Drug-resistant Tuberculosis: The urgent need for better, shorter and more tolerable treatment regimens

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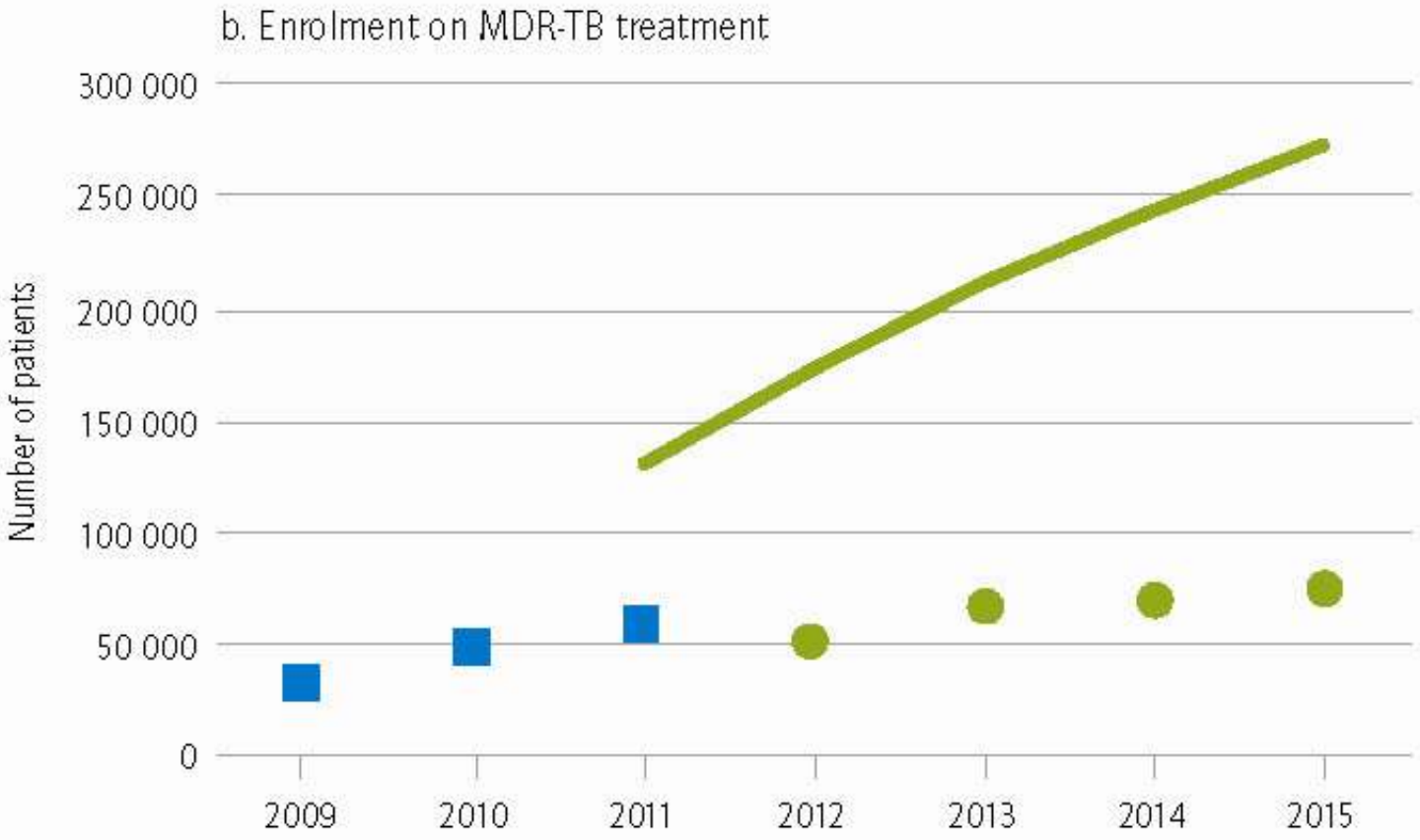
MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

DR-TB treatment scale up needed!

~650,000 prevalent cases globally



WHO TB Report Oct 2012

Current DR-TB treatment (WHO)

Group name	Anti-tuberculosis agent	Abbreviation
Second-line parenteral agent (injectable anti-tuberculosis drugs)	kanamycin amikacin capreomycin	Km Amk Cm
Fluoroquinolones	levofloxacin moxifloxacin gatifloxacin ofloxacin	Lfx Mfx Gfx Ofx
Oral bacteriostatic second-line anti-tuberculosis drugs	ethionamide prothionamide cycloserine terizidone *p*-aminosalicylic acid	Eto Pto Cs Trd PAS
Group 5 drugs	clofazimine linezolid amoxicillin/clavulanate thioacetazone clarithromycin imipenem	Cfz Lzd Amx/Clv Thz Clr Ipm

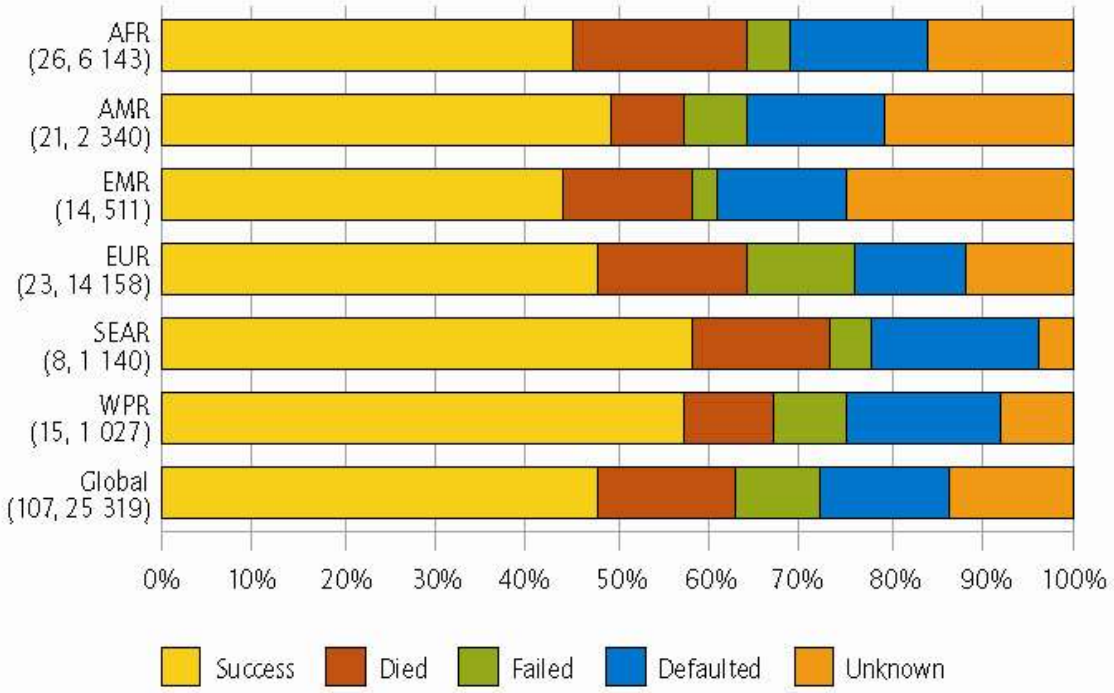
- ❑ At least 4 second-line drugs likely to be effective
- ❑ Injectable drug for at least 8 months
- ❑ Total treatment duration at least 20 months

Evidence for current regimens...

- No randomised controlled trials
- Most drugs used off-label
- Most would not be approved for use under current regulatory requirements
- WHO recommendations for DR-TB treatment are all rated at **“very low quality evidence”**

Global DR-TB treatment outcomes

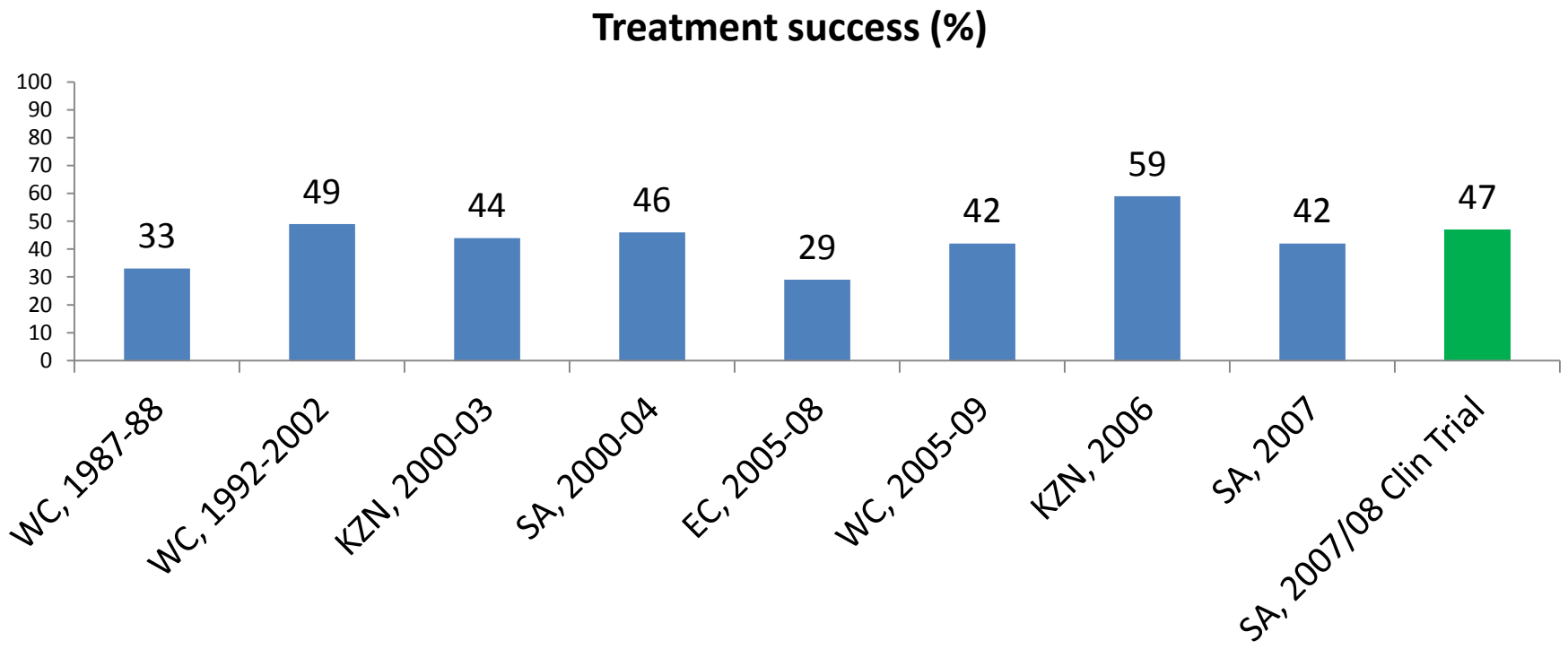
FIGURE 4.8 **Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2009 cohorts.** The number of countries reporting outcomes for at least one case, followed by total cases with outcome data, shown beside each bar.



- ~30,000 enrolled on treatment in 2009
- Less than 50% treatment success globally and in African region
- High rates of death, failure and default throughout

WHO TB Report. Oct 2012

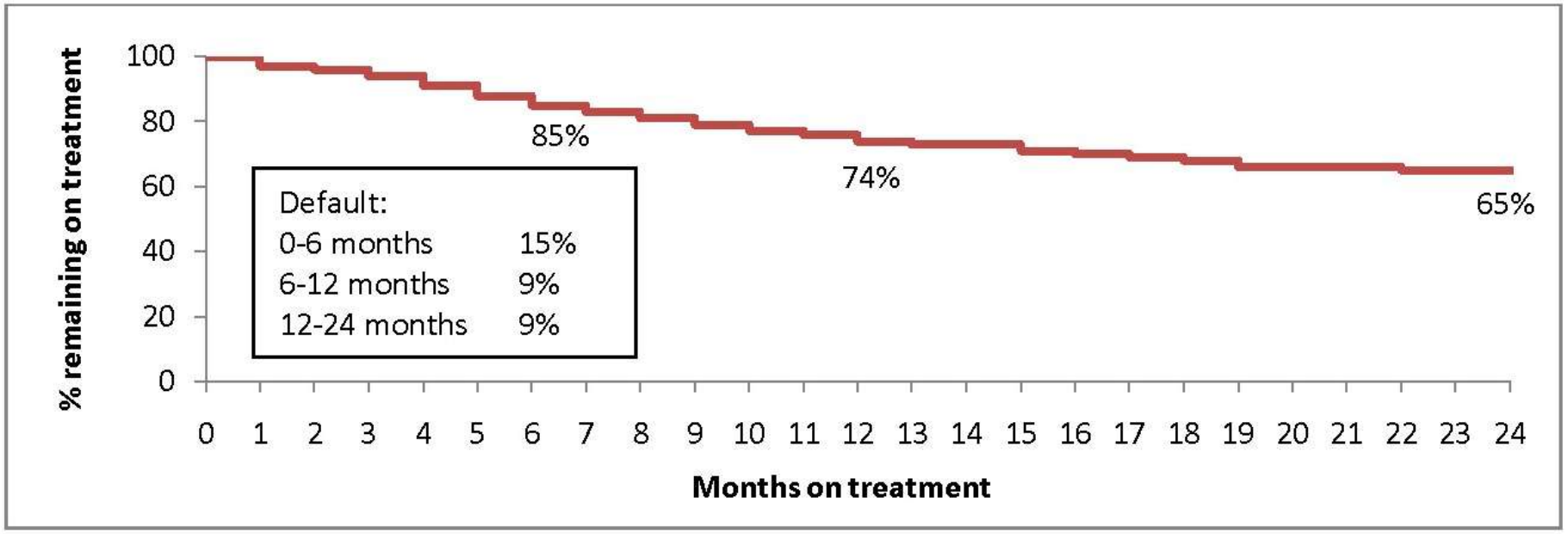
DR-TB treatment success in South Africa



- Very poor outcomes overall
- High rates of mortality and default

Schaaf et al Trop Med Int Hlth 1996, Shean et al IJTBLD 2008, Brust et al IJTBLD 2010, Farley et al PLoS One 2011, Odendaal et al PHA SA newsletter, Aug 2012, Khayelitsha DR-TB programme, O Donnel et al IJTBLD 2009, Kvasnovsky et al JAIDS 2011, NDOH data, reported 2011, Diacon et al AAC 2012, Brust et al IJTBLD 2012

Treatment default in Khayelitsha

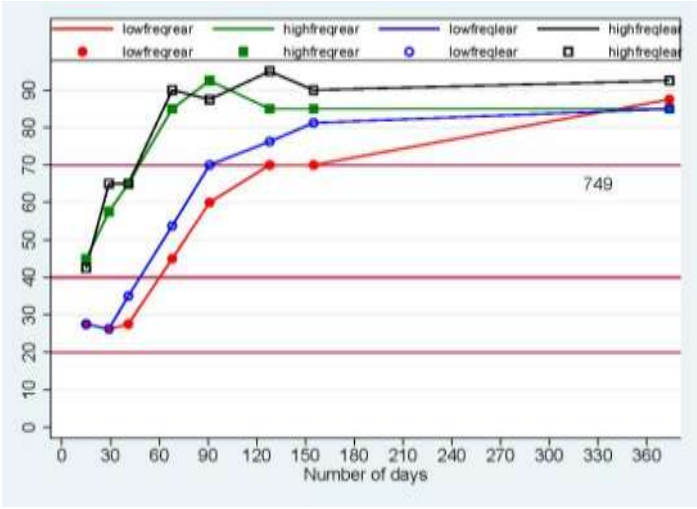


- Default throughout treatment
- Injectable in first 6 months probably increases default
- Treatment fatigue is a major issue

Side effects of treatment

- Painful injections
- Hearing loss due to the injectable drugs (~30% of patients in some settings)
- Nausea and vomiting
- Kidney failure
- Psychiatric side effects (depression, paranoia)
- Hepatitis
- Peripheral neuropathy (tingling, numbness, pain)
- Side effects often additive with HIV drugs

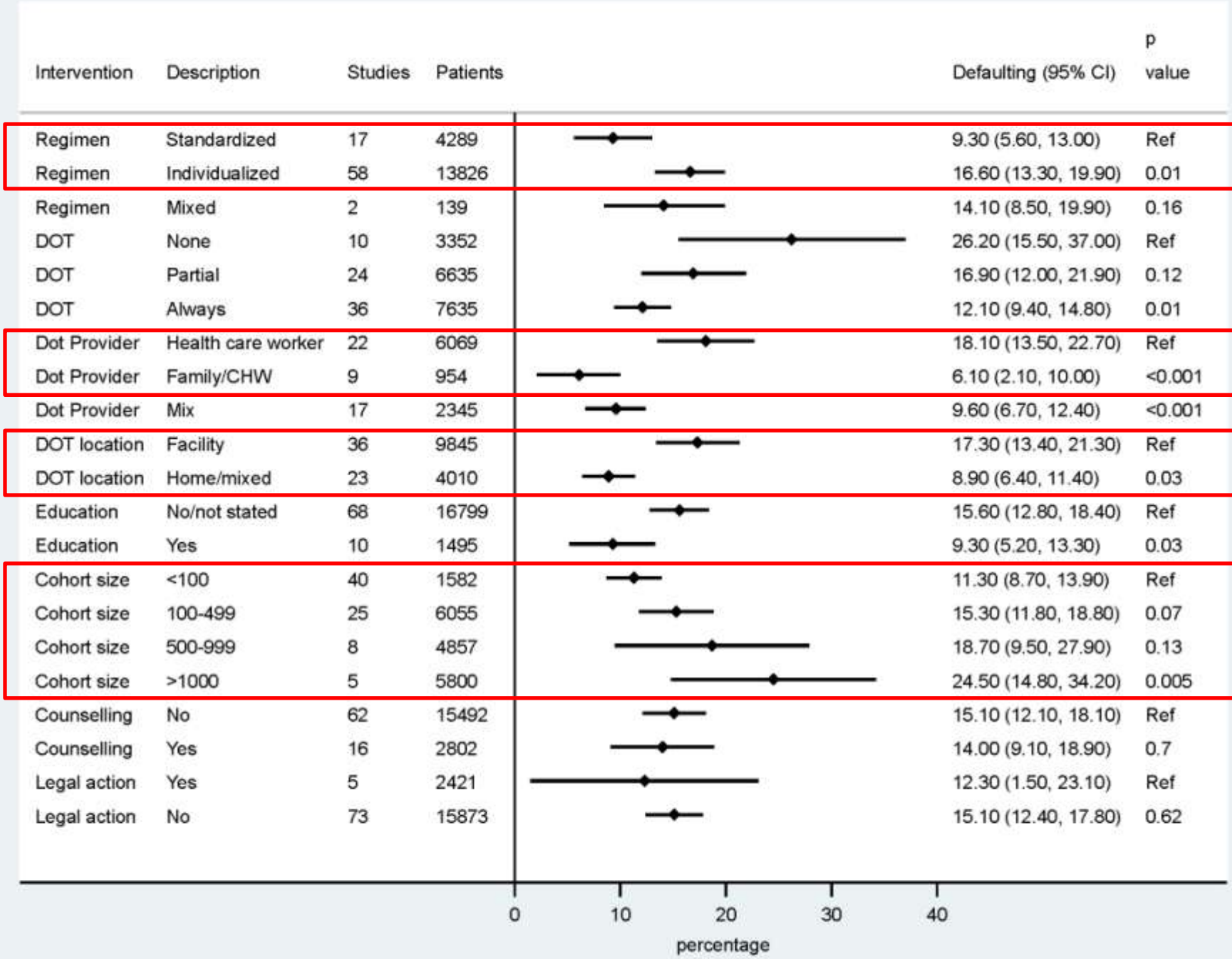
Hearing loss with treatment

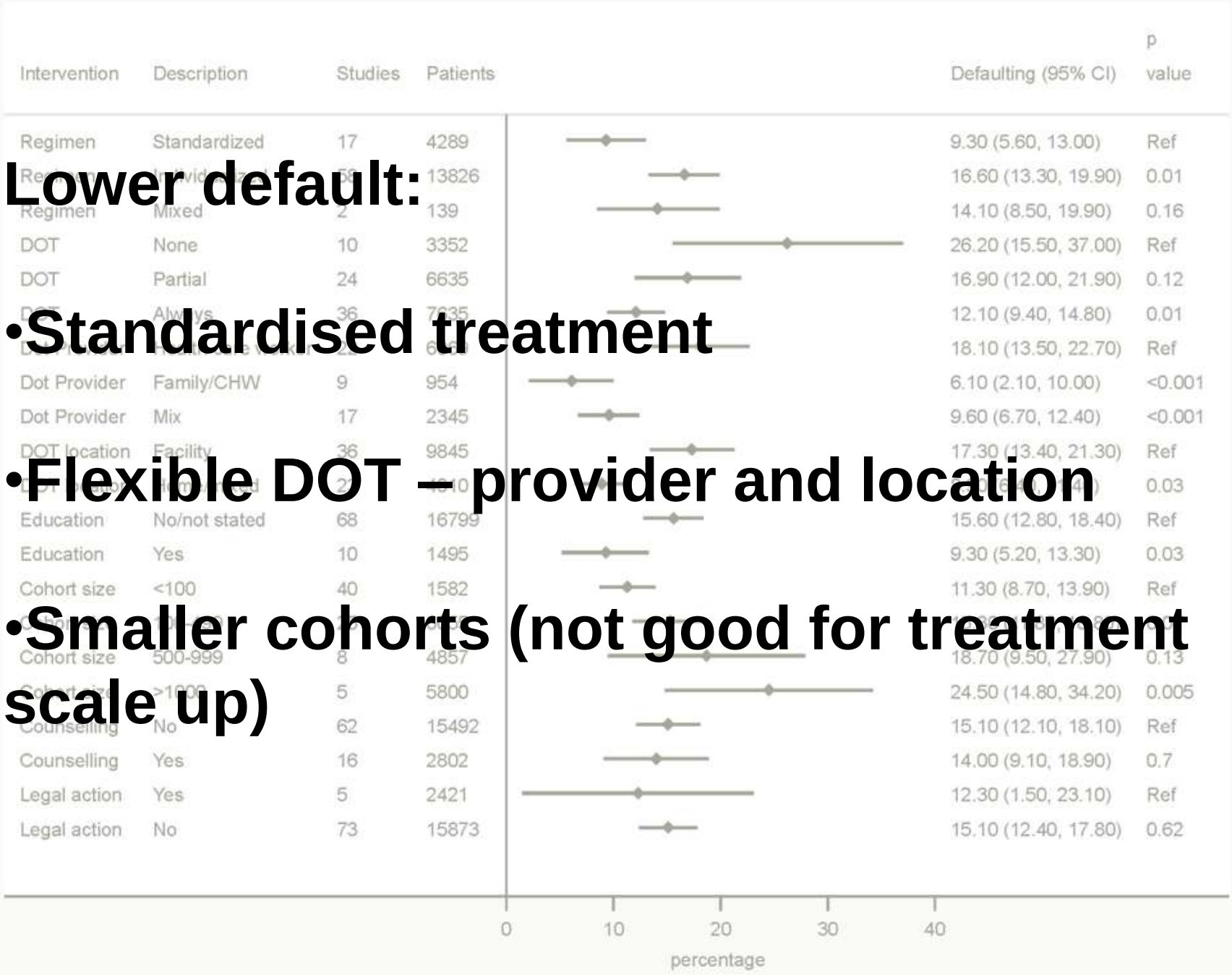


Treatment default: tolerability

Tocsek et al Int J TB Lung Dis, in press

- Systematic review of DR-TB treatment outcomes specifically looking at default
- 75 studies, 18,294 patients, 31 countries
- **Overall 15% default (range 1- 56%)**
- Extremely heterogeneous
- Look at factors (programmatic level) predicting default


Intervention
Description
Studies
Patients
Defaulting (95% CI)
p value
Regimen Standardized 17 4289 9.30 (5.60, 13.00) Ref
Regimen Individualized 58 13826 16.60 (13.30, 19.90) 0.01
Regimen Mixed 2 139 14.10 (8.50, 19.90) 0.16
DOT None 10 3352 26.20 (15.50, 37.00) Ref
DOT Partial 24 6635 16.90 (12.00, 21.90) 0.12
DOT Always 36 7635 12.10 (9.40, 14.80) 0.01
Dot Provider Health care worker 22 6069 18.10 (13.50, 22.70) Ref
Dot Provider Family/CHW 9 954 6.10 (2.10, 10.00) <0.001
Dot Provider Mix 17 2345 9.60 (6.70, 12.40) <0.001
DOT location Facility 36 9845 17.30 (13.40, 21.30) Ref
DOT location Home/mixed 23 4010 8.90 (6.40, 11.40) 0.03
Education No/not stated 68 16799 15.60 (12.80, 18.40) Ref
Education Yes 10 1495 9.30 (5.20, 13.30) 0.03
Cohort size <100 40 1582 11.30 (8.70, 13.90) Ref
Cohort size 100-499 25 6055 15.30 (11.80, 18.80) 0.07
Cohort size 500-999 8 4857 18.70 (9.50, 27.90) 0.13
Cohort size >1000 5 5800 24.50 (14.80, 34.20) 0.005
Counselling No 62 15492 15.10 (12.10, 18.10) Ref
Counselling Yes 16 2802 14.00 (9.10, 18.90) 0.7
Legal action Yes 5 2421 12.30 (1.50, 23.10) Ref
Legal action No 73 15873 15.10 (12.40, 17.80) 0.62
0
10
20
30
40
percentage



Lower default:

- **Standardised treatment**
- **Flexible DOT – provider and location**
- **Smaller cohorts (not good for treatment scale up)**

We need a new regimen!

- Some new drugs are close to approval
- Do we wait for an entirely new regimen?
- Conventional approach 20+ years
- Drug combination approach – half this, but still too long
- Or use combination of new, existing and re-purposed drugs to develop our ‘best guess’ regimen
- Both short term and long term goals are needed

Which drugs to choose?

New:

- Bedaquiline (TMC207)
- OPC-67683 (Delamanid)
- PNU-100480
- SQ-109
- PA-824

Re-purposed:

- Linezolid
- Clofazamine
- High dose INH

Existing:

- Fluoroquinolones
- Injectables
- Ethionamide
- Terizidone
- PAS

Existing drugs: Individual patient meta analysis

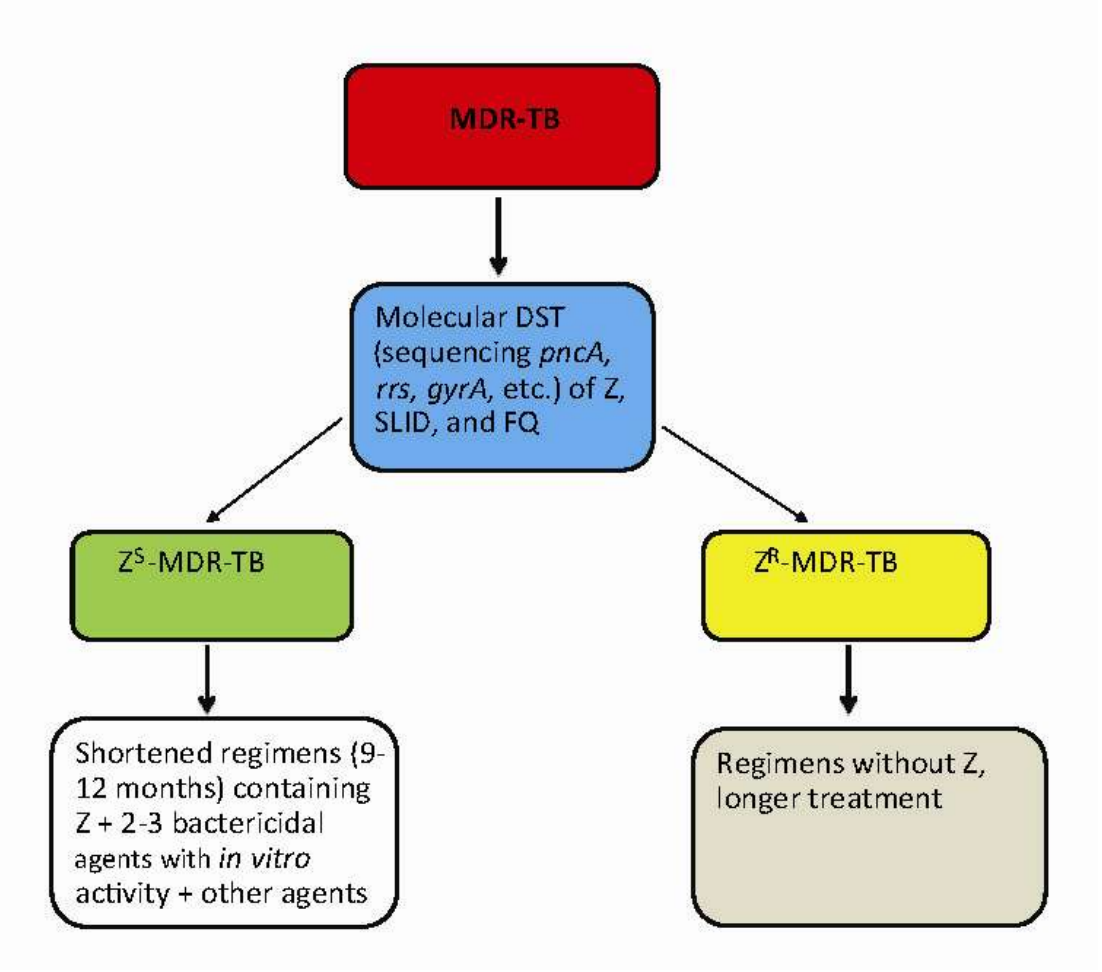
Ahuja et al PLoS Medicine 2012

- 9,000+ MDR-TB patients
- Range of settings and treatment strategies

Choice of drugs?	Odds ratio – success vs fail/rel/death/def
Kanamycin vs capreomycin	**1.3 (1.1-1.6)**
Kanamycin vs **no** injectable	1.3 (0.7-2.5)
Capreomycin vs **no** injectable	1.1 (0.4-3.2)
Later gen FLQ vs **no** FLQ	**2.8 (1.3-6.1)**
Later gen FLQ vs Oflox	**2.1 (1.2-3.9)**
Ethionamide	**1.7 (1.5-2.0)**

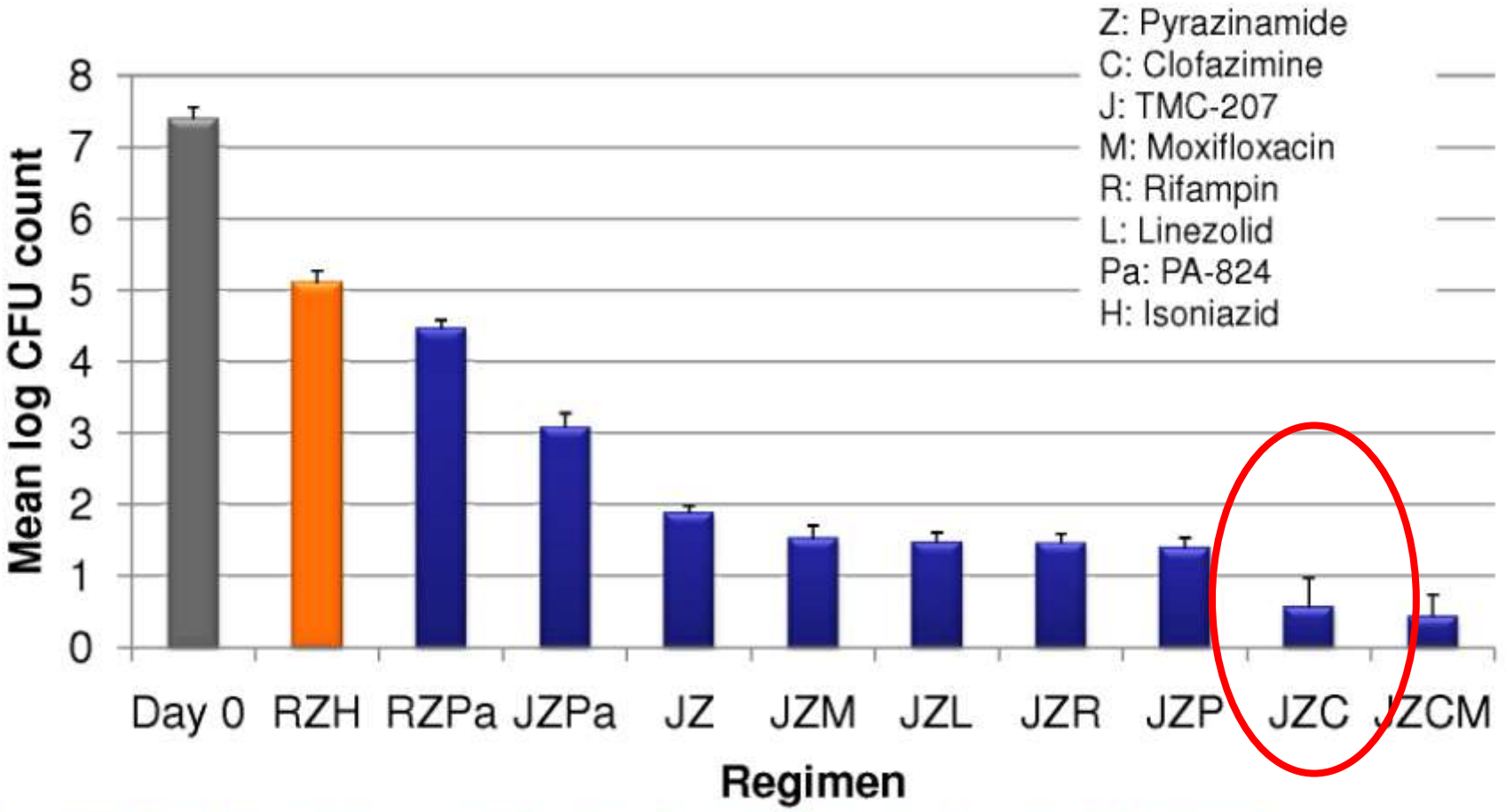
Pyrazinamide susceptibility: shorter treatment?

- PZA enables shortening of first-line TB treatment
- Potential synergistic activity with existing and new TB drugs
- Improved cult conversion with phenotypic PZA susceptibility
- May enable shortening of DR-TB regimens (if susceptible)



Zhang et al Emerg Mic and Inf 2012

Re-purposed drugs: Clofazimine (mouse data)



*Mouse TB infection model: aerosol infection, 2-week before Rx, 4 weeks of treatment

TB Alliance 2011

The Bangladesh regimen (clofazimine)

Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun[1,2], Aung Kya Jai Maug[3], Md Abdul Hamid Salim[3], Pankaj Kumar Das[3], Mihir Ranjan Sarker[3], Paul Daru[3], and Hans L. Rieder[1,4]

[1]International Union Against Tuberculosis and Lung Disease, Paris, France; [2]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; [3]Damien Foundation Bangladesh, Dhaka, Bangladesh; and [4]Institute of Social and Preventive Medicine, University of Zurich, Switzerland

Most successful regimen:

- Intensive phase (4 months min): Gfx,**Cfz**, EMB, PZA, Proth, Kan, high dose INH
- Continuation phase: Gfx,**Cfz**, EMB, PZA
- Total duration 9 months min
- 88% treatment success

Am J Respir Crit Care Med Vol 182. pp 684–692, 2010
Originally Published in Press as DOI: 10.1164/rccm.201001-0077OC on May 4, 2010
Internet address: www.atsjournals.org

A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis

Int J TB Lung Dis 2008

S. K. Katiyar,* S. Bihari,* S. Prakash,*† M. Mamtani,† H. Kulkarni†

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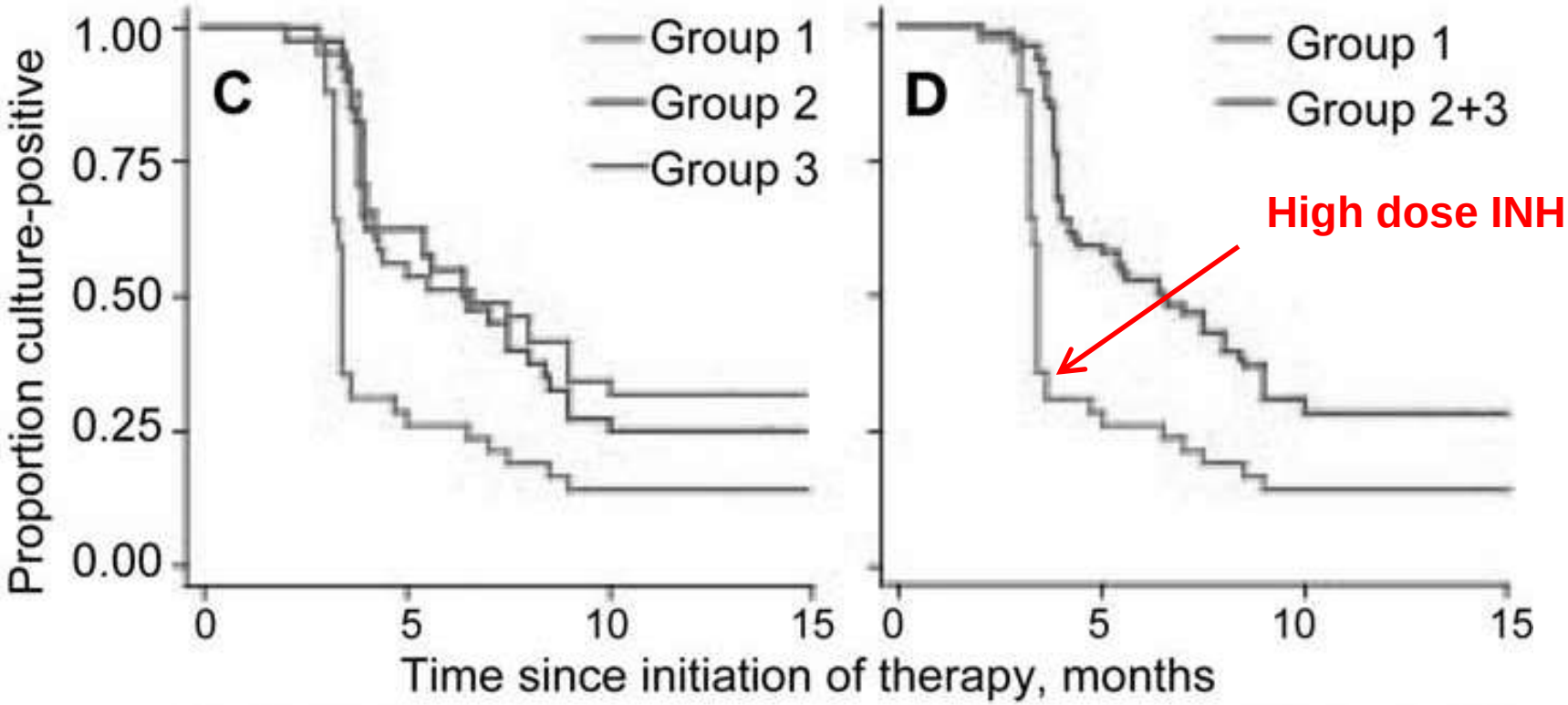
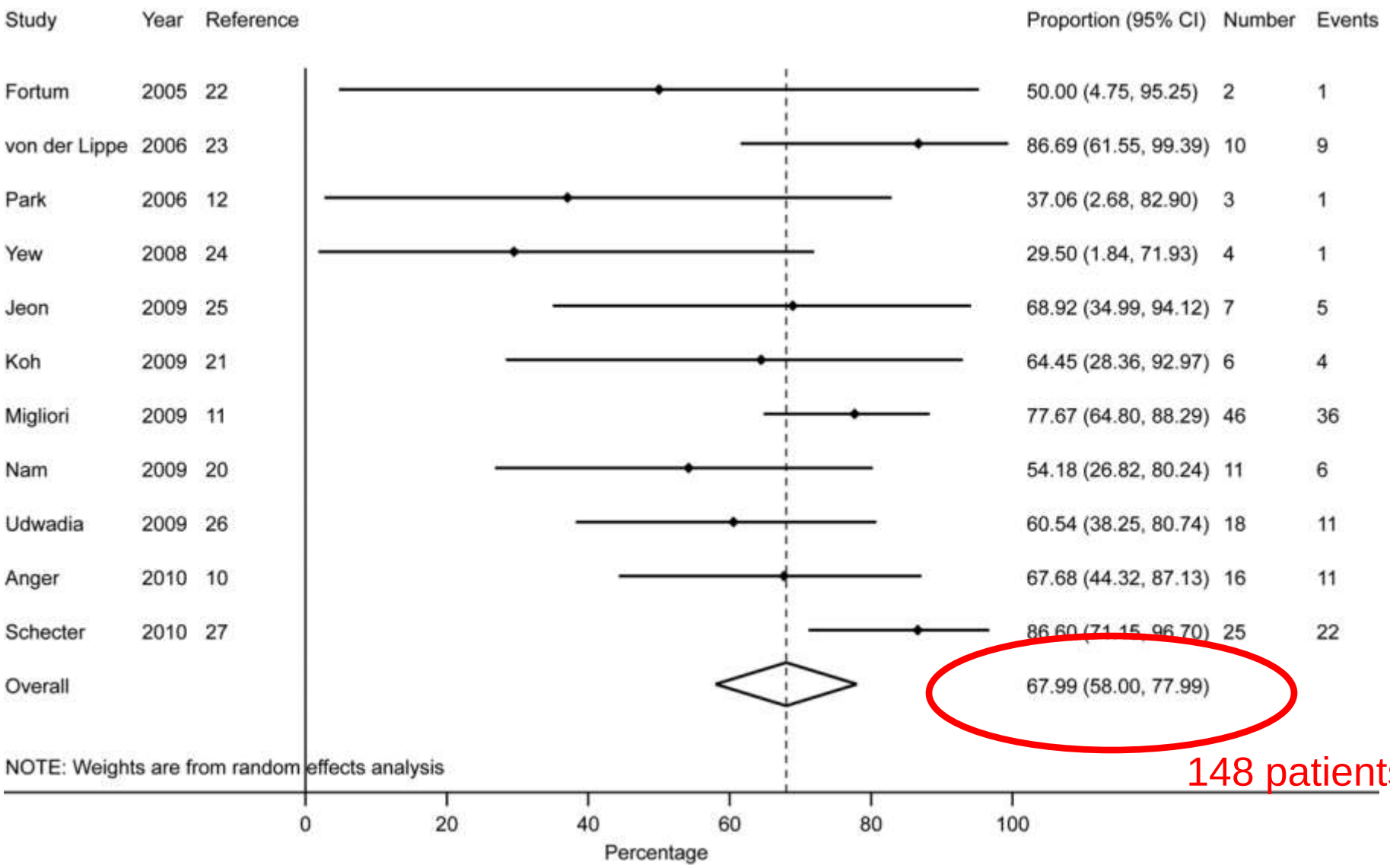


Linezolid for complicated DR-TB: systematic review



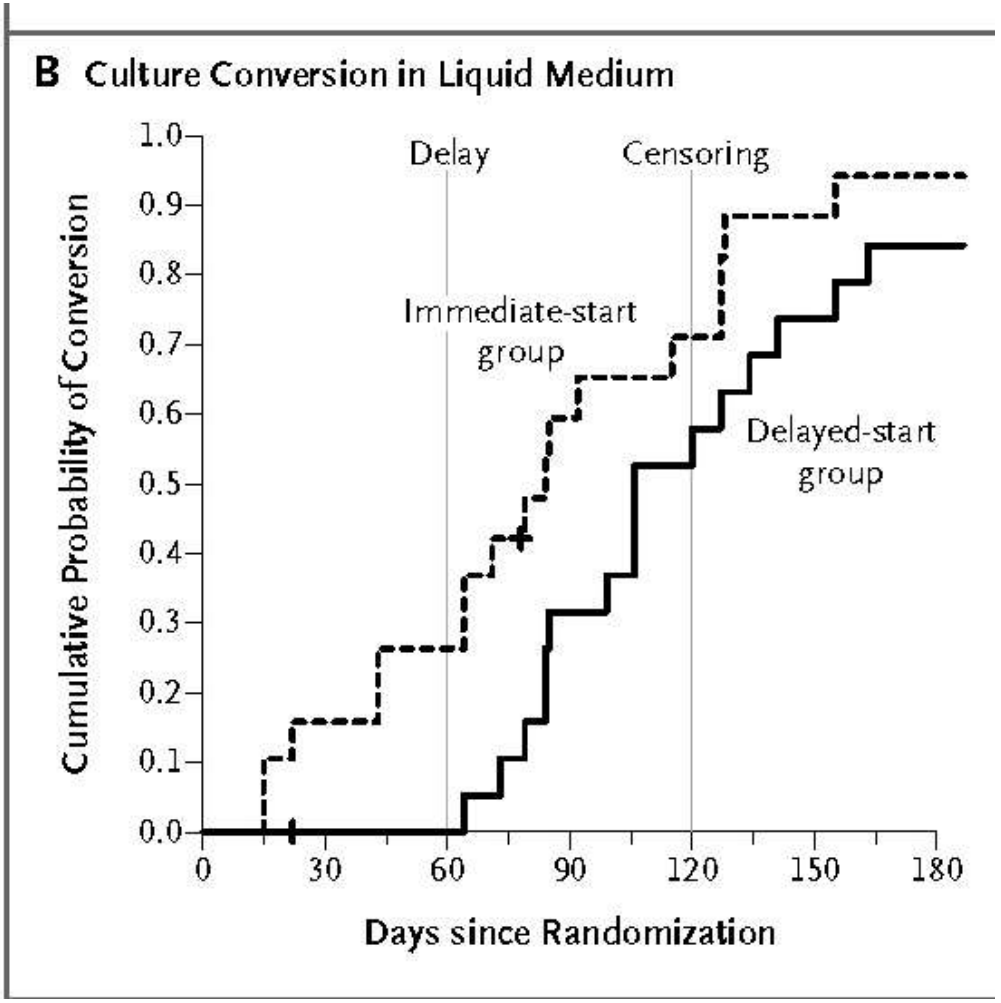
148 patients

Cox & Ford, Int J TB Lung Dis, 2012

Linezolid for chronic XDR-TB: clinical trial

Lee et al NEJM 2012

- 38 XDR-TB patients
- Previously unresponsive to treatment
- 87% culture conversion within 6 months
- 82% sig AEs
- 300 mg daily may be acceptable



Key principles for a new regimen

- At least one new class of drug
- Minimum 3 effective drugs?
- Not combining drugs of the same class
- No injectables?
- Broad backbone that can be used for MDR and XDR
- Simple dosing
- Limited side effects
- Shorter duration (6-9 months?)
- Minimal interaction with ART

Regimen options?

- Need to start treatment on Rif resistance result only
- Start with strong regimen containing more drugs than will be needed
- Change treatment when further DST results become available (phenotypic and genotypic)
- Easier to withdraw drugs than to add

??? Bedaquiline, Delamanid, Moxifloxacin, Clofazimine, Pyrazinamide, high dose Isoniazid, (Linezolid, ethionamide?)

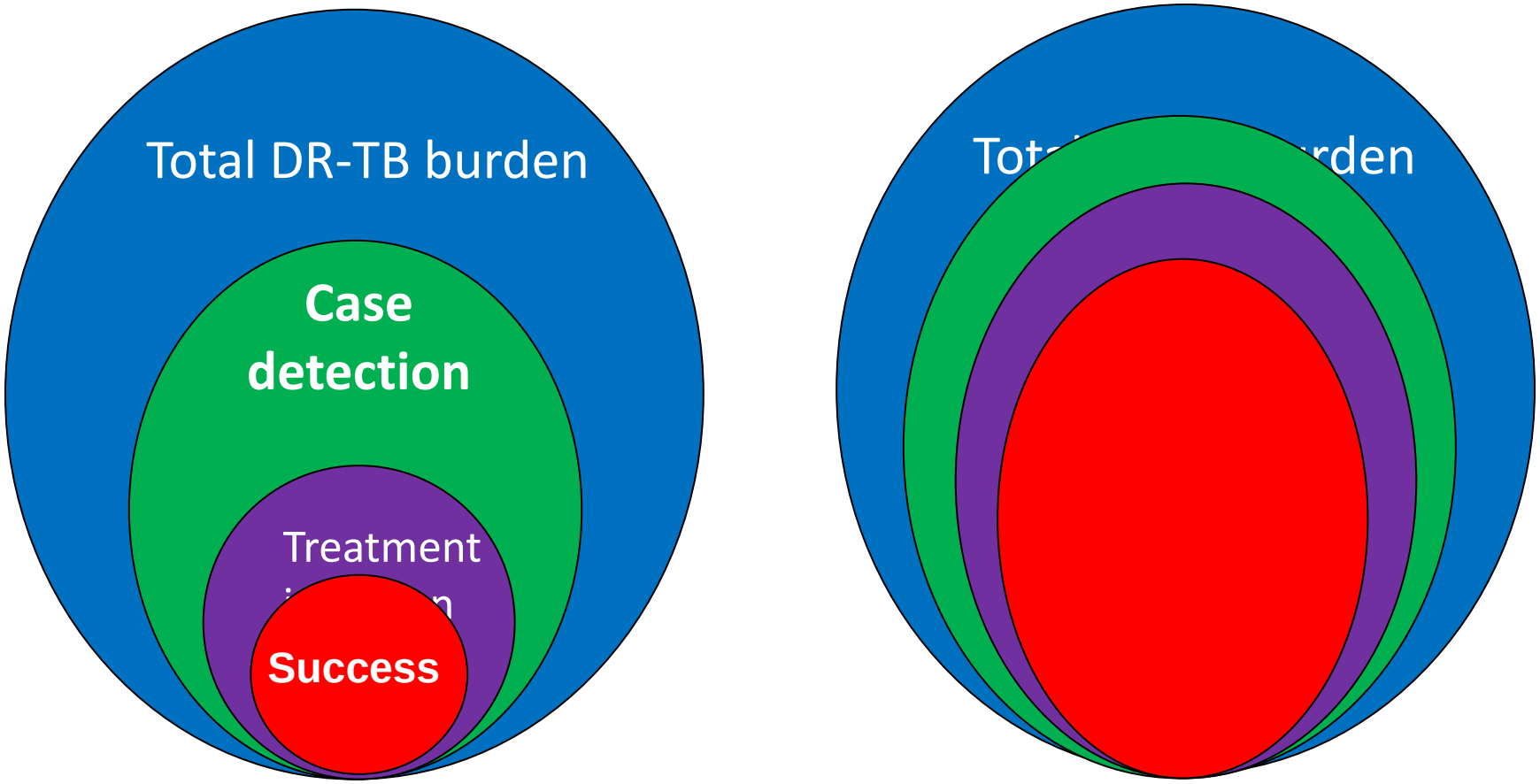
Pragmatic trials required

- Pharmaceutical companies design trials to get their own new drugs registered.
- They are not primarily interested to design a new regimen
- Therefore the regimens that are tested in clinical trials are often not the most practicable in high burden, programmatic settings

Potential trade-offs?

	Benefits	Trade-offs
Shorter duration	•Reduced default •Easier monitoring •Decreased cost	Reduced efficacy Increased relapse
No injectable	•Improved tolerability and default •Less adverse events •Easier health service implementation •Decreased cost	Reduced efficacy?
More than one potentially cardiotoxic drug	Increased efficacy Overall improved survival	Potential risk of sudden death in a few

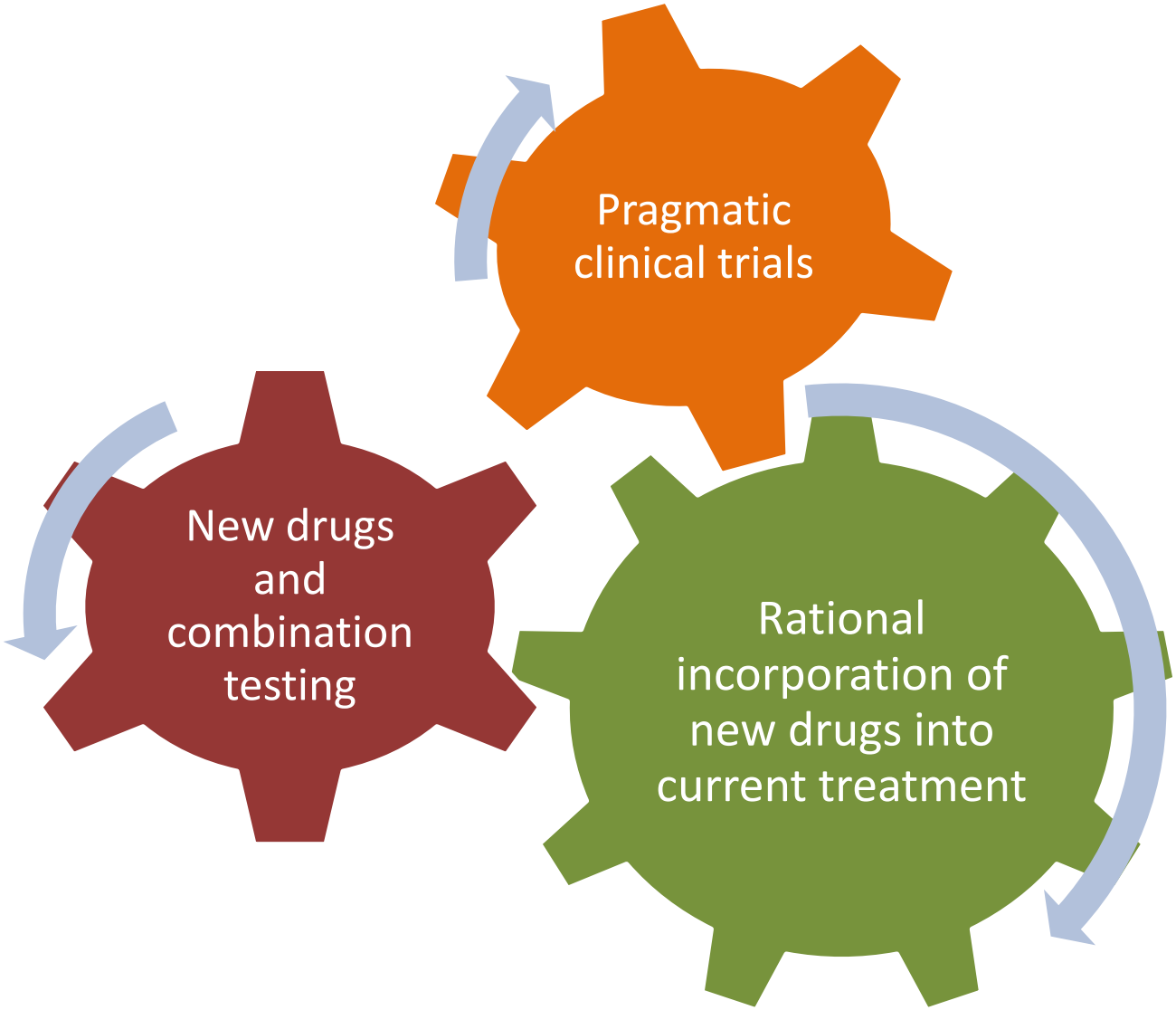
Overall impact…



Current: ~10,000 deaths/year

Better regimen: ~5,000 deaths/year

Concurrent approaches required



Summary

- Current treatment not good enough
- Regimen change is urgently needed
- New drugs are close to available
- Need to use these new drugs in the best possible regimens that take into account tolerability and duration in addition to efficacy
- Pragmatic clinical trials that reflect programmatic conditions are needed

Keeping things in perspective...

"With no controlled trials, to base therapy on anecdotal treatment successes with linezolid could be dangerous"

Chang et al Lancet Infect Dis July 2012

"...trials are rarely conducted in conditions that genuinely reflect programmatic conditions"

Nunn Int J TB Lung Dis 2010

Acknowledgments

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