Data on TB regimens – what next?

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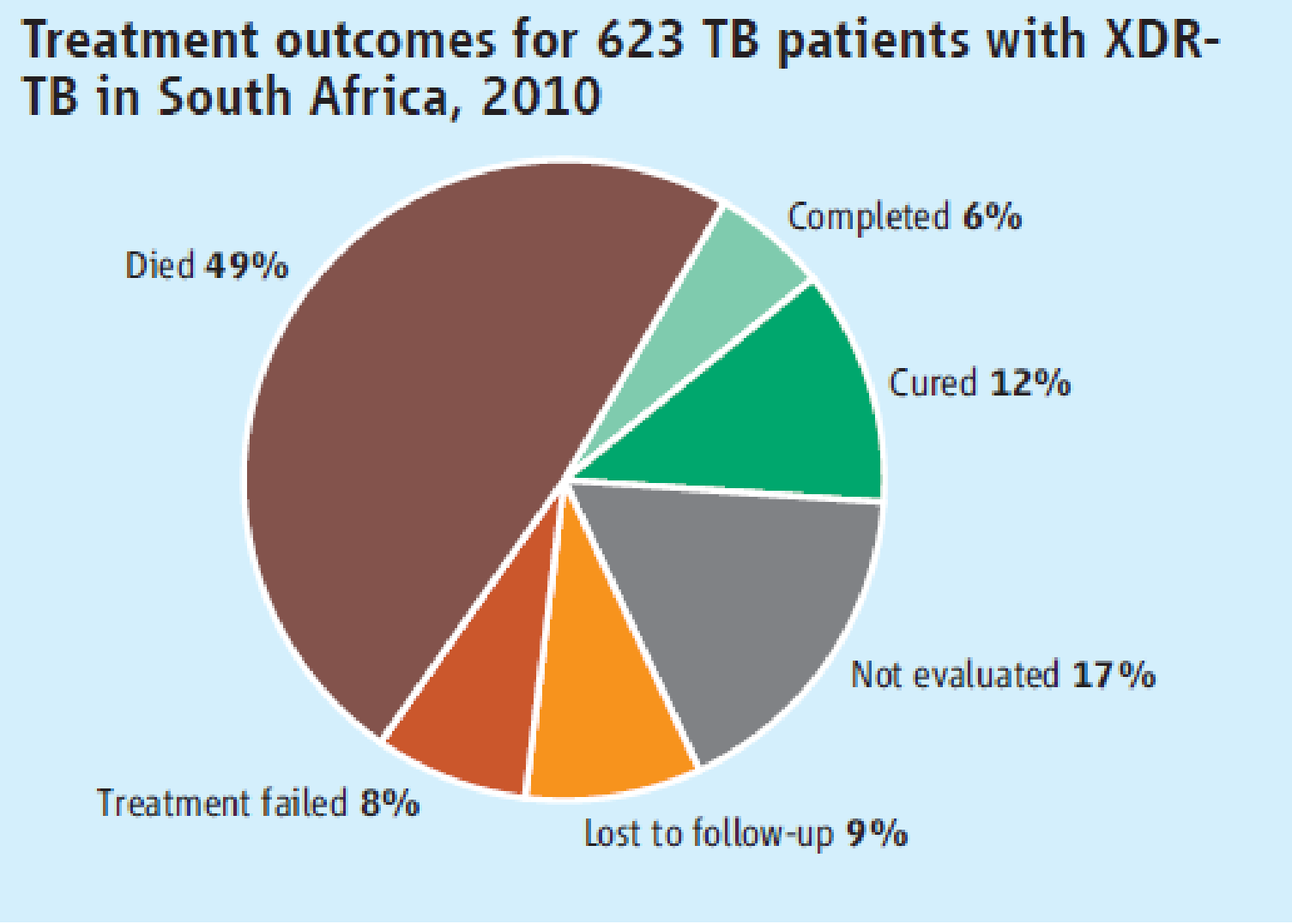
MEDECINS SANS FRONTIERES

- 21-yr old HR Mx student
- HIV neg, primary XDR-TB
- 3 mths MDR Tx (went deaf), 6 mths XDR Tx in hospital, culture reconverted at month 10

- 19-yr old engineering student
- HIV neg, primary XDR-TB
- 4 months MDR Tx before Dx

- 32-yr old mother of one
- HIV pos, primary pre-XDR-TB (Ami)
- 4 mths Reg I Tx, one month MDR Tx before Dx

SA: XDR-TB treatment outcomes



Source: WHO TB report 2013

Existing:

- Fluoroquinolones
- Injectables
- Ethionamide
- Terizidone
- PAS

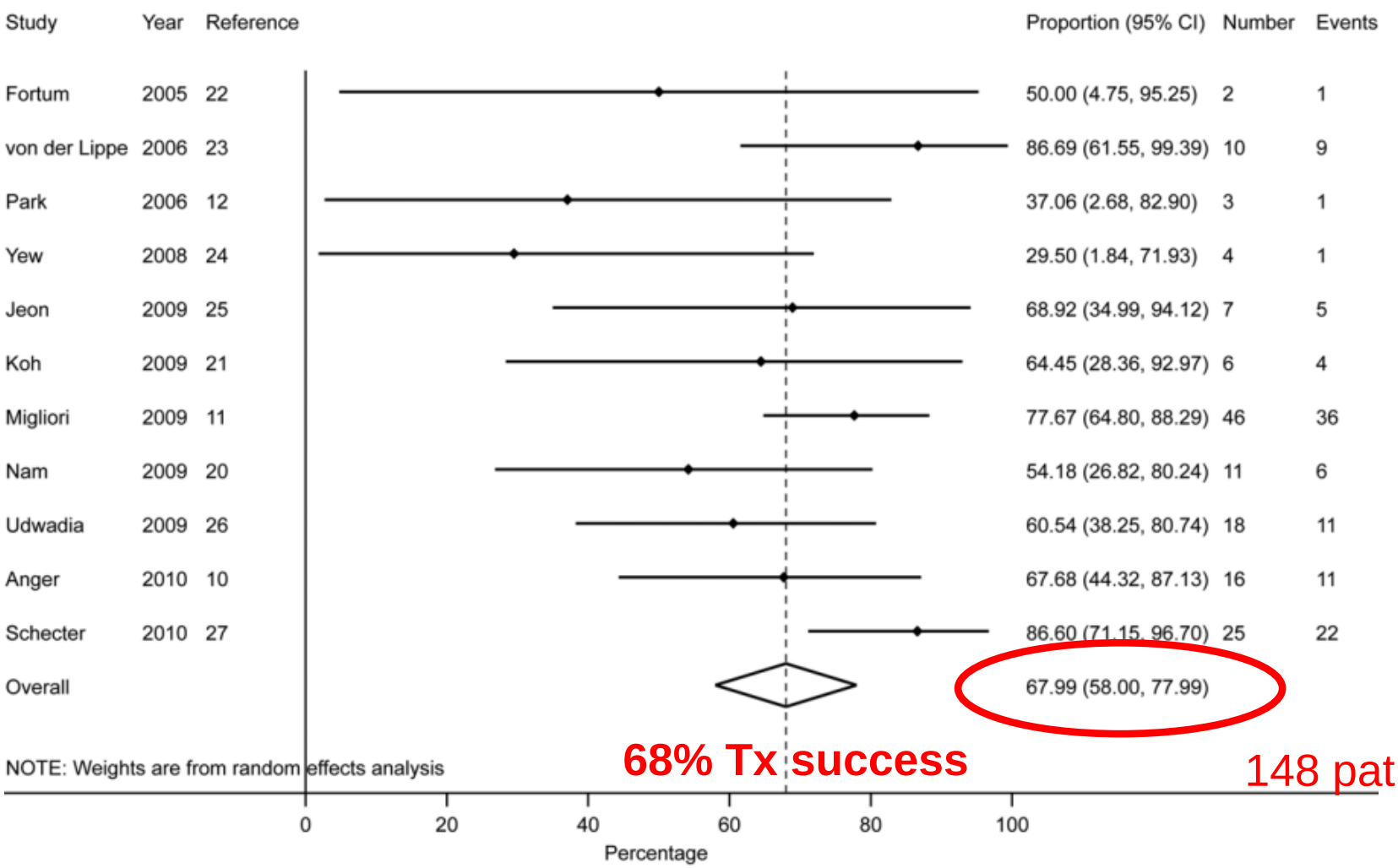
Re-purposed:

- **Linezolid**
- Clofazimine
- High dose INH

New:

- **Bedaquiline**
- Delaminid
- PA-824
- PNU-100480
- SQ-109

LINEZOLID
Systematic Review



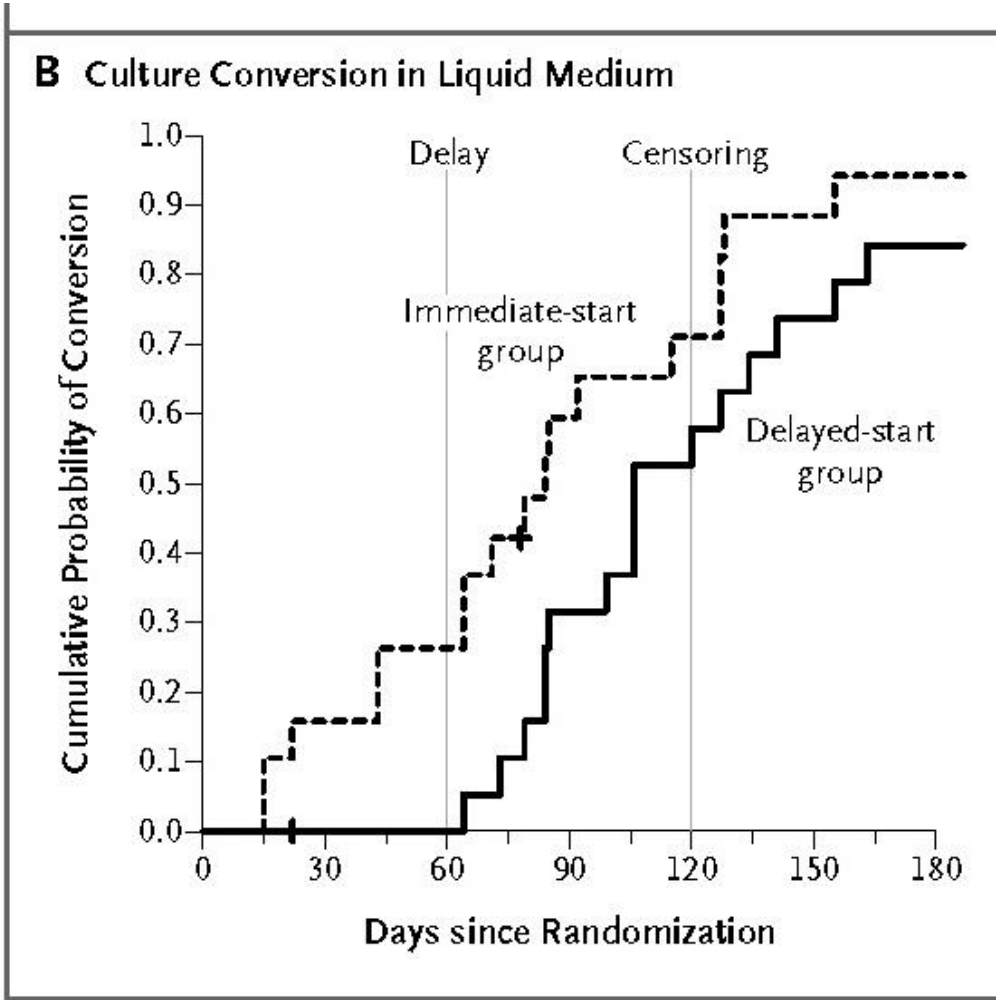
68% Tx success

148 patients

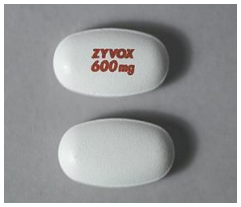
Cox & Ford, Int J TB Lung Dis, 2012

Linezolid for chronic XDR-TB: clinical trial

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



Lee et al, NEJM 2012



Linezolid Access Barriers

FIX THE PATENT LAWS!

- Pfizer holds a monopoly on linezolid sales in SA
- No alternative generic registered yet

Purchaser	Supplier	Price (600 mg tablet)
SA Government	Pfizer	R 287.9*
SA Private Sector	Pfizer	R 715.24**
Global Fund	Hetero	**R74 *** **

*Expired antibiotics tender price
**Single Exit Price
***not available in South Africa

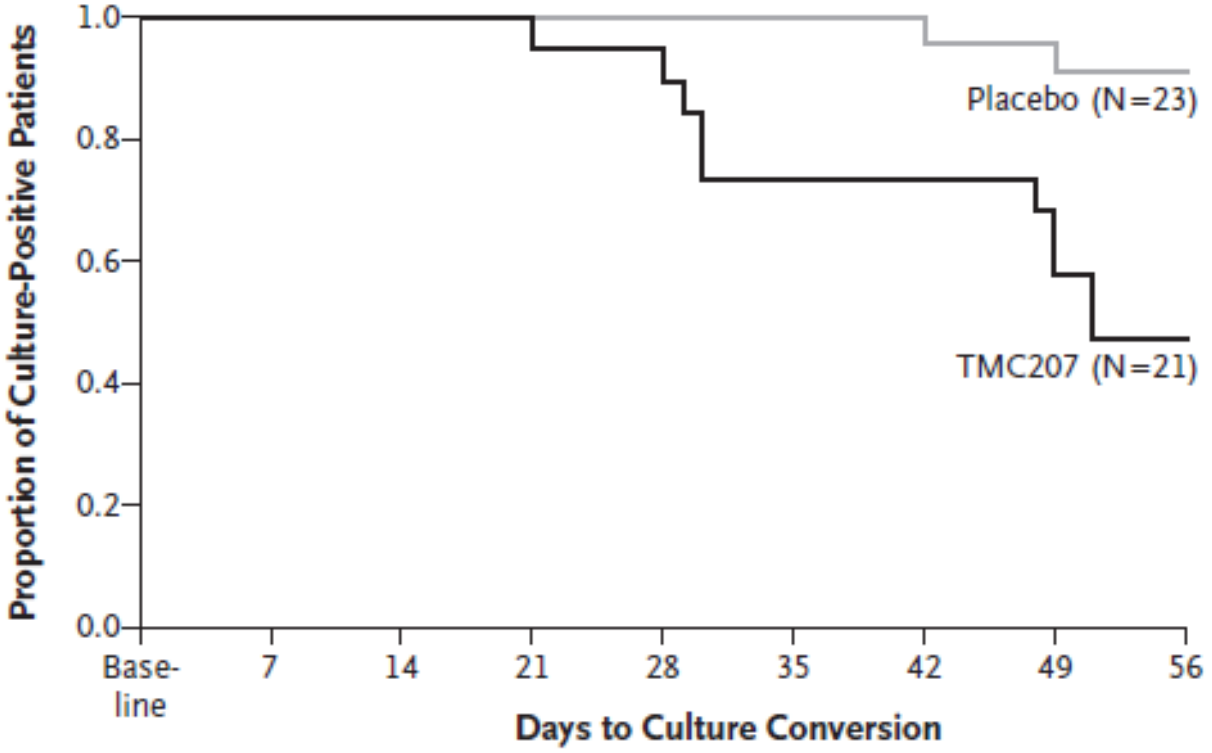
With mark-ups, MSF in South Africa pays approximately ***R123,000 per patient*** *for a 6-month supply of linezolid*

BEDAQUILINE

- First new drug for TB in 50 years
- Diarylquinolone compound
- New mechanism of action:
  - specifically inhibits ATP-synthase in mycobacteria
- Long terminal half life of ~5 months
- Toxicities:
  - QT prolongation and raised hepatic enzymes

Bedaquiline (TMC207)

Phase 2 results



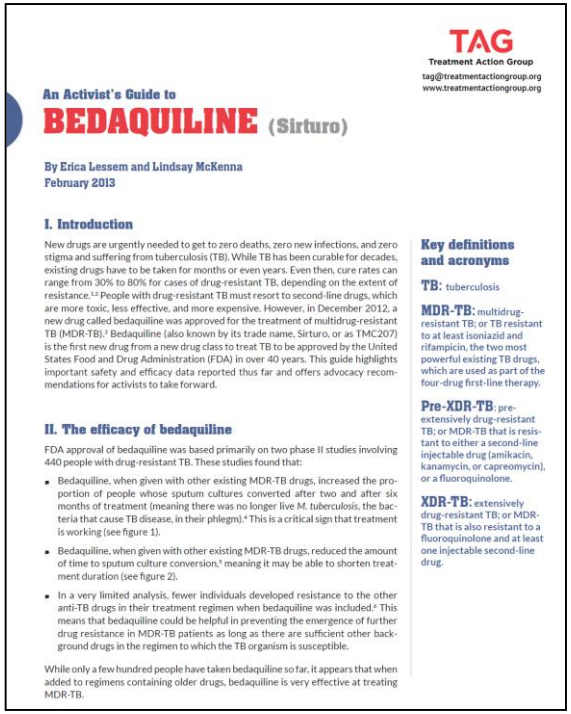
No. at Risk							
Placebo					22	21	
TMC207	19	18	16			13	11

- ❑No cross-resistance
- ❑No additional side effects
- ❑Less acquired drug resistance during treatment

Diacon et al, NEJM 2009, and Diacon et al AAC 2012

Access to Bedaquiline

- US FDA granted accelerated approval of BDQ in 2012 for DR-TB
- MCC registration in SA still pending
- Cost in SA? ~R10,000 for 6-month course



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An Activist's Guide to
BEDAQUILINE (Sirturo)

By Erica Lessem and Lindsay McKenna
February 2013

I. Introduction

New drugs are urgently needed to get to zero deaths, zero new infections, and zero stigma and suffering from tuberculosis (TB). While TB has been curable for decades, existing drugs have to be taken for months or even years. Even then, cure rates can range from 30% to 80% for cases of drug-resistant TB, depending on the extent of resistance.[1,2] People with drug-resistant TB must resort to second-line drugs, which are more toxic, less effective, and more expensive. However, in December 2012, a new drug called bedaquiline was approved for the treatment of multidrug-resistant TB (MDR-TB).[3] Bedaquiline (also known by its trade name, Sirturo, or as TMC207) is the first new drug from a new drug class to treat TB to be approved by the United States Food and Drug Administration (FDA) in over 40 years. This guide highlights important safety and efficacy data reported thus far and offers advocacy recommendations for activists to take forward.

II. The efficacy of bedaquiline

FDA approval of bedaquiline was based primarily on two phase II studies involving 440 people with drug-resistant TB. These studies found that:

- Bedaquiline, when given with other existing MDR-TB drugs, increased the proportion of people whose sputum cultures converted after two and after six months of treatment (meaning there was no longer live *M. tuberculosis*, the bacteria that cause TB disease, in their phlegm).[4] This is a critical sign that treatment is working (see figure 1).
- Bedaquiline, when given with other existing MDR-TB drugs, reduced the amount of time to sputum culture conversion,[3] meaning it may be able to shorten treatment duration (see figure 2).
- In a very limited analysis, fewer individuals developed resistance to the other anti-TB drugs in their treatment regimen when bedaquiline was included.[4] This means that bedaquiline could be helpful in preventing the emergence of further drug resistance in MDR-TB patients as long as there are sufficient other background drugs in the regimen to which the TB organism is susceptible.

While only a few hundred people have taken bedaquiline so far, it appears that when added to regimens containing older drugs, bedaquiline is very effective at treating MDR-TB.

Key definitions and acronyms

TB: tuberculosis

MDR-TB: multidrug-resistant TB; or TB resistant to at least isoniazid and rifampicin, the two most powerful existing TB drugs, which are used as part of the four-drug first-line therapy.

Pre-XDR-TB: pre-extensively drug-resistant TB; or MDR-TB that is resistant to either a second-line injectable drug (amikacin, kanamycin, or capreomycin), or a fluoroquinolone.

XDR-TB: extensively drug-resistant TB; or MDR-TB that is also resistant to a fluoroquinolone and at least one injectable second-line drug.

http://www.treatmentactiongroup.org/tb

- BDQ accessible in SA only through **BCAP** for selected pre-XDR and XDR patients with PTB

THE IDEAL REGIMEN

1. At least one new class of drug
2. Contains 3 to 5 effective drugs (minimum 3), each of them from a different class of drugs
3. No injectables
4. Broad backbone that can be used for MDR and XDR
5. Simple dosing schedule
6. Limited side effects profile requiring limited monitoring
7. Shorter duration (aiming at 6 months but max 9 months)
8. Minimal interaction with ART

http://www.who.int/bulletin/volumes/92/1/13-122028.pdf

Challenges for regimen trials

- Pharmaceutical companies design trials to get the new drug registered
- They are not designing the best possible regimen
- Patents on individual drugs may hinder research into better regimens

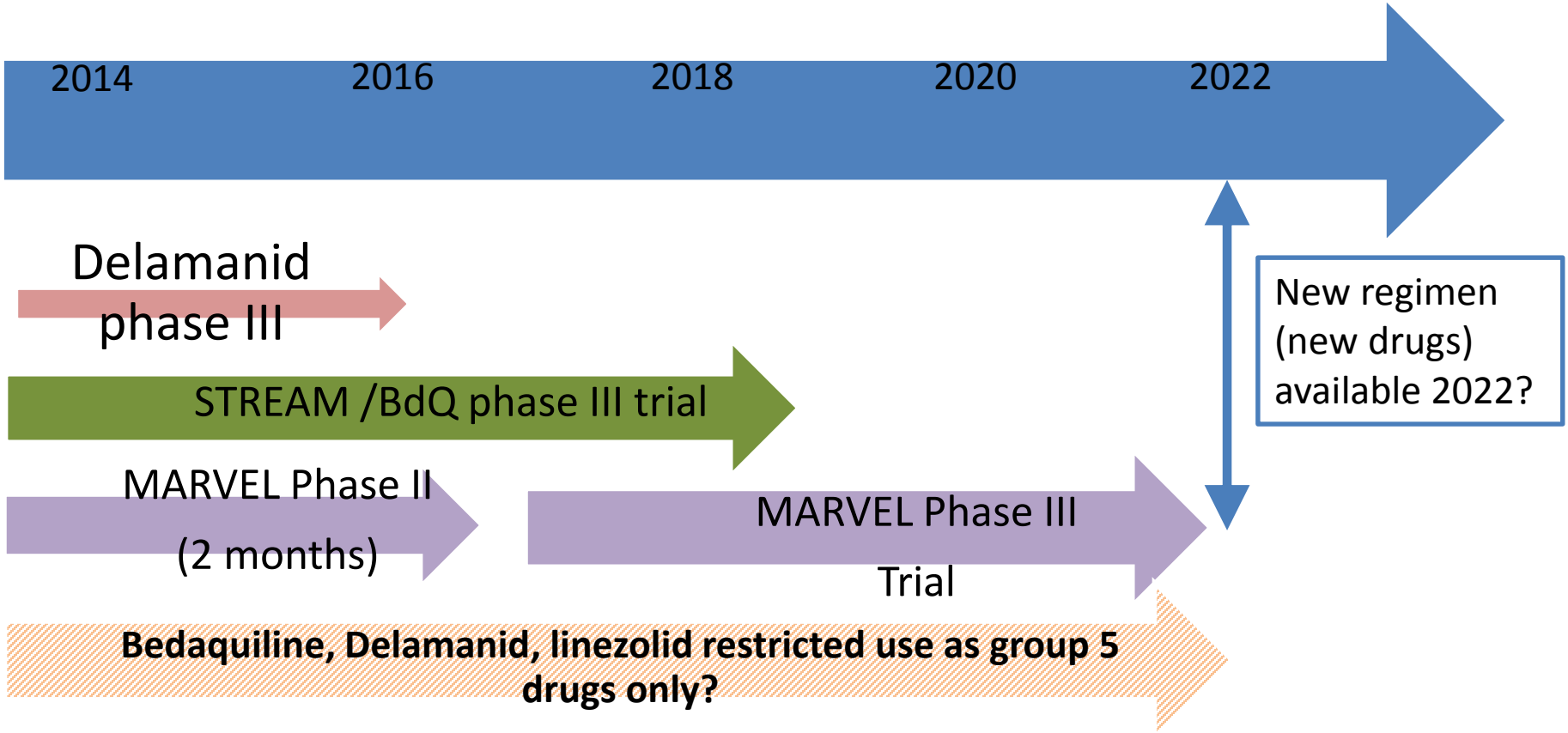
- Hard to find funding for pragmatic trials that will work in real program settings
- Limited trial capacity in high DR-TB burden settings

Trial	Regimen	Injectable	Treatment duration	Current status
Delaminid (Otsuka)	Delaminid (OPC67683) and OBT	Yes (6-8 mths)	Standard (18-24 mths)	Phase III, ongoing
STREAM (MRC)	Modified Bangladesh regimen (Gfx/Cfz/E/Z/ Pto/Ka/hdINH) vs WHO std regimen	Yes (4-6 mths)	9 mths	Recruitment ongoing
Bedaquiline (Janssen)	Bedaquiline into 2 additional arms of STREAM trial	Yes (4 mth) No	6 mths 9 mths	Recruitment ongoing
PaMZ	PA-824/Moxi/PZA (4-6mths) vs RHZE for DS-TB; one arm MDR	No		Not yet enrolling
MARVEL (ACTG)	BDQ/PA-824/PZA/LZD +/- Lfx	No	6 mths	Protocol being finalised
PaBZ (TB Alliance)	BDQ/PA-824/PZA for DS-TB; Mfx added for one MDR arm	No		Not yet enrolling
NIX-TB	BDQ/PA-824/LZD for XDR-TB	No	6-9 mths	Not yet enrolling
OPTI-Q	High dose Lfx and OBT for MDR	Yes (6 mths)	Standard (18-24 mths)	Not yet enrolling
DDI study (ACTG)	BDQ / DEL interaction (to assess for future regimen options)	-	-	Approved

Overview of trials

- http://www.resisttb.org/?page_id=1602

Results of trials unlikely to be available v soon:



1. What do we do in the meantime?

MDR regimens

- Robust standard regimen for all new RR-TB cases, ensure at least 4 effective drugs
- Low threshold for modification of MDR regimen if inadequate (need alternative drugs available)
- Identify MDR failure early and amend regimen

The standard MDR regimen (SA)

PZA / Kana / Mfx / Tzd / Eto

- Is PZA reliable? – no DST
- INH mutations: inhA – is Eto effective?
- Evidence for Tzd?
- 10% XDR prevalence – Ka +/or Mfx ineffective?
  - Only detected later if 2nd line DST followed up

- **Are we driving development of XDR TB…??**

A slightly more empiric approach

- Suggested initial MDR regimen on GXP RR-TB:

PZA / EMB / Kana / Mfx / Tzd / Eto / hdINH

- EMB – well tolerated and potentially effective in 50%
- Modify when INH mutation info available:
  - inhA > remove Eto
  - katG > remove hdINH
  - both > use alternative (PAS/Cfz), and request 2nd line LPA to r/o XDR early

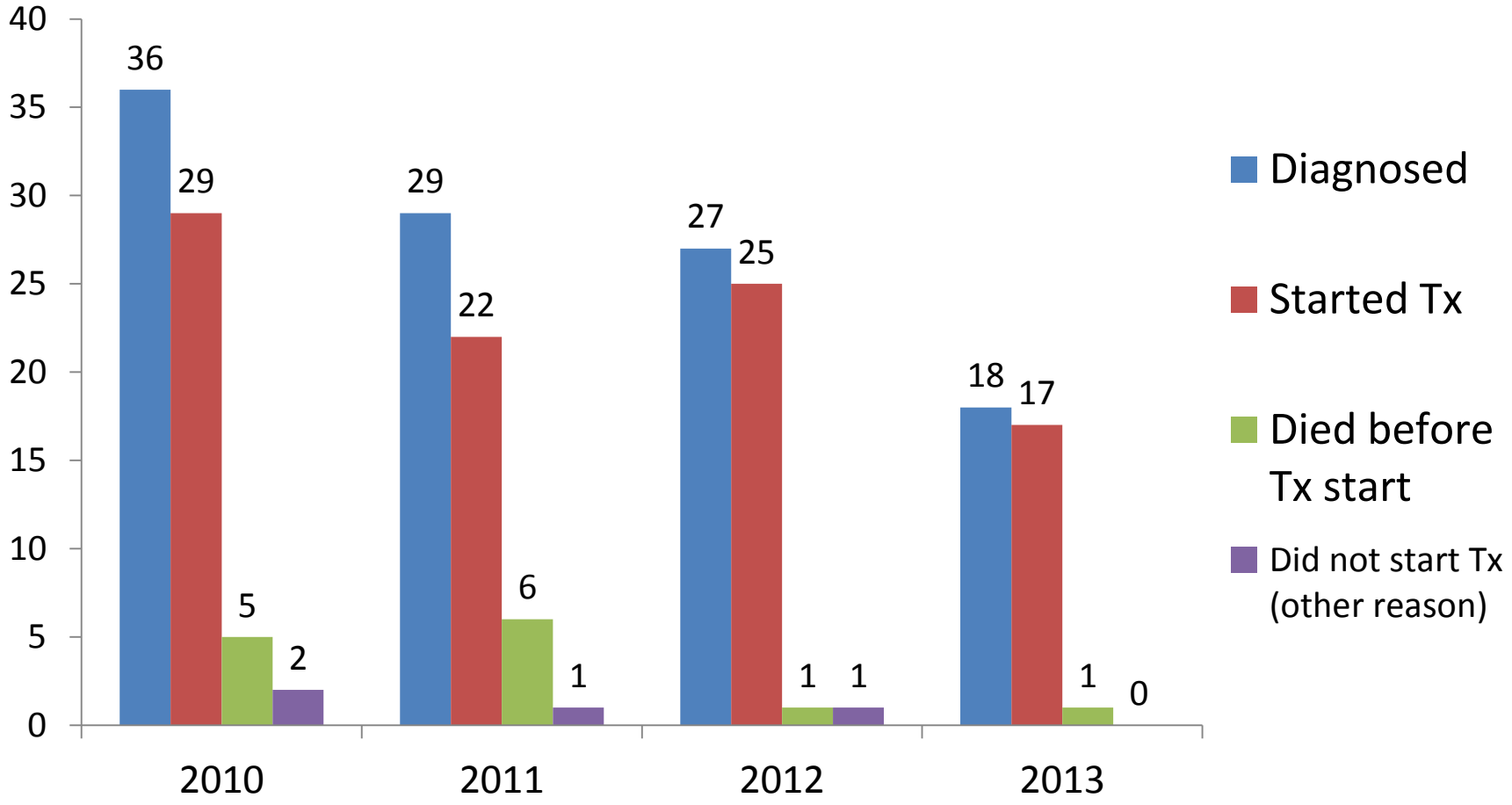
- If any drug not tolerated, consider substitution early:
  - LZD / PAS / Cfz

2. What do we do in the meantime?

XDR regimens

- One chance at providing an effective regimen
  - no use ‘saving’ drugs for salvage regimens
- Access effective drugs and start treatment asap
- Use rapid diagnostics to detect XDR early
  - MDR treatment is inadequate for XDR, may lead to development of further resistance

Cases with **pre-XDR or XDR-TB** Khayelitsha 2010-2013



>85% started DR-TB treatment; 12% died before start

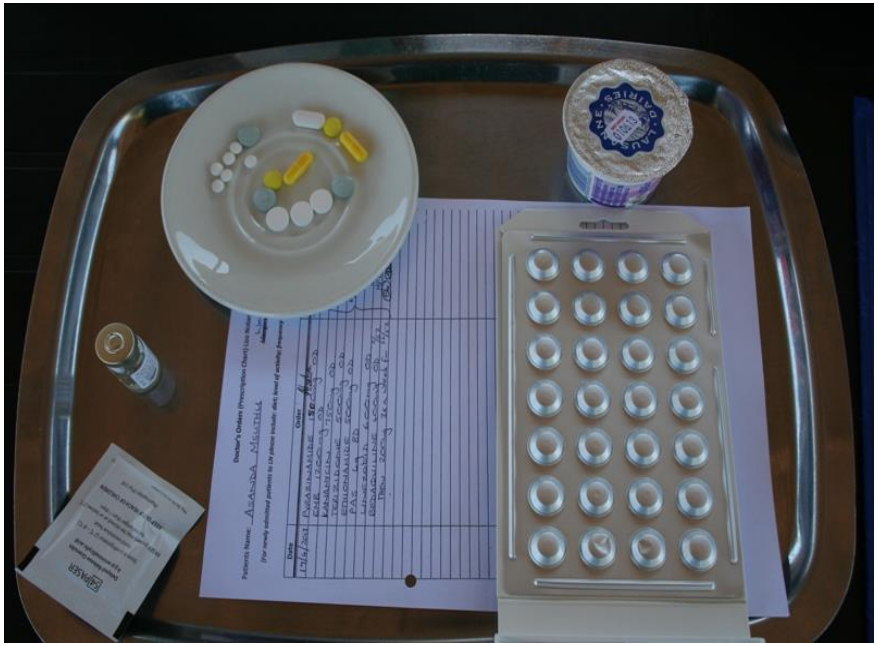
"Strengthened Regimen" pilot

- Since July 2011:
  - pre-XDR or XDR-TB results identified (clinics, NHLS, MSF)
  - MDR failure (delayed conversion or reconversion) referred

- Clinically stable patients with good compliance on MDR treatment are offered modified regimens in PHC

- Drug regimens **individually tailored**
  - DST pattern; genotyping results
  - Prior Tx history
  - Co-mordities and concomitant meds
- Agreed by TB hospital clinicians and local experts

- **Drugs** sourced:
  - Z/E/Ka/Mfx/Tzd/Eto (PHC)
  - hdLfx and hdINH (PHC)
  - Cm, Cfz, PAS (TB hospital)
  - LZD from MSF
  - (BDQ from BCAP…)



BDQ Clinical Access Programme

- BCAP – mix between a clinical trial and CU
  - no comparison arm
  - allows access to BDQ (in an OBR) for pre-XDR and XDR patients with limited treatment options
  - eligible patients presented to Clinical Committee
  - progress and adverse events closely monitored
- Specific eligibility criteria
  - MDR excluded, but HIV pts on ART included

Patients NOT eligible for BCAP

- MDR
- EPTB – hip / sternum etc
- Uncontrolled HIV
- Poly-resistance – e.g. INH and Ofx
- Age under 18yrs
- XDR failure

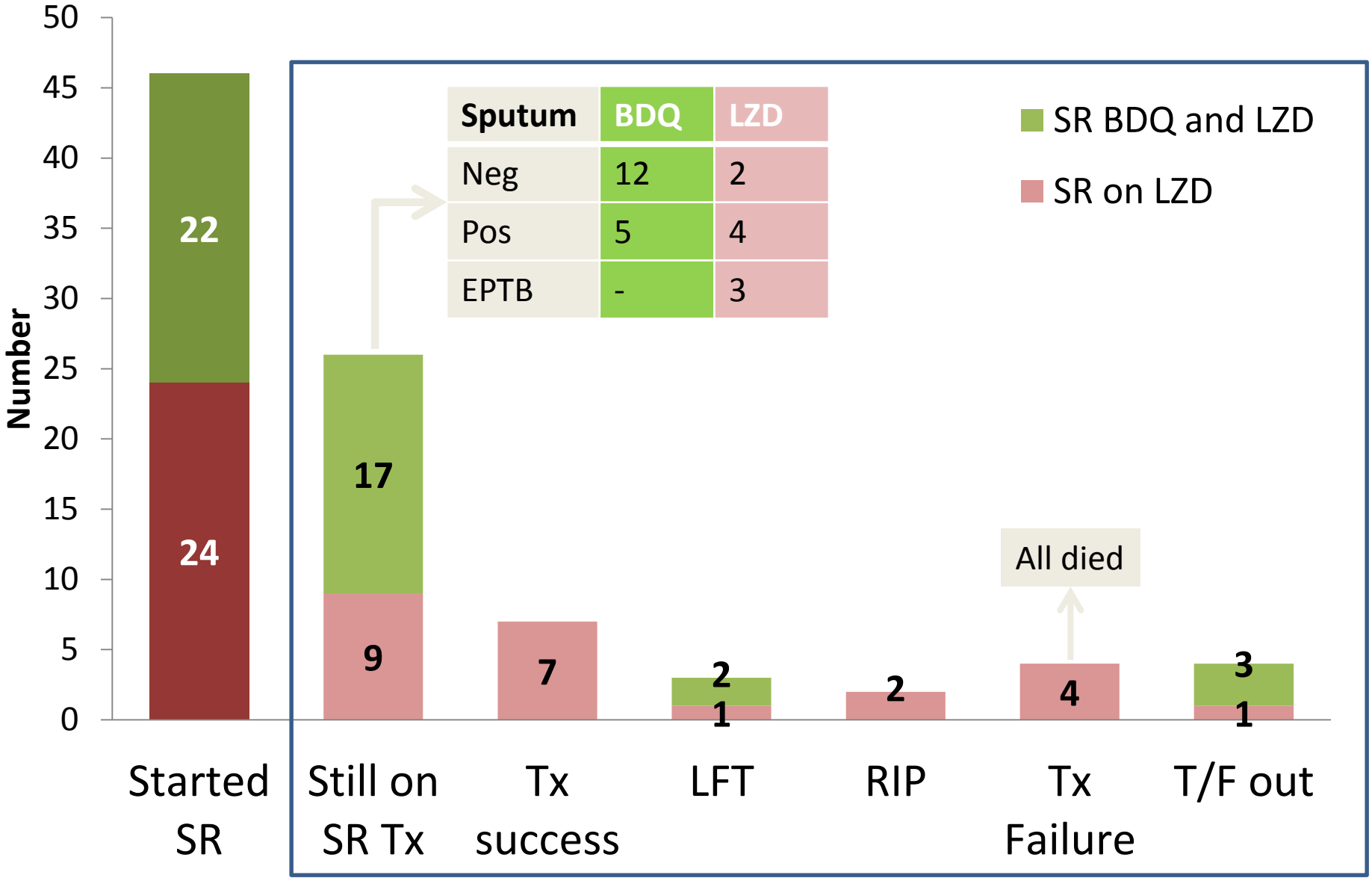
- In Khayelitsha, these patients may still be offered LZD as part of Strengthened Regimen pilot

Description of Khay SR cohort

- 46 pts enrolled on SR in Khayelitsha to date

	SR with LZD		SR with LZD and BDQ	HIV STATUS	
				Pos	Neg
XDR	5 PTB	1 EPTB	4 PTB	6	4
PRE-XDR	10 PTB	3 EPTB	18 PTB	15	16
MDR failure	4		0	3	1
Poly-resistant	1 (Rif + Ofx)		0	-	1
TOTALS	**24**		**22**	**24**	**22**

Strengthened regimen patients since July 2011: Interim outcomes August 2014



FUTURE…

- Empiric regimen for all RR-TB
- Tailor down according to DST

Benefits	Downsides
• Strong initial regimen for all • Covers all R patterns • Can remove drugs if not tolerated without compromising regimen • Improved culture conversion?	• Cost for all RR-TB pts • Pill burden • Interactions with ARVs • Toxicity for some

Summary

- Current DR-TB regimens not good enough
- Need to improve access to newly available and repurposed drugs for better regimens
- Need to urgently implement use of better available drugs to improve regimens while waiting for regimen trials results

QUESTIONS?

Acknowledgements:
SR patients in Khayelitsha
MSF Khayelitsha staff
CoCT and PGWC
NDOH and BCAP