Nix-TB trial

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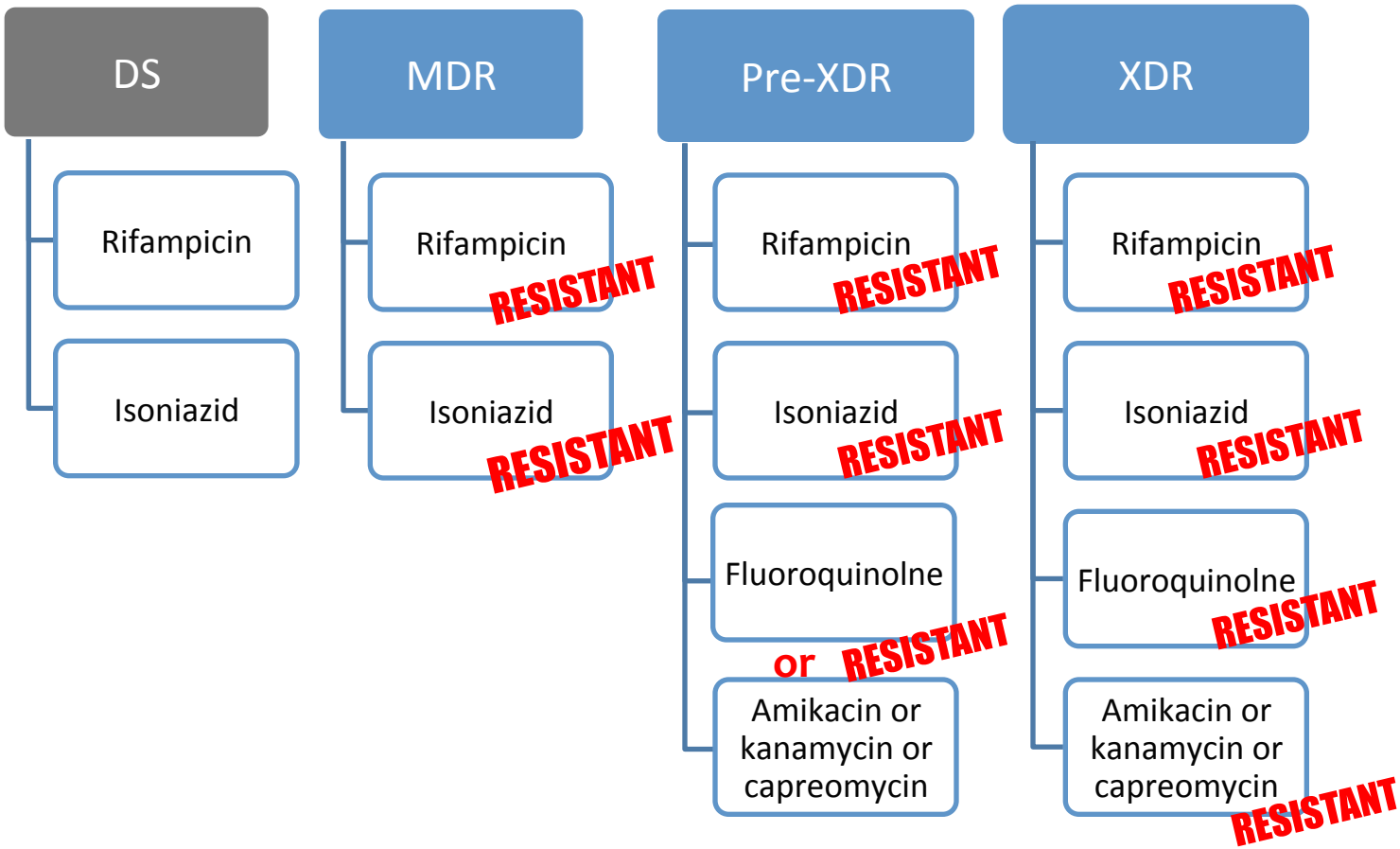
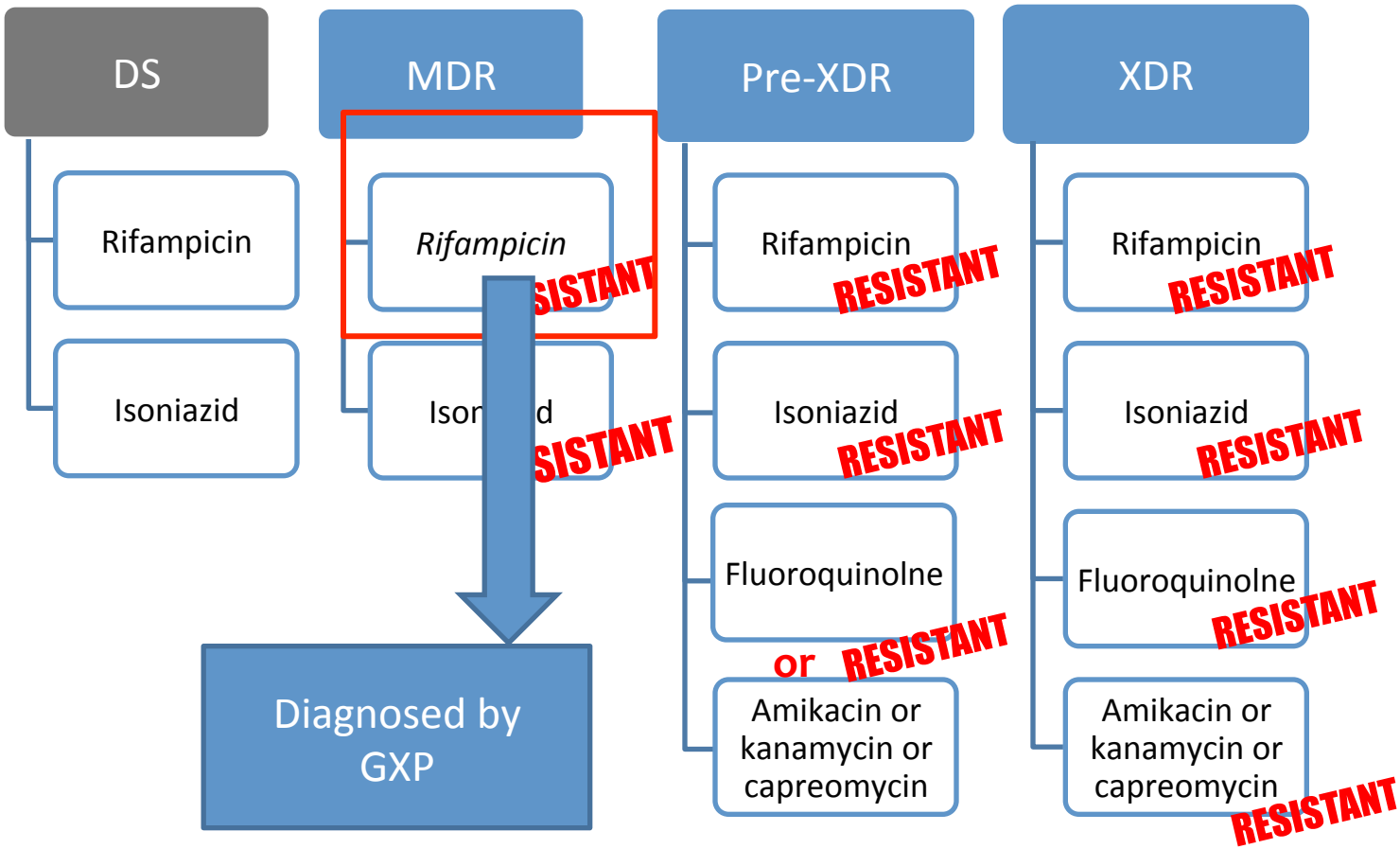
- What is XDR TB?
- How big is the problem?
- What is prognosis?
- What are current treatment options?
- What is the Nix trial?

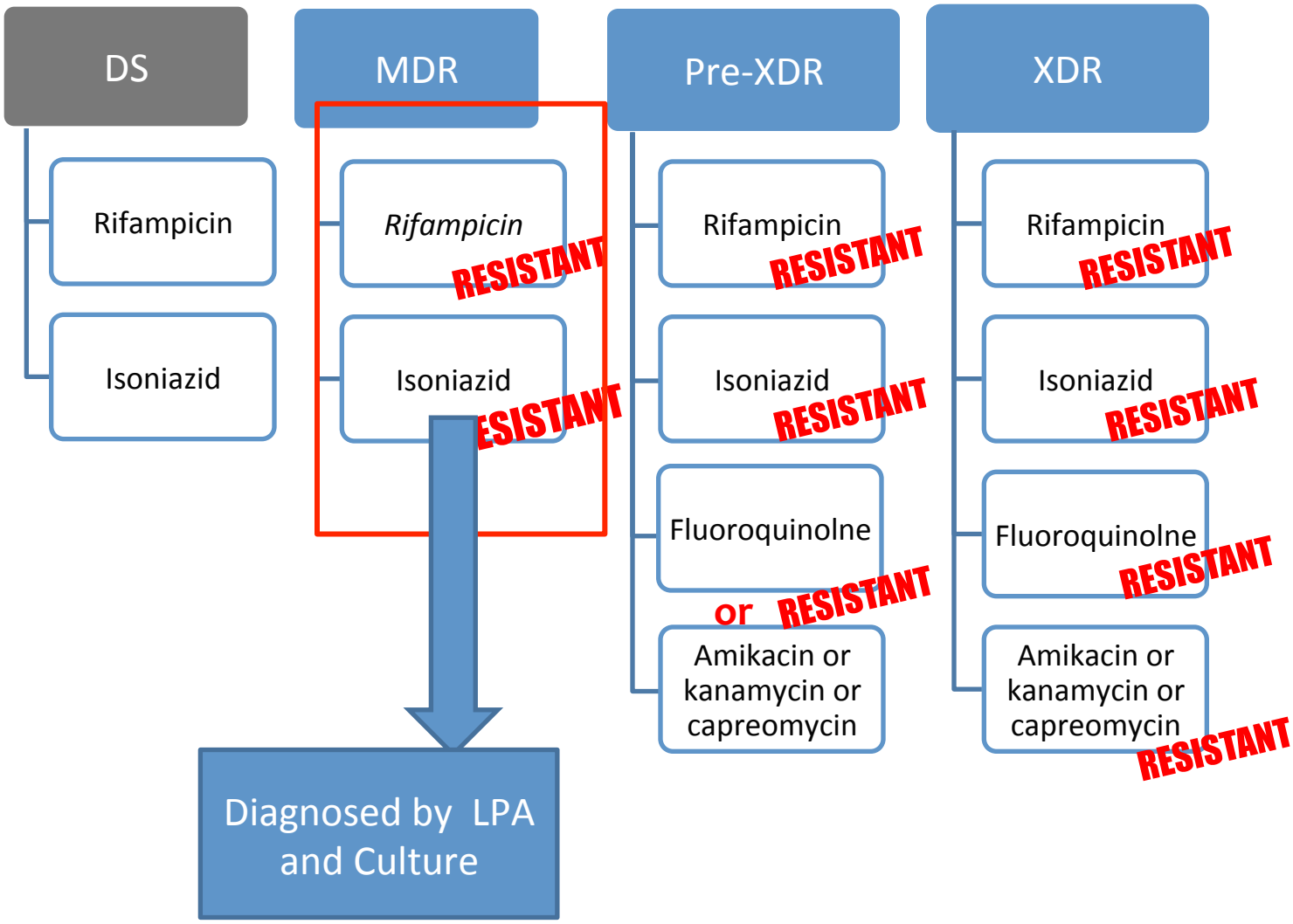
TB resistance



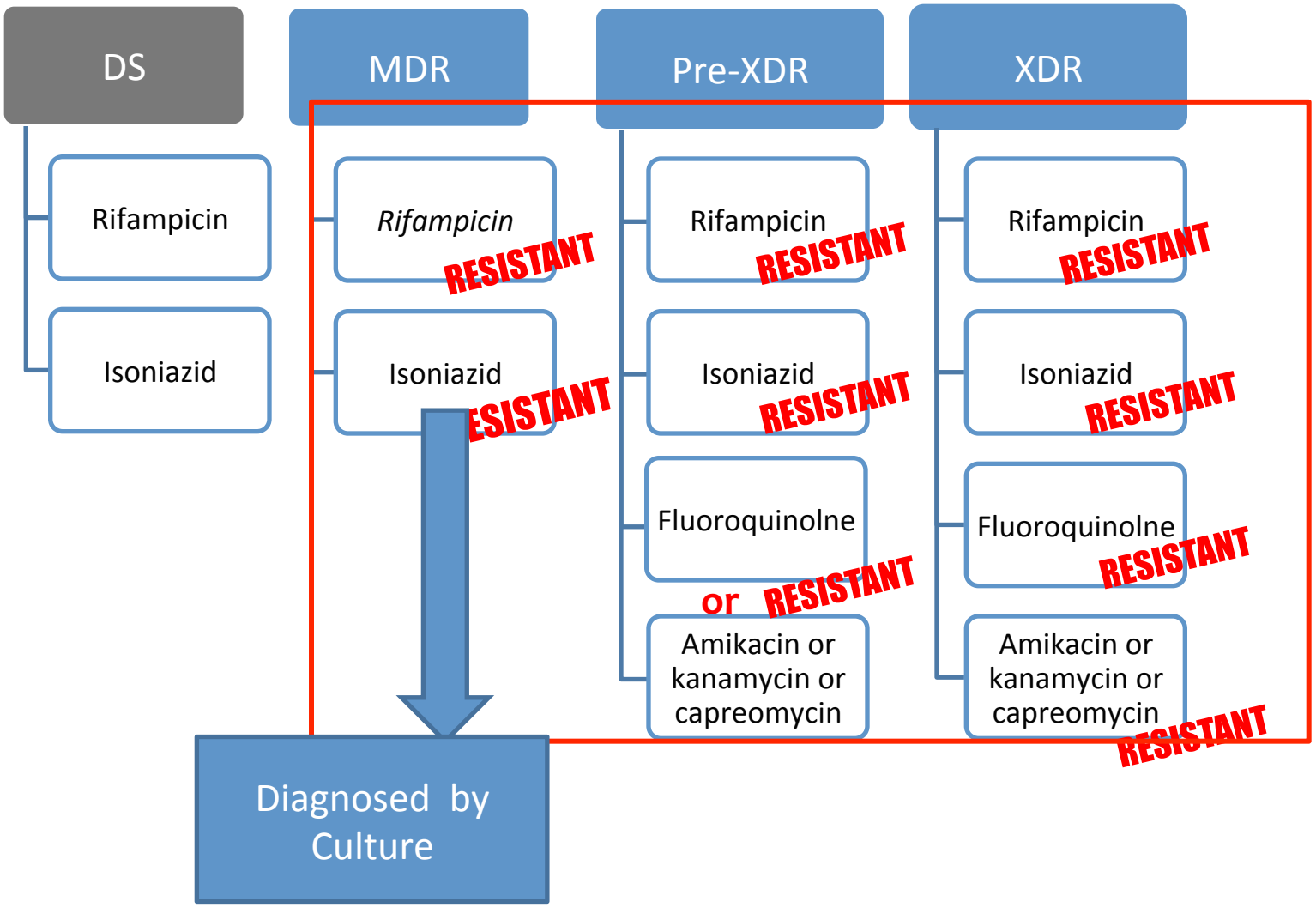
TB resistance



TB resistance



TB resistance

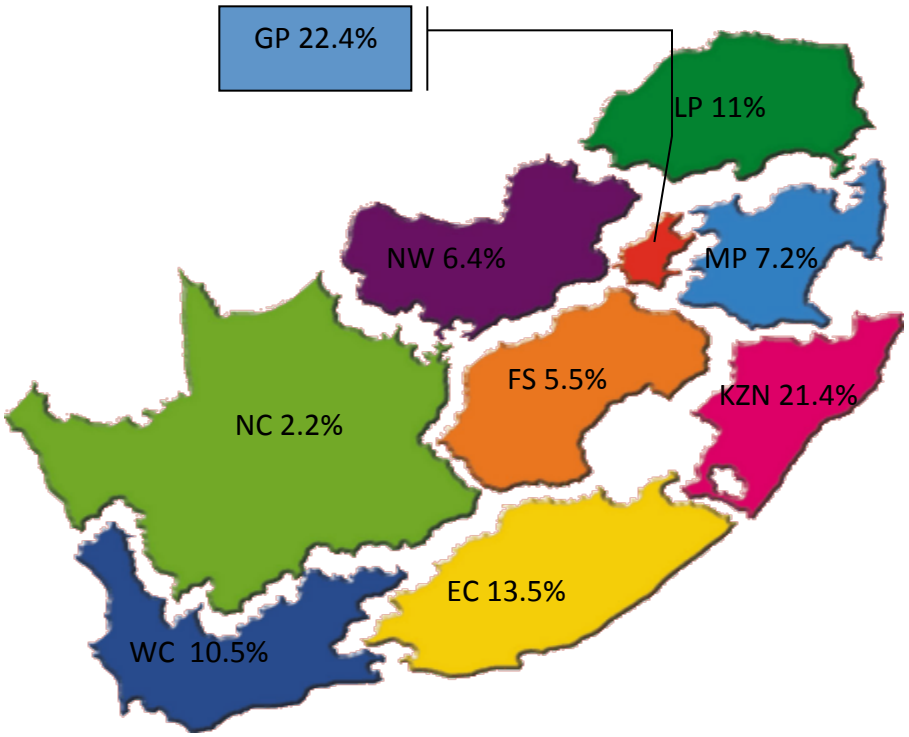


How big is the problem?

Snap shot of South Africa

- Population: 50, 586 757
  - Provinces – 9
  - Districts - 53
  - Sub districts - 253
  - Health facilities – 4790

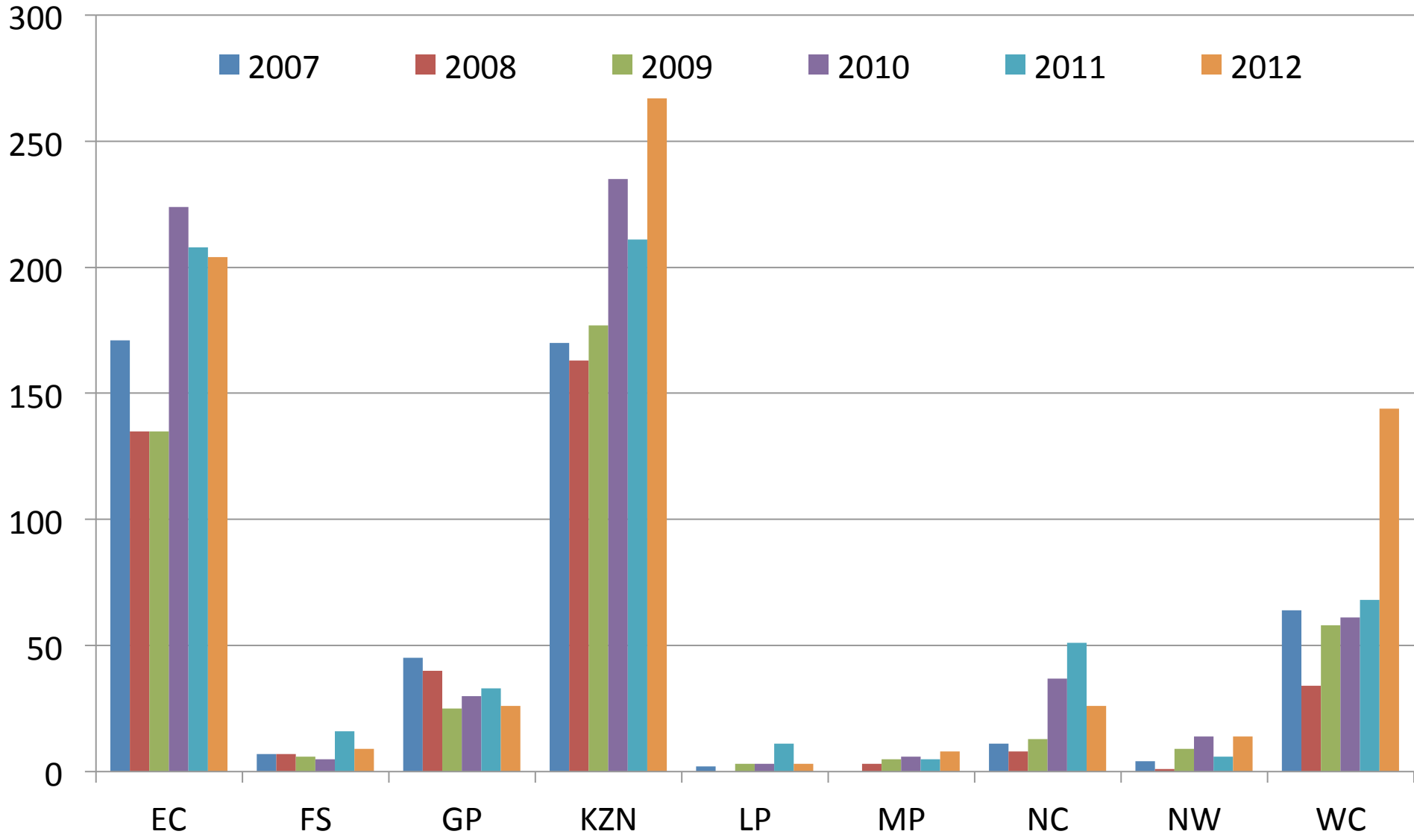
- MDR-TB beds: Approx. 3,000
- DR-TB treatment sites: 578



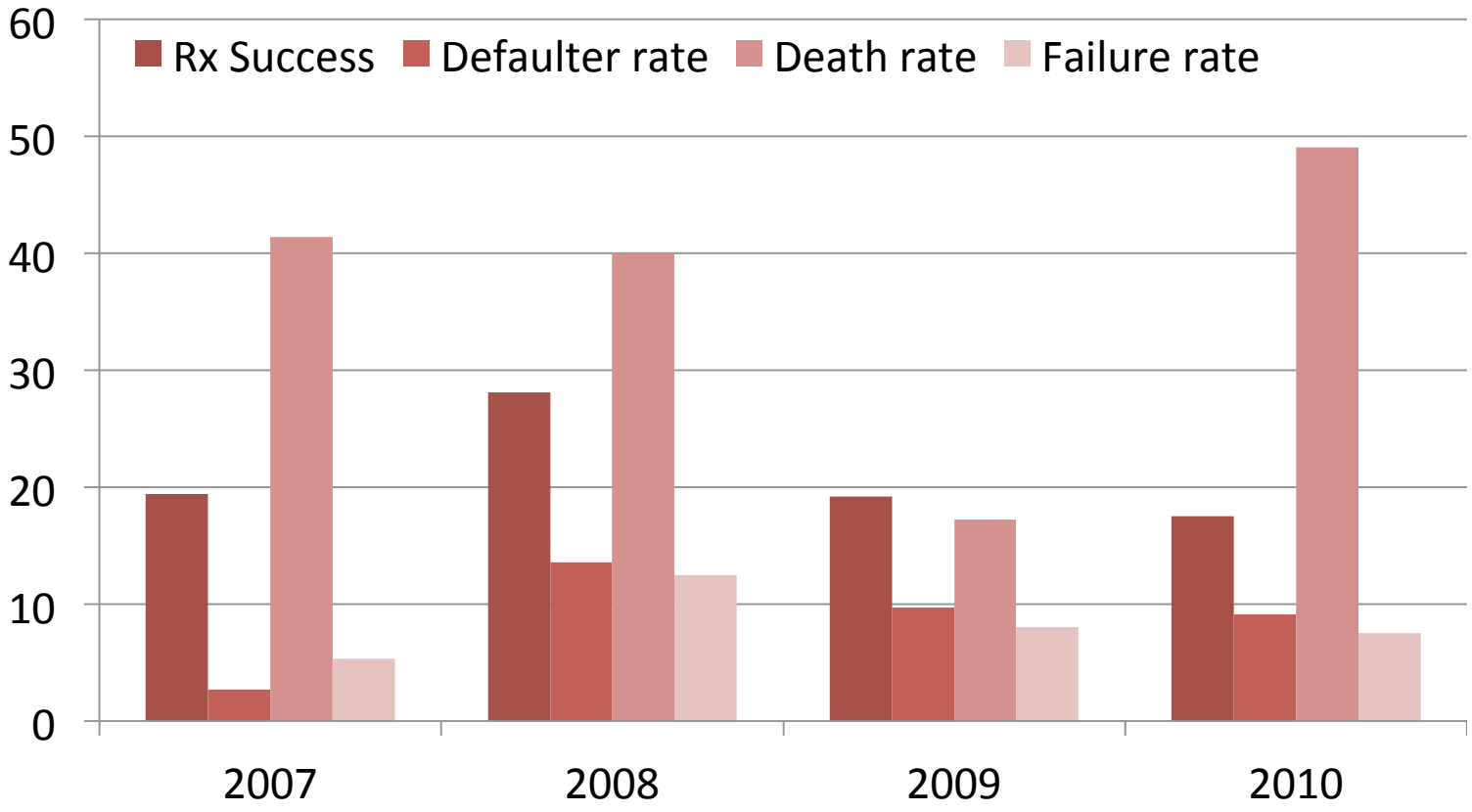
TB Burden in South Africa

- **TB** patients initiated on treatment **decreasing**: **406,082 to 332,170** (2009 and 2013)
- Treatment success rate: **80,9 %** for 2012 DS cohort
- **MDR-TB** numbers initiated on treatment **doubled** between **2010 and 2013** (5,313 to 10,719)
- MDR-TB treatment success rate of **49 %** (2012 cohort > 8,000)
- XDR-TB treatment success rate is **20 %**

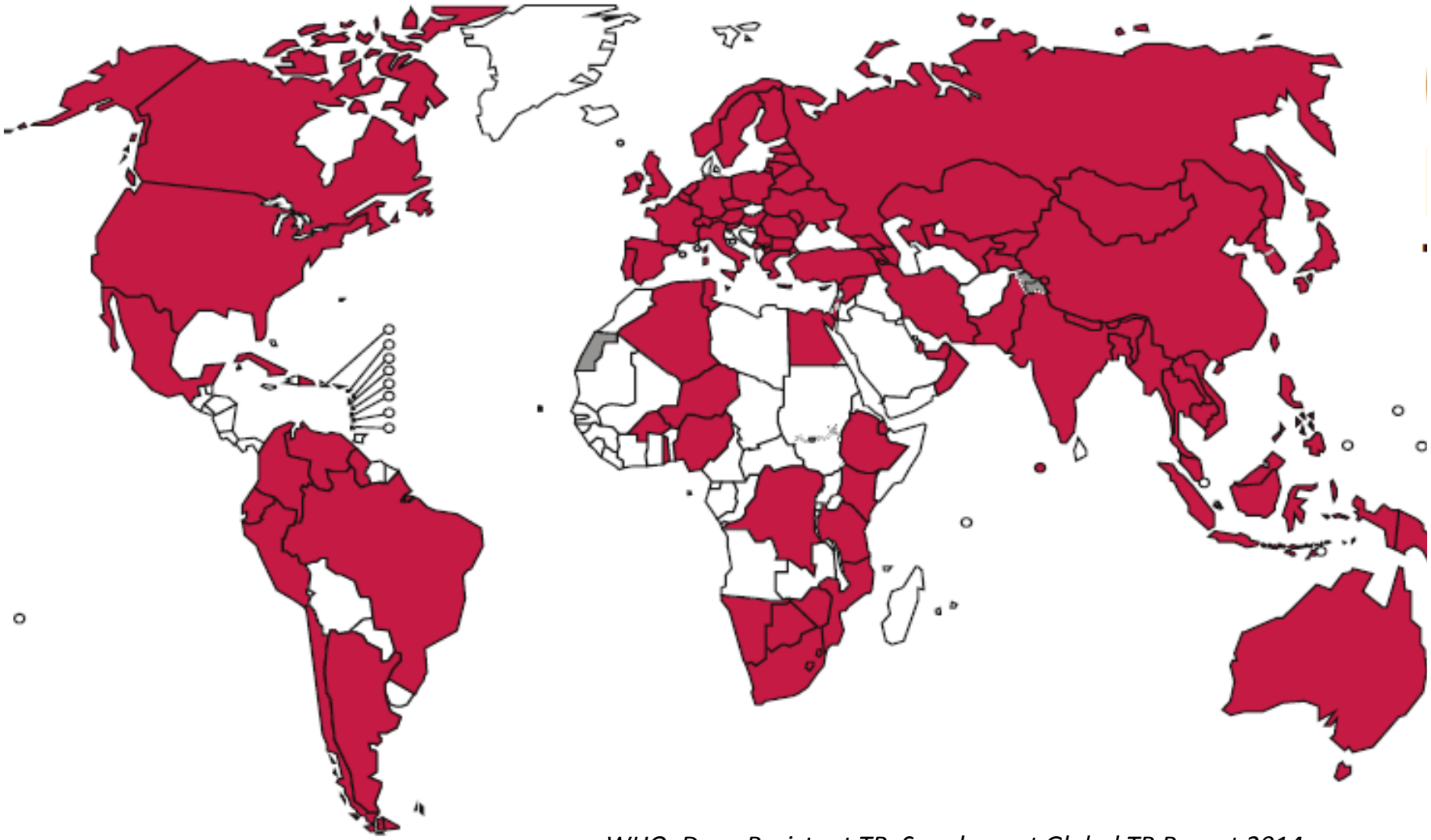
XDR- TB Started on treatment



XDR-TB Treatment Outcomes (24 months)



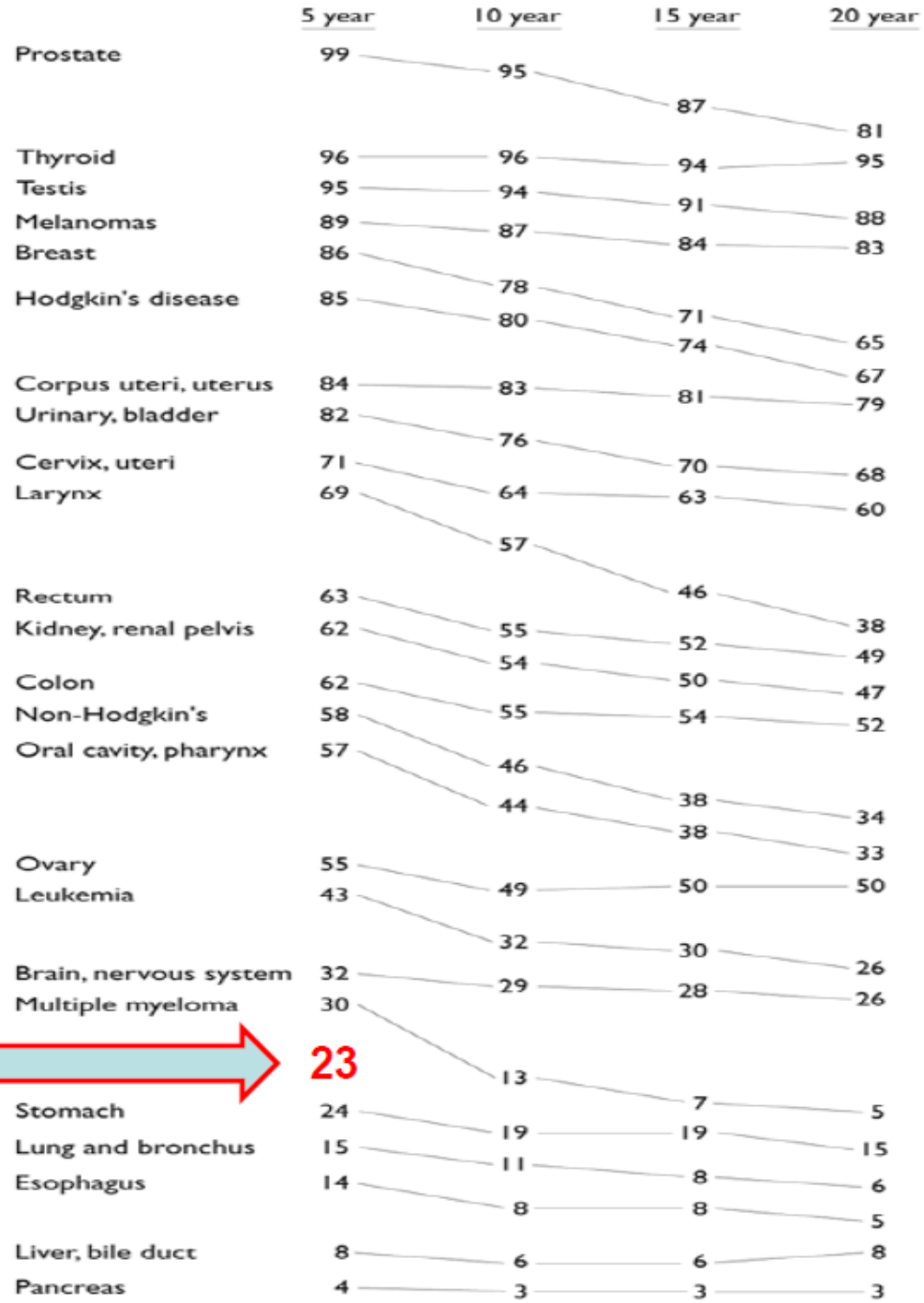
Countries (in Red) that had Notified at least One Case XDR-TB, by end 2013



WHO. Drug-Resistant TB. Supplement Global TB Report 2014

Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis

Adapted from Brenner H (2002); The Lancet, 360; 1131-1135
by Edward Tufte (http://www.edwardtufte.com)



XDR-TB → 23

Courtesy: Jaramillo E, WHO

Why do people get XDR TB?

- Original cases were due to non- adherence
- Now at least 79% of cases are transmitted

Current treatment of XDR TB

- Based on Resistance tests and prior exposure to other TB drugs
- Duration is at least 24 months

Current treatment of XDR TB

- Commonly used drugs
  - Capreomycin- injectable agent, cross resistance is high to other injectable
  - PAS- poor side effect profile
  - PZA, terizidone, ethionamide etc. dependant of prior exposure them.
  - Newer drugs available in some countries

    Bedaquiline

    Linezolid

    Delaminid

What would be the ideal regimen?

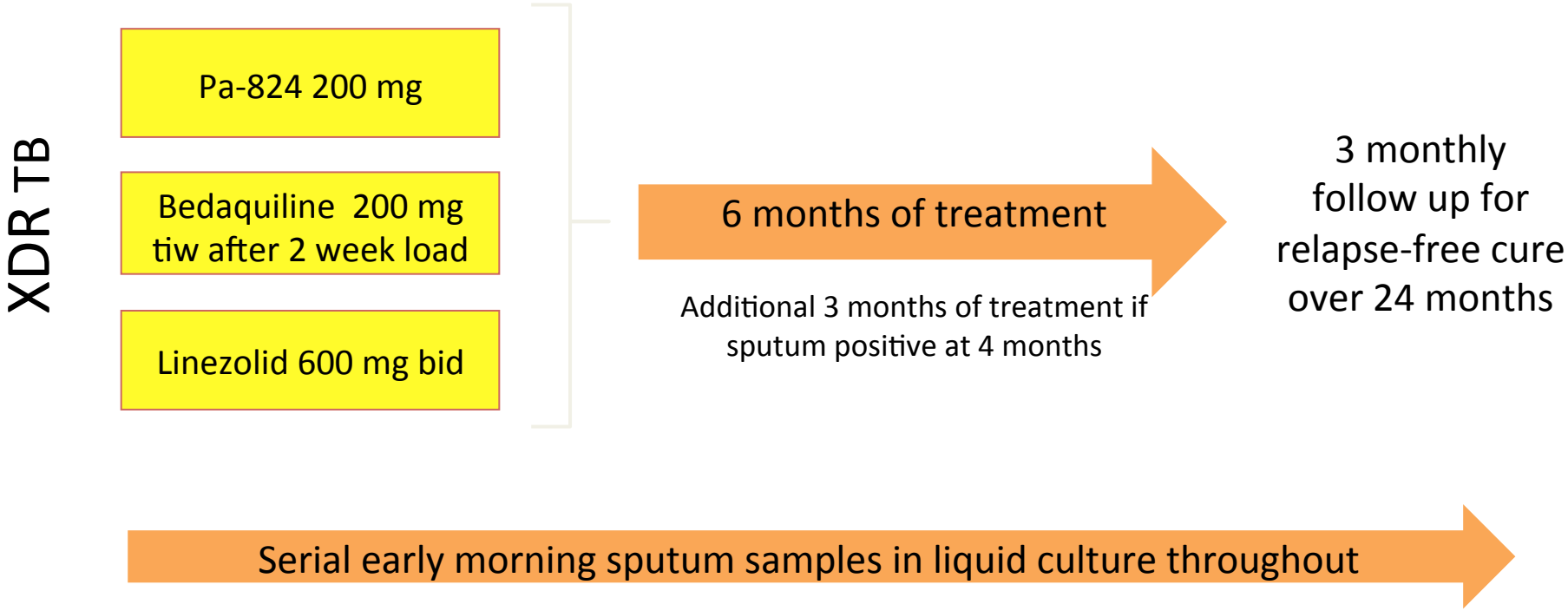
- Safe and effective
- Shorter and injection free
- Three new drugs to which there is no resistance

Nix-TB Rescue Study

A Phase 3 open-label trial assessing the safety and efficacy of bedaquiline plus Pretomanid (PA-824) plus linezolid in subjects with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant / non-responsive multi-drug resistant tuberculosis (MDR-TB).

Nix-TB Rescue

- Patients with XDR TB or Who Have Failed MDR Treatment



Sites: Durban, Sizwe, Brooklyn Chest, SA

Nix-TB Objective and Primary Endpoint

- Objective
  - To evaluate the efficacy, safety, tolerability and pharmacokinetics of bedaquiline plus PA-824 plus linezolid after 6 months of treatment (option for 9 months for subjects who remain culture positive at month 4) in Subjects with either pulmonary XDR tuberculosis, treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

- Primary Endpoint
  - Incidence of bacteriologic failure or relapse or clinical failure through follow up until 24 months after the end of treatment.

Nix-TB
Safety and Tolerability Endpoints

- All cause mortality.
- Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented by severity (DMID Toxicity Grade), drug relatedness and seriousness, leading to early withdrawal and leading to death.
- Quantitative and qualitative clinical laboratory result measurements
- Quantitative and qualitative measurement of ECG results
- Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2] lens opacity classification and grading).
- Changes in ophthalmic exam for visual acuity and color vision
- Changes noted in peripheral neuropathy signs and symptoms

Analyses, DSMC Meetings

- Exploratory Analyses:
  - Evaluate whether any of the secondary endpoints predicts relapse free cure.
  - Sub-analysis of populations by HIV status and CD4 count.
  - Correlation of Time over mitochondrial protein synthesis inhibition (MPS50) with linezolid toxicity (The MPS50 will be an assumed value from the literature).
- DSMC Meetings & Futility Analyses:
  - Frequent DSMC meetings to review safety/efficacy and futility.
    - Safety/Efficacy

    DSMC Meetings will be held at least every 6 months

    Ad hoc meetings can/will be held if there are concerns with safety or efficacy between these meetings

    - Futility

    Interim analyses for futility will be performed for every 20 patients who reach the primary efficacy endpoint, treatment failure (that is, bacteriologic failure, or relapse, or clinical failure).