LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Isoniazid preventive therapy in settings of drug resistance: what do we know and what could be done?

Alison Grant

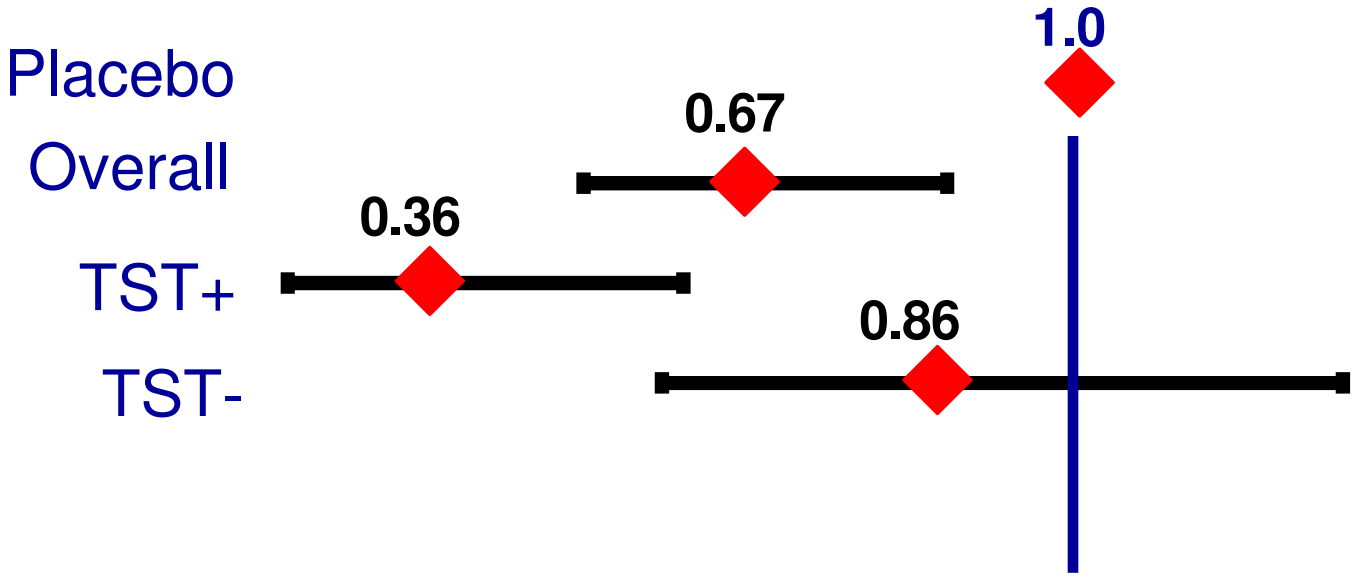
LSHTM

What do we know?

- Isoniazid preventive therapy (IPT) works!

Effect of IPT on TB:

meta-analysis of clinical trials in PWHIV



Akolo 2010, Cochrane review

What do we know?

- IPT works in settings where there is isoniazid resistance

IPT vs. RZ, Haiti, 1990-4

prevalence any H resistance, new TB cases: 17%

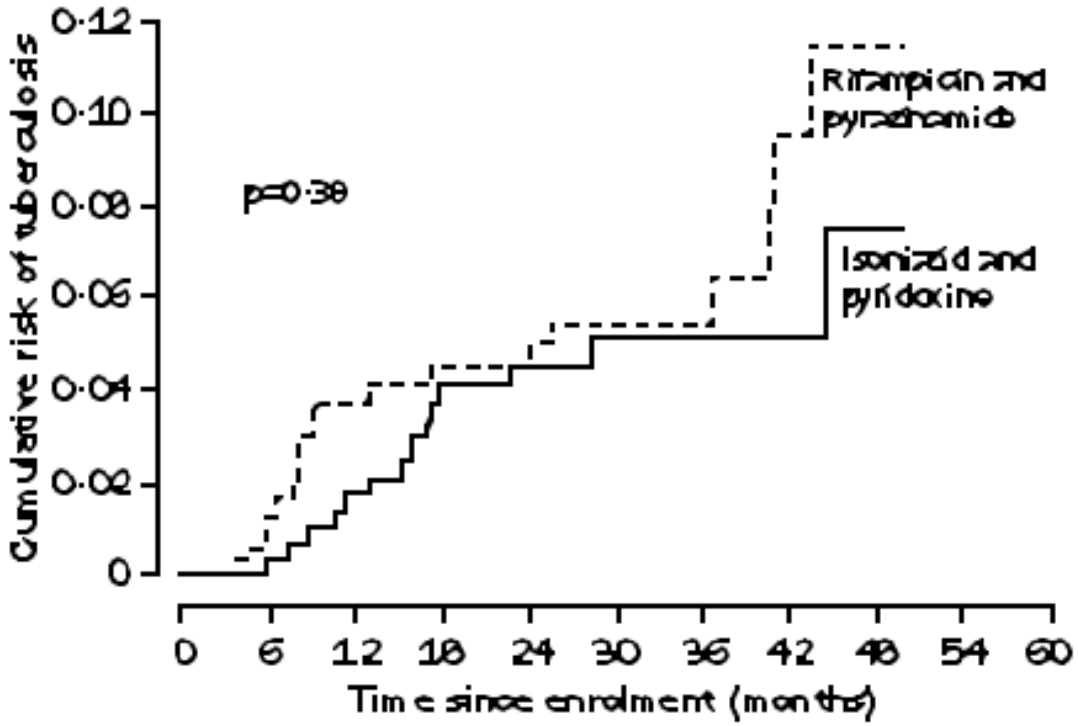
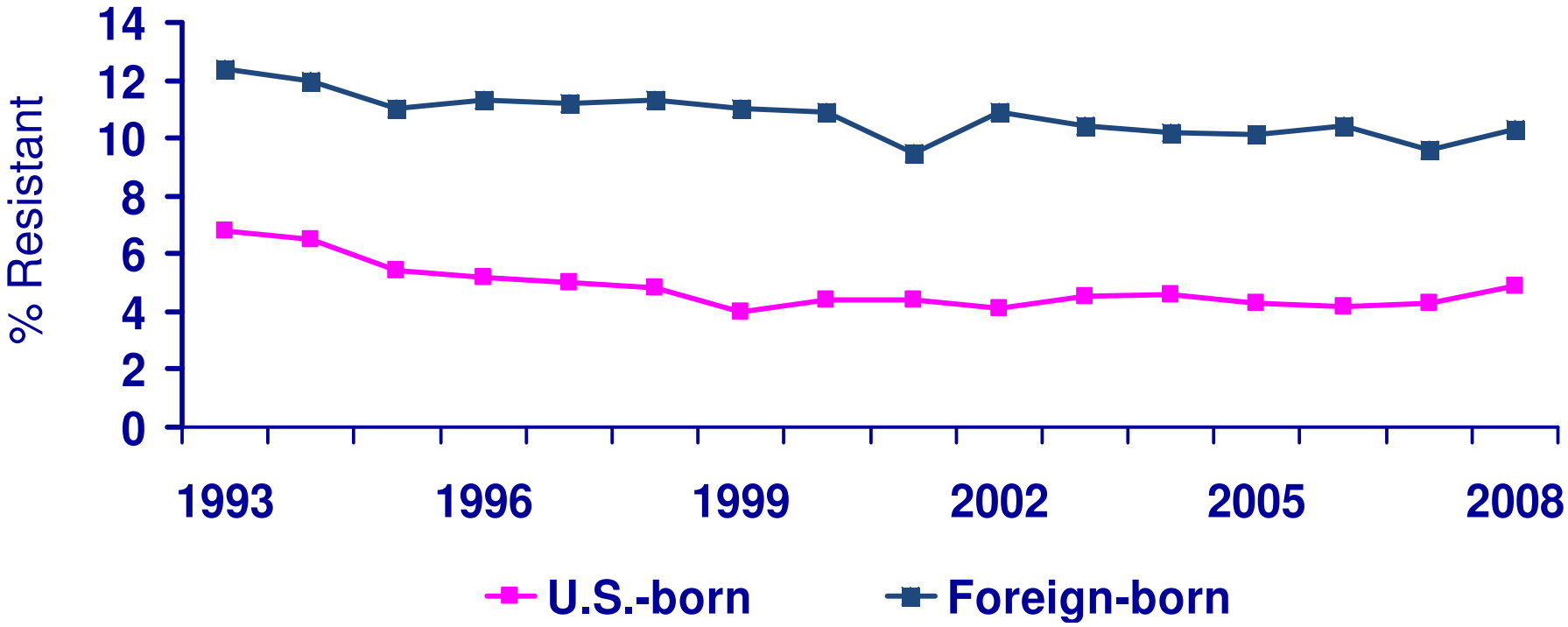


Figure 2: **Kaplan-Meier plot of proportions of patients developing confirmed, probable, or possible tuberculosis by treatment regimen**

Halsey, Lancet 1998;351:786; Chaisson ARRCCM 1996;154:1034

Primary Isoniazid Resistance in U.S.-born vs. Foreign-born Persons United States, 1993–2008*



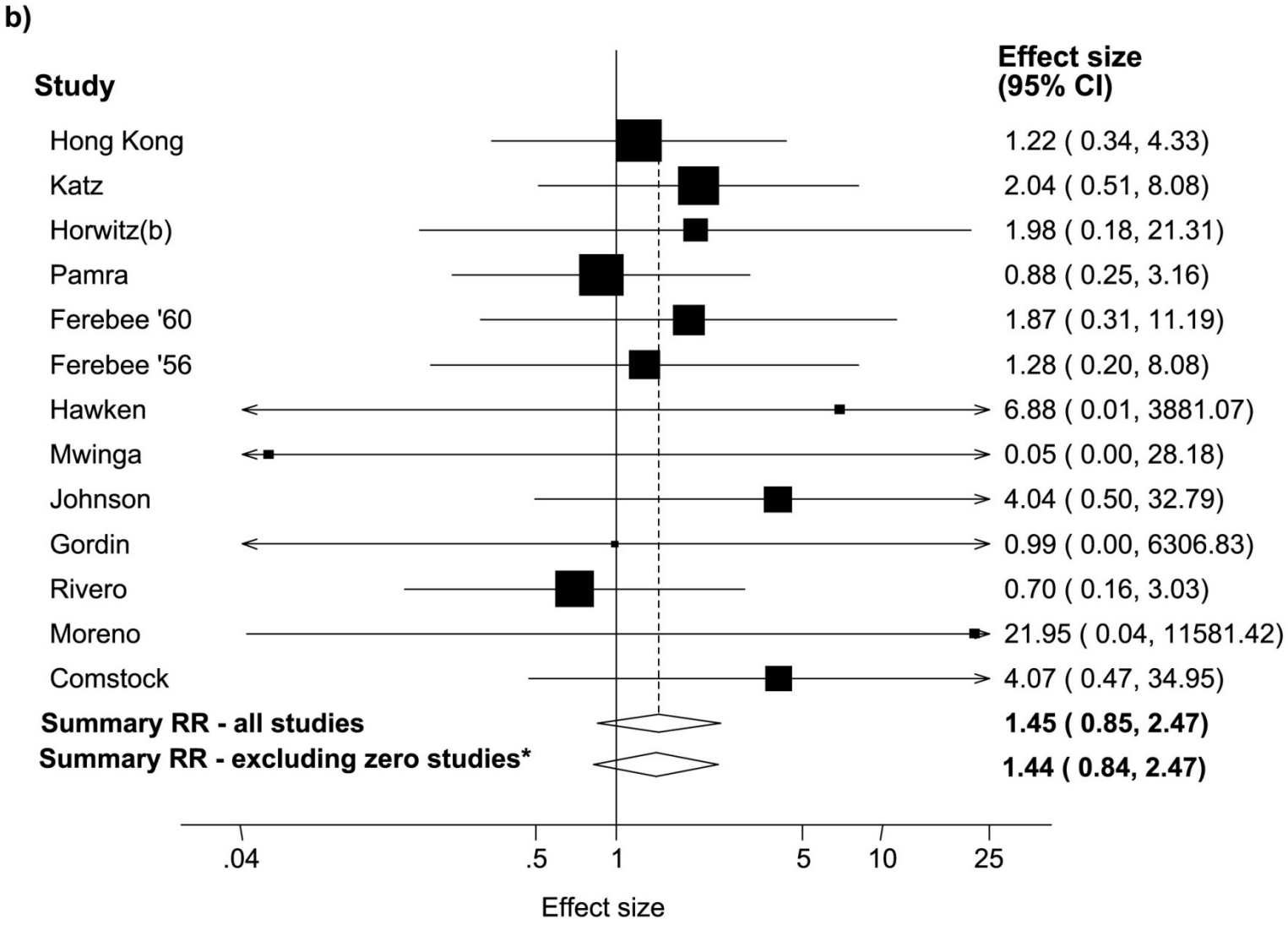
*Updated as of May 20, 2009.

Note: Based on initial isolates from persons with no prior history of TB.

What do we know?

- IPT does not promote isoniazid resistance when used to treat latent TB infection
  - in latent TB few organisms, dividing slowly, hence low risk of selecting drug-resistance mutant

Meta-analysis, incidence of isoniazid resistance, IPT vs. no IPT



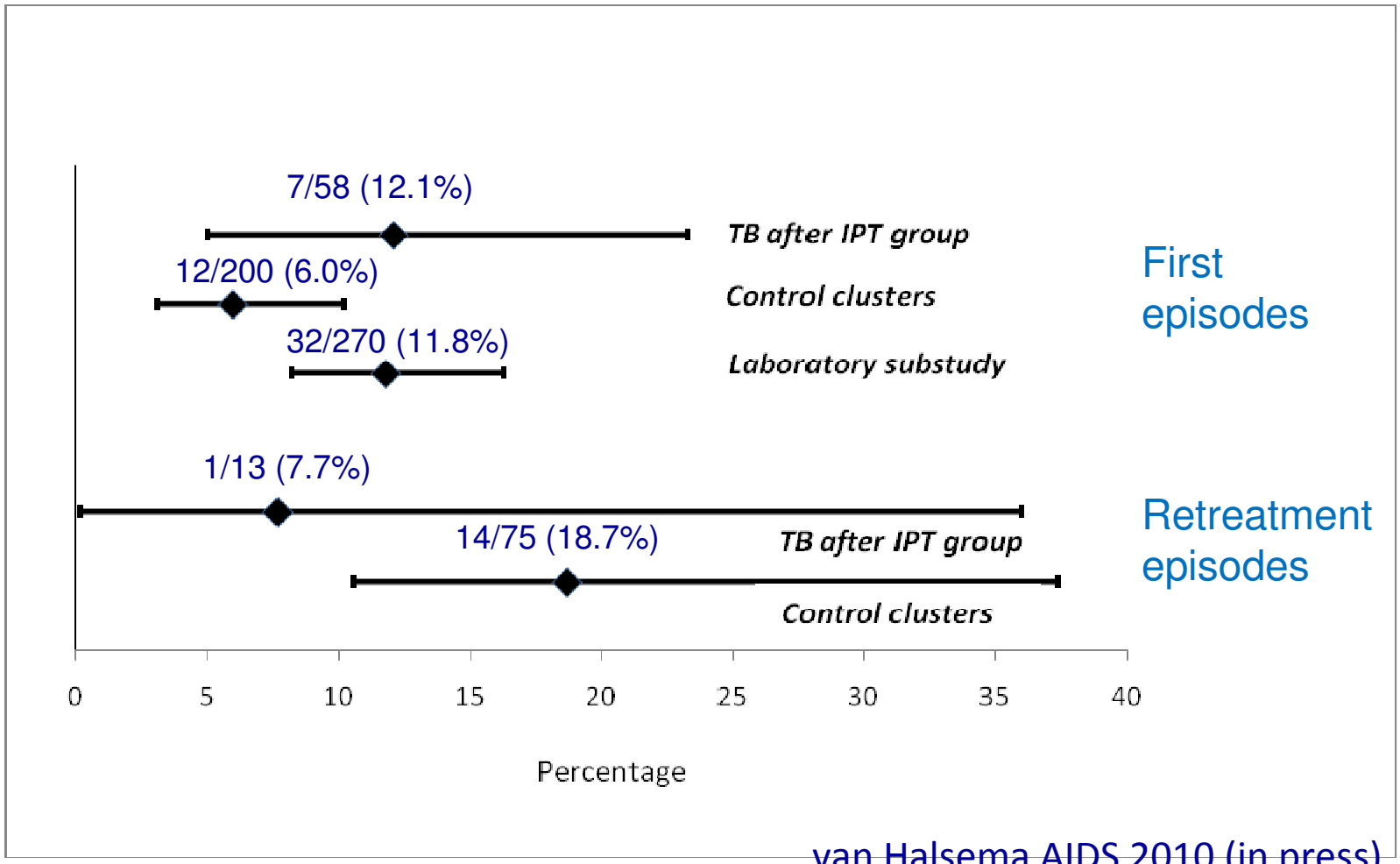
Balcells Emerg Infect Dis 2006;**12**:744

Isoniazid resistance after IPT: data from Thibela TB

- case series from Thibela TB (cluster-randomised trial of community-wide IPT)
  - 126 gold miners (125 men, median 43y) developing active TB after receiving IPT
  - 89/103 (86.4%) had HIV infection
  - median CD4 (n=51) 196 cells/mm^3
  - drug susceptibility results available for 71 (58 new, 13 retreatment)

van Halsema AIDS 2010 (in press)

Prevalence of any isoniazid resistance in TB episodes after IPT (bars=95% CI)



van Halsema AIDS 2010 (in press)

What do we know?

- IPT does not promote isoniazid resistance when used to treat latent TB infection
  - unless a person with active TB is given isoniazid monotherapy
  - thus importance of screening to exclude active TB prior to IPT

What are we less sure about?

- IPT ineffective in individual with latent INH-resistant TB

What are we less sure about?

- IPT ineffective in individual with latent INH-resistant TB
- though not all INH resistance is equal:

Gene	Gene function	Role	Mechanism	% resistant strains	Degree of resistance conferred	Overcome with high dose INH?
kat G	catalase-peroxidase	pro-drug conversion	inhibition of mycolic acid biosynthesis and other effects	50-95%	high	no
inh A	enoyl ACP reductase	drug target		8-43%	low	yes

adapted from Zhang IJTLD 2009;13:1320

What are we less sure about?

- who has latent infection with a resistant strain?
- best data from studies of contacts of drug-resistant TB cases
- contacts with latent TB infection may not have the same strain /resistance pattern as the index case

Household contacts may not have the same resistance pattern as index

- Retrospective cohort, Rio de Janeiro, Brazil, 1988-92
- 64 index cases with resistance to >1 drug
- 17/218 HIV neg household contacts developed TB
- 13/17 culture + with DST:
  - 6 (46%) identical DST to index case
  - 4 (31%) resistance, with different pattern
  - 3 (23%) fully susceptible

Kritski AJRCCM 1996;153:331

Household contacts may not have the same resistance pattern as index

	MDR index case	XDR index case
Contacts culture+ with DST	26	29
Fully sensitive	2 (8%)	2 (7%)
MDR	14 (54%)	8 (28%)
XDR	10 (38%)	19 (66%)

data from KwaZulu Natal, South Africa: Moll et al, Union conference, Cancun 2009

IPT may have some effect even in contacts of MDR index cases

- Among TST+ (>10mm) contacts of MDR index cases (Brazil, 1988-92):
  - no IPT: active TB in 13/145 (9.0%)
  - IPT: TB in 2/45 (4.4%) (OR 0.46, 95% CI 0.07-2.32)
    - 2 cases post IPT both had MDR strains, as did index cases

Kritski AJRCCM 1996;153:331

What are we less sure about?

1: what are the risks vs. benefits of IPT for people with HIV in settings of high prevalence of isoniazid resistance?

- no evidence about threshold prevalence of INH resistance at which IPT risks exceed benefits

What could be done?

- Review data:
  - outcomes from IPT programmes among PWHIV in settings of high prevalence of isoniazid resistance

IPT use where isoniazid resistance, new cases, >15%

country	year of resistance survey	prevalence any isoniazid resistance, new TB cases	started IPT, 2008
Dominican Republic	1995	19%	443
Georgia	2006	23%	301
Kazakhstan	2001	42.8%	656
Mozambique	1999	16.5%	724
Vietnam	2006	19%	500

WHO drug resistance survey 2008;
IPT data courtesy WHO

What are we less sure about?

2: what to do for contacts of MDR index cases

- almost no data
- inconsistent international guidelines
  - WHO 2006: follow up, no chemoprophylaxis
  - ATS/CDC 2000: if high risk, ZE or Z plus Fq
  - American Academy Pediatrics: 2 drugs to which index case susceptible
  - SA expert advice for HIV+ or child contacts: Fq plus E or ethionamide plus high dose H (Schaaf 2009)
- accordingly, national guidelines also inconsistent (Cain 2010)
- consensus that more data are needed

Research priorities

- case registries of MDR contacts who are treated
- formal trials of regimens for MDR contacts
  - e.g. Fq /E or ethionamide /high dose H vs. placebo or vs. isoniazid alone

Research priorities

- trials among MDR contacts of new agents?
- e.g. TMC 207: diarylquinoline, inhibits mycobacterial ATP synthetase

  - phase 2 RCT of 5-drug second line regimen + TMC207 x8w vs. placebo reduced time to culture conversion
  - also has activity in non-replicating mycobacteria

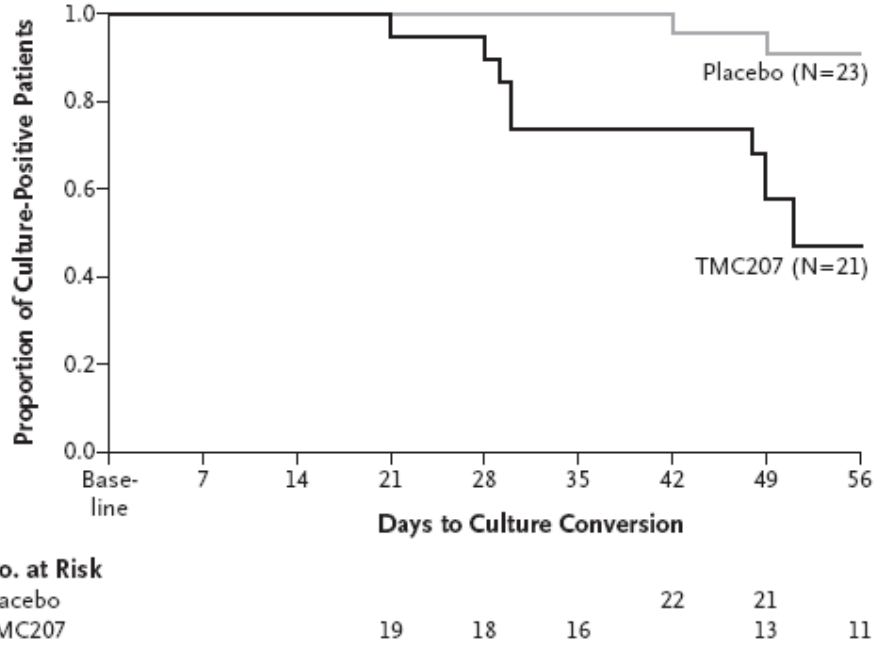


Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.

Proportions of positive cultures were determined according to the myco-bacteria growth indicator tube (MGIT) system.

Diacon NEJM 2009;360:2397

Research priorities

- trials among MDR contacts of new agents e.g. TMC207 vs. placebo or vs. IPT
  - advantages: potentially great for participants, who currently have few options
    - relatively small studies
    - could evaluate single agent as monotherapy
  - disadvantage: low power to detect rare adverse events

Research priorities

- more data please!

Acknowledgements

- Gavin Churchyard
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Effect of IPT on prevalence of resistance