Overview

- Background
- Tuberculosis
  - Epidemiology
  - Drugs
  - Diagnostics
  - Vaccines
  - HDT
  - Research priorities
- Buruli ulcer
- Leprosy
- Priorities for research
- Conclusion
Mycobacterial diseases of poverty

- Tuberculosis, leprosy and buruli ulcer are
  - Infectious diseases of poverty
  - Caused by mycobacteria
  - Treatable and preventable
  - Associated with disability and stigma
  - Require further research to reduce morbidity, stigma, mortality and burden of disease
Tuberculosis
Tuberculosis

Epidemiology
Drugs
Diagnostics
Vaccines
Research priorities
Tuberculosis

**Epidemiology**

**Drugs**

**Diagnostics**

**Vaccines**

**Research priorities**
Estimated TB incidence, 2012
Proportion of new TB cases with MDR TB
MDGs and Stop TB targets

- 2015: reduce prevalence of and deaths due to TB by 50% compared to 1990 baseline

- 2050: eliminate TB as a public health problem (defined as <1 case per 1 million population per year)
Global trends in TB

Incidence

Prevalence

Mortality

(Global TB report, 2013)
## Progress towards 2015 targets

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
<th>Prevalence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLOBAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>Met</td>
<td>Not on track</td>
<td>On track</td>
</tr>
<tr>
<td><strong>WHO REGION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African (AFR)</td>
<td>Met</td>
<td>Not on track</td>
<td>Not on track</td>
</tr>
<tr>
<td>Americas (AMR)</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
</tr>
<tr>
<td>Eastern Mediterranean (EMR)</td>
<td>Met</td>
<td>Not on track</td>
<td>On track</td>
</tr>
<tr>
<td>European (EUR)</td>
<td>Met</td>
<td>Not on track</td>
<td>Not on track</td>
</tr>
<tr>
<td>South-East Asia (SEAR)</td>
<td>Met</td>
<td>On track</td>
<td>On track</td>
</tr>
<tr>
<td>Western Pacific (WPR)</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
</tr>
</tbody>
</table>

(Countdown to 2015. Global TB report supplement)
Tuberculosis

Epidemiology
Drugs
Diagnostics
Vaccines
Research
priorities
Tuberculosis

Epidemiology

Drugs

Diagnostics

Vaccines

Research

priorities

• Pipeline
• Phase II studies
• Phase III studies
• PK studies
• Treatment of LTBI
• HDT
Tuberculosis

- **Pipeline**
  - Phase II studies
  - Phase III studies
  - PK studies
  - Treatment of LTBI
  - HDT

Epidemiology

Drugs

Diagnostics

Vaccines

Research priorities
Global TB drug pipeline

- **Early Stage Development**
  - CPZEN-45
  - DC-159a
  - Q203
  - SQ609
  - SQ641
  - TBI-166

- **GLP Tox.**
  - PBTZ169
  - TBA-354

- **Phase I**
  - AZD5847\(^N\)
  - Bedaquiline\(^NcR\)
  - Linezolid
  - PA-824\(^Nc\)
  - Rifapentine
  - SQ-109\(^N\)
  - Sutezolid\(^N\)

- **Phase II**
  - Delamanid\(^NR\)
  - Gatifloxacin\(^c\)
  - Moxifloxacin\(^c\)
  - Rifapentine\(^R\)

**Chemical classes:** fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

---


2. Drug candidate currently in combination regimen in clinical testing

3. Submitted for approval or approved by stringent regulatory authority (i.e., FDA, EMA, WHO Prequalification)

4. New chemical entity
## TB treatment priorities

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-Susceptible TB</td>
<td>Shorter, simpler therapy</td>
</tr>
<tr>
<td>Drug-Resistant TB</td>
<td>Fully oral, shorter and safer therapy</td>
</tr>
<tr>
<td>TB/HIV co-Infection</td>
<td>few or no DDI with ARVs</td>
</tr>
<tr>
<td>LTBI with DS TB</td>
<td>Shorter, safer therapy</td>
</tr>
<tr>
<td>LTBI with DR TB</td>
<td>Short, efficacious &amp; Safe</td>
</tr>
</tbody>
</table>
Tuberculosis

- Epidemicology
- Drugs
- Diagnostics
- Vaccines
- Research priorities

- Pipeline
- **Phase II studies**
- Phase III studies
- PK studies
- Treatment of LTBI
- HDT
• Greater proportion converted their culture (48% vs 9%)
• Most AEs mild/moderate
• Unexplained deaths up to 2 years after treatment
The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin Grobusch, M.D., D.T.M.&H., Ramonde Patientia, M.D., Roxana Rustomjee, M.D., Ph.D., Liesl Page-Shipp, M.D., Christoffel Pistorius, M.D., Rene Krause, M.D., Mampedi Bogoshi, M.D., Gavin Churchyard, M.B., Ch.B., Amour Venter, Nat.Dip.Med.Tech.(Micro), and Christopher M. Beare, M.D., M.R.C.P. (Lond.)

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis
Interim policy guidance
Delamanid: 8 week culture conversion rate

A. Mycobacterial Growth Indicator Tube System

- Placebo: 29.6% (37/125)
- 100 mg, twice daily: 45.4% (64/141)
- 200 mg, twice daily: 41.9% (57/136)

P-values: 0.04, 0.008

B. Solid Medium

- Placebo: 33.6% (38/113)
- 100 mg, twice daily: 53.8% (64/119)
- 200 mg, twice daily: 65.2% (75/115)

P-values: <0.001, 0.002
Linezolid for XDR TB

Culture conversion: immediate vs delayed start group
79% vs 35% respectively

Clinically significant AEs observed in 82%

Lee et al. NEJM. 2012
NC001: 14 day EBA of PA824, bedaquiline, pyrazinamide & moxifloxacin

(Diacon et al. Lancet. 2012)
# Phase II trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose RPT (TBTC29X)</td>
<td>10mg, 15mg, 20mg in S+ TB patients</td>
<td>Safe. At highest dose 100% C- at 8 weeks Phase III trial indicated</td>
</tr>
<tr>
<td>High dose rifampicin EBA</td>
<td>10, 20, 25, 30 mg/kg</td>
<td>Well tolerated &amp; trend towards reduced CFUs with higher doses</td>
</tr>
<tr>
<td>NC002 (8wk SSCC)</td>
<td>M, PA200,Z-DS TB M, PA100,Z-DS-TB M, PA200,Z-DR TB</td>
<td>Results will be available soon</td>
</tr>
<tr>
<td>NC003 (EBA)</td>
<td>Combinations of Clofazamine, bedaquiline, PA824, PZA</td>
<td><em>Results to be presented at Union Conference</em></td>
</tr>
<tr>
<td>AZD-5847</td>
<td>EBA</td>
<td>Evaluating 4 doses</td>
</tr>
<tr>
<td>MAMS-TB-01</td>
<td>HRZQ&lt;sub&gt;low&lt;/sub&gt;, HRZQ&lt;sub&gt;high&lt;/sub&gt;, HR&lt;sub&gt;20&lt;/sub&gt;ZQ&lt;sub&gt;high&lt;/sub&gt;, HR&lt;sub&gt;20&lt;/sub&gt;ZM</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>
Tuberculosis

Epidemiology

Drugs

Diagnostics

Vaccines

Research

priorities

- Pipeline
- Phase II studies
- **Phase III studies**
- PK studies
- Treatment of LTBI
- HDT
Rifaquine: study regimens

- **Rifampicin**, Isoniazid, Ethambutol, Pyrazinamide

- **Rifampicin**, **Rifapentine**, Moxifloxacin

- **Rifampicin**, **Rifapentine**, Moxifloxacin

Months:
- 2
- 4
- 6

Rifapentine and Moxifloxacin given 1-weekly

Rifapentine and Moxifloxacin given 2-weekly
Rifaququine trial: proportion unfavourable

![Graph showing absolute difference from control for MITT and Per-Protocol, with 6% margin of non-inferiority. The graph compares 6-month and 4-month periods.]
## Phase III trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oflotub DS TB</td>
<td>2RHGZ/HR</td>
<td><em>LB presentation at Union conference</em></td>
</tr>
<tr>
<td>ReMOX DS TB</td>
<td>2RMEZ/4HR 2RHMZ/4HR</td>
<td><em>Results soon</em></td>
</tr>
<tr>
<td>Delamanid MDR TB</td>
<td>OBR+OPC-67683/placebo (6m)</td>
<td>MDR TB Enrolling</td>
</tr>
<tr>
<td>Bedaquiline MDR TB</td>
<td>Short BR + TMC207 /placebo</td>
<td>Entire Rx duration</td>
</tr>
<tr>
<td>STREAM MDR TB</td>
<td>Mox, CLO, Eb, PZA, INH, Prot, Kanamcyin</td>
<td>Compared to standard Enrolling</td>
</tr>
</tbody>
</table>
Tuberculosis

- **Epidemiology**
- **Drugs**
- **Diagnostics**
- **Vaccines**
- **Research priorities**

- Pipeline
- Phase II studies
- Phase III studies
- **PK studies**
- Treatment of LTBI
- HDT
“Today we are calling on the world to recognize that we can’t fight AIDS unless we do much more to fight TB as well”
Drug interactions with ART

- **Delamanid** has lower DDI risk
  - must be taken twice a day
- Sutezolid: not tested with ART
- **EFV ▼ BDQ** conc. by > 20%
- **EFV ▼ PA-824** conc. by ~30%
- Enzyme induction by high-dose rifampin or rifapentine may be similar to standard-dose rifampin

(Source: Kelly Dooley)
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- EFV $\downarrow$ PA-824 conc. by $\sim 30$
- Enzyme induction by high-dose rifampin or rifapentine may be similar to standard-dose rifampin

(Source: Kelly Dooley)
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“All who mix with tuberculosis patients got infected, but remained well so long as they took care of themselves and kept the soil in a condition unfavourable for the growth of the seed.”
Continuous IPT results in durable reduction in TB risk, while taking it

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Intention to treat</th>
<th>Per Protocol</th>
</tr>
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<tr>
<td><strong>Martinson</strong></td>
<td>S. Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST+</td>
<td></td>
<td><strong>26%</strong></td>
<td><strong>58%</strong>*</td>
</tr>
<tr>
<td><strong>Samandari</strong></td>
<td>Botswana</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td><strong>43%</strong></td>
<td></td>
</tr>
<tr>
<td>TST+</td>
<td></td>
<td><strong>74%</strong></td>
<td><strong>100%</strong></td>
</tr>
<tr>
<td>TST-</td>
<td></td>
<td><strong>25%</strong></td>
<td></td>
</tr>
</tbody>
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(Martinson NEJM. 2011; * Reduction for TB & deaths)  (Samandari Lancet. 2011)
Continuous IPT results in durable reduction in TB risk, while taking it

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<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

(Martinson NEJM. 2011; * Reduction for TB & deaths)  (Samandari Lancet. 2011)
TB rates increase soon after stopping IPT

6H vs 36H in PWHIV in Botswana

(TST positive participants)

In-trial n=468

Post-trial (no IPT) n=395

Days after enrolment

Days after trial end

(Tsamandari, CROI2012)
IPT with ART: a randomised controlled trial

South Africa

- HR: 0.63 (95% CI 0.41-0.94)
- Deaths were similar between arms (3.0% vs. 2.1%, p=0.29)
- The risk of stopping IPT due to grade 3 or more raised ALT was 2.13 (95% CI 0.97-4.67)

(Rangaka et al, AIDS2012)
IPT with ART: a randomised controlled trial in South Africa

Effect of IPT with ART by TST or IGRA status

<table>
<thead>
<tr>
<th>TST status</th>
<th>TB rates (100 person years)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>INH</td>
<td></td>
</tr>
<tr>
<td>TST positive</td>
<td>2.8</td>
<td>2.6</td>
</tr>
<tr>
<td>TST negative</td>
<td>4.1</td>
<td>1.7</td>
</tr>
<tr>
<td>IGRA positive</td>
<td>3.9</td>
<td>3.0</td>
</tr>
<tr>
<td>IGRA negative</td>
<td>3.4</td>
<td>1.7</td>
</tr>
</tbody>
</table>

(Rangaka. Poster 189LB)
IPT promotion in 29 HIV clinics in Rio de Janeiro, Brazil reduced TB incidence/death at a clinic-level.

<table>
<thead>
<tr>
<th>Primary Analysis</th>
<th>% reduction</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>475</td>
<td>0.87 (0.69-1.10)</td>
<td>0.24</td>
</tr>
<tr>
<td>TB/Death</td>
<td>1313</td>
<td>0.74 (0.64-0.85)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Thibela TB: duration of IPT effect at individual level

63% reduction in TB incidence during 9m of IPT

(Fielding CROI 2012)
### Effectiveness

#### TB incidence

Among employees in the primary outcome measurement:

<table>
<thead>
<tr>
<th></th>
<th>TB</th>
<th>Person years</th>
<th>Rate/100 pyo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>887</td>
<td>29,352</td>
<td>3.02</td>
</tr>
<tr>
<td>Control</td>
<td>856</td>
<td>29,015</td>
<td>2.95</td>
</tr>
</tbody>
</table>

**Incidence rate ratio**

- **Unadjusted**: 1.00 (95% CI 0.75-1.34)
- **Adjusted***: 0.96 (95% CI 0.76-1.21)

*Adjusted for individual level variables gender, age, surface/underground work, and cluster level variables of silicosis and ART prevalences TB case notification rate 12-months prior to cluster enrolment and pre-randomisation strata.
Short course rifamycin based regimens have similar efficacy as 6-months IPT in PWHIV

TST+ South Africans

3RPT/INH (900mg/900mg weekly×12)

(Martinson NEJM. 2011)
Weekly high dose 3HP is non-inferior to 9H

Study 26: High risk persons in US, Canada, Brazil & Spain

N=7731
Weekly high dose 3HP vs. 9H in HIV-infected persons not on ART
(N=393)

- In study 26, only 3% of participants were HIV+
- Enrolment of HIV+s extended to assess tolerability
- In MITT analysis, participants receiving 3HP
  - Had higher completion rates (89% vs 65%, p=0.04)
  - Fewer AEs (≥1) (22 vs. 40%; p=0.004)
  - Less hepatotoxicity (2% vs. 6%; p=0.03)

(Sterling et al, AIDS2012, MOAB0302)
Rifapentine preventive therapy trials

- Study 33 (iAdhere) 3HP given by DOTS, Self-administered, self-administered with SMS reminder
- A5279.
  - A phase III trial of daily RPT and INH for one month among PWHIV and LTBI in HBCs
  - No PK issues noted with concomitant RPT & EFV
- Sanofi (NCT01690403)
  - PK study of rifapentine on Atripla in HIV+s
Tuberculosis

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HDT: mechanisms of actions

- Enhance protective immunity
- Facilitate access or activity of chemotherapeutic agents to the bacilli, by disrupting bacteriostatic pathways or fibrosis
- Enhance autophagy
Role of adjunctive HDT

- Shortening the duration of TB treatment
- Improving treatment success of DS & DR TB
- Reducing clinical complications
- Reducing rate of recurrent TB

(Source: R Wallis)
Month 2 culture status and duration as predictors of relapse

Wallis, *PLoS ONE* 2013
Acceleration of TB culture conversion by anti-TNF therapy

Wallis, CID 2005;41:201
Tuberculosis

- Epidemiology
- Drugs
- Diagnostics
- Vaccines
- Research

Priorities:
- Pipeline
- WHO endorsed
- WHO not endorsed
- Early development
- Point of care
Tuberculosis

**Epidemiology**

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Global TB diagnostics pipeline

[Diagram showing the timeline and levels of TB diagnostics, including methods such as liquid culture and DST, Xpert MTB/RIF, LED microscopy, and POC tests.]
Tuberculosis

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Assay Procedure for the MTB/RIF Test

1. Sputum liquefaction and inactivation with 2:1 sample reagent

2. Transfer of 2 ml material into test cartridge

3. Cartridge inserted into MTB-RIF test platform (end of hands-on work)

4. Sample automatically filtered and washed

5. Ultrasonic lysis of filter-captured organisms to release DNA

6. DNA molecules mixed with dry PCR reagents

7. Seminested real-time amplification and detection in integrated reaction tube

8. Printable test result

Time to result, 1 hour 45 minutes
Xpert MTB/RIF for detection of TB and rifampicin resistance

(WHO Expert meeting report for use of Xpert MTB/RIF, 2013)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacing microscopy as initial test for TB</td>
<td>88%</td>
<td>99%</td>
</tr>
<tr>
<td>Add on following negative microscopy</td>
<td>68%</td>
<td>99%</td>
</tr>
<tr>
<td>Rifampicin resistance</td>
<td>95%</td>
<td>98%</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>79%</td>
<td>98%</td>
</tr>
<tr>
<td>Children</td>
<td>66%</td>
<td>98%</td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>81%</td>
<td>98%</td>
</tr>
</tbody>
</table>
Xpert sensitivity for ETB

(A) Sensitivity by sample type

- Tissue
- Gastric fluid
- Cerebrospinal fluid
- Lymph node
- Pleural fluid

Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Composite reference standard</th>
<th>Culture reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric fluid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural fluid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(WHO Expert meeting report for use of Xpert MTB/RIF, 2013)
WHO recommendations for Xpert

- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults presumed to have MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence).

- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults presumed to have TB. (Conditional recommendation acknowledging resource implications, high-quality evidence).
Xpert for TB- Evaluating a New Diagnostic

A cluster randomised trial evaluating patient, programme & population level impact of Xpert
**XTEND: early mortality**

- Median follow-up: 3.3 months (IQR 2.1 - 3.7)
- During follow-up: 17 deaths, 97.2 person-years (py)
- Overall mortality rate: 17.5 per 100py

Kaplan-Meier mortality plot, among clinic attendees suspected of TB (n=380)
Tuberculosis

- Epidemiology
- Drugs
- Diagnostics
- Vaccines
- Research
- Priorities

- Pipeline
- WHO endorsed
- **WHO not endorsed**
- Early development
- Point of care
<table>
<thead>
<tr>
<th>Model: Crudu. JCM, 2012</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>87.6%</td>
<td>99.2%</td>
</tr>
<tr>
<td>Smear negative</td>
<td>79.8%</td>
<td>99.2%</td>
</tr>
<tr>
<td><strong>Rifampicin resistance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>94.3%</td>
<td>96.0%</td>
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<tr>
<td>Smear negative</td>
<td>90.7%</td>
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<tr>
<td><strong>Isoniazid resistance</strong></td>
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<tr>
<td>Overall</td>
<td>95.8%</td>
<td>88.9%</td>
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<tr>
<td>Smear negative</td>
<td>93.5%</td>
<td>82.3%</td>
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</table>
## GenoType MTBDRsl

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<tr>
<th>Drug</th>
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<tbody>
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</tbody>
</table>
Determine LAM lateral flow assay (Alere)

- uses Determine testing platform
- No sample processing; results in 25 minutes
- Analytical sensitivity reported to be 0.25 ng/ml
- Reporting scale: no band (neg), 1+ to 5+ (pos)
## Determine TB-LAM

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>N</th>
<th>Setting</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peter, 2012</td>
<td>335</td>
<td>Inpatients</td>
<td>45%</td>
<td>96%</td>
</tr>
<tr>
<td>Lawn, 2012</td>
<td>516</td>
<td>ART clinic</td>
<td>28%</td>
<td>52%</td>
</tr>
<tr>
<td>Dorman S, 2012</td>
<td>561</td>
<td>Outpatients</td>
<td>45%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inpatients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Tuberculosis

- Epidemiology
- Drugs
- Diagnostics
- Vaccines
- Research
- Priorities

- Pipeline
- WHO endorsed
- WHO not endorsed
- **Early development**
- Point of care
TB diagnostics: early development

Volatile organic compounds
- BreathLink, Menssana Research, USA
- Prototype breath analyzer device, Next Dimensions Technology, USA

Molecular technologies
- Alere Q, Alere, USA
- B-SMART, LabCorp, USA
- Gendrive MTB/RIF ID, Epistem, UK
- LATE-PCR, Brandeis University, USA
- GeneXpert XDR cartridge, Cepheid, USA
- TruArray MDR-TB, Akkoni, USA
- INFINITIMTB Assay, AutoGenomics, USA
TB diagnostics: early development

Culture-based technologies
- BNP Middlebrook, NanoLogix, USA
- MDR-XDR TB Color Test, FIND, Switzerland/Imperial College, UK
- TREK Sensititre MYCOTB MIC plate, Trek Diagnostic Systems/Thermo Fisher Scientific, USA

Other technologies
- TB Rapid Screen, Global BioDiagnostics, USA
- TBDx, Signature Mapping Medical Sciences, USA
Rationalizing the use of Xpert: the role of automated microscopy

**TBDx: automated smear microscopy**

- automatically loads slides
- conventional fluorescence microscope
- Autofocuses and digitally captures images
- Reads 300 fields of view
- Computerised algorithms classifies slides as +ve/–ve
Rationalizing the use of Xpert: the role of automated microscopy

TBDx

- Negative/scanty 1+
- Scanty 2-9+
- Smear positive

Xpert MTB/Rif

- Neg
- Pos

No TB

TB

(Islam. Union LB presentation)
Rationalizing the use of Xpert: the role of automated microscopy

TBDx

Smear positive

scanty 2-9+

Xpert MTB/Rif

Pos

TB

Neg

No TB

Negative/ scanty 1+

(Ismail. Union LB presentation)
Tuberculosis

Epidemiology
Drugs
Diagnostics
Vaccines
Research
priorities

- Pipeline
- WHO endorsed
- WHO not endorsed
- Early development
- Point of care
The long & winding road to TB treatment

- Infectious
- Has symptoms
- Attends health centre
- TB test sent
- TB test result
- Treatment start
- TB cured

infectiousness

(A Grant. AIDS2012)
Earlier testing is TB prevention.

- Infectious
- Has symptoms
- Attends health centre
- TB test
- TB test result
- Treatment start
- TB cured

(A Grant. AIDS2012)
Point of care diagnostic

- Hospital
- TB diagnostic center
- Primary Health Clinic
- Home

Point of care test
Point of care Xpert in PHCs in Africa

- 5 sites
- Randomised to
  - 758 microscopy
  - 744 Xpert
- TB related morbidity similar, due to common use of empiric treatment

(Theron et al. Lancet. 2013)
Population level impact of same-day microscopy & Xpert MTB/RIF

(Dowdy et al, PLOS One, 2013)
Tuberculosis

- Epidemiology
- Drugs
- Diagnostics
- Vaccines
- Research
- Priorities
Tuberculosis

Epidemiology

Drugs

Diagnostics

Vaccines

Research priorities

• Vaccination strategies
• Pipeline
• Phase II
• Phase Iib/III
• Blueprint
• BCG revaccination
Tuberculosis

- Epidemiology
- Drugs
- Diagnostics
- Vaccines
- Research priorities

- Vaccination strategies
- Pipeline
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- Phase Iib/III
- Blueprint
- BCG revaccination
TB Vaccine strategies

Pre-exposure vaccines

BCG priming (infant)

Sub-unit Vaccine Boost (infant or ado)

Therapeutic vaccines

Post-exposure vaccines

Level of immunity

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

Source: L. Abu Raddad et al, PNAS 2009
Tuberculosis

Epidemiology
Drugs
Diagnostics
**Vaccines**
Research
priorities

- Vaccination strategies
- **Pipeline**
  - Phase II
  - Phase IIb/III
  - Blueprint
# Global TB Vaccine Pipeline

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdAg85A</td>
<td>VPM 1002</td>
<td>MVA85A/AERAS-485</td>
<td><em>M. Vaccae</em></td>
</tr>
<tr>
<td>McMaster, CanSino</td>
<td>Max Planck, VPM, TBVI, Serum Institute</td>
<td>Oxford, Aeras, EDCTP</td>
<td>Anhui Longcom</td>
</tr>
<tr>
<td>MTBVAC</td>
<td>H1+IC31</td>
<td>H1+IC31</td>
<td>IT</td>
</tr>
<tr>
<td>TBVI, Zaragoza, Biofabri</td>
<td>SSI, TBVI, EDCTP, Intercell</td>
<td>SSI, TBVI, EDCTP, Intercell</td>
<td></td>
</tr>
<tr>
<td>ID93+GLA-SE</td>
<td>RUTI</td>
<td>RUTI</td>
<td></td>
</tr>
<tr>
<td>Infectious Disease Research Institute (IDRI), Aeras</td>
<td>Archivel Farma, S.L.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crucell Ad35/MVA85A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crucell, Oxford, Aeras</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prime</td>
<td>Boost</td>
<td>Post-infection</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Prime</td>
<td>Boost</td>
<td>Post-infection</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56, ID93</td>
<td>H56/AERAS-456</td>
<td>H56/AERAS-456</td>
<td></td>
</tr>
<tr>
<td>rBCG: VPM 1002</td>
<td>+IC31</td>
<td>+IC31</td>
<td></td>
</tr>
<tr>
<td>Killed WC or Extract: Mw, RUTI</td>
<td>SSI, Aeras, Intercell</td>
<td>SSI, sanofi-pasteur, Aeras, Intercell</td>
<td></td>
</tr>
<tr>
<td>Viral-vectored: MVA85A, AERAS-402, AdAg85A</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56, ID93</td>
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</tbody>
</table>

**June 2013**

**TB Vaccine Types**
- Viral-vectored: MVA85A, AERAS-402, AdAg85A
- Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56, ID93
- rBCG: VPM 1002
- Killed WC or Extract: Mw, RUTI

**Stop TB Partnership**

**Working Group on New TB Vaccines**
Tuberculosis

Epidemiology

Drugs

Diagnostics

Vaccines

Research

priorities

• Vaccination strategies
• Pipeline
• **Phase II**
• Phase IIb/III
• Blueprint
VPM1002 in HIV-exposed infants

• Live recombinant rBCG
• Phase IIa:
  • HIV-uninfected newborns: safe & immunogenic
  • HIV exposed and unexposed newborns: safety and immunogenicity study planned
Tuberculosis

Epidemiology
Drugs
Diagnostics
Vaccines
Research
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- Vaccination strategies
- Pipeline
- Phase II
- **Phase IIb/III**
- Blueprint
MVA85A Efficacy in BCG vaccinate infants

(McShane, Lancet, 2013)
MVA85A Efficacy in BCG vaccinate infants

McShane, Lancet, 2013)
## DarDar study: M vaccae in HIV-infected adults

### Table 1. Protection against HIV-associated TB in the DarDar Trial

<table>
<thead>
<tr>
<th>TB endpoints</th>
<th>Vaccine $n$</th>
<th>Placebo $n$</th>
<th>Hazard ratio (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated</td>
<td>7</td>
<td>13</td>
<td>0.52 (0.21–1.34)</td>
<td>0.16</td>
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<tr>
<td>Definite</td>
<td>33</td>
<td>52</td>
<td>0.61 (0.39–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Probable</td>
<td>48</td>
<td>40</td>
<td>1.17 (0.76–1.80)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; TB = tuberculosis; CI = confidence interval.

*(von Reyn et al. AIDS, 2010)*
## TB Vaccine efficacy trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Strategy</th>
<th>Type</th>
<th>Sponsors</th>
<th>Status</th>
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<tr>
<td><em>M. vaccae</em></td>
<td>Immunotherapeutic</td>
<td>Whole-cell <em>M. vaccae</em></td>
<td>AnHui Longcom</td>
<td>Phase III pending</td>
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<tr>
<td>MVA85A/AERAS-485</td>
<td>Prime-boost</td>
<td>Viral vector</td>
<td>Oxford University, Aeras</td>
<td>Phase IIb in HIV+s Enrolling</td>
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<tr>
<td>M72 + AS01</td>
<td>Prime-boost</td>
<td>Adjuvanted subunit</td>
<td>GSK, Aeras</td>
<td>Phase Iib Pending</td>
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Tuberculosis

Epidemiology

Drugs

Diagnostics

Vaccines

Research

Priorities

- Vaccination strategies
- Pipeline
- Phase II
- Phase Iib/III
- Blueprint
TB vaccine blueprint

Keys to progress

• Creativity in research & discovery
• Correlates of immunity & biomarkers for TB vaccines
• Clinical trials: harmonization and cooperation
• Rationale selection of TB vaccine candidates
• Critical need for advocacy, community acceptance & funding

(Brennan, Tuberculosis, 2012)
TB vaccine blueprint

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**TB vaccine blueprint**

**Keys to progress**

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- Correlates of immunity & biomarkers for TB vaccines
- Clinical trials: harmonization and cooperation
- Rationale selection of TB vaccine candidates
- Critical need for advocacy, community acceptance & funding

- Explore novel approaches to identifying biomarkers
- Introduce novel assays
- Identify signatures of efficacy

(Brennan, Tuberculosis, 2012)
Tuberculosis

Epidemiology
Drugs
Diagnostics
Vaccines
Research
priorities
TB research priorities
Buruli Ulcer
Buruli ulcer: background

- Buruli ulcer is a neglected but treatable tropical disease
- Caused by subcutaneous infection with *Mycobacterium ulcerans*
- Slowly progressing disease
  - often painless
  - begins as a nodule
  - life-long deformity may occur
- Early diagnosis and treatment are key to preventing disabilities
- Children and the elderly appear most susceptible
Buruli ulcer: burden of disease

- Globally, 26,000 cases recorded b/w 2004-2008
- Greatest burden in Africa
  - Primarily in remote, rural areas
  - Prevalence in Ghana and Benin range from 50 - 3,500 cases per 100,000
Buruli ulcer: reservoir & mode of transmission

- Although classified as an environmental mycobacterium, does not live freely in the environment
- Occupies specific (vertebrate and invertebrates) hosts
- Infection associated with swamps and slow-flowing water
- Transmitted to humans by an unknown mechanism
  - Mosquitoes may be involved in transmission (in Australia)
Buruli ulcer: diagnosis

- Direct smear examination
- Culture
- Polymerase chain reaction
- Histopathology
- There is no rapid point-of-care test
Buruli Ulcer: treatment and prevention

- Rifampicin & streptomycin/amikacin x 8wks
  - Oral regimen: rifampicin & clarithromycin or ciprofloxacin or moxifloxacin for 3 months
- Surgery to remove necrotic tissue, cover skin defects and correct deformities
- There is no vaccine against *BU*
  - BCG offers short-term protection
Leprosy
Leprosy: background

- Caused by *M leprae*
- Leading infectious cause of disability
- Delayed diagnosis results in increased risk of nerve damage.
- Stigma an important feature in many cultures
Leprosy: epidemiology

- 250,000 cases/year
- Prevalence fallen substantially
- Transmission continues

(Rodrigues, 2011, Lancet ID)
Leprosy: clinical

- Caused by chronic granulomatous inflammation in skin and peripheral nerves

Classification

- WHO (skin lesions: <6, 6+)
- Ridley-Jopling
  - Tuberculoid disease
    - good cell-mediated immune response
    - few lesions with no detectable mycobacteria
  - Lepromatous leprosy
    - anergic to *M. leprae*
    - multiple lesions with mycobacteria present
- Borderline leprosy types
Leprosy: treatment

- Paucibacillary disease
  - rifampicin and dapsone x6m
- Multibacillary disease
  - rifampicin, dapsone, clofazimine x 12m
- Alternative regimen
  - Rifampicin, oxfloxacin and minocycline X1 month
- Infectiousness reduced after starting treatment
- Relapse rate: 2-3 per 100 person years
- Immune-mediated reactions
  - Occur in 30% of patients with multibacillary disease
  - Steroids are the main treatment
Leprosy: prevention

- Chemoprophylaxis reduces risk in household contacts
  - Rifampicin single dose
  - Rifampicin 2 doses, ofloxacin, minocycline
- Vaccination with BCG protects people from developing leprosy
- Search for subunit protein vaccine been facilitated by the sequencing of *M. leprae*
- There is no suitable animal model
Priorities for mycobacterial research

- Integrated research priorities
- Multidisciplinary
<table>
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<th>TDR: Global research priorities for TB, leprosy and buruli ulcer</th>
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<tbody>
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<td>Improve diagnostics for infection, disease and drug resistance for TB, leprosy and buruli ulcer, especially point of care tests</td>
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<tr>
<td>Develop improved treatment and prevention regimens (based on current and new drugs) for TB, leprosy and buruli ulcer</td>
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<tr>
<td>Identify and validate biomarkers that facilitate development of vaccines, diagnostics and drugs for TB, leprosy and buruli ulcer</td>
</tr>
<tr>
<td>Increase understanding of the pathogenesis of TB, leprosy and buruli ulcer to fuel discovery of drugs, vaccines and diagnostics</td>
</tr>
<tr>
<td>Increase understanding of the burden of disease, the modes of transmission and the impact of public health interventions for TB, leprosy and buruli ulcer</td>
</tr>
<tr>
<td>Develop novel vaccines and optimise current vaccines for TB, leprosy and buruli ulcer</td>
</tr>
<tr>
<td>Evaluate and optimise strategies to improve case finding and reduce barriers to treatment access for TB, leprosy and buruli ulcer</td>
</tr>
<tr>
<td>Optimise implementation of preventive therapy (for TB and leprosy), TB infection control and patient centred TB management, especially drug resistant TB</td>
</tr>
<tr>
<td>Evaluate and optimise new and current strategies to quantify, prevent and minimise disability and stigma resulting from TB, leprosy and buruli ulcer</td>
</tr>
<tr>
<td>Evaluate strategies to strengthen health systems to support control of TB, leprosy and buruli ulcer</td>
</tr>
</tbody>
</table>
What are the barriers?

“we ... activists recoiled from the formaldehyde-enshrouded world of TB science .... so different from the vibrant and ever forward thrusting vitality of HIV science”
Continuum of TB research

Basic research for discovery

Development of new tools (diagnostic tests, drugs, vaccines)

Implementation operational research

Monitoring Evaluation of impact Epidemiology & modelling
Multidisciplinary approach

- Bioinformatics
- Social science
- Pathogenesis/Biomarkers
- Clinical trial
- Modeling/Cost-effectiveness
- Pharmacogenomics
Conclusion

- TB, leprosy and buruli ulcer remain important public health problems
- Elimination of TB, leprosy and buruli ulcer is possible
- New diagnostics, drugs and vaccines are required to reduce morbidity, mortality and burden of disease