Drug-resistant TB in South Africa: Better treatment needed

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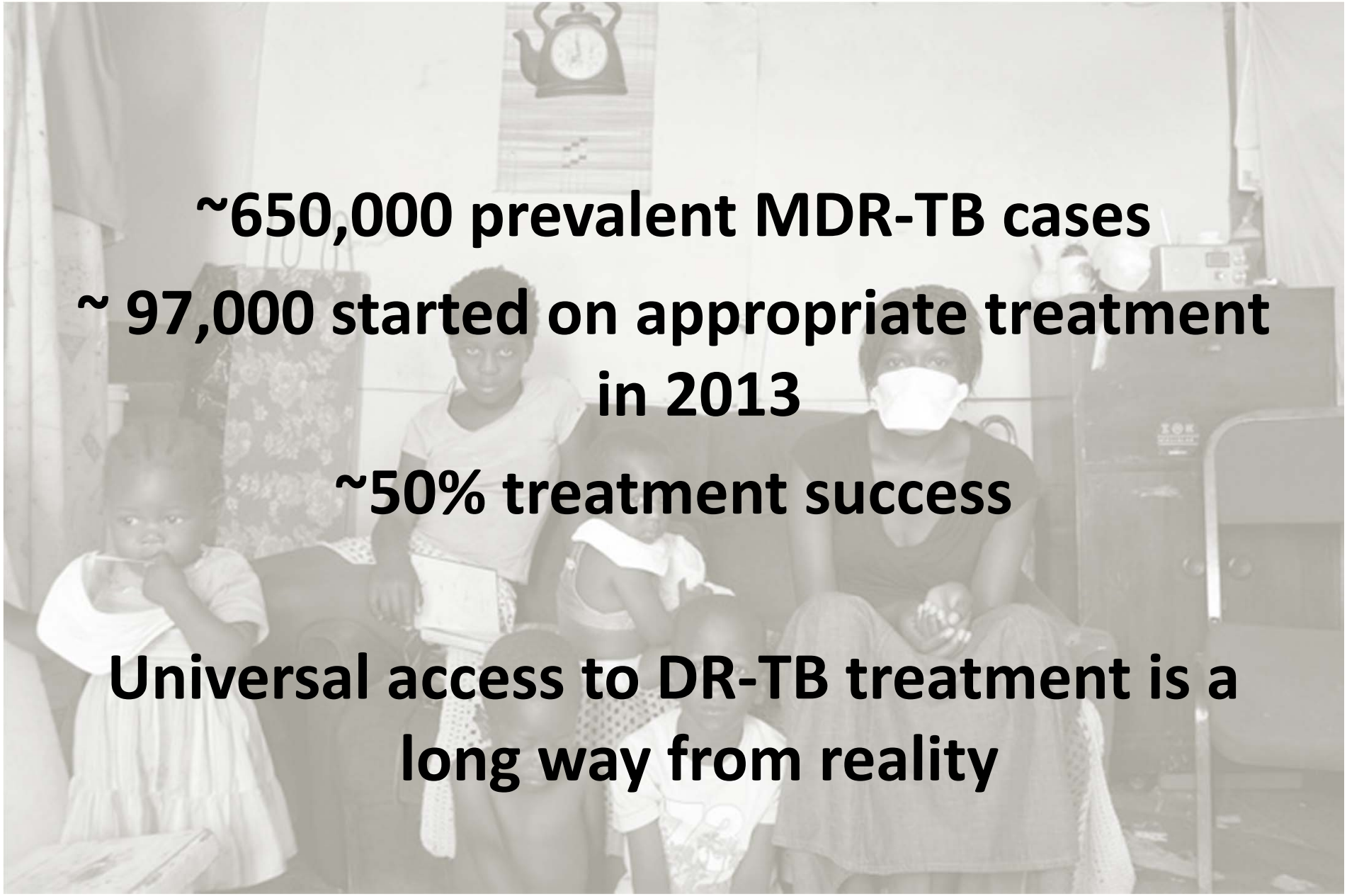


~650,000 prevalent MDR-TB cases

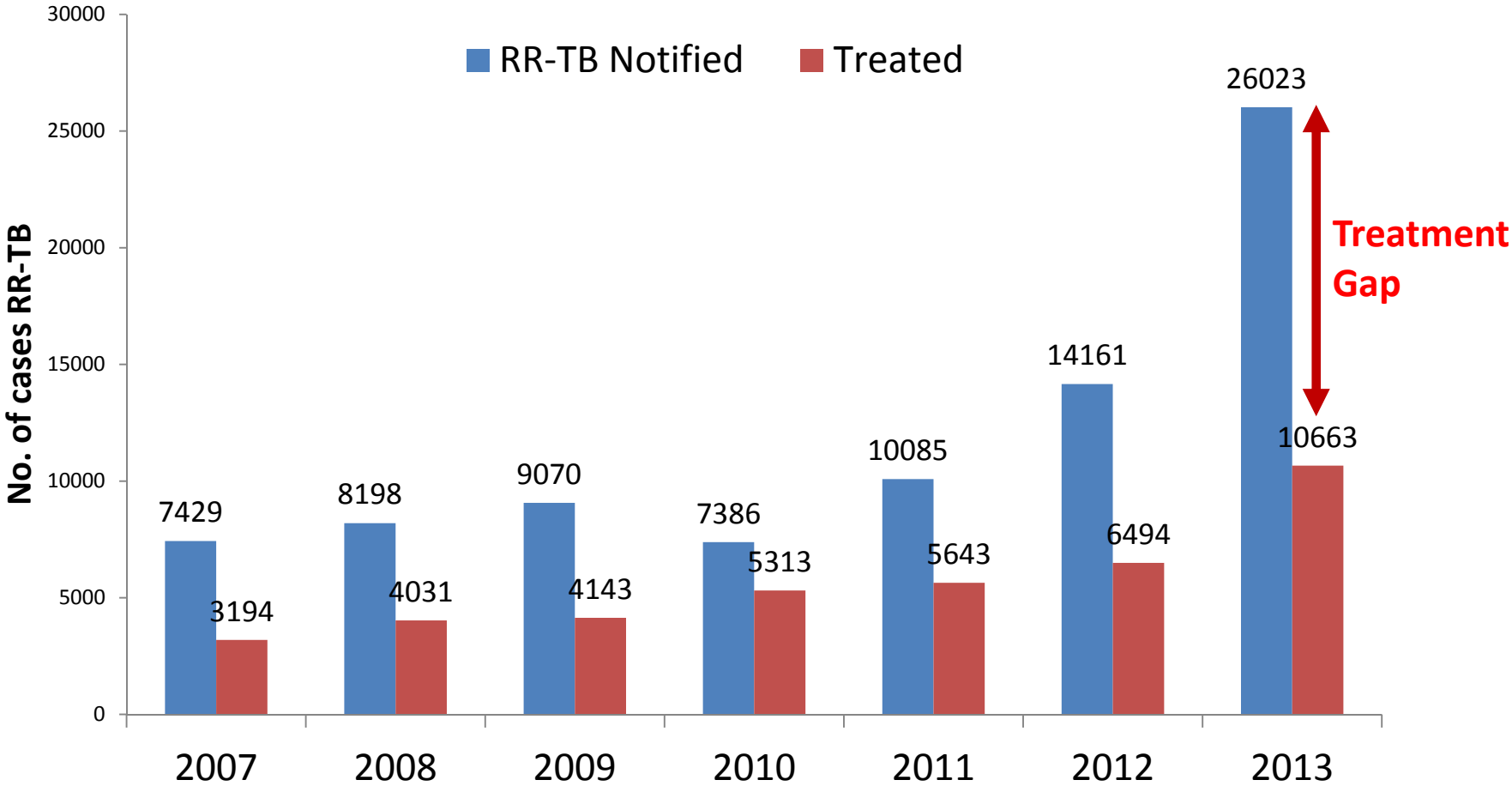
~ 97,000 started on appropriate treatment in 2013

~50% treatment success

Universal access to DR-TB treatment is a long way from reality

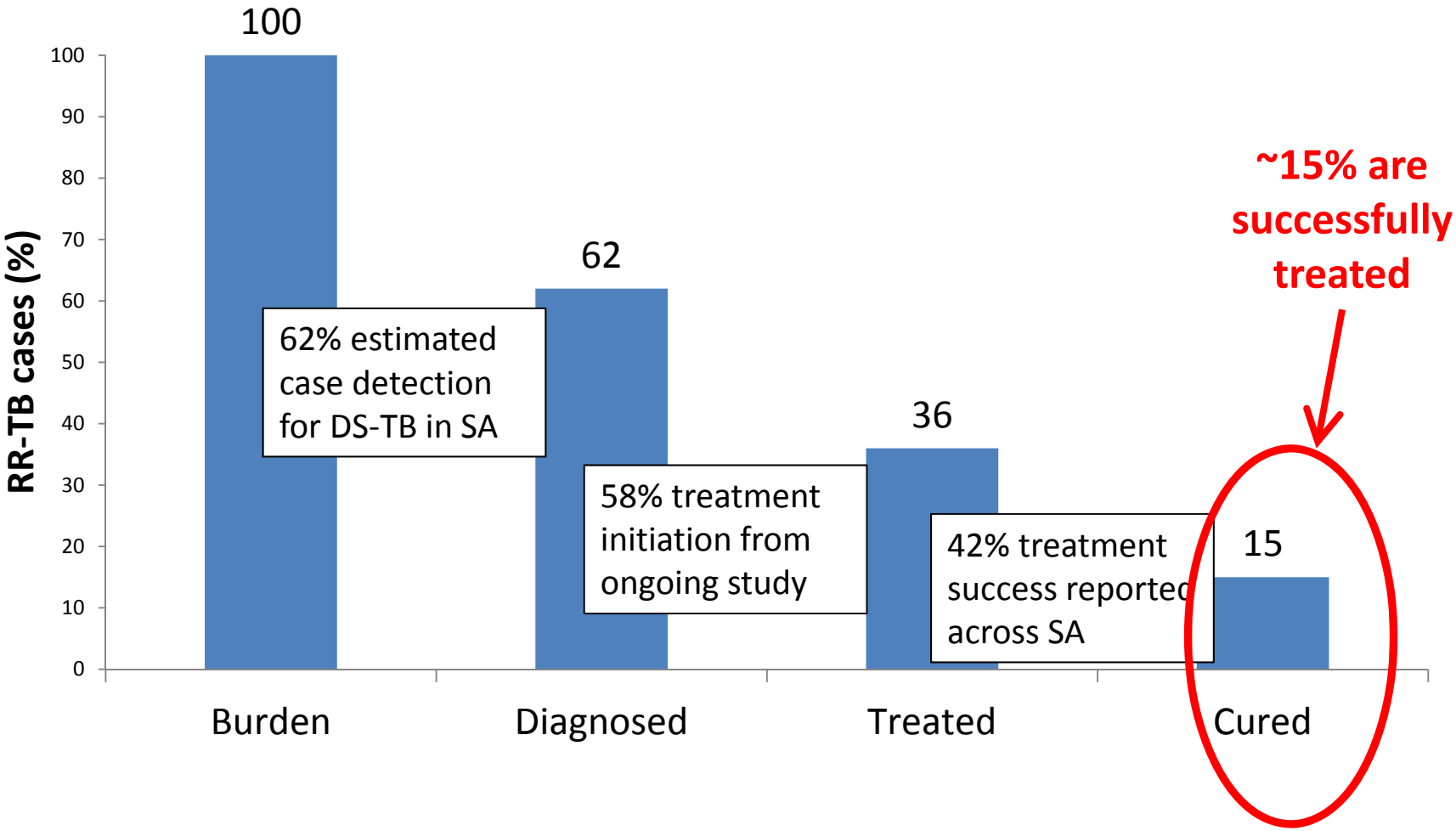
South Africa

RR-TB = rifampicin-resistant tuberculosis

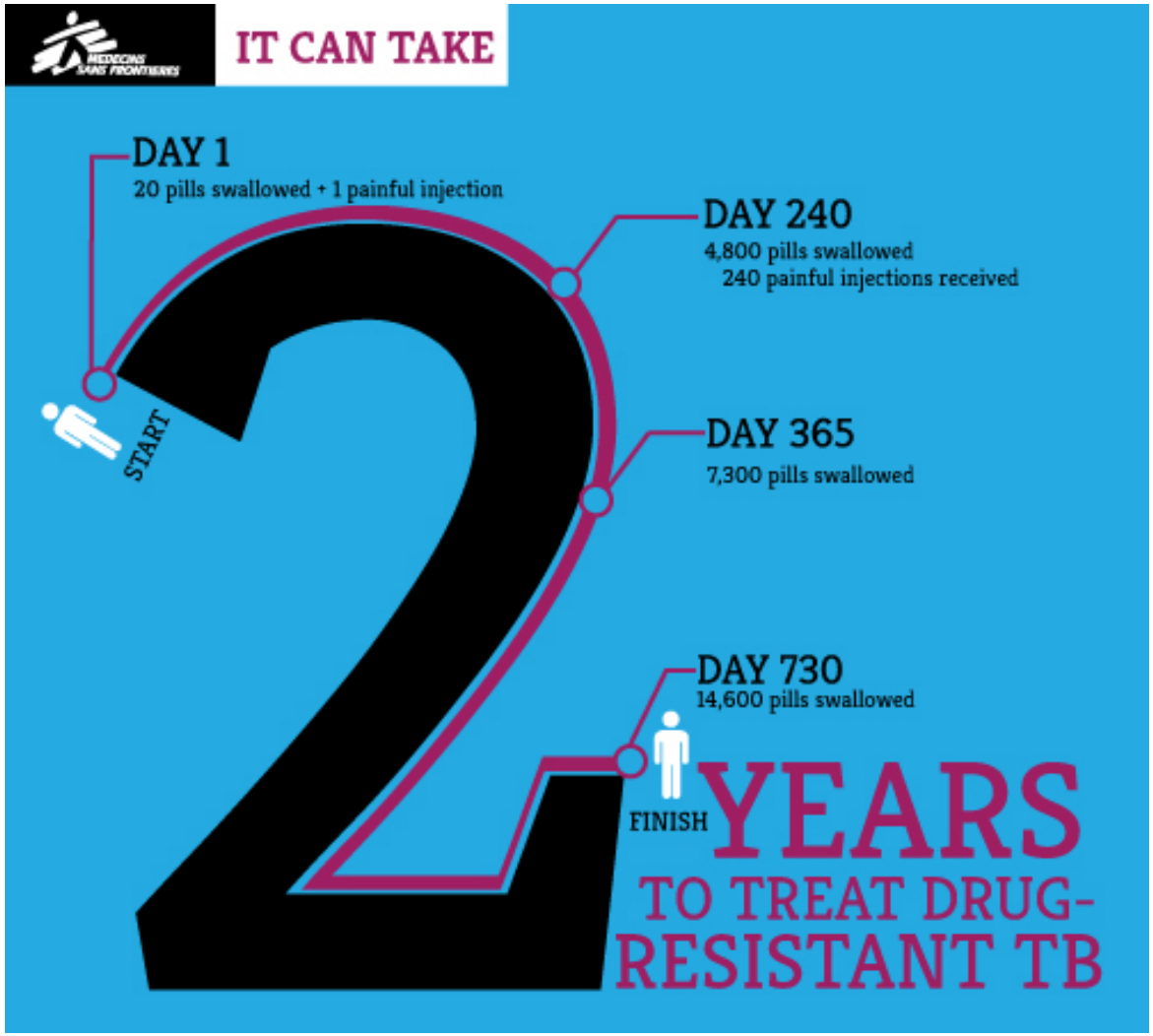


Source: South African NDoH and WHO

Diagnosis and treatment cascade (RR-TB)



Currently recommended treatment



Second-line drugs	**Year discovered**
PAS	1948
Cycloserine	1955
Kanamycin	1957
Ethionamide	1960
Capreomycin	1963
Moxifloxacin*	1996

*Moxifloxacin used in South Africa from 2012

Barriers to treatment

- Lab capacity, lack of diagnostics
- Cost of drugs/treatment
- **Poor treatment regimens/outcomes**
- **Complexity and length of treatment**
- **Lack of appropriate models of care to enable scale up**
- Lack of guidance internationally
- Lack of funds and political commitment

Key principles for a new regimen (aka the wishlist)

- No injectables
- Broad backbone that can be used for MDR and XDR (start with any Rif resistance – Xpert)
- Simple dosing
- Limited side effects (improved tolerability)
- Shorter duration (6-12 months)
- Minimal interaction with ART
- Can be used to treat children

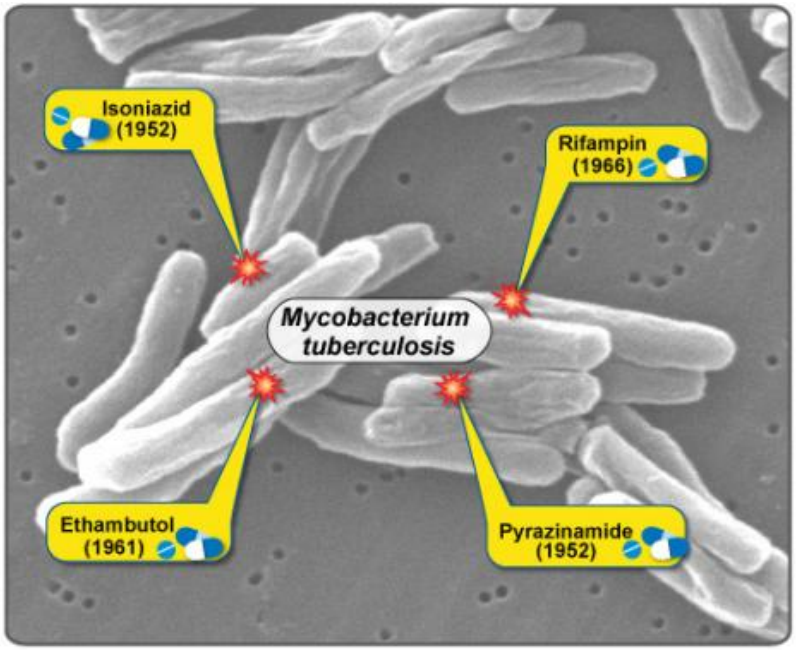
New and re-purposed drugs

New:

- Bedaquiline (TMC207)
- Delamanid (OPC-67683)
- PA-824 (combination PaMZ)

Re-purposed:

- Linezolid
- Clofazimine



Multidrug treatment is essential for TB

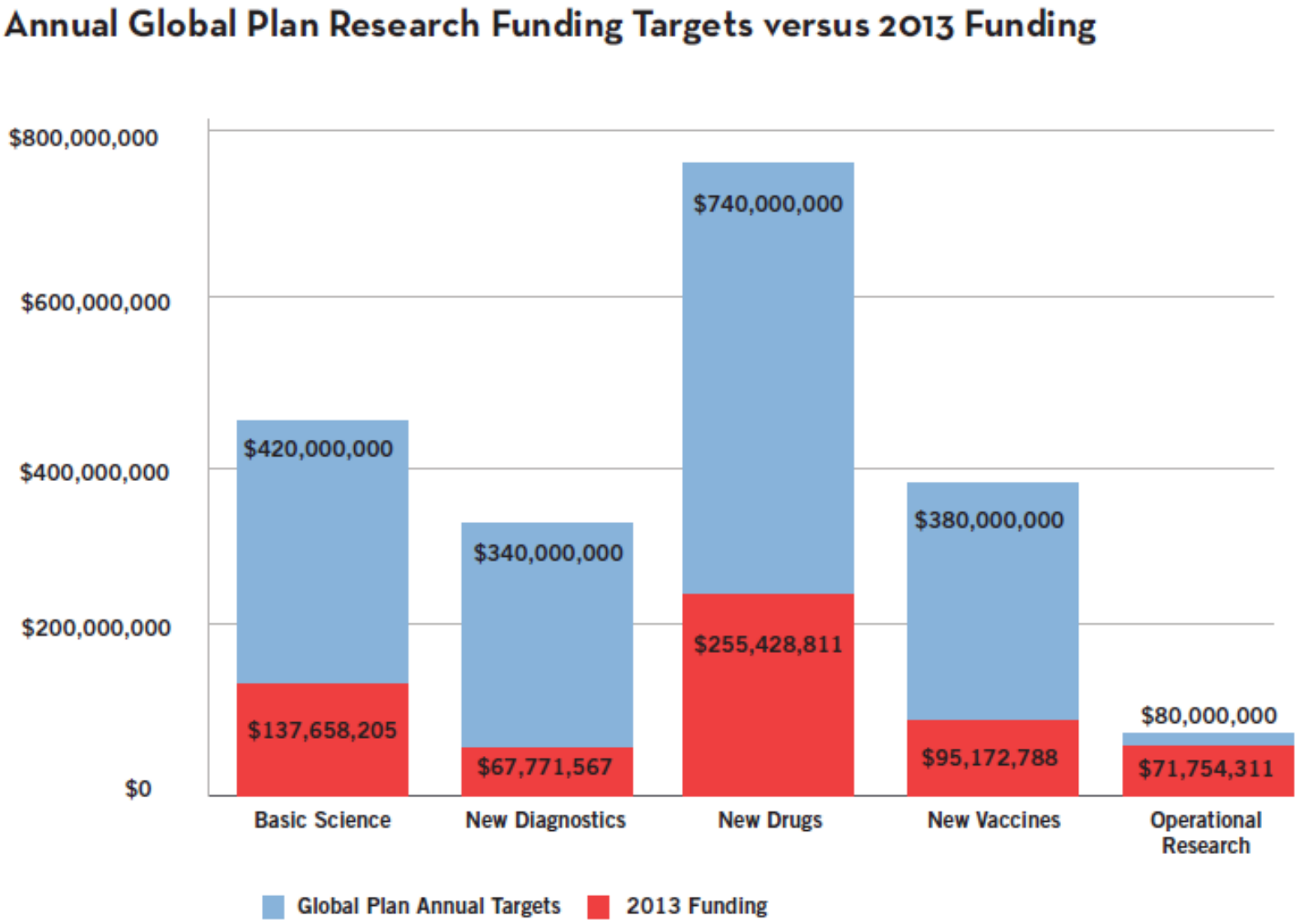
A new regimen would/could…

- Improve individual treatment outcomes (reduce mortality)
- Allow improved access to treatment
- Reduce burden on the health system
- Reduce further community transmission

Stages required

1. Drug development (basic science)
2. Bringing new drugs to market (conducting trials for regulatory approval)
3. Development and testing of new regimens – suitable for programmatic use in high burden settings
4. Roll out of new regimen

Drug development: TB R&D funding



TAG, TB funding trends 2005-13, Oct 2014

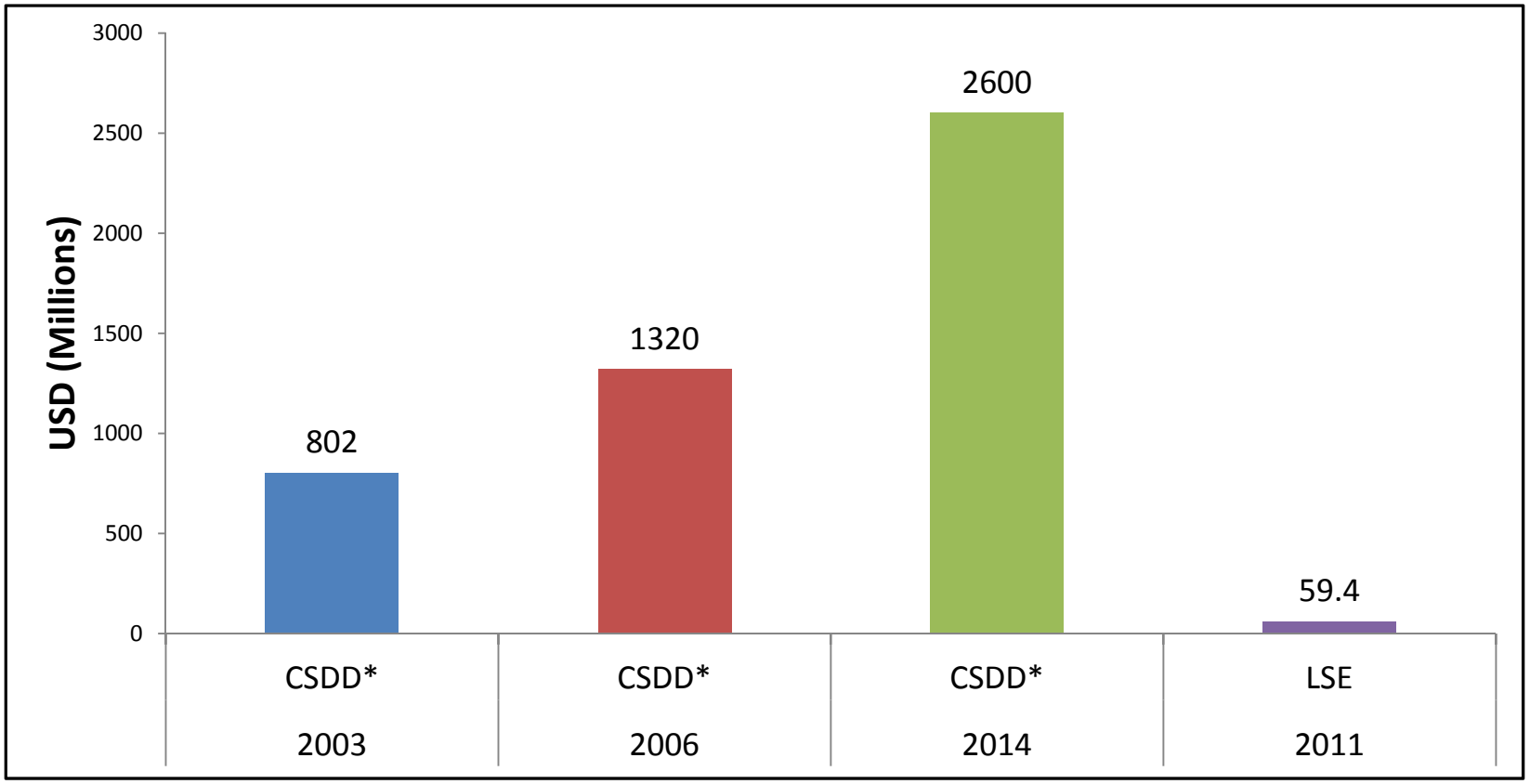
Top funders (2013)

Rank	Funding (USD)	Name
1	158,797,248	US National Institutes of Health
2	147,923,878	Bill and Melinda Gates Foundation
3	58,717,259	Otsuka Pharmaceuticals (producer of Delamanid)
4	36,656,765	Other NIH institutes
5	24,640,072	UK DFID
34	2,248,534	SA Medical Research Council
64	316,776	SA Dept Science and Technology
78	143,548	SA National Research Foundation

- Private contribution decreasing over time
- Large pharma companies withdrawing from TB research
  - Pfizer – 2012
  - AstraZeneca – 2013
  - Novartis - 2014

TAG, TB funding trends 2005-13, Oct 2014

Cost of bringing a drug to market



*Pharma funded research institute

DiMasi et al J Health Economics 2003, Light & Warburton LSE Biosocieties 2014

Current clinical trials (new combinations): Phase 3

Trial	Sponsor	Patients	regimen	Current status
STREAM	IUATLD	MDR-TB	New and repurposed drugs Incorporating BDQ arm	Ongoing New arm not yet started
STAND TB	BMGF/TB Alliance	DS-TB and MDR-TB	Pa-824/ Moxi / PZA (PaMZ)	Not yet started
Nix-TB	TB Alliance	XDR-TB/TDR-TB	All new drugs: BDQ, Pa-824, Sutezolid	In planning (not funded)
NEXT RCT	UCT/ SA MRC	MDR-TB	BDQ, LZD and existing drugs	Not yet started
END-TB	MSF/PIH	MDR-TB/XDR-TB	BDQ, DEL and existing drugs	In planning
PRACTECAL	MSF	MDR-TB/XDR-TB	BDQ, DEL and existing drugs	In planning

Trial results not likely until 2020 at the earliest

Clinical trials capacity limited:

- trial sites with sufficient patient numbers and infrastructure
- trial sponsors with experience and funding

Uptake of new regimens in high burden settings

- Regulatory approval of each new drug often required in each country
- Reliant on WHO guidance
- Desire for trial/programmatic data from each country before widespread rollout
- High cost of new drugs (cost effectiveness analysis required)
- Capacity for monitoring and evaluation (pharmacovigilance)

Bedaquiline (BDQ): the first new TB drug in 40 years

Date	Milestone
2005	Evidence of BDQ activity against TB in mice
2008	Phase 2a study of early bactericidal activity in humans
2009	Early results of phase 2b study (2 months BDQ) in humans
Mar, 2012	Final results of phase 2b study
Dec, 2012	FDA grants approval to market BDQ in the US (conditional on phase 3 trial results)
Mar, 2013	SA NDoH starts BDQ access programme (4 approved sites)
Jun, 2013	WHO releases guidance on appropriate use (for patients with pre-XDR or XDR-TB)
Oct, 2014	SA MCC approves BDQ
2015	SA NDoH plans access to BDQ for 3000 patients in 2015
2020	Phase 3 trial results expected

Can access to better treatment for DR-TB be aided by exploring the right to benefit from scientific progress?

Discussion