Σύγχρονη διαγνωστική προσέγγιση-αντιμετώπιση φυματίωσης

Σαμπατάκου Ελένη
HISTORY of Tuberculosis

- Spinal Tuberculosis in Egyptian Mummies History dates to 1550 – 1080 BC
  Identified by PCR
- 460 BC
  Hippocrates, Greece
  First clinical description: Phthisis / Consumption
- 1650-1900 AD
  White plague of Europe, causing one in five deaths
Diagnostic discoveries

• 24th March 1882 (Robert Koch) TB Day
  – Discovery of staining technique that identified Tuberculosis bacillus
  – Definite diagnosis made possible and thus treatment could begin
• 1890 (Robert Koch)
  – Tuberculin discovered
  – Diagnostic use when injected into skin
• 1895 (Roentgen)
  – Discovery of X-rays
  – Early diagnosis of pulmonary disease
Pharmacological discoveries

• 1908-1920 (Calmette and Guerin)
  – Vaccine (BCG)
    • Attenuated strain Mycobacterium Bovis
• 1943
  – Streptomycin developed
• 20th November 1944
  – Critically ill TB patient injected dramatically recovered
Why is it so difficult?

TB prevalence
- Risk factors:
  - HIV
  - Diabetes
  - Poverty
  - Malnutrition
  - Smoking
  - Alcohol
  - Gender
  - Genetics?
- Immunology
  - Latency, 1/3 of world population is infected

TB mortality
- Diagnosis
  - Clinical diagnosis difficult
  - Smear 50% sensitivity
  - Chest x-ray non-specific
  - Lack of point-of-care test
- Treatment
  - Availability
  - Adherence
    - Pill burden
    - Duration
HIV/AIDS and TB

- HIV weakens the immune system, so a Tuberculosis infection is more likely.
- Because of this, everyone who has HIV is tested for Tuberculosis.
- Tuberculosis is the leading cause of death in HIV patients around the world.
- In 2009, of the 1.7 million people who died of tuberculosis, 400,000 (24%) of them were living with HIV.
Nobody is absolutely Immune to Tuberculosis
Reported TB Cases
United States, 1982–2010*

*Updated as of July 21, 2011
Primary MDR TB
United States, 1993 – 2010*

*Updated as of July 21, 2011
Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Mode of Treatment Administration in Persons Reported with TB United States, 1993 – 2008*

*Updated as of July 21, 2011. Data available through 2008 only.

**Percentage of total cases in persons alive at diagnosis, with an initial regimen of one or more drugs prescribed, and excluding cases with unknown mode of treatment administration.

Directly observed therapy (DOT); Self-administered therapy (SA)
Completion of TB Therapy
United States, 1993 – 2008*

* Updated as of July 21, 2011. Data available through 2008 only.
Note: Includes persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die during therapy. Excludes persons with initial isolate rifampin resistant, or patient with meningeal disease, or pediatric patient (aged ≤15) with miliary disease or positive blood culture.
TB Rates in Countries of Birth

2010

Per 100,000

Source: World Health Organization
Κατανομή συχνότητας ανά εθνικότητα, Ελλάδα 2004-2010
Ηλικιακή κατανομή δηλωθέντων κρουσμάτων ανά εθνικότητα, Ελλάδα, 2004-2010
22 Countries Account for 80% of Global TB Cases

Estimated number of new TB cases (all forms)

- No estimate
- 0–999
- 1000–9999
- 10 000–99 999
- 100 000–999 999
- 1 000 000 or more
HIV-TB COINFECTION

RESOURCE-RICH

RESOURCES-RICH

ACCESS TO
HEALTH SERVICES

SUBSAHARAN AFRICA

HIV-TB COINFECTION

COMMON

RESOURCE-POOR

USUALLY
GOOD

USUALLY
POOR

Highest:
- TB incidence rates
- HIV prevalence rates
- children in SSA have greatest burden of HIV-TB co-infection
What is multidrug-resistant tuberculosis (MDR TB, XDR TB)?

- Multidrug resistance (MDR) TB
- $R \geq$ isoniazid and rifampicin

- Extensively drug resistant (XDR) TB
  MDR plus a fluoroquinolone and one second-line injectable drug (amikacin, kanamycin, capreomycin)
• Nine million people suffer from tuberculosis
• Two million people die each year.
• Tuberculosis accounts for one-third of Aids deaths worldwide every year.
• Globally, there have been just 347 identified cases of XDR-TB, mainly in the former USSR and in Asia
Killer TB Hits Gauteng

Woman who left hospital could be spreading disease to unsuspecting people

By Jillian Green

A young Joburg woman carrying a deadly incurable strain of TB is walking the streets and possibly infecting scores of unsuspecting people.

The woman, whose identity has not been revealed, was diagnosed with the killer strain of extensively drug-resistant TB, XDRTB, last Friday after laboratory tests at the Siyanda Tropical Diseases Hospital in Edenvale.

“Take your drugs and go and look for her. She is a danger to society,” the director of HIV and TB at the Gauteng Department of Health, Dr Dambudzo Moto, told The Star last night.

XDRTB is different from normal TB in that it is resistant to most—if not all—nine drugs available to treat the bacteria successfully.

And unlike normal TB, which can be cured, once people are infected with the virulent strain, they will die in likelihood succumbing to the infection and die.

Because of the high incidence of HIV in South Africa, the emergence of XDRTB has the potential to kill millions of South Africans.

The strain has claimed the lives of 52 out of 55 patients confirmed to have the disease in KwaZulu Natal.

The Joburg woman is the latest confirmed case of XDRTB in the country and the first in Gauteng, in the latest outbreak, according to Moto.

ON ALERT: A nurse wears a mask during The Star’s tour of Siyanda Tropical Diseases Hospital in Edenvale, east of Joburg, yesterday. A woman found to be resistant to seven of the nine drugs used to treat TB discharged herself from the hospital before her test results were known.

By Jo Khobzi

TB adviser for the Gauteng Department of Health, Dr Dirk Koegelenberg, said the province did not have a clearer policy in dealing with patients refusing treatment.

“It would be unconstitutional to remove the patient from the hospital,” he said.

But Dr Karin Weyer, research director for TB at the SA Medical Research Council, said calling for test cases to be done in the Constitutional Court, saying there was a need to balance the rights of patients.
% MDR TB in Previously Treated Cases

Lithuania 53.3%
Kazakhstan 56.4%
Russia (Ivanovo) 58.1%
Drug susceptible TB

MDR-TB 1990

Resistance to H&R –
Treatable with 2nd line drugs

XDR-TB 2006

Resistance to 2nd line drugs – Treatment options seriously restricted

Total DR ?

Resistance to all available drugs – No treatment options

*or limited resistance manageable with 4 drug regimen - DOTS

The Return to a Pre-antibiotic Era
Antibiotics usually used to treat TBC

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>FORMULATION</th>
<th>STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAZID</td>
<td><img src="image1" alt="Isoniazid" /></td>
<td><img src="image2" alt="Isoniazid structure" /></td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td><img src="image3" alt="Rifampin" /></td>
<td><img src="image4" alt="Rifampin structure" /></td>
</tr>
<tr>
<td>ETHAMBUTOL</td>
<td><img src="image5" alt="Ethambutol" /></td>
<td><img src="image6" alt="Ethambutol structure" /></td>
</tr>
<tr>
<td>PYRAZINAMIDE</td>
<td><img src="image7" alt="Pyrazinamide" /></td>
<td><img src="image8" alt="Pyrazinamide structure" /></td>
</tr>
</tbody>
</table>

Help Your Antibiotics Do Their Job

- Take as directed
- Finish the full prescription even if you are feeling better
- Help prevent antibiotic resistance
Genes Associated with INH and RIF Resistance

- **RIF** resistance
  - *rpoB* core region (>95%)

- **INH** resistance
  - *katG, inhA, ahpC, ndh* (85%)
  - *unknown* (10-15%)
# Table of drugs used for the treatment of Tuberculosis.

<table>
<thead>
<tr>
<th>First line drugs</th>
<th>Second line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential</td>
<td>Old</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>Streptomycin</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New rifamycins
Rifabutin
Rifapentine
<table>
<thead>
<tr>
<th>Second Line</th>
<th>Third Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aminoglycosides</td>
<td>• Augmentin</td>
</tr>
<tr>
<td>– (Streptomycin)</td>
<td></td>
</tr>
<tr>
<td>– Amikacin/Kanamycin</td>
<td>• Imipenem</td>
</tr>
<tr>
<td>• Capreomycin</td>
<td></td>
</tr>
<tr>
<td>• Fluoroquinolones</td>
<td>• Clarithromycin</td>
</tr>
<tr>
<td>• Cycloserine</td>
<td>• Linezolid</td>
</tr>
<tr>
<td>• Ethionamide</td>
<td>• Clofazimine</td>
</tr>
<tr>
<td>• PAS</td>
<td></td>
</tr>
</tbody>
</table>
**Building a Treatment Regimen for MDR-TB**

**Step 1**

Begin with any first-line agents to which the isolate is susceptible.

Add a fluoroquinolone and an injectable drug based on susceptibilities.

- **Use any available**
  - **First-line drugs**
    - Pyrazinamide
    - Ethambutol

- **PLUS**
  - **One of these**
    - Fluoroquinolones
      - Levofloxacin
      - Moxifloxacin

- **PLUS**
  - **One of these**
    - Injectable agents
      - Amikacin
      - Capreomycin
      - Streptomycin
      - Kanamycin
TREATMENT OF MDR/XDR TB

• **4 months** of intensive phase (5 drugs)
  – Kanamycins
  – Ethionamide
  – Pyrazinamide
  – Ofloxacin
  – Cycloserine or Ethambutol

• **18 months** of continuation phase (3 drugs)
  – Ethionamide
  – Ofloxacin
  – Cycloserine or Ethambutol
## Cross-resistance for Second-line Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cross Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>None</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>None</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Kanamycin*</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>All Fluoroquinolones</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>None</td>
</tr>
<tr>
<td>PAS</td>
<td>None</td>
</tr>
<tr>
<td>Linezolid</td>
<td>None</td>
</tr>
</tbody>
</table>

*50% of strains; may not be true cross-resistance*
Who is this man?
TB Patient Is Isolated After Taking Two Flights

By LAWRENCE K. ALTMAN
Published: May 30, 2007

Federal and international officials are tracking down passengers and crew members on two trans-Atlantic flights earlier this month who may have been exposed to a man infected with an exceptionally dangerous form of tuberculosis.
Tuberculosis and HIV Infection: Partners in Human Tragedy

John G. Bartlett
Johns Hopkins University School of Medicine, Baltimore, Maryland

The Journal of Infectious Diseases 2007;196:S124–5
Διαγνωστικές δυσχέρειες

ALTERNATIVE DIAGNOSIS
- Bacterial infections
- Fungal infection
- PCP
- NTM
- Lymphoma
- Kaposi’s sarcoma

Drug resistance
13/141 in Cape Town cohort of TB-IRIS suspects had MDR
or Rifampicin monoresistance

DRUG REACTION
especially if hepatic involvement
Evidence-based TB Diagnosis
Toolbox for Diagnosis of Latent TB

- History
- CXR
- TST
- IGRAs

No Gold Standard!
Diagnosis

- Sputum
- X-ray chest
- Sputum culture
X- Ray Findings
Symptoms

What are the symptoms of TB?

- Fever
- Fatigue
- Weakness
- Weight loss
- Night sweats

Symptoms of pulmonary TB include:

- Coughing
- Pleurisy (pain when taking deep breaths)
- Coughing up blood⁴.
Current diagnostic test for latent TB

- Diagnosis of latent TB relies on the tuberculin skin test.

- 101 years old
  - Developed 1907 by Charles Mantoux

- The oldest diagnostic test still in use.

The skin test enters its 6th decade of use. (Canada 1957)
Reading the Tuberculin Skin Test

• Read reaction 48-72 hours after injection

• Measure only induration

• Record reaction in millimeters
IGRA

„T-cell interferon-γ release assays“

Flow-Cytometry

ELISPOT Assay
T-SPOT.TB

ELISA
QuantiFERON

Cytokine-induction

PPD
ESAT-6/CFP-10/TB7.7
Negative controls
Positive controls, i.e. PHA/SEB

8h ≥1ml

8-10ml

24h

3ml
Antigens: IGRAs vs. PPD

- Purified protein = derivative (PPD)

- Quantiferon
  - QFT-TB
  - QFT-Gold
  - QFT-Gold In-tube (IT) ESAT-6, CFP-10, TB7.7

- T-spot ESAT-6, CFP-10

Antigens

Mtb PPD, MAC PPD
ESAT-6, CFP-10
ESAT-6, CFP-10, TB7.7
Species Specificity of ESAT-6 and CFP-10

### Tuberculosis complex

<table>
<thead>
<tr>
<th>Species</th>
<th>ESAT</th>
<th>CFP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M tuberculosis</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>M africanum</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>M bovis</strong></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### BCG substrain

- gothenburg: -
- moreau: -
- tice: -
- tokyo: -
- danish: -
- glaxo: -
- montreal: -
- pasteur: -

### Antigens specific to Mtb Complex
- **M tuberculosis**
- **M africanum**
- **M bovis**

Not found in any of the BCG substrains used in global vaccines.
A word about IGRA boosting

- No “boosting” as we use the term with PPD (ie. True infections have false negative test at first, then positive when done as two-step test)

- BUT: PPD done at least 7 days prior to IGRA may “boost” subsequent IGRA result (no boost at 3 days after PPD)
  - More often in IGRA+, clinical impact?

[Van Zyl Smit et al, Am J Respir Crit Care Med, April 2009]
How does immunosuppression influence the IGRA and TST?

Microscopy and Culturing still a top priority
Diagnosis of Pulmonary TB

Cough 3 weeks

If 1 positive, X-ray and evaluation

AFB X 3

If negative:
Broad-spectrum antibiotic 10-14 days

If symptoms persist, repeat AFB smears, X-ray

If consistent with TB

Anti-TB Treatment

If 2/3 positive:
Anti-TB Rx
Διάγνωση TB

- πτύελα x 3 για AFB και καλ/γεια
- Θετικά πτύελα 50-80% για AFB σε + καλ/γεια
- >6 εβδομάδες για καλ/γεια (Loewenstein-Jensen, Middlebrook 7H10, 7H11)
- 7-21 ημέρες σε υγρά υλικά
- Mantoux test
Drug Susceptibility Testing

• Culture-based methods
  – Proportion method
    • Solid media
    • Liquid media (bactec 460, 960)

• Molecular methods
The RD1-encoded antigen Rv3872 of Mycobacterium tuberculosis as a potential candidate for serodiagnosis of tuberculosis

P. Mukherjee¹, M. Dutta¹, P. Datta¹, A. Dasgupta¹, R. Pradhan², M. Pradhan², M. Kundu¹, J. Basu¹ and P. Chakrabarti¹

Clin Microbiol Infect 2007; 13: 146–152
# Nucleic acid amplification assays

## Comparison of different CDATs for detection of MTB in clinical samples

<table>
<thead>
<tr>
<th>CDAT</th>
<th>Amplification method</th>
<th>Amplification target</th>
<th>Sample vol (µL)</th>
<th>Detection</th>
<th>Assay time (h)</th>
<th>Automation</th>
<th>IAC</th>
<th>Sensitivity&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Specificity&lt;sup&gt;b&lt;/sup&gt;</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMTD2</td>
<td>TMA</td>
<td>16S RNA</td>
<td>450</td>
<td>Chemiluminescence</td>
<td>2.5</td>
<td>No</td>
<td>No</td>
<td>+++</td>
<td>+++</td>
<td>Yes</td>
</tr>
<tr>
<td>AMPLICOR</td>
<td>PCR</td>
<td>16S DNA</td>
<td>100</td>
<td>Colorimetric</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>+++</td>
<td>+++</td>
<td>Yes</td>
</tr>
<tr>
<td>LCx</td>
<td>LCR</td>
<td>PAB</td>
<td>500</td>
<td>Fluorimetric</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>+++</td>
<td>+++++</td>
<td>No</td>
</tr>
<tr>
<td>DTB</td>
<td>SDA</td>
<td>IS6110</td>
<td>500</td>
<td>Fluorimetric (ET)</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>+++</td>
<td>+++++</td>
<td>No</td>
</tr>
<tr>
<td>LiPA</td>
<td>Nested PCR</td>
<td>RpoB gene</td>
<td>500</td>
<td>Colorimetric</td>
<td>12</td>
<td>Yes</td>
<td>No</td>
<td>+++</td>
<td>+++++</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup> Abbreviations: TMA, transcription-mediated amplification; LCR, ligase chain reaction; PAB, protein antigen.

<sup>b</sup> ++++, good; ++++, very good.
### M. tuberculosis detection in clinical samples by molecular methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Target</th>
<th>Detection method</th>
<th>Sensitivity in respiratory samples (%)</th>
<th>Sensitivity in extra respiratory samples (%)</th>
<th>Overall specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMTD2</td>
<td>16S rRNA</td>
<td>Chemiluminometric</td>
<td>80-100</td>
<td>60-90</td>
<td>95-100</td>
</tr>
<tr>
<td>LCx</td>
<td>b antigenic protein</td>
<td>Fluorimetric</td>
<td>80-90</td>
<td>65-80</td>
<td>90-100</td>
</tr>
<tr>
<td>AMPLICOR</td>
<td>16S rRNA</td>
<td>Colorimetric</td>
<td>75-100</td>
<td>45-60</td>
<td>90-100</td>
</tr>
<tr>
<td>BD ProbeTec</td>
<td>IS6110 and 16S rRNA</td>
<td>Fluorimetric</td>
<td>55-100</td>
<td>30-80</td>
<td>45-100</td>
</tr>
<tr>
<td>INNO-LIPA v2</td>
<td>IR16S-23S</td>
<td>Colorimetric</td>
<td>50-95</td>
<td>60-80</td>
<td>90-100</td>
</tr>
<tr>
<td>GenoType Direct</td>
<td>23S rRNA</td>
<td>Colorimetric</td>
<td>60-95</td>
<td>60-80</td>
<td>95-100</td>
</tr>
<tr>
<td>PCR real time</td>
<td>16S rRNA</td>
<td>Fluorimetric</td>
<td>70-90</td>
<td>65-85</td>
<td>85</td>
</tr>
</tbody>
</table>

* In smear negative samples the sensitivity is reduced in a 50%
NAA- summary

• rapid diagnosis of smear negative
• Able to identify 50-60% of smear -ve culture +ve cases
• Distinguish M.tb from NTM in smear +ve cases
• They are able to detect nucleic acids from both living and dead
• A major limitation of NAA: no drug-susceptibility information.
• NAA should always be performed in conjunction with microscopy and culture
• Very high degree of quality control required
CDC Updates Guidelines for Nucleic Acid Amplification Techniques to Diagnose Tuberculosis

- NAAT results should be interpreted in conjunction with the AFB smear results.
- NAAT and smear positive: start Rx despite pending culture results. PPV 95%
- Smear negative, NAAT positive: use clinical judgment to either treat or await culture
Genotype® MTBDRplus Hybridization-Strip

from specimens

Hillemann D, Rüsch-Gerdes S, Richter E.
Application of the Genotype MTBDR assay directly on sputum specimens.
Molecular Methods
Drug Resistance

• Reverse hybridization
  – Line probe assays
• RNase Cleavage
• Diagnostic Sequencing (Genotyping)
Xpert MTB/RIF

• A new PCR-based TB fast, sensitive, and automated. An accurate diagnosis can be obtained in less than 2 hours by adding a reagent to a sputum sample and, 15 minutes later, pipetting it into a cartridge that is inserted into the diagnostic instrument for 1–2 minutes.
Drug Susceptibility testing
So what is new?

1. Vaccines
2. Tackling risk factors
3. New diagnostics
4. Preventive measures
5. Treatment in pipeline
Modified dosing of rifampin

Higher-dose rifampin for the treatment of pulmonary tuberculosis: a systematic review

K. R. Steingart,* S. Jotblad,† K. Robsky,† D. Deck,‡ P. C. Hopewell,*§ D. Huang,§ P. Nahid*§
# 1. Vaccines

<table>
<thead>
<tr>
<th>Description</th>
<th>Developmental stage</th>
<th>Sponsor or funder</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA85A Attenuated strain of vaccinia expressing Ag85A</td>
<td>Phase 1 completed and phase 2 continuing; phase 2b in infants started</td>
<td>Wellcome Trust, Aeras, Emergent BioSolutions</td>
</tr>
<tr>
<td>rBCG30 BCG overexpressing Ag85B</td>
<td>Phase 1 completed</td>
<td>University of California, Los Angeles; Aeras</td>
</tr>
<tr>
<td>AERAS-402 Non-replicating Ad25 expressing Ag85A, Ag85B, and TB10.4</td>
<td>Phases 1 and 2 continuing</td>
<td>Aeras</td>
</tr>
<tr>
<td>AdAg85A Non-replicating Ad5 expressing Ag85A</td>
<td>Phase 1</td>
<td>McMaster University</td>
</tr>
<tr>
<td>M72 Recombinant fusion (Mt39 and Mt32) in AS02 and AS01 adjuvant systems</td>
<td>Phases 1 and 2 completed; additional trials continuing</td>
<td>GlaxoSmithKline, Aeras, Tuberculosis Vaccine Initiative</td>
</tr>
<tr>
<td><strong>H1-IC31</strong> Recombinant fusion of Ag85B-ESAT-6 in IC31 adjuvant</td>
<td>Phase 1 completed</td>
<td>Statens Serum Institut, Tuberculosis Vaccine Initiative</td>
</tr>
<tr>
<td>H1-CAF01 Recombinant fusion of Ag85B-ESAT-6 in CAF01 adjuvant</td>
<td>Phase 1 continuing</td>
<td>Statens Serum Institut, Tuberculosis Vaccine Initiative</td>
</tr>
<tr>
<td>H4-IC31 (AERAS-404) Recombinant fusion of Ag85B-TB10.4 in IC31 adjuvant</td>
<td>Phase 1 completed</td>
<td>Statens Serum Institut, Aeras</td>
</tr>
<tr>
<td>rBCGΔUreC:Hly (VPM1002) BCG with an endosome escape mechanism</td>
<td>Phase 1 completed</td>
<td>Vakzine Projekt Management, Tuberculosis Vaccine Initiative, Max Planck Institut</td>
</tr>
<tr>
<td>RUTI Detoxified <em>M tuberculosis</em> in liposomes</td>
<td>Phase 1 completed</td>
<td>Archivel Farma</td>
</tr>
<tr>
<td>M vaccae Inactivated <em>M vaccae</em></td>
<td>Phase 3 completed</td>
<td>National Institutes of Health</td>
</tr>
</tbody>
</table>
Vaccine strategies

• Pre-exposure, boost, therapeutic
4. New treatments

• Existing drugs:
  – Rifapentine, linezolid, gatifloxacin, moxifloxacin

• Pipeline drugs:
  – PNU-100480 – oxazolidinone, Pfizer
  – AZD-5847 – oxazolidinone, AstraZeneca
  – SQ-109 – ethambutol derivative, Sequella
  – TMC207 – diarylquinoline, Tibotec
  – PA-824 – nitroimidazole, Novartis
  – Opc67683 – nitroimidazo-oxazole, Otsuka
4. New treatments

- Adjunctive therapy
  - Multivitamin supplementation
    - Major trial in Malawi: no effect
  - The vitamin D story
    - Major trial in Bissau: No effect on clinical score or mortality, but mean sputum conversion time 29 days in vitamin D arm vs 38 days in placebo (NS)
      - London trial: 36 vs 43 days to sputum conversion
        - Only significant in VDR subgroup
Many more powerful hands needed to Control Tuberculosis
A WORLD FREE OF TB

• WHO is working to dramatically reduce the burden of TB, and halve TB deaths and prevalence by 2015, through its Stop TB Strategy and supporting the Global Plan to Stop TB.
Contribute your Knowledge, Wisdom, to prevent spread and control of Tuberculosis