

Treatment options and outcome in the management of M/XDR-TB

Jean-Pierre Zellweger, MD

Swiss Lung Association

Annecy, 15 Sept 2015

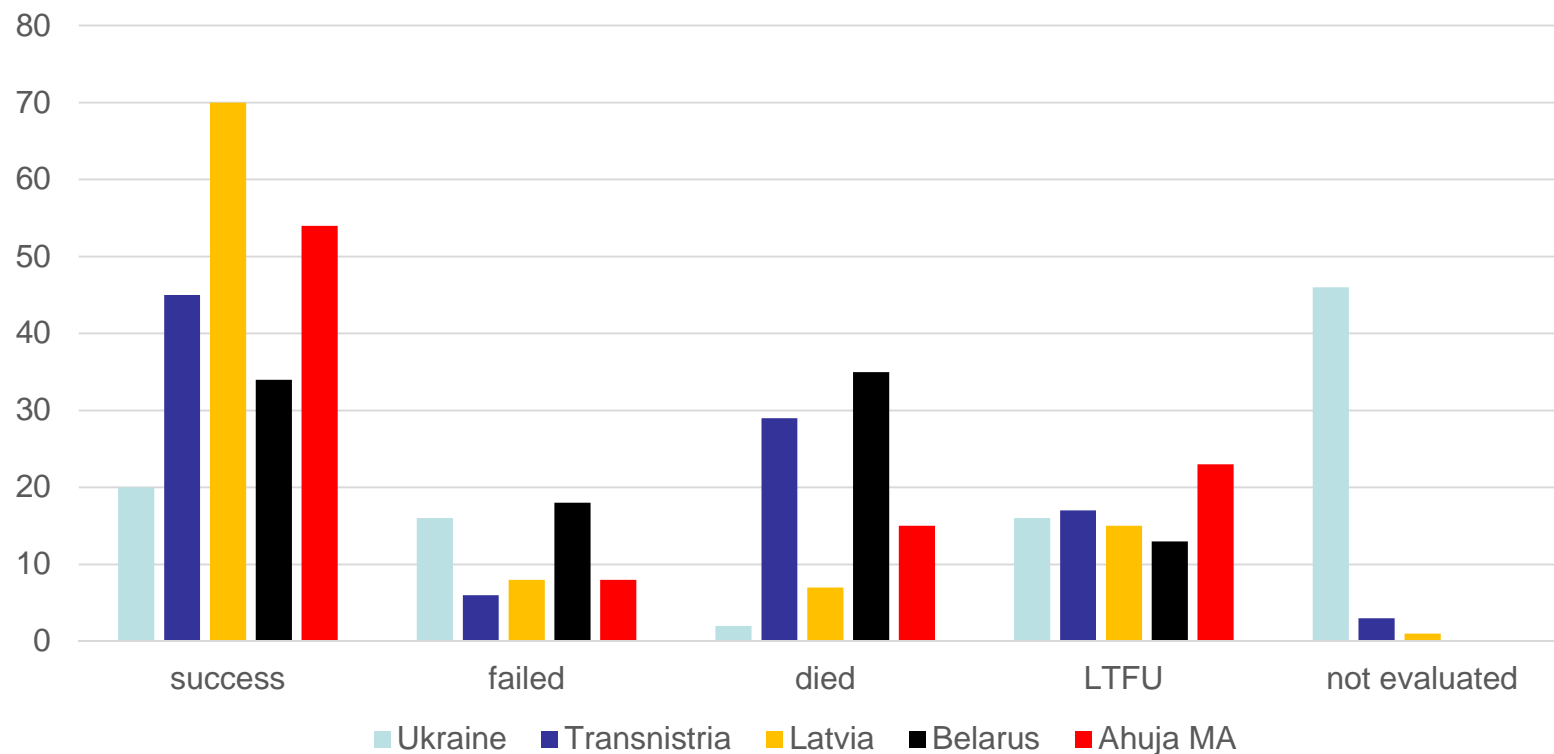
M/XDR-TB: Outcome of treatment

2

- The outcome of treatment – if known – is still below the expected standards
- Main issue: **high rate of failure and default** => ongoing transmission to the local population

Outcome of treatment of MDR-TB

3

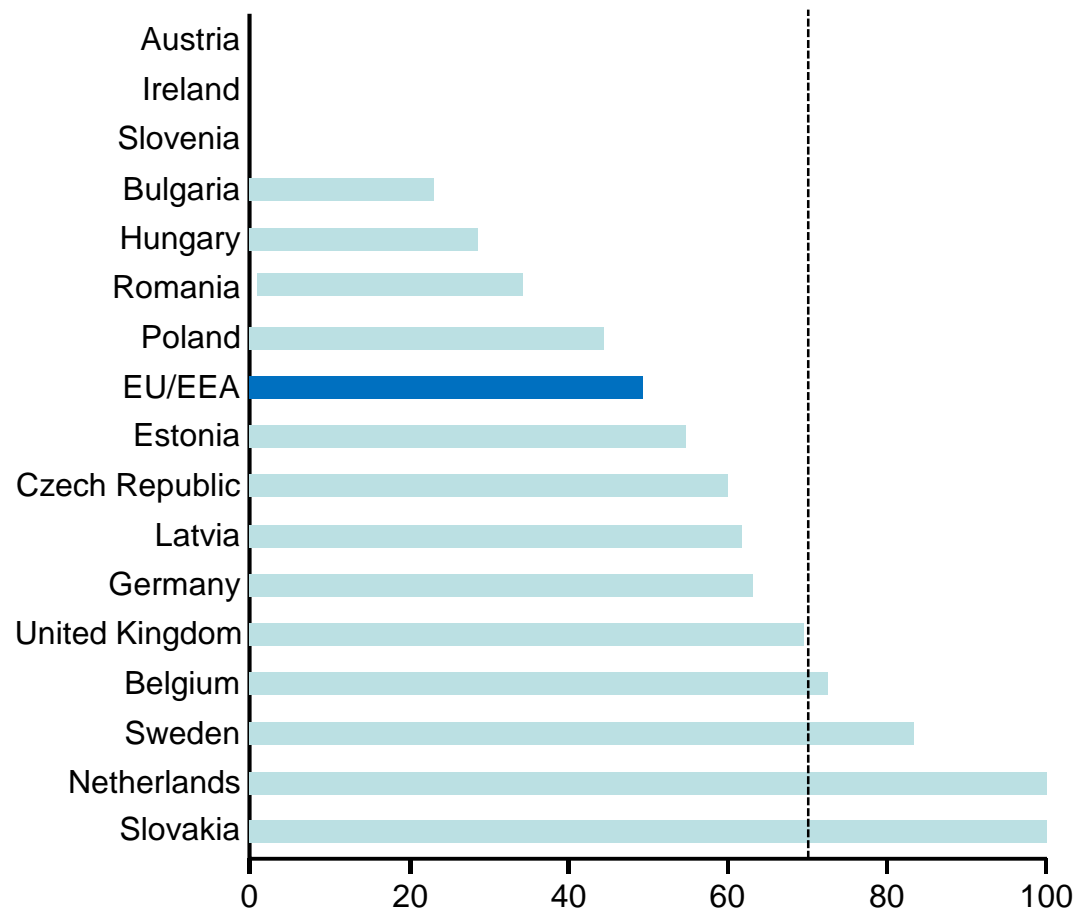


Sources:

Ahuja SD, PLoS Medicine August 2012 | Volume 9 | Issue 8 | e1001300

Public Health Action, 2014;4,suppl. 2

Treatment success rate of new culture-positive MDR-TB reported in Europe (2008)



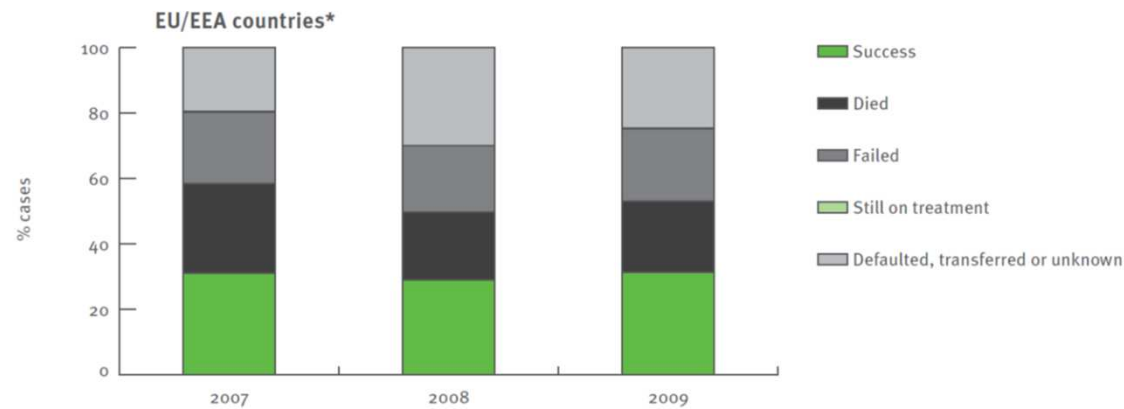
ECDC report 2012



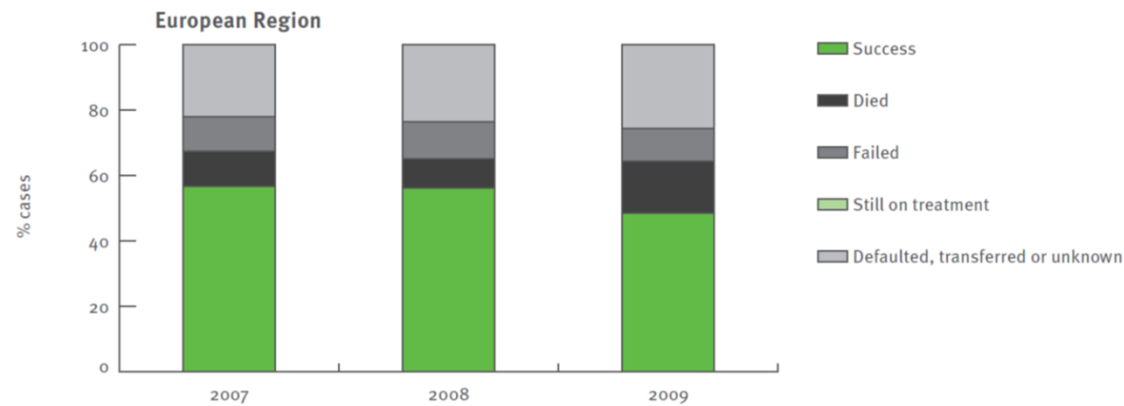
Outcome of treatment of MDR-TB (Europe)

5

Figure 9: Treatment outcome after 24 months of MDR-TB cases, Europe, 2007–2009



* Excluded: Finland, France, Greece, Liechtenstein, Luxembourg, Portugal, Spain



Open issues in the management of M/XDR-TB

6

- Management of DSTB is standardised and based on accepted evidences
- Management of M/XDR-TB is individualised based on assumptions and expert opinions, due to the complexity of settings and paucity of evidences
- The following are not (yet) known:
 - the real size of the problem
 - the burden of disease
 - the best options for diagnosis
 - the optimal treatments

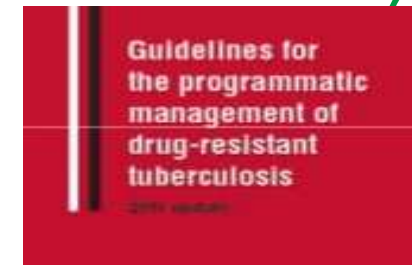
M/XDR-TB: current choice of treatment

- Current consensus:

- 1 injectable
(NOT streptomycin)
- 1 fluoroquinolone
(NOT ciprofloxacin)
- 3 others, potentially
active drugs

- The controversies:

- pyrazinamide?
- ethambutol?
- isoniazid in high
dose?
- duration of the
intensive
phase?
- duration of the
full treatment?



Falzon D, et al. Eur Respir J 2011;38:516–28
Guidelines for clinical operational management of drug-resistant tuberculosis. Available at:
http://www.theunion.org/what-we-do/publications/technical/english/mdr-tbguide_6-19-13_web.pdf
Lange C, et al. ERJ Express 2014; doi: 10.1183/09031936.00188313

M/XDR-TB treatment: which second-line drugs?

8

- Indications to most of the second-line drugs are unclear
 - Linezolid
 - Clofazimine
 - Co-amoxycilline
 - Meropenem-clavulanate
 - Cotrimoxazole
 - Thioridazine

M/XDR-TB: duration of treatment

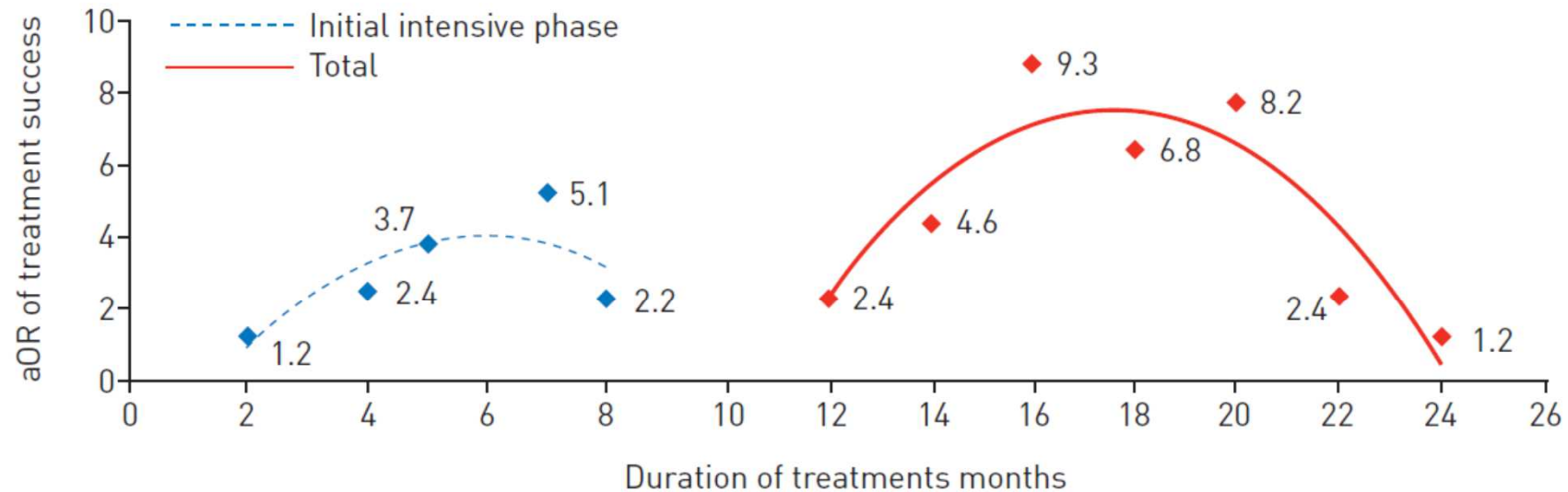
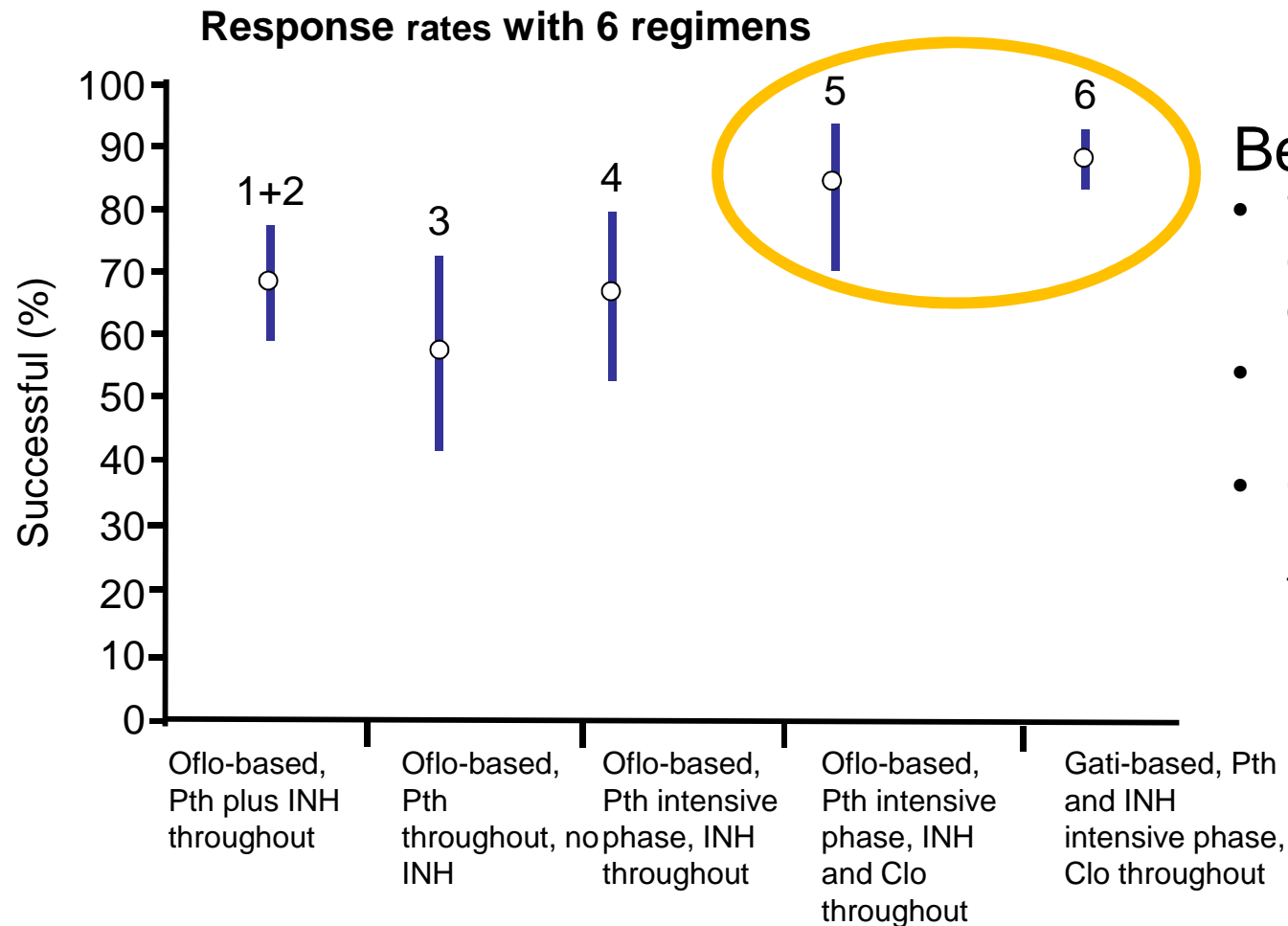


FIGURE 3 Association of the duration of initial intensive phase and total treatment with adjusted odds of treatment success in patients with multidrug-resistant tuberculosis. aOR: adjusted odds ratio. Data from [178].

Note: only 14% of patients included in this meta-analysis had access to quinolones!

From: Ahuja, SD, PLoS Medicine 2012;9(8):e1001300

MDR-TB treatment: The first «Bangladesh study»



10

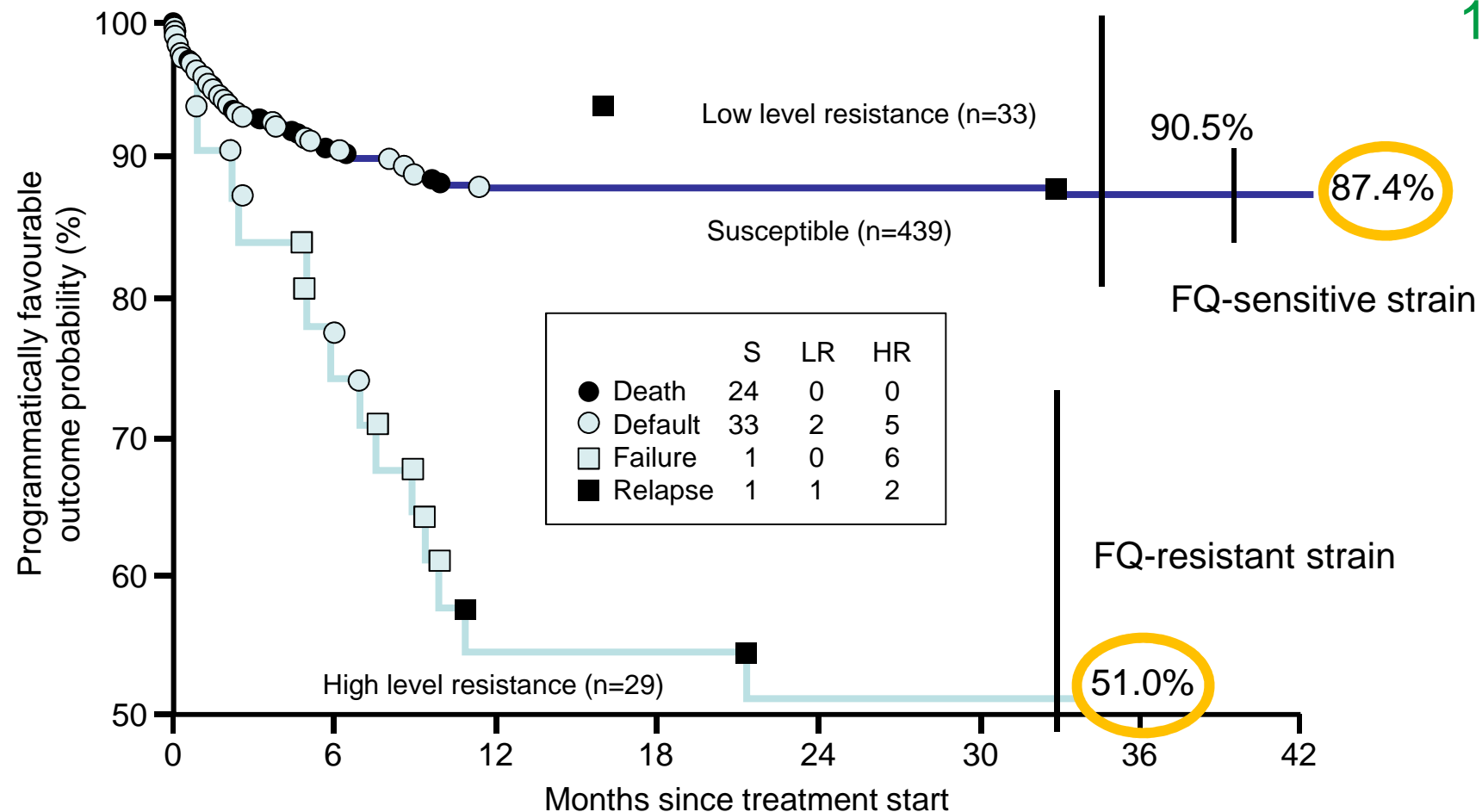
Best outcome if

- 7 drugs until conversion, then 4 drugs for 5 months
- Isoniazid intensive phase
- Clofazimine and pyrazinamide throughout

Clo, clofazimine; Gati, gatifloxacin; INH, isoniazid;
Oflo, ofloxacin; Pth, prothionamide

Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684-92

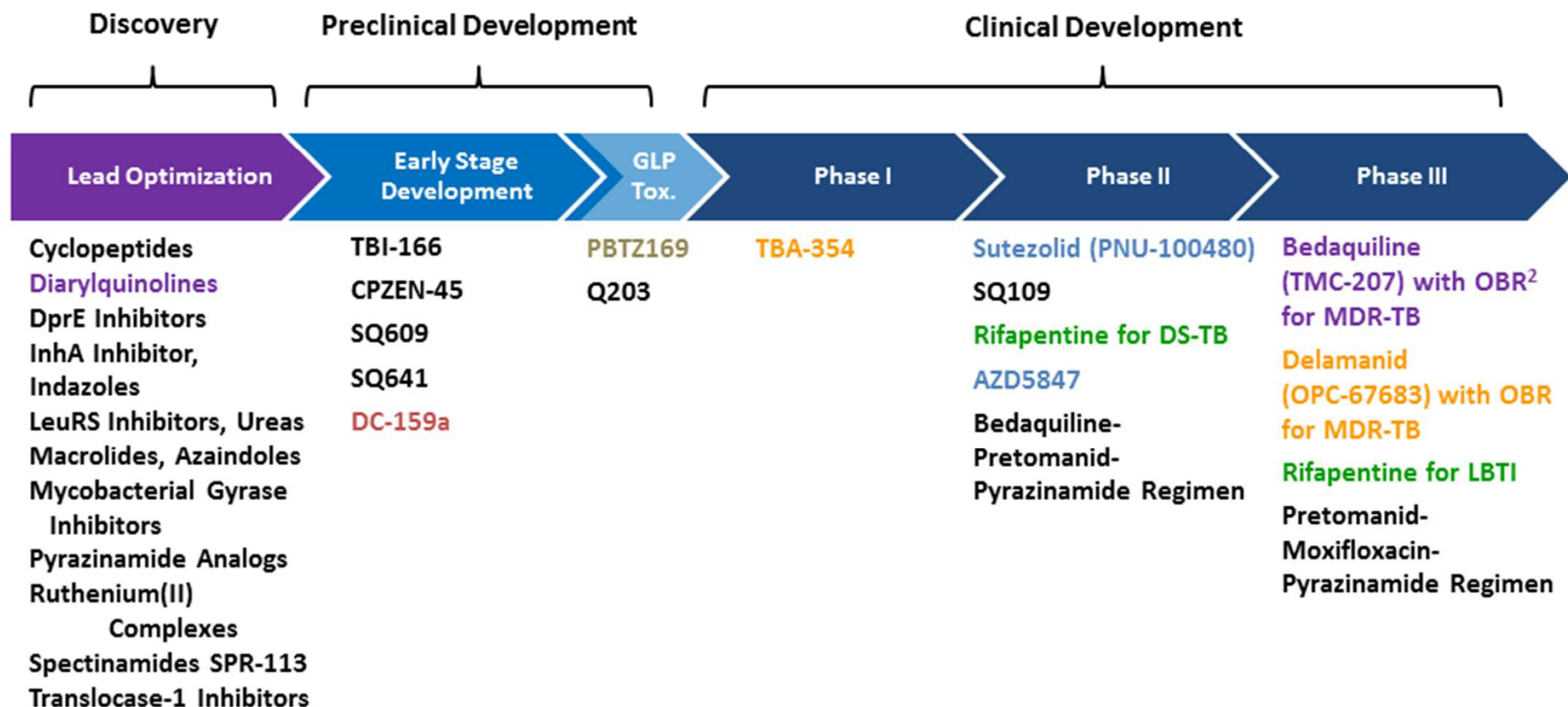
MDR-TB treatment: The second «Bangladesh study»



FQ, fluoroquinolone; HR, high level resistance;
LR, low-level resistance; S, susceptible to ofloxacin
and/or gatifloxacin at the standard critical concentration

Aung KJ, et al. Int J Tuberc Lung Dis 2014;18:1180-7

Global TB Drug Pipeline ¹



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

¹Details for projects listed can be found at <http://www.newtbdrugs.org/pipeline.php> and ongoing projects without a lead compound series identified can be viewed at <http://www.newtbdrugs.org/pipeline-discovery.php>

²OBR = Optimized Background Regimen



www.newtbdrugs.org

Updated: February 2015

Re-emergent drugs:

13

- Fluoroquinolones
- Clofazimine
- Meropenem-clavulanate (as amoxicilline-clavulanate)
- Linezolid

M/XDR-TB treatment: new drugs

14

- Two new drugs have been launched in 2013 and 2014 (bedaquiline = Sirturo® and delamanid = Deltyba®)
- The clinical experience is limited
- Potential drug/drug interactions and adverse events may be a problem
- Combination of both drugs or combination with quinolones is not recommended (QT prolongation)
- Cost may be a problem
- Creation of resistant strains must be avoided!

Bedaquiline (Sirturo®):



15

- Bactericidal activity exceeds isoniazid and rifampicin
- Decreased time to culture conversion, and improved culture conversion rates compared to placebo
- QT prolongation, concerns about combination with other quinolones, clofazimine and delamanid
- Approved by FDA and EMA
- May be added to a WHO-recommended regimen
 - an effective treatment with 4 second-line drugs cannot be designed
 - there is documented evidence of resistance to fluoroquinolones

**The use of
bedaquiline in
the treatment of
multidrug-resistant
tuberculosis**

Interim policy guidance

Delamanid (Deltiya®):



- Mycobacterial cell wall inhibitor
- Long-term treatment (>2 months) in addition to usual regimen for MDR-TB is associated with higher favourable outcome (74.5% vs 55% in placebo group, 1% vs 8.3% in resistance rate)
- Possible QT prolongation, ECG monitoring recommended
- Conditional approval for MDR-TB treatment
- May be added to a WHO-recommended regimen with
 - high risk of poor outcome
 - additional resistance to fluoroquinolones

The use of delamanid in the treatment of multidrug-resistant tuberculosis

Interim policy guidance

Non-antibiotic treatment of MDR-TB (1)

17

- Immunostimulation:
 - Thioridazide
 - Interferon-Gamma
 - Cell-based immunotherapy
- Enhancement of natural cellular mechanisms
- Disruption of the granuloma formation (better penetration of antituberculous drugs): steroids

Non-antibiotic treatment of MDR-TB (2)

18

- Vit D (compensation of deficiency)
- Vaccination
 - Pre-exposure
 - Post-exposure/infection
 - After disease outbreak
- Surgery
- Smoking cessation!!!

Availability of second-line drugs

19

- The best Guidelines are useless if the drugs are not available and affordable
- The best drugs are useless if the patients do not tolerate them

M/XDR-TB: prevention

20

- MDR-TB is a problem because errors have been committed and are perpetuated
- MDR-TB is frequently detected late, because of failure of first-line standard therapy (no sputum conversion after 2-3 months)
- MDR-TB is still transmitted unnecessarily to other patients, staff and relatives (half of the patients with MDR-TB are **new** cases!)
- As long as these errors will not be acknowledged and corrected, there will be no prospect for control and a decrease in Europe

What is the cause of MDR-TB?

21

Classical theory:

- intermittent or erratic treatment selects the resistant mutants, which replace the sensitive strains
- **Blame the system / the doctor / the patient**

What is the cause of MDR-TB?

22

Alternative theory:

- Some drugs circulate in low levels and therefore do not exert their bactericidal effect, even if perfectly ingested
- Some drugs do not penetrate as expected in the granulomas
- Blame the pharmacology / the drug / the dose / the route

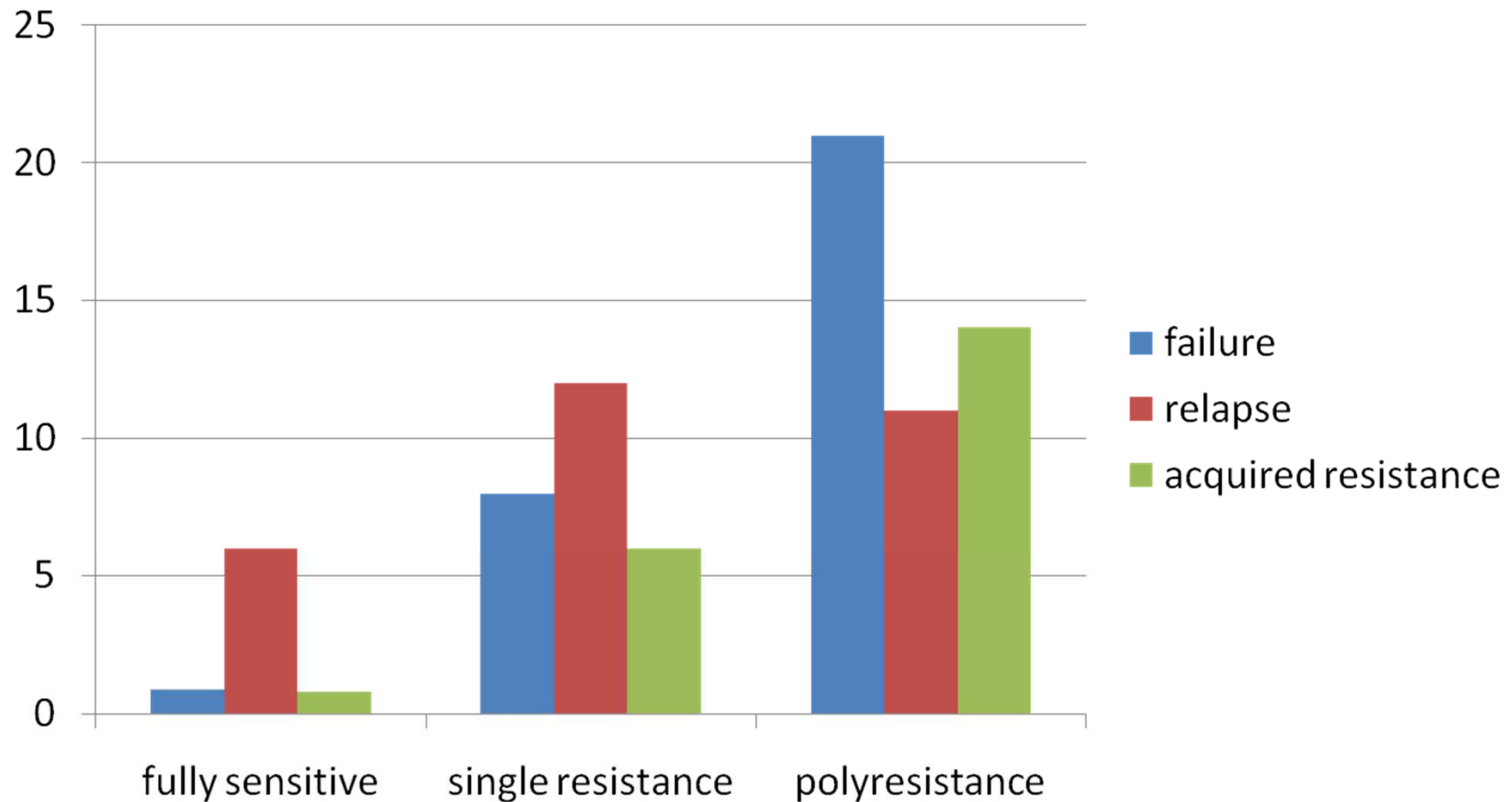
M/XDR-TB: conclusions (1)

23

- The majority of MDR-TB cases can be treated
- The treatment should include
 - Optimal use of existing first- and second-line drugs
 - Targeted use of new drugs
- Avoid the amplification of resistance (do not miss H resistance!)
- Drug level monitoring may play an important role
- Infection control measures are crucial (decrease transmission)

Failure, relapse and acquired drug resistance by initial strain sensitivity

24

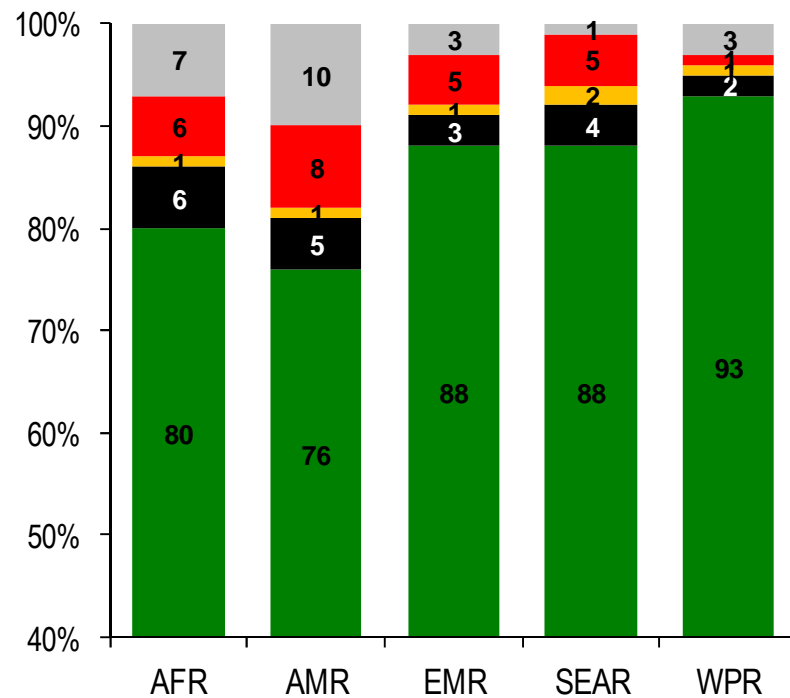


Lew W, Ann Int Med 2008;149:123-134

Treatment outcome by WHO Region, 2010

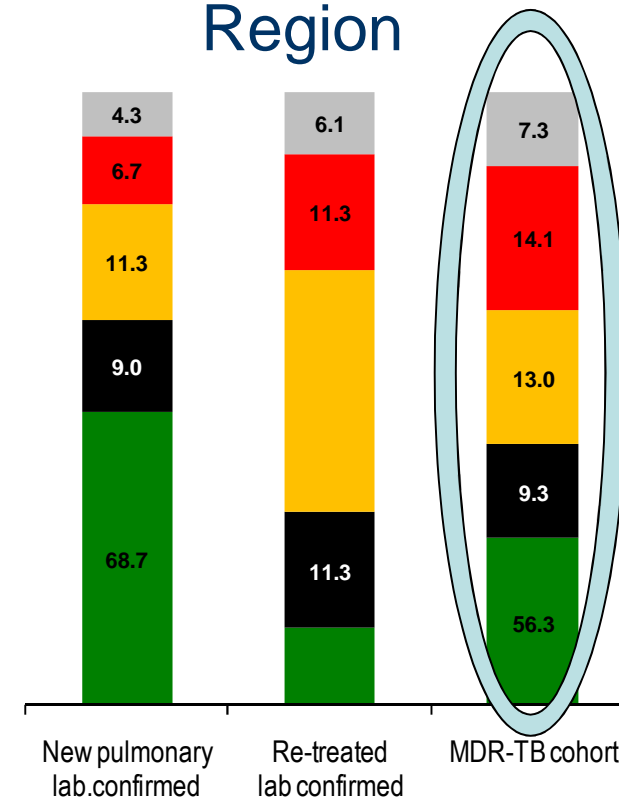
25

Other WHO Regions



Not evaluated
 Defaulted
 Failed
 Died
 Successfully treated

WHO European Region



M/XDR-TB: conclusions (2)

26

- The main issue is the prevention of the emergence of new cases, by appropriate treatment of drug-sensitive cases, to avoid relapses and failure.
- The treatment of MDR-TB should not divert resources from adequate treatment of drug-sensitive TB

If not...

27

