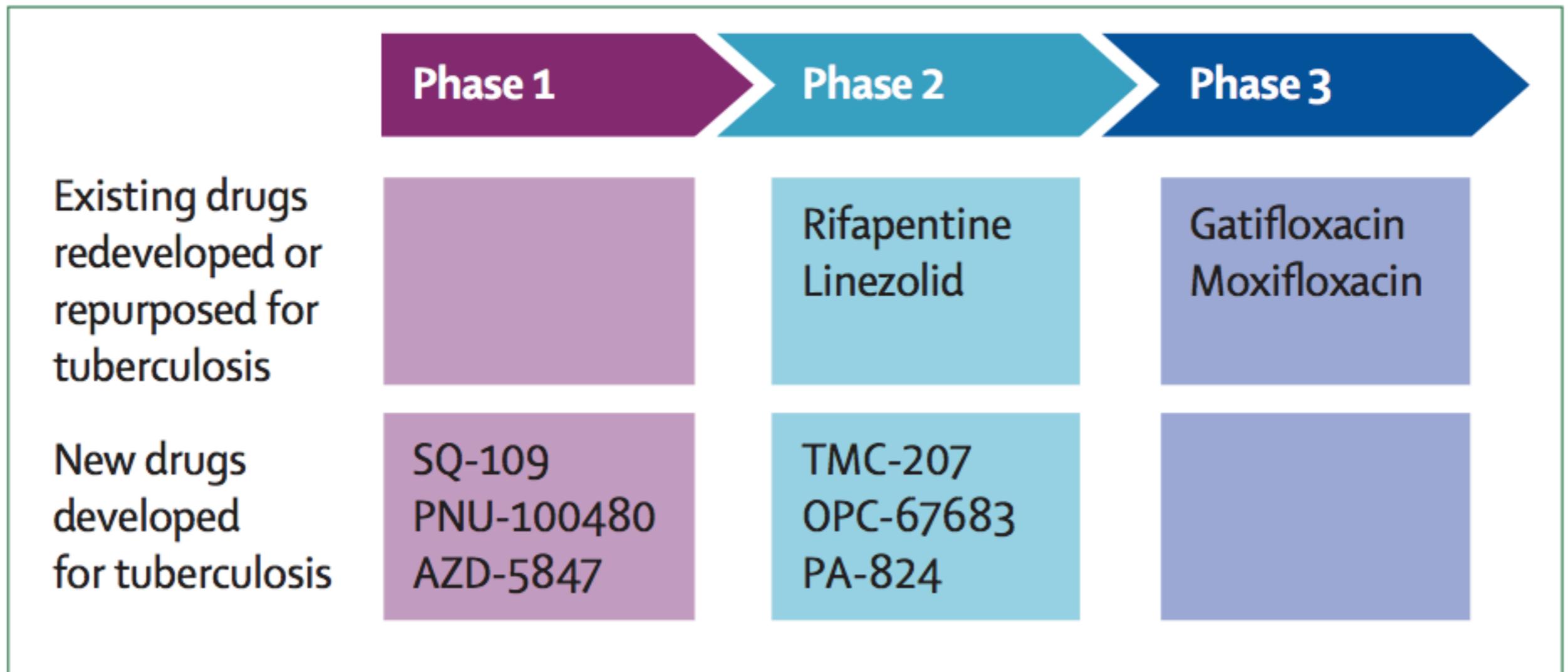
- Key drug in the treatment of MDR-TB
- Substitution for first-line drugs when necessary
- Trial under way to see if use of quinolones substituting for other standard drugs can shorten total duration of therapy

# Rifamycins

- Rifapentine
  - Trial to use in short course therapy for latent tuberculosis
  - Trial to combine with moxifloxacin to shorten treatment duration to 4 months
- Rifampin- studies to use higher dosing in treatment
- Rifabutin- used as substitute for rifampin in HIV patient, access in many regions is a problem

# Linezolid

- Has been used successfully in XDR-TB
- Side effects are a limiting factor



**Figure 1: Compounds in clinical development for the treatment of active tuberculosis**

# Status of New Drugs

- TMC-207: bactericidal, effective in clinical trial against MDR-TB
- OPC-67683: impressive in vitro activity, clinical trial in MDR-TB underway
- PA-824: excellent in vitro activity, bactericidal, clinical trials underway
- PNU-100480: an oxazolidinone, human safety/ mycobacterial activity trial completed

# Summary

- Tuberculosis remains a significant medical problem in the world
- The combination of lack of advancement of diagnostic/treatment options and the lack of resources in many regions in the world threaten the progress we have made against tuberculosis
- New technological breakthroughs and new drugs are tools that may lead to significant progress in tuberculosis control
- There is a possibility of eradicating tuberculosis