

17TH ANNUAL CONFERENCE OF THE
BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association
BHIVA

Dr Nick Paton
MRC Clinical Trials Unit, London

6-8 April 2011, Bournemouth International Centre

**Tuberculosis:
New drugs and diagnostic
approaches – at last**
Nick Paton MD FRCP
MRC CTU, London

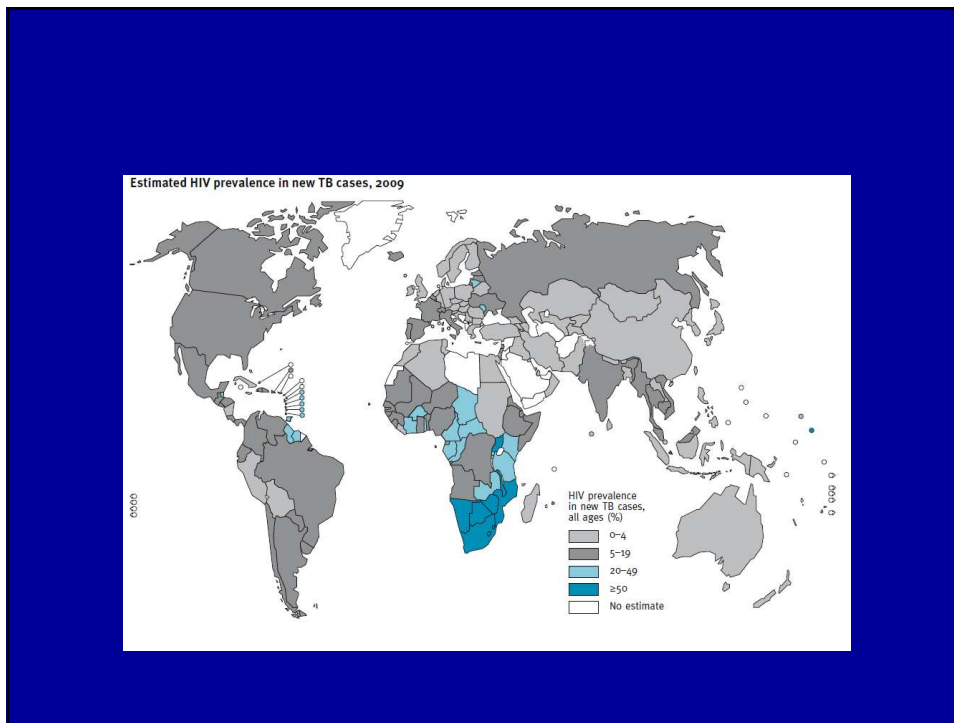
MRC adult HIV trials portfolio

- **Optimising treatment in early chronic HIV disease**
 - Early antiretroviral therapy
 - Hydroxychloroquine / anti-inflammatory therapy
- **Optimising first-line therapy**
 - Protease inhibitor monotherapy
 - Raltegravir-based dual therapy
 - Third drug class + nutrition + OI prophylaxis
- **Optimising second-line therapy**
 - Raltegravir-based dual therapy / PI monotherapy
- **Co-infections**
 - Tuberculosis, Hepatitis B, Hepatitis C



“I am in the process of exploring the possibility... of utilizing our HIV/AIDS clinical trials networks for the implementation of similar clinical trials capacities for TB as well as other infectious diseases.”

--- Pacific Health Summit,
June 17, 2009



MRC's role in TB treatment trials



Austin Bradford Hill

1947-48
Streptomycin trial



Philip D'Arcy Hart

1948-86
Tuberculosis
Research Unit



Wallace Fox

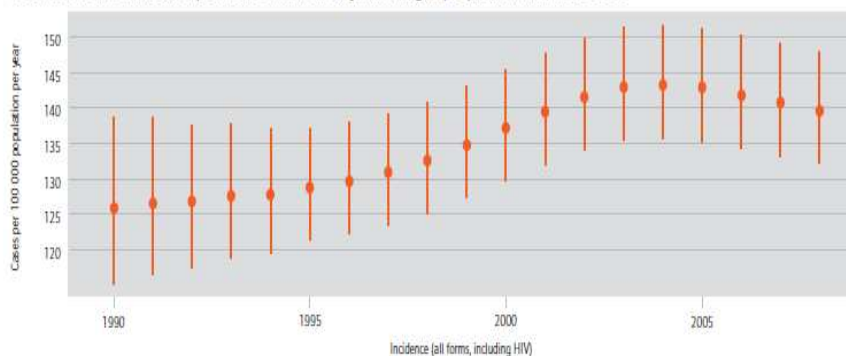
1970 1st Trial of
short course
chemotherapy



Denny Mitchison

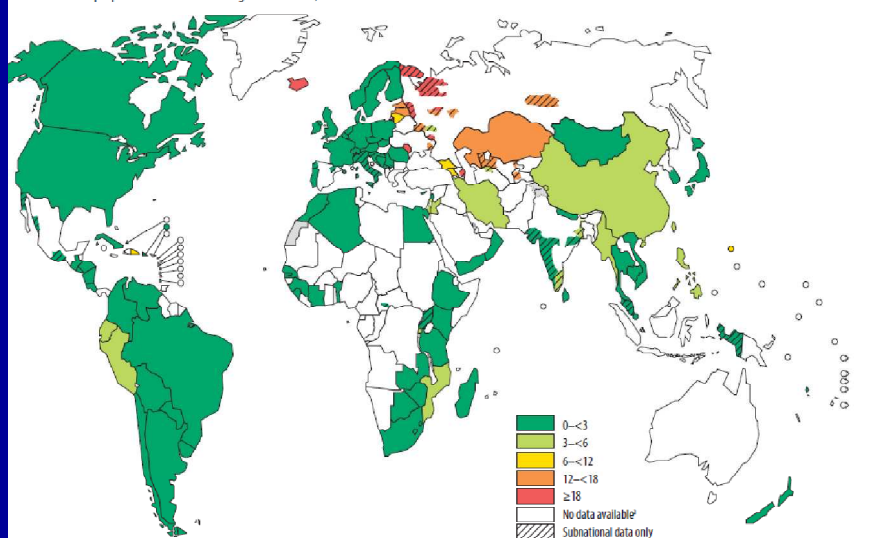
ReMox, Rifaquin,
STREAM

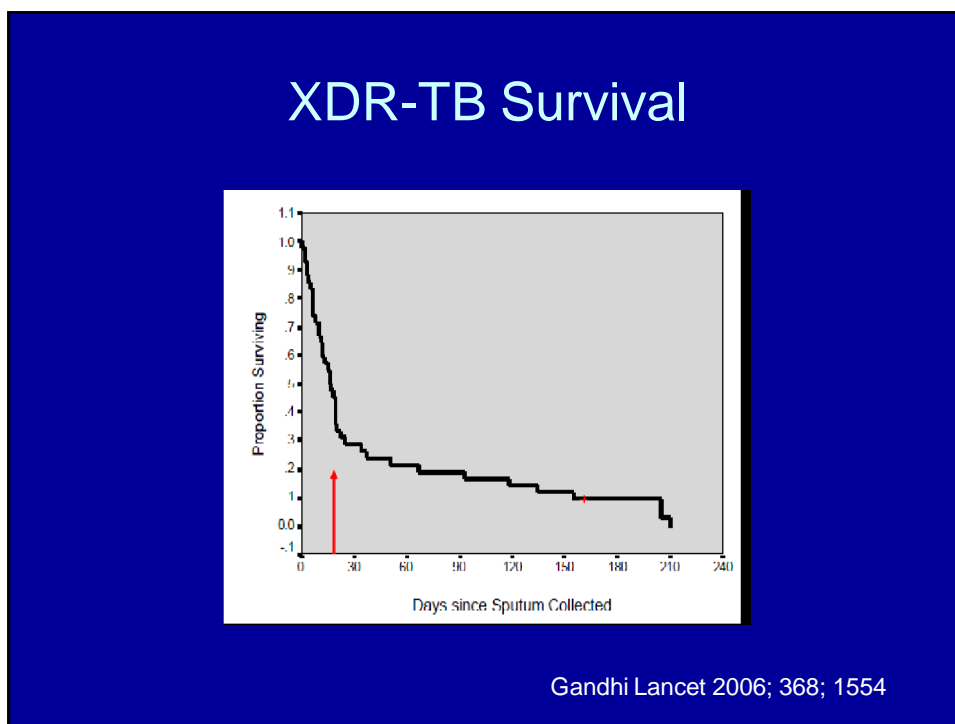
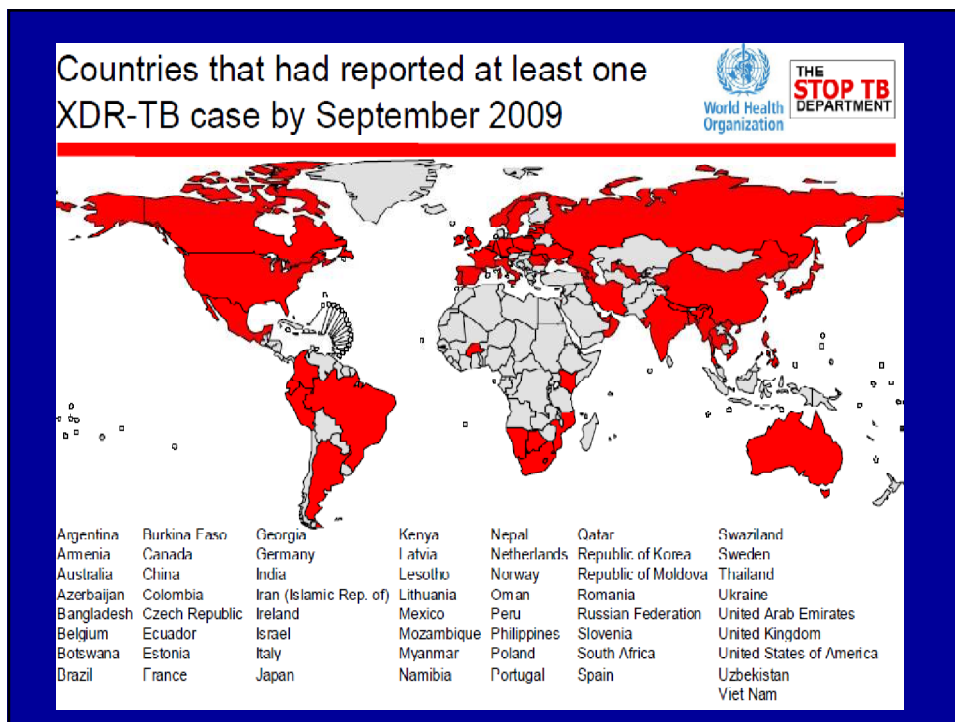
FIGURE 24
Global rates of TB incidence, prevalence and mortality, including in people with HIV, 1990-2008



MDR-TB in new TB cases

Distribution of proportion of MDR-TB among new TB cases, 1994-2009





(X)XDR-TB

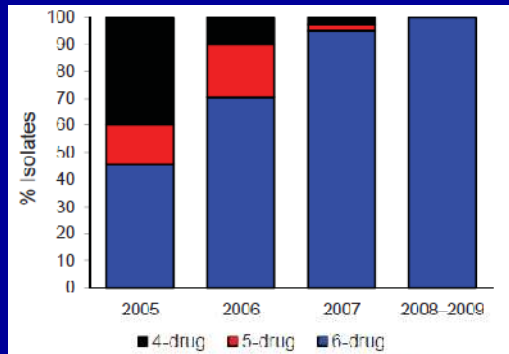
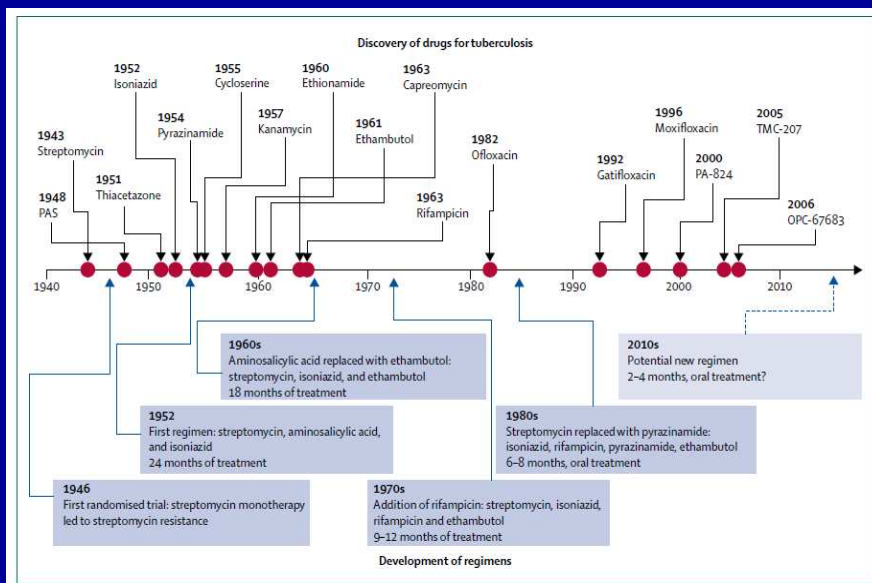
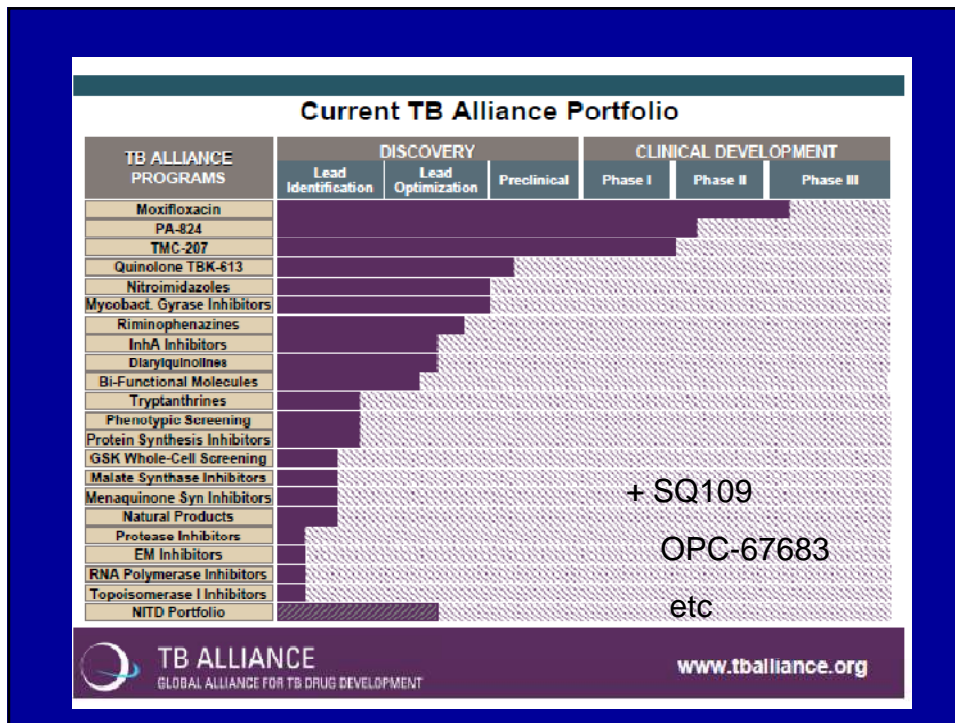


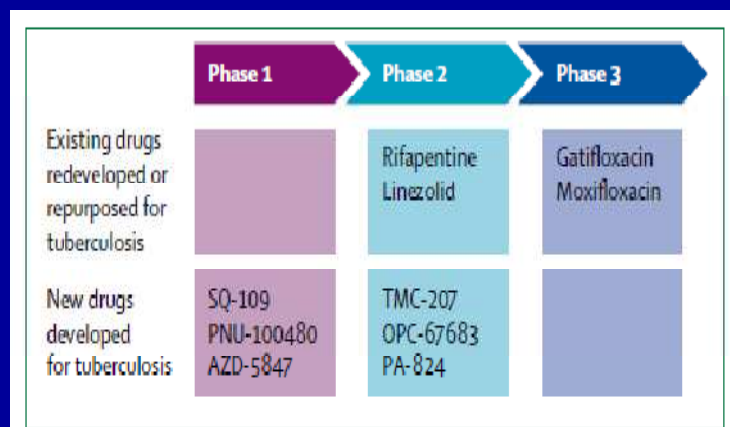
Figure 1. Drug resistance among extensively drug-resistant tuberculosis isolates from Tugela Ferry, South Africa, 2005–2009. 4-drug resistance = isoniazid (INH), rifampin (RIF), ofloxacin (OFL), and kanamycin (KM); 5-drug resistance = INH, RIF, OFL, KM, and ethambutol (EMB) or streptomycin (SM); 6-drug resistance = INH, RIF, OFL, KM, EMB, and SM. Column for 2008–2009 indicates study population.

Shah et al; EID 2011, 17, 510-513





TB drugs in clinical development



MoA of TB Drugs in Development

Multiple Targets

- PA-824
- OPC-67683

DNA Gyrase

- Gatifloxacin
- Moxifloxacin
- TBK-613

Cell-Wall Synthesis

- SQ-109
- Meropenem-Clavulanate*
- CPZEN-45*
- BTZ-043

ATP Synthase

- TMC-207

RNA Polymerase

- Rifapentine

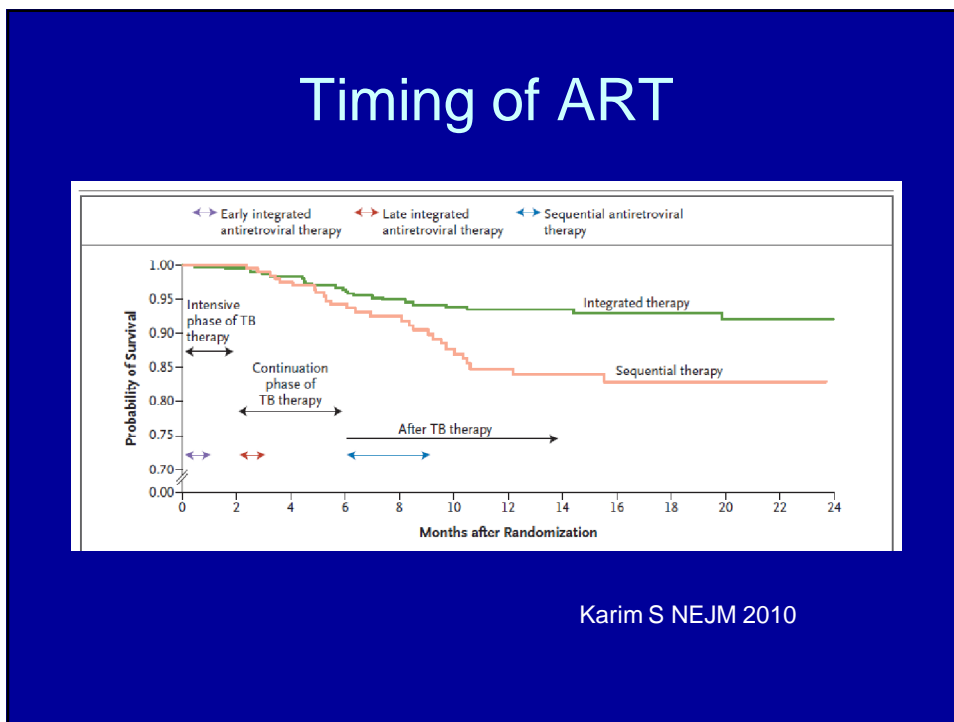
Ribosome

- Linezolid
- PNU-100480
- AZD-4563

* Not orally active

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

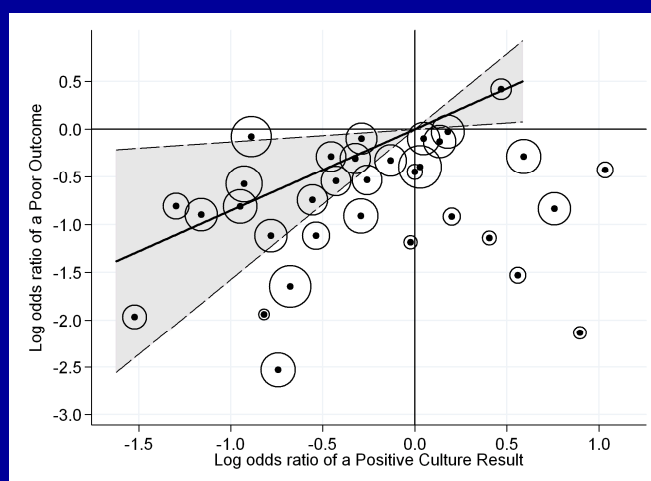
www.tballiance.org



Biomarkers

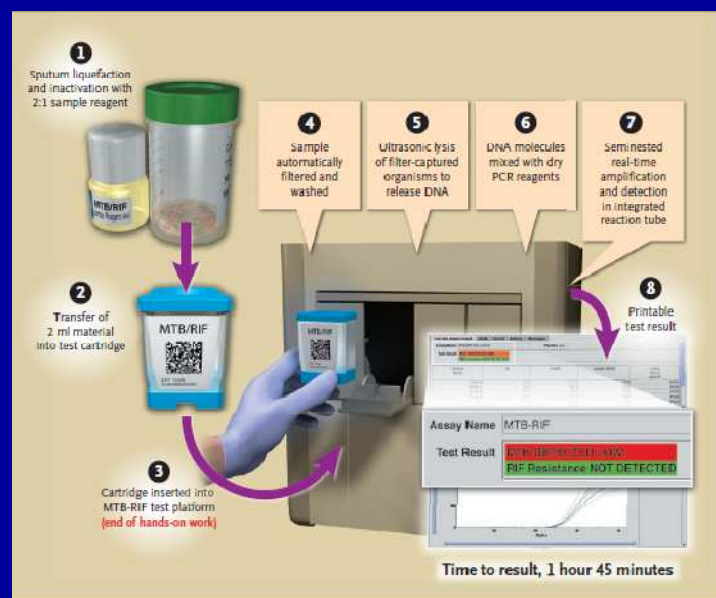
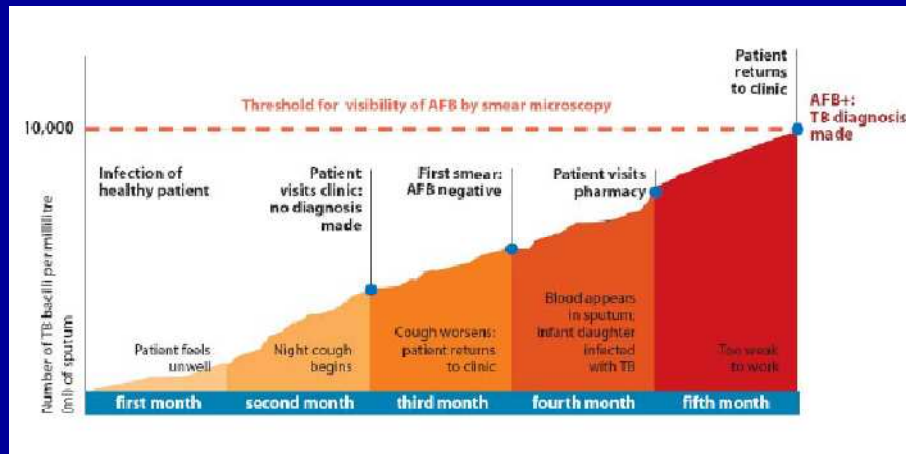
- Need TB biomarkers as predictors of reactivation and cure →
 - Use as surrogate endpoint
 - Accelerate dose selection trials
 - Shorten duration of follow up in clinical trials

2-month sputum culture conversion and TB outcome



Phillips, pers. communication

TB diagnosis



Boehme NEJM 2009; 363; 1005-15