New TB regimens and the need for new approaches to drug susceptibility testing

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TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Outline

- TB Alliance and the drug development pipeline
- Resistance and DST algorithms
- Turning theory into diagnostic development

TB Alliance Vision

Current Treatment

6-30
Months

New Treatments in Development

2-4
Months

Our Vision

7-10
Days

Success will require novel drug combinations

Current Therapy and Unmet Needs

	Drug Sensitive TB	M(XDR)-TB	TB/HIV co-infection	Latent TB Infection	Children
Current Therapy	4 drugs taken for 6 or more months	Injections and drugs taken for more than 2 years, poorly tolerated	Drug-drug interactions with ARVs	9 months of isoniazid	Formulations not adequately dosed
Unmet Needs	Shorter, simpler therapy	More effective, shorter, safer simpler regimens	Co-administration with ARVs	Shorter, more easily tolerated therapy	Regimens and formulations with correct dose

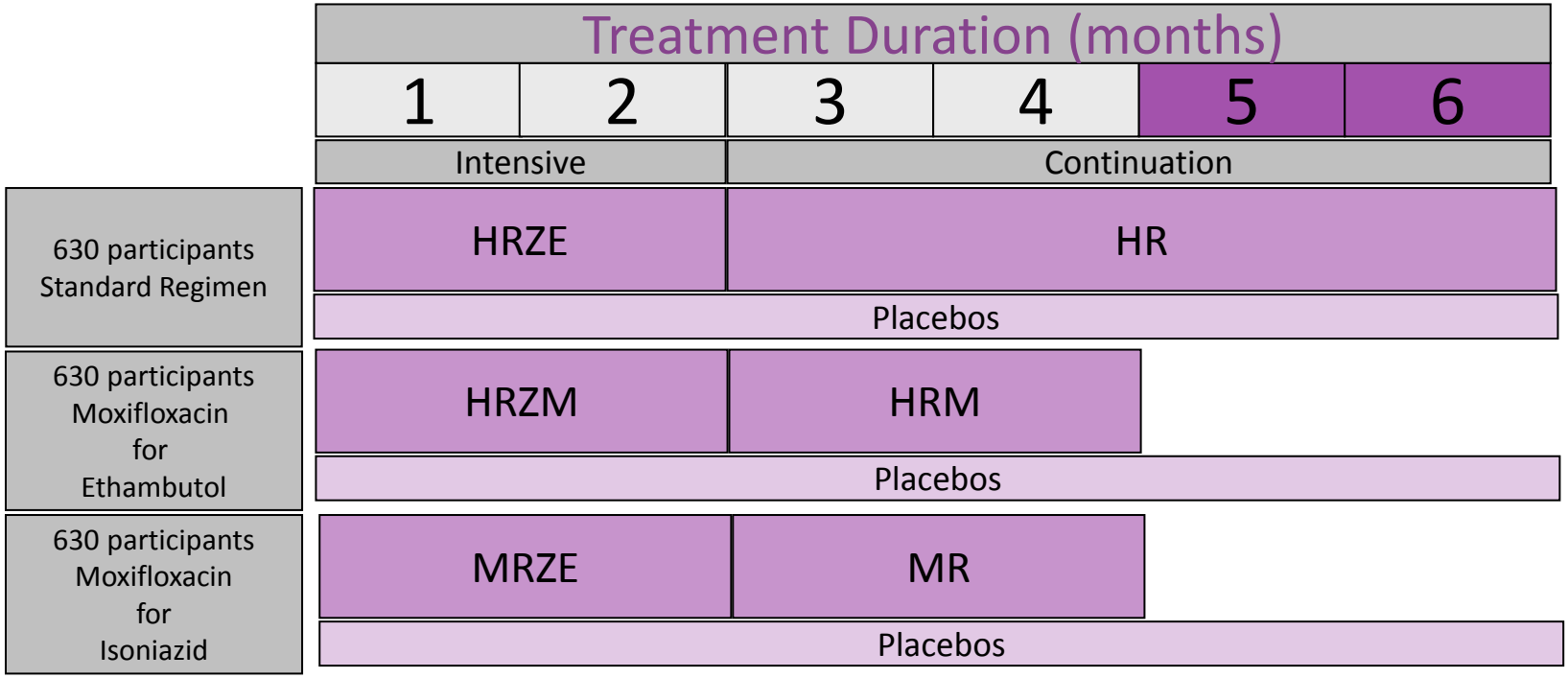
No new drugs for TB in more than 40 years

Timeline for country availability of new TB drugs and regimens

- 2013+: Bedaquiline (TMC-207; Janssen/Tibotec) and delamanid (OPC-67683; Otsuka) for MDR-TB
  - Based on Phase II results: adding new drug for 6 months on top of existing MDR-TB regimen
  - Phase III trial will take several years
- 2014+: Dispersible first-line (HRZE) FDCs for pediatric use
- 2015: REMoxTB regimens (moxifloxacin) for drug-sensitive TB
- 2018+: PaMZ for drug-sensitive TB AND some MDR-TB

Phase 3 REMox TB Trial Design

Randomized, Double-blind; Non-inferiority



All participants followed for 12 months post-treatment

H = isoniazid; M = moxifloxacin; R = rifampin; Z = pyrazinamide; E = ethambutol

1931 patients enrolled in China, India, Kenya, Malaysia, Mexico, South Africa, Tanzania, Thailand, Zambia

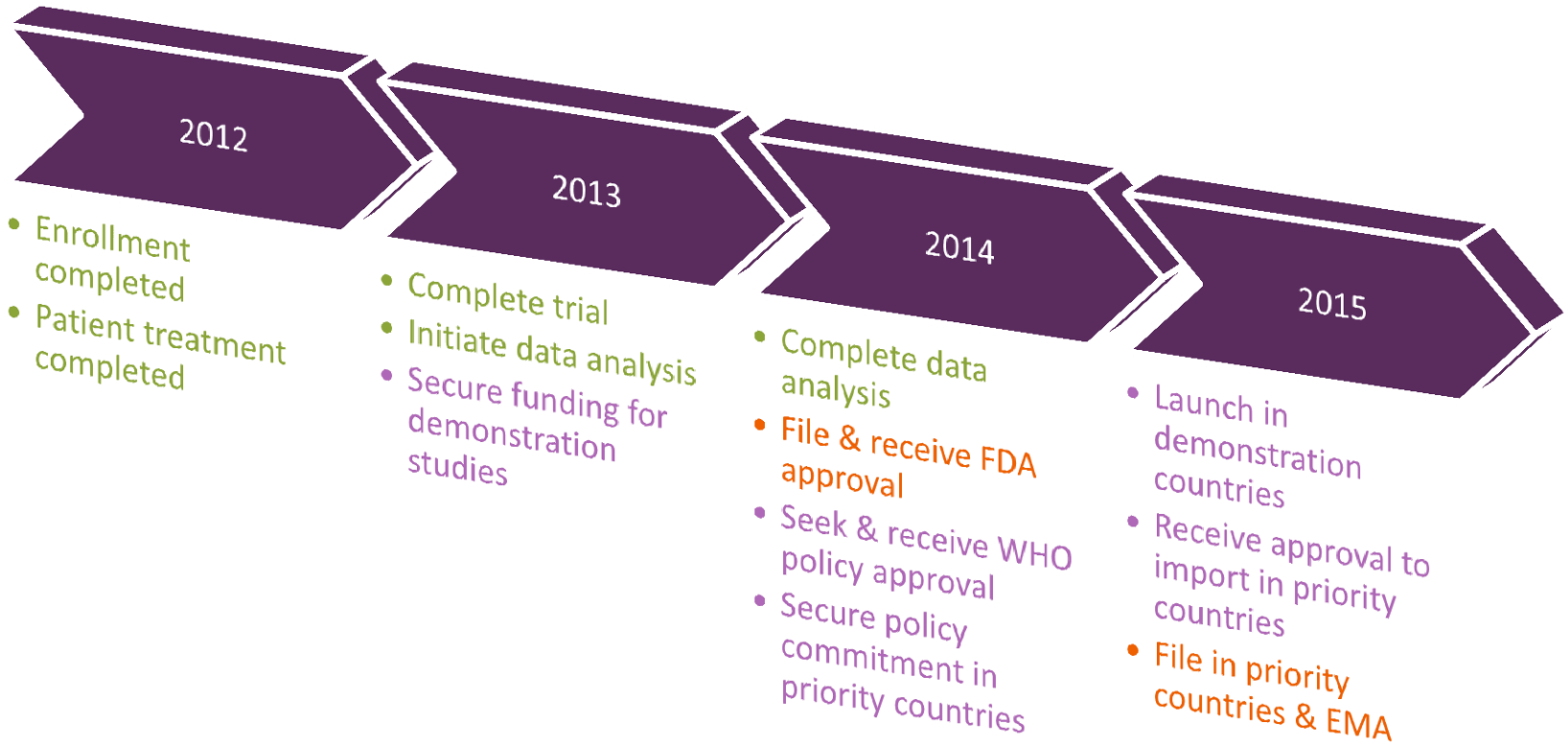
Benefits of REMox Regimen

Shorten Treatment from 6 to 4 months

- Treatment outcome benefits (potentially higher effective cure rates & less emergence of MDR-TB)
  - Increased adherence/reduced drop-out
  - Less resistance to drugs in regimen (e.g. isoniazid or ethambutol)
- Health Systems benefits
  - Reduced cost in healthcare utilization (at any one time in Bangladesh, ~53,000 active patients instead of 80,000)
- Patient benefits
  - Reduced out of pocket costs (fewer visits)
  - Less time exposed to side effects

Timeline for REMox TB

Clinical, Regulatory and Market Access activities in brief



Value Proposition of PaMZ

Potential benefits from PaMZ

- TIME
  - Reduce treatment duration from 6 months (first line) or 18-24 months (MDR-TB) to 4 months.
- TREATMENT OUTCOMES
  - Eliminate interaction with ARVs with removal of R from regimen
  - Treat some (10-67%) of MDR patients with shorter, safer, cheaper, more efficacious regimen with fewer side effects and no injections
- SUPPLY MANAGEMENT
  - Single weight band for all patients
  - No technical barrier to being made into FDC
  - All oral, no refrigeration
- COST
  - For DS-TB: Tradeoff similar to REMoxTB, i.e., higher drug costs but reduced cost of delivery
  - For MDR-TB: Drug costs and delivery costs both dramatically reduced
  - Patient out of pocket costs reduced

Questions for Adoption

What countries may need to know about drug resistance

- What is the background, *population-based* resistance to drugs in the combination?
- Based on modeling, what *individual* drug susceptibility testing (DST) – with what kind of sensitivity and specificity – will be needed?
- What is the likely availability of those DST diagnostics?
  - Developed
  - In field use
  - At national & district levels

Current DST is focused on the needs of the current regimen – but what will be needed for the future?

Resistance exists: the question is how to deal with it

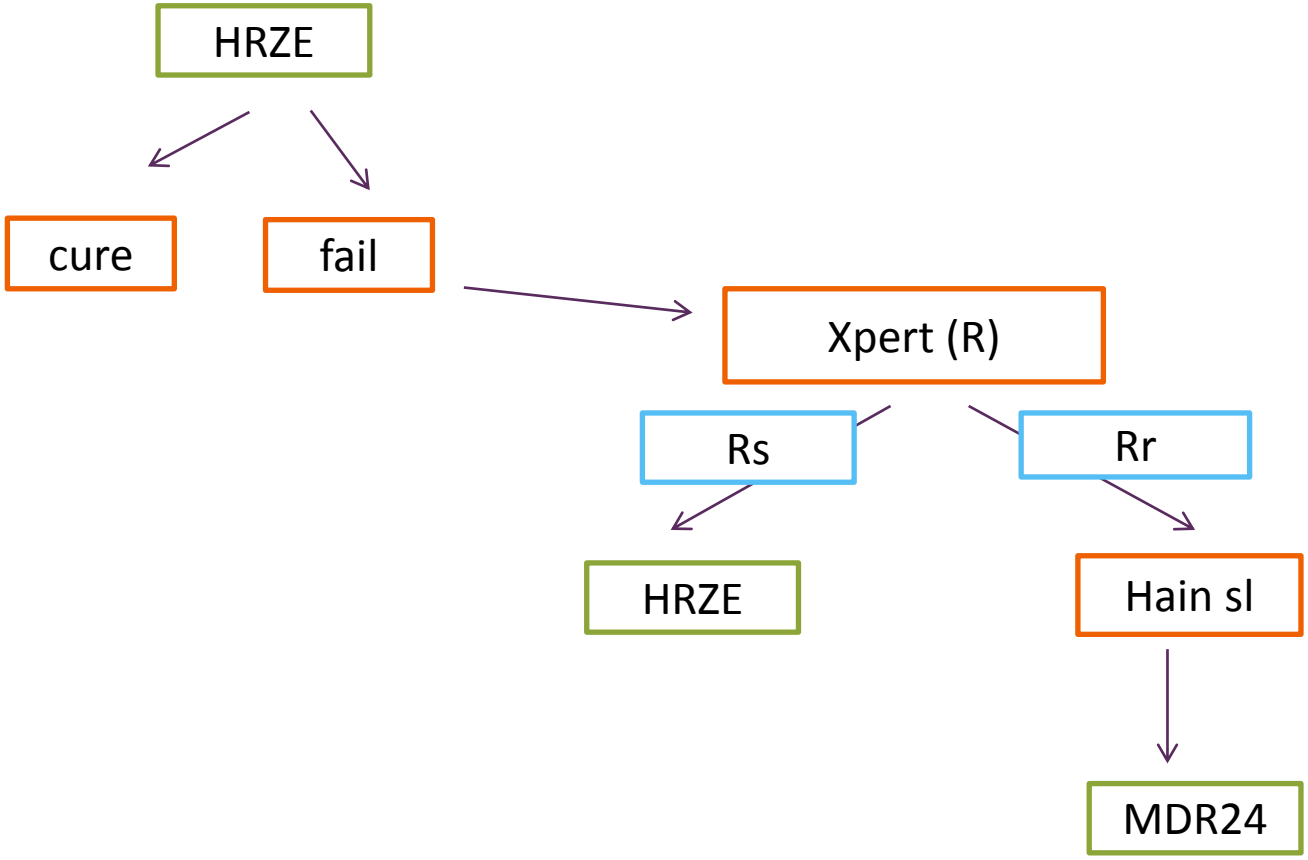
- H resistance among new cases of 15% is not unusual.
- R resistance among new cases: 3% is typical.
- Z resistance among non-MDR-TB cases: around 3%.
- FQ resistance among non-MDR-TB cases appears to be ~1-2%, though data here are particularly sparse.
- Resistance to FQ and Z appears to be higher in Asia than in Africa – possibly due to the more extensive private sector TB drug use in Asia.
- Z resistance rates among MDR-TB range from 33-90%.

Test everybody for everything?

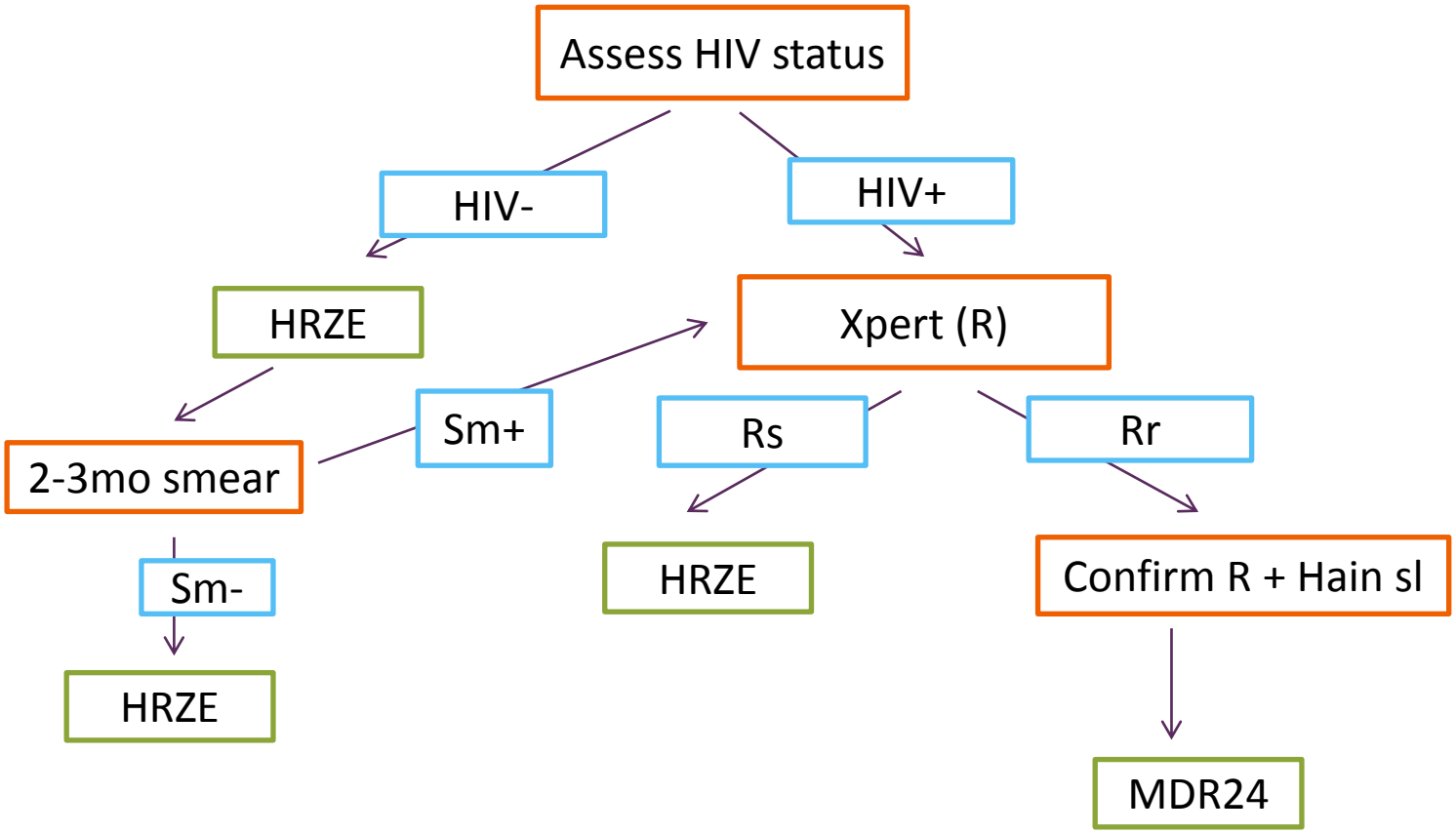
It's not that simple

- Xpert uptake not just for DST ability, but often for TB detection
- Many high burden countries have insufficient resources to do DST on all suspects or patients
- If resistance prevalence is low, false positives (and need for confirmatory testing) would be high
- Trade-off:
  - DST increases knowledge of patient's clinical status
  - But DST increases burden on health system and patient
- **If DST results in greater travel costs, multiple visits and diagnostic delays, it will reduce patient retention and may result in worse outcomes.**

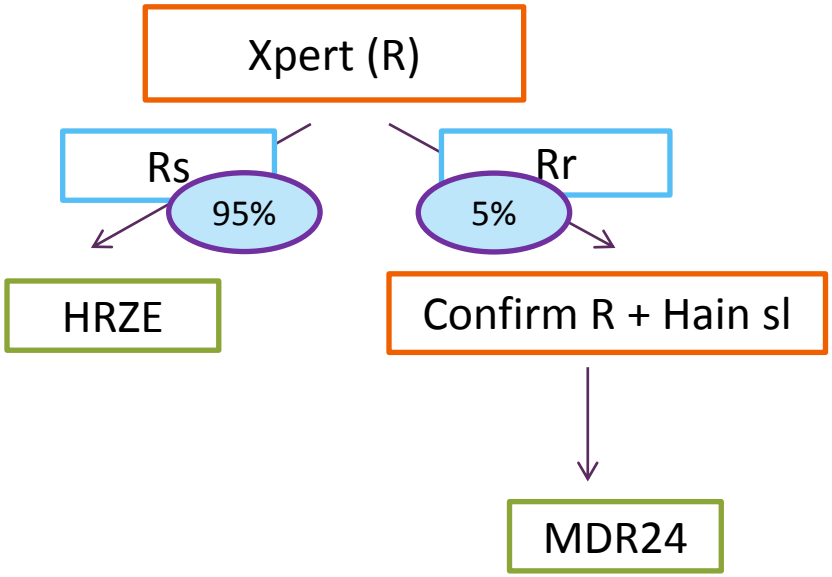
Current treatment algorithm: many countries



Current treatment algorithm: Some high HIV-burden countries



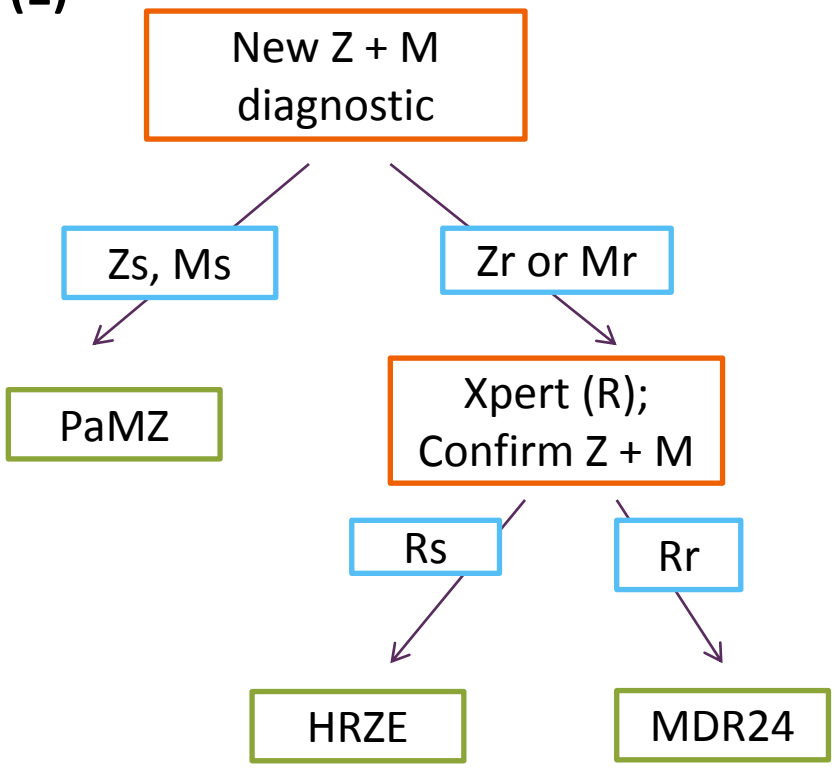
Current treatment algorithm: South Africa



Potential algorithms for PaMZ

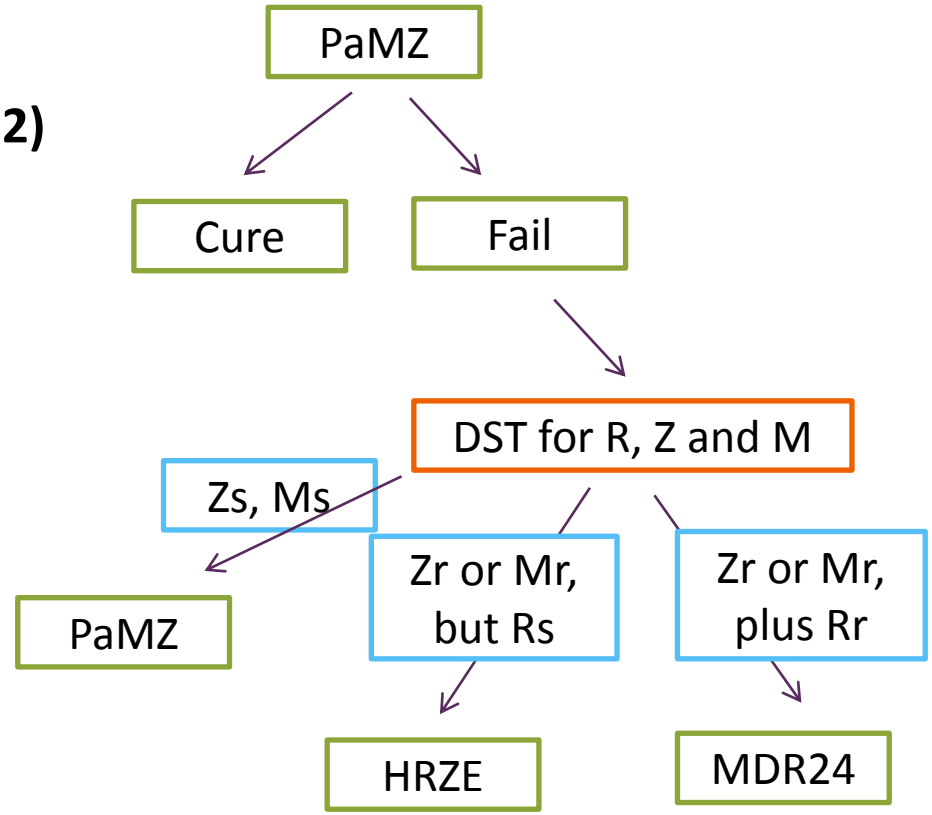
1) Test all for R & M; or 2) presumptive treatment for all

(1)



Safe but expensive, complex and difficult logistics

(2)

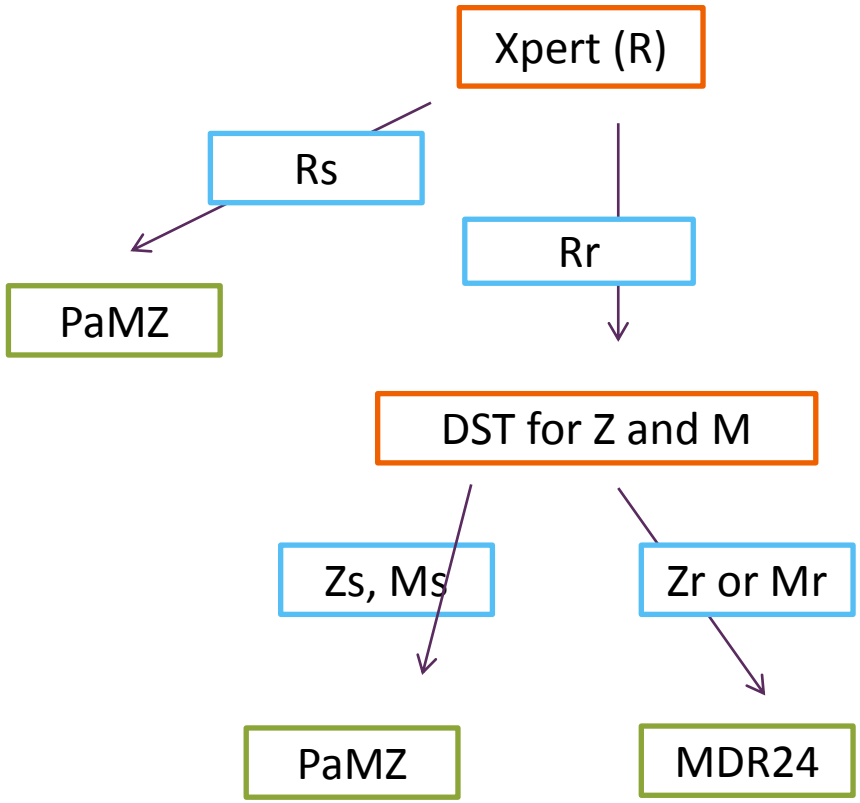


Cheaper, simpler, but more risk of resistance generation

Potential algorithm for PaMZ (cont)

Before M/Z DST, do triage based on R DST

(3)



Cheaper, simpler, and safer, but still risk of M resistance generation

- Prioritizes Z and M testing for those at higher risk;
- Presumptive PaMZ treatment is now for "DS-TB" (non-MDR-TB) cases, rather than for "new" cases.
- But still a risk that M has only 1 active companion drug.

Conclusions on DST algorithms

- For M:
  - Upfront DST may not be needed or advisable in sub-Saharan Africa, if they have M resistance in new cases of ~1%
  - This may be a closer call in Asia, if they have higher prevalence of M resistance among new cases.
- For Z:
  - Baseline resistance among new cases may be ~3% everywhere (i.e., somewhat higher than for M). This, plus concern about exposing M to an inadequate regimen, may increase pressure for upfront Z DST.
  - How low would Z resistance have to be in new cases (algorithm #2) or non-MDR-TB cases (algorithm #3) for presumptive PaMZ treatment to be OK?
- For both:
  - Fast test = molecular test. Achieving a high PPV with a molecular test may be more challenging for M and Z than it is currently for R (not all mutations known, or known to be specific to resistant strains). If PPV is low, either reserve DST for high risk subpopulation and/or need confirmatory testing of positives .

What diagnostics developers need

- Specifications:
  - which drugs;
  - surveillance, screening or stand-alone test;
  - what sensitivity and specificity required;
  - What decentralization required.
- Market size/demand:
  - What resistance prevalence is the cut-off for adoption; therefore which countries adopt
  - Where the diagnostic is placed in algorithms – therefore what percentage of TB suspects or patients get tested

Two-fold challenge in predicting demand

- Prediction
  - Predicting new regimen adoption is hard;
  - Predicting new DST adoption is hard;
  - Predicting new regimen + new DST adoption is much harder.
- Chicken and egg
  - Diagnostic companies only willing to develop new DST if new regimens are adopted.
  - But adoption of new regimens relies on availability of new DST assays

Pathway for action

- Enabling science
  - Define which mutations correlate with in vitro resistance *and* have clinical impact
  - Establish a strain bank to use for testing of new assays
- Surveillance
  - Establish more baseline values for fluoroquinolone resistance among new patients, and Z resistance among new and MDR-TB patients
- Modeling impact
  - Model trade-offs between speed, accuracy, price, and technical specs of DST assays
  - Model different DST algorithms (e.g., DST for all, DST for retreatment/failure cases only, or use of novel regimens without DST). Above what threshold of resistance prevalence would more widespread DST be advisable?
- Assay development
  - Finalize target product profiles, so developers have a clear pathway forwards
  - Use both existing platforms (e.g., FQr via Xpert) and new platforms

Co-development of drugs and diagnostics is the way forwards!