ACHIEVING CONVERGENCE BETWEEN EMERGING TREATMENT REGIMENS AND DIAGNOSTICS

8 December, 2014, National Institute for Research in TB, Chennai. **"Evaluation of new TB diagnostics: A capacity building workshop for public sector institutions in India"**

Puneet Dewan, BMGF India Country Office

CORE ISSUE

- Diagnostic manufacturers need to be informed in advance
  - Type of TB diagnostics they should invest in
  - Potential market size for these products
  - Pre and Post-launch market preparation activities
- Target product profiles (TPPs)
  - Align the needs of end-users with the specifications and performance and operational characteristics targets to meet

DIAGNOSTICS TPP DEFINED

5. Next-generation drug-susceptibility testing at microscopy centres

Table 11. Delphi survey results for proposed key characteristics of a next-generation drug-s

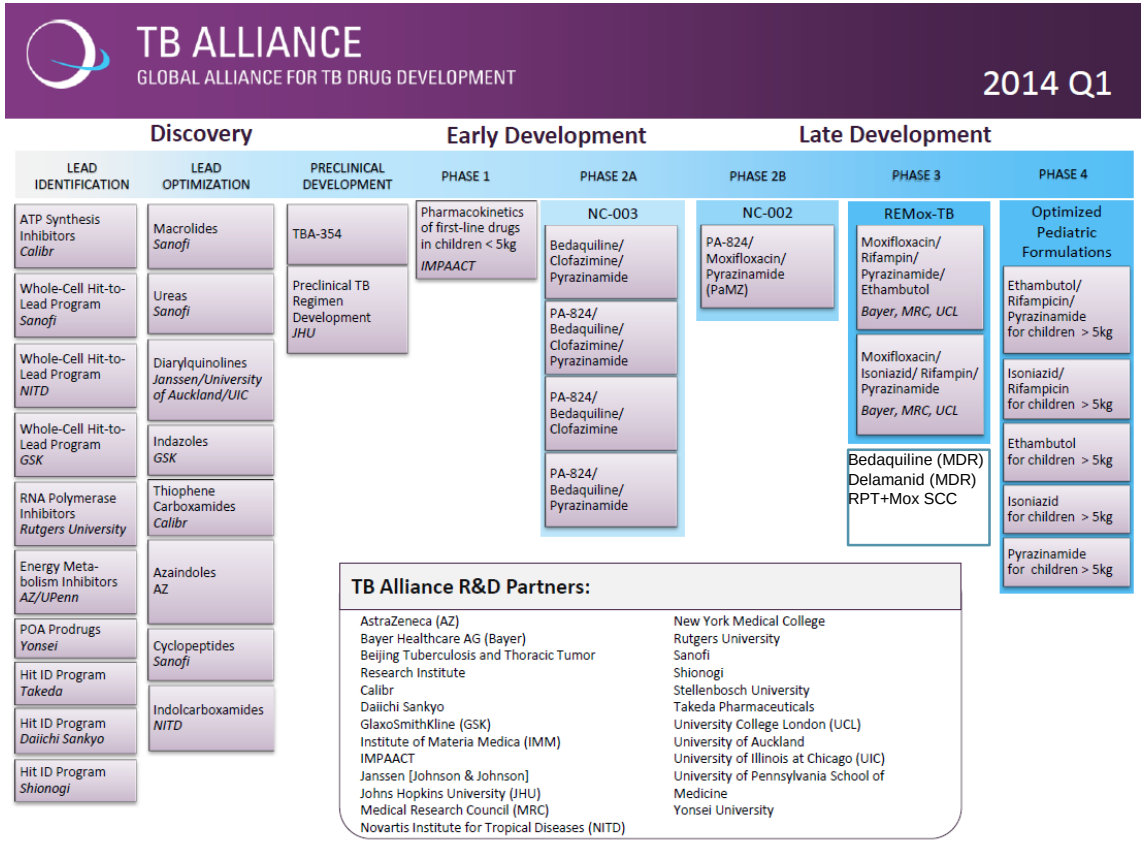
Characteristic	Optimal requirements	% (range) agreeing with the optimal requirements for the characteristic[a]	Minimal requirements	% (range) agreeing with the minimal requirements for the characteristic[a]
1 Priority of anti-TB agents for testing	In order of decreasing importance: 1. RIF 2. FQs 3. PZA 4. INH 5. AG and CAP	87% (72–89%)	In order of decreasing importance: 1. RIF 2. MOX	85% (70–87%)
2 Diagnostic sensitivity of DST	Should have >95% sensitivity for detecting resistance to RIF, FQ, PZA, INH and AGs when compared with phenotypic liquid culture DST	79% (66–82%)	Should have >95% sensitivity for detecting resistance to RIF and >90% sensitivity for detecting resistance to MOX when compared with phenotypic liquid culture DST	72% (60–77%)

Testing for resistance to PZA

- The inclusion of PZA in the optimal requirements was not questioned, although concerns were raised over the feasibility of testing for resistance to PZA at the specified performance characteristics.
- Some participants also advocated for the inclusion of PZA in the minimal requirements, given the importance of PZA in novel regimens.
- Knowledge about the molecular basis of resistance to PZA is limited, and given the large number of single-nucleotide polymorphism (SNPs) associated with resistance, the tests would likely have to be performed in a separate, additional step.
- It was considered whether resistance to RIF could be used as a proxy for resistance to PZA, given the good negative predictive value of susceptibility to RIF (that is, if a strain is susceptible to RIF then it is likely to be susceptible to PZA). However, the positive predictive value was considered to be too variable to be useful, and it would limit the use of PaMZ because depending on the epidemiological setting, up to 70% of patients could be treated with PaMZ rather than with MDR-TB therapy.
- If detection of resistance to PZA is not included initially with other resistance tests but only as a reflex test – for example, if it is used when resistance to RIF is detected – then the market volume would be small (essentially, it would be only patients with MDR-TB), which would limit the industry's interest in such a test.

http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

NEW DRUGS AND REGIMENS EMERGING THAT DIAGNOSTICS MANUFACTURERS SHOULD PREPARE FOR



RECENT ADVANCES HIGHLIGHT THE POTENTIAL FOR SHORTER AND MORE EFFECTIVE TB REGIMENS FOR DS AND DR PATIENTS

PaMZ
All DS, ~25% of MDR patients

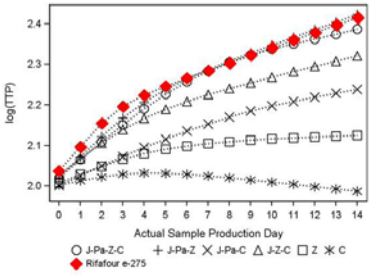
- **4-6 month** PaMZ regimen
- Advanced to **Phase 3 trial**
- PaMZ is as effective in MDR (susceptible to M and Z) as the 6 month standard therapy in DS TB

Study Arm	Days to Culture Conversion Solid Liquid	
M-PA200-Z	28	42
M-PA100-Z	28	49
M-PA200-Z-MDR	35	56
Rifafour	35	56

Ready early as 2018

JPaZ
All DS & ~50% of MDR TB patients

- **4-6 month** JPaZ regimen
- Advanced to **Phase 2b trial**[3]
- JPaZ is as effective as standard therapy in DS TB and expected to be effective in MDR patients resistant to fluoroquinolones



Potentially ready in 2020

"Universal Regimen"
All DS and MDR TB patients

- Potential **4 month regimen**
- Combination of **3 new drugs**: bedaquiline, Pa-824 and an oxazolidinone
- Preclinical data suggests high efficacy

Addition of U or L to combinations with J and/or PA-824 (interim results)
Proportion (%) of mice relapsing after treatment

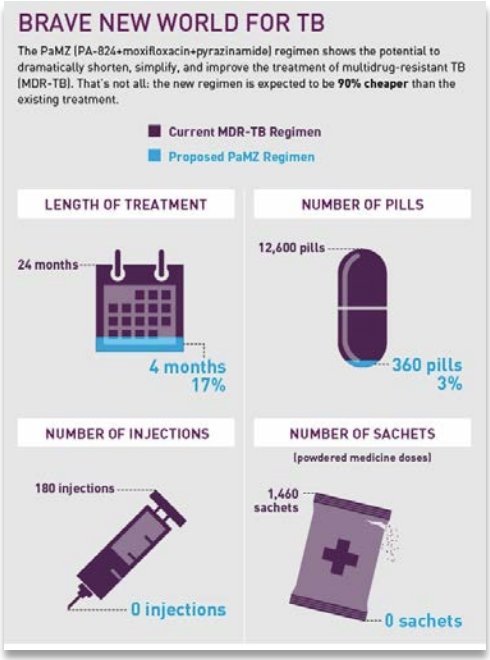
Regimen	2 months	3 months	4 months
2RHZ/4RH	ND	13/15 (87%)	Pend (20)
Jpa	15/15 (100%)	10/15 (67%)	Pend (20)
JPaU	14/20 (70%)	**1/14 (7%)**	
JPaL	12/15 (80%)	**0/14 (0%)**	Pend (20)

Not ready before 2022

1 Ariey F et al, Nature 505, 50–55 (02 January 2014);
2 Preliminary results from the SMRU and MORU;
Source: Image obtained from Ariey F et al, Nature 505, 50–55 (02 January 2014)
Sutezolid (U); Linezolid (L); Bedaquiline (J)

PAMZ PHASE 3 CLINICAL TRIAL TO BEGIN LATE 2014

PaMZ = PA-824 + Moxifloxacin + Pyrazinamide



New Tuberculosis Drug Regimen Will Move to Landmark Phase 3 Clinical Trial

STAND trial will test the first regimen designed to significantly shorten and simplify the treatment of drug-sensitive and drug-resistant TB

Based on positive results from earlier clinical studies, TB Alliance is advancing the first-ever drug regimen designed to treat both drug-sensitive and some forms of multi-drug resistant tuberculosis (TB) to a global Phase 3 clinical trial.

The announcement by Bill Gates, co-chair of the Bill & Melinda Gates Foundation, accompanied a commitment of significant funding by the Gates Foundation to determine the safety and efficacy of the new drug regimen, which is known as PaMZ. Mr. Gates called on other organizations to support the effort to develop new treatments for TB, a disease that kills an estimated 1.3 million people annually and remains a leading cause of death globally, especially among people who are co-infected with HIV.

"The results from early phase research suggest that this new drug regimen could provide the breakthrough we need to accelerate progress against this deadly and dangerous disease," said Mr. Gates. "PaMZ could dramatically reduce the time required to cure drug-resistant TB from two years to just six months, and it could cut the cost of curing drug-resistant TB in low-income countries from thousands of dollars to just a fraction of that cost. Now we need funders to step forward to make next-generation TB drugs like PaMZ a reality."

Source: http://www.tballiance.org/portfolio/regimen/pamz

WORKING ASSUMPTION ON PAMZ BIOMARKERS AND TIMING

Commercial Prelaunch Activities

Launch Activities

PaMZ biomarkers published

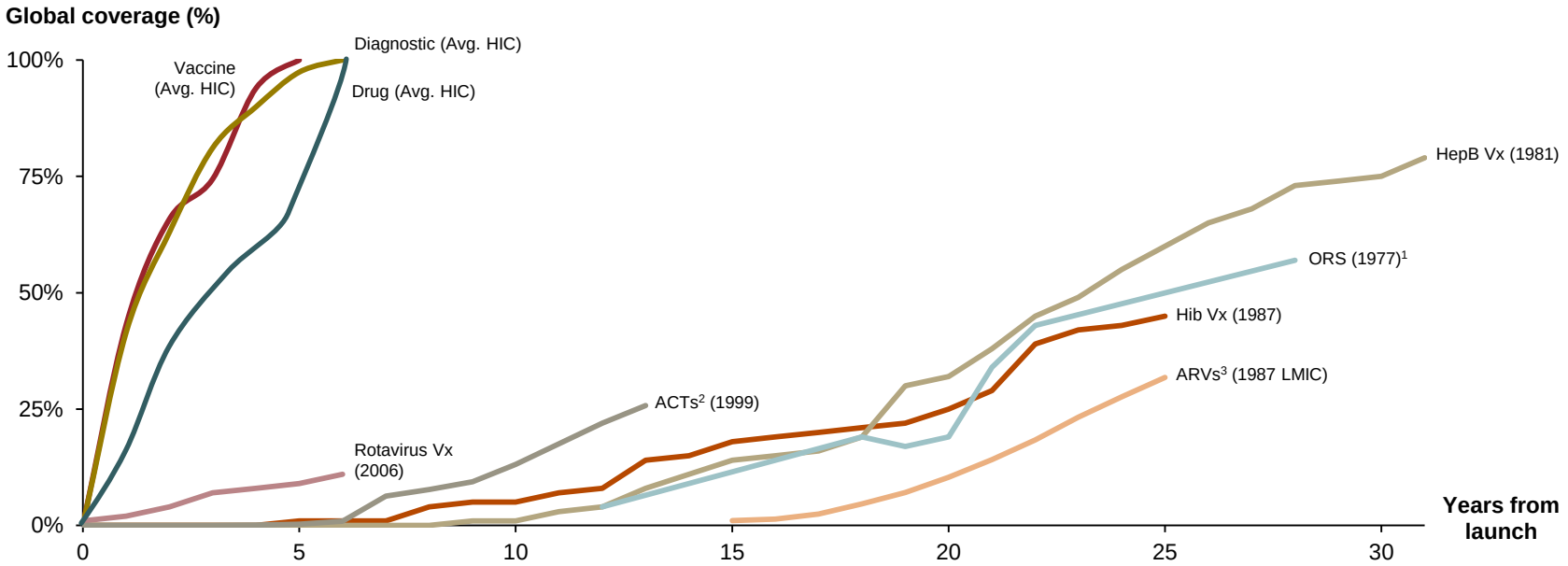
PaMZ Rx Launched

2014	2015	2016	2017	2018	2019

IMPLICATIONS OF NEW REGIMENS FOR TPP

- After brief engagement, pharma industry again quietly dis-investing from new TB drug and regimen development
  - Looking for public sector / non-profits to pay the bill
  - Low risk tolerance
- Imminent displacement of existing regimens is very unlikely; existing TPP
- Beyond RPO-B; Multiplexed DST are essential
- DST panel for drugs (PZA, PA-824/Delamanid/BDQ) need to be available early and open source to diagnostics industry

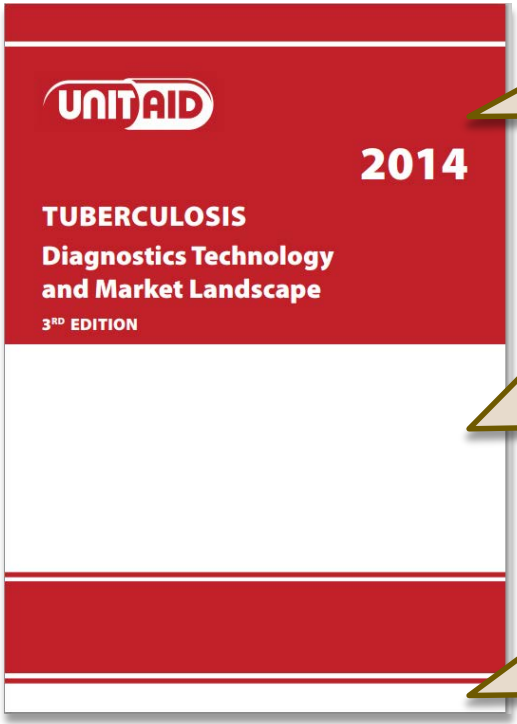
CRITICAL HEALTH INTERVENTIONS EXPERIENCE SLOW UPTAKE AND LOW COVERAGE



Legend: Product (launch year). LMIC: Lower- and middle- income countries. HIC: High income countries. Avg: Average from launch date

More information on sources and approach available upon request. 1. All ORS data is taken from previous BCG document. Average of 49 countries reporting ORS rates 1999-2005, weighted by population under 15 years old 2. This uptake estimate assumes that the total anti-malarial market: is1.2B pa. (Based on Dalberg analysis of anti-malarial market). This is significantly more than the annual cases of malaria which are estimated to be ~400M pa (WHO). It is an open question, also dependent on the diagnostic paradigm, whether reaching 100% of the malaria treatment volumes should be a public health goal 3. Coverage calculated using 2013 WHO guidelines that recommend use of ARVs if CD4 count lower than 500. Past estimates were based on lower CD4 thresholds.

MARKET INFRASTRUCTURE IN SUPPORT OF NEW TB DIAGNOSTICS IS LESS THAN IDEAL

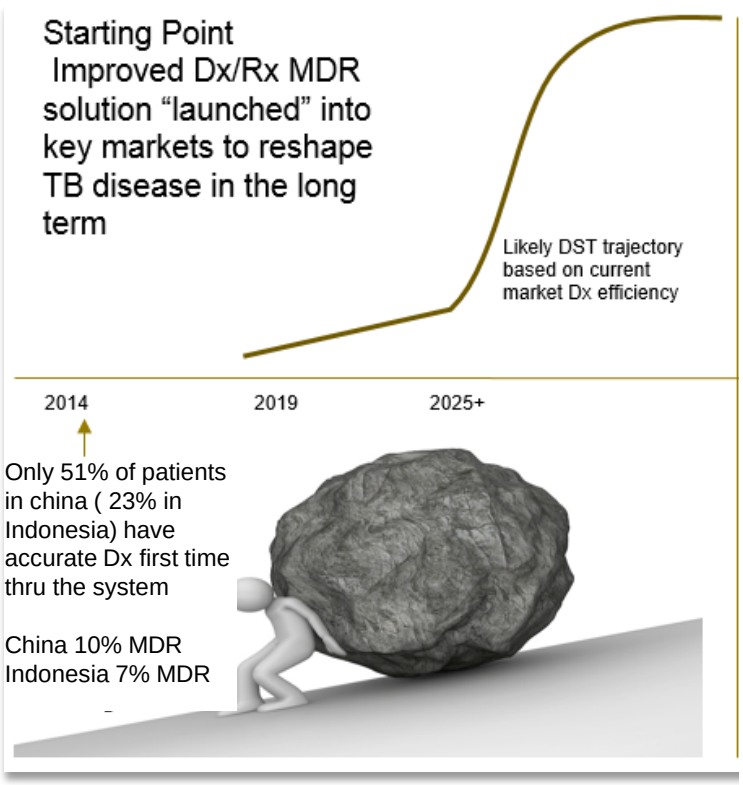


*"**Lack of sufficient field evidence** deters widespread uptake of next-generation NAATs."*

*"Emerging data suggest that the impact of Xpert® MTB/RIF on TB transmission and mortality may be limited because of widespread **empiric therapy, weak health systems and lack of adequate linkages between diagnosis and treatment/follow-up."***

*"Develop or refine **novel approaches to engage private sector** care providers, including **innovative business models** that leverage market-based incentives for appropriate TB diagnosis."*

STARTING POINT IN TB IS LESS THAN IDEAL



SO-WHAT?

Demand for molecular TB diagnostics is low… and without market based momentum

SO TO CREATE A VIABLE COMMERCIAL MARKET FOR ALL NEW MOLECULAR TESTS WE NEED TO LOOK BEYOND TECHNOLOGY

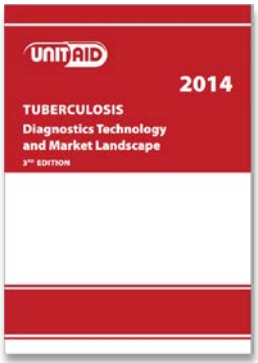
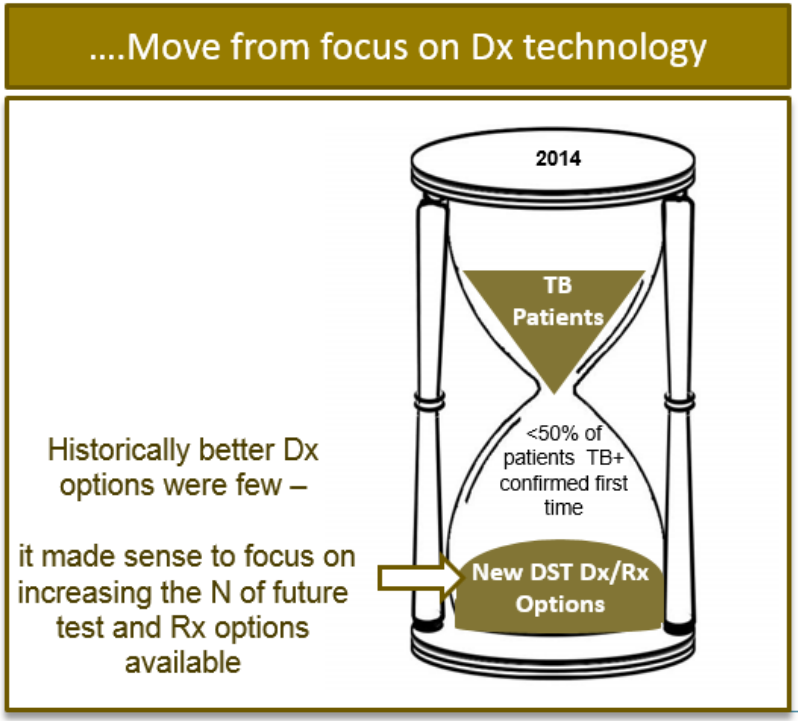


Figure 1. Patient pathway to diagnosis and care, with common barriers and potential interventions

	Exposure	Infection	Active TB	Patient recognizing symptoms	Accessing care	Health worker recognizing symptoms	TB Diagnosis	TB Treatment and notification
Barriers			• Lack of knowledge, poor information • Misperceptions • Stigma, Perceived poor quality services	• Distance • Cost of transportation, testing • Loss of wages • Time spent, opportunity costs	• Lack of proper training • Poor index of suspicion for TB	• Insensitive screening algorithms • Insensitive tests • Delays to give results	• Weak linkages between public/private sectors • Poor internal reporting systems • Drug stockouts	
Possible Interventions			• Awareness raising • Mass media • Community engagement • Information and education	• Expanded coverage • Community outreach • Mobile clinics • Task shifting	• Systematic facility screening • Better training • Improved screening algorithms	• Improved diagnostics • Improved screening algorithms	• Engagement of all care providers • Improved information and supply systems	

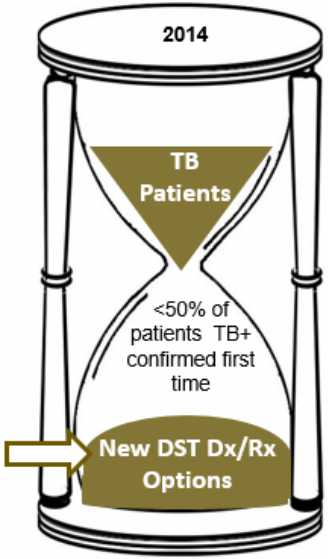
Adapted from Uplekar et al. 2013

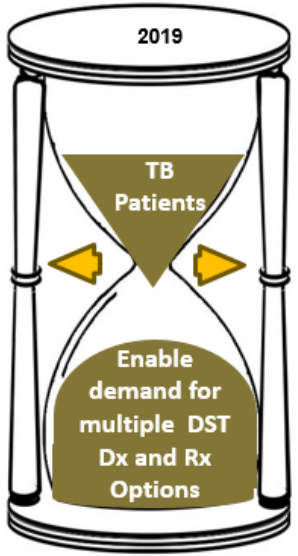
HISTORICAL FOCUS HAS CORRECTLY BEEN ON TECHNOLOGY



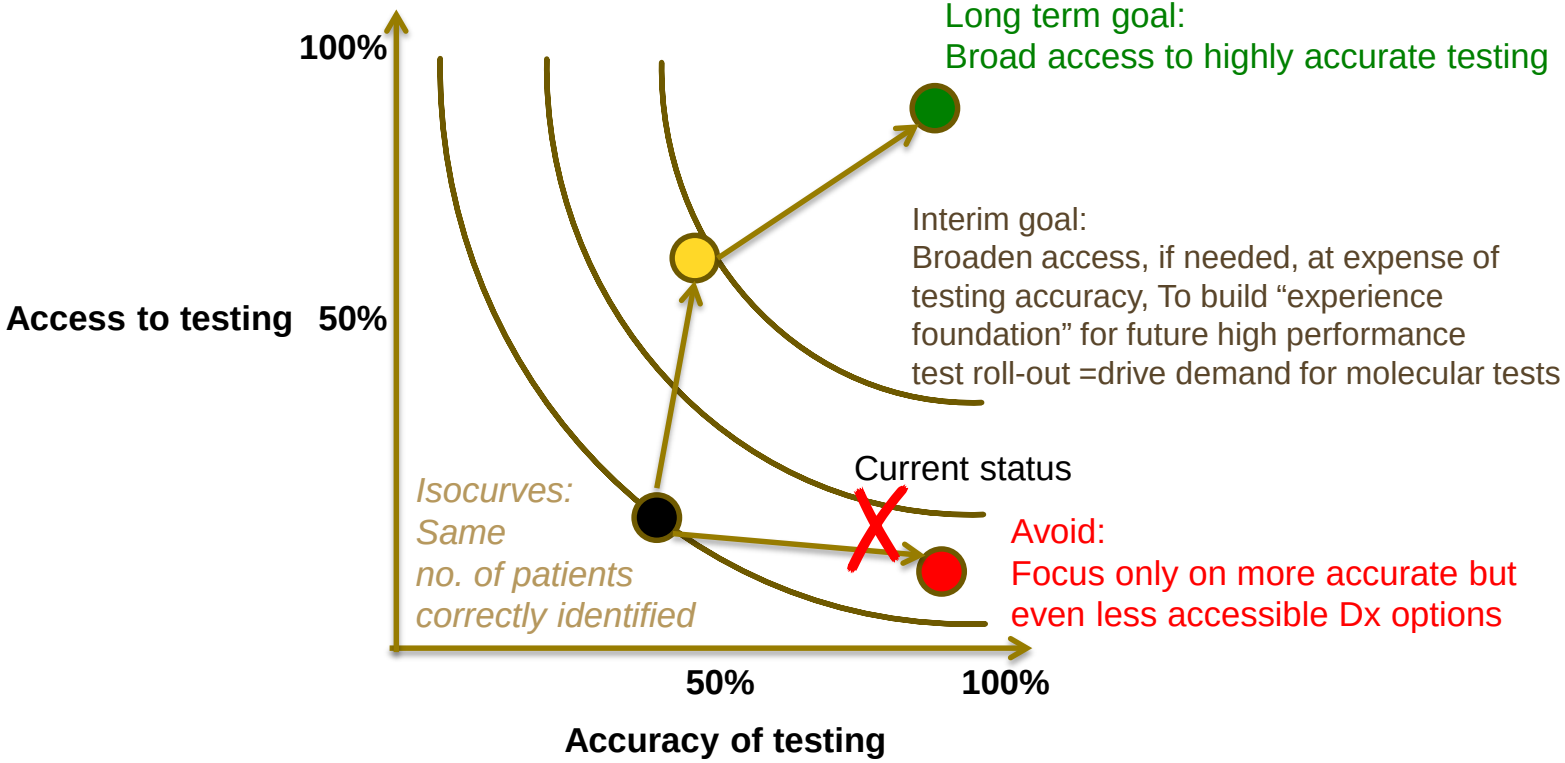
EQUAL FOCUS FROM HEREON ON DEMAND CREATION

….Move from focus on Dx technology	….to demand (functioning market) creation
Historically better Dx options were few – it made sense to focus on increasing the N of future test and Rx options available	Commercial focus should shift in near term to infrastructure for demand creation – and widening the patient access to molecular testing

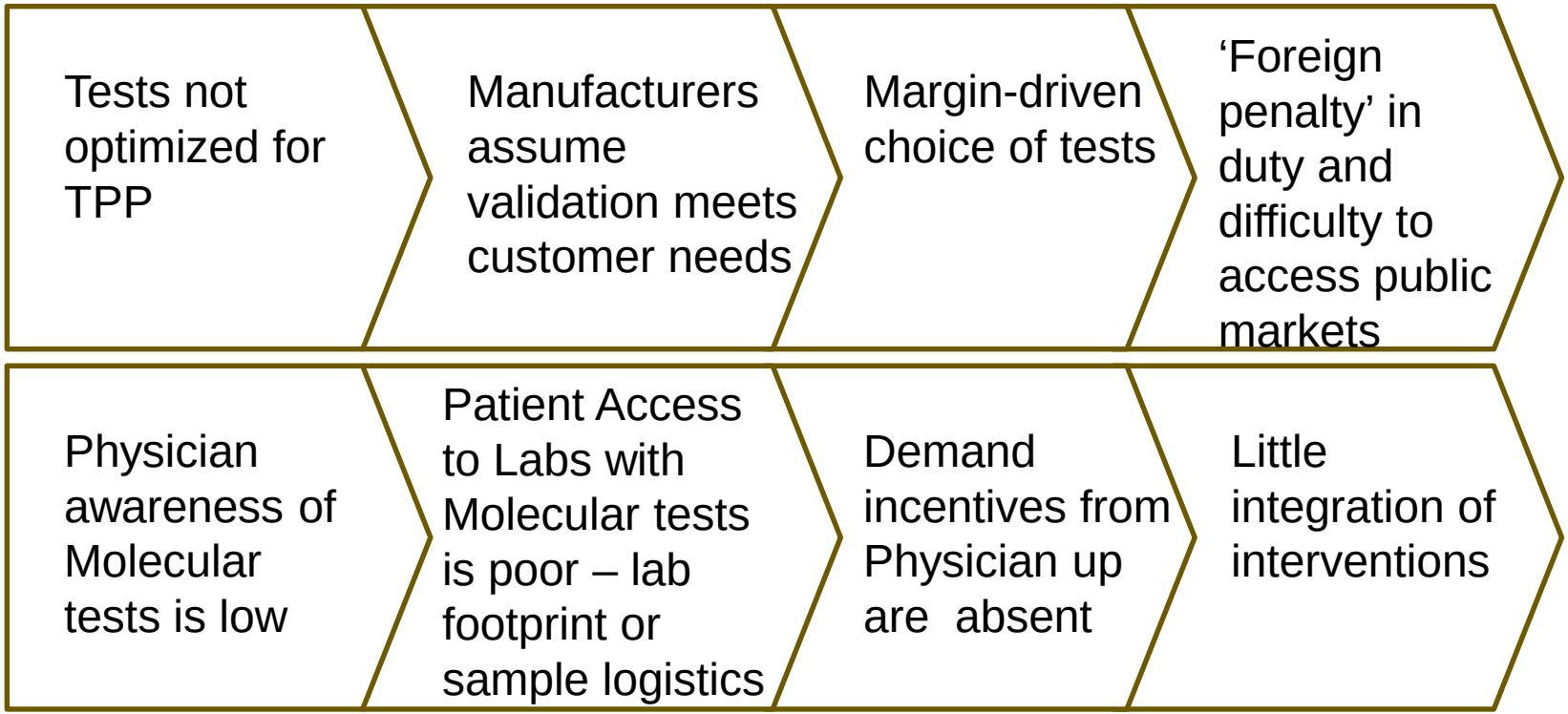




NOW NEED TO SHIFT TO MOVING UP THE "PATIENTS IDENTIFIED" ISOCURVE, NOT JUST OPTIMIZE ONE AXIS

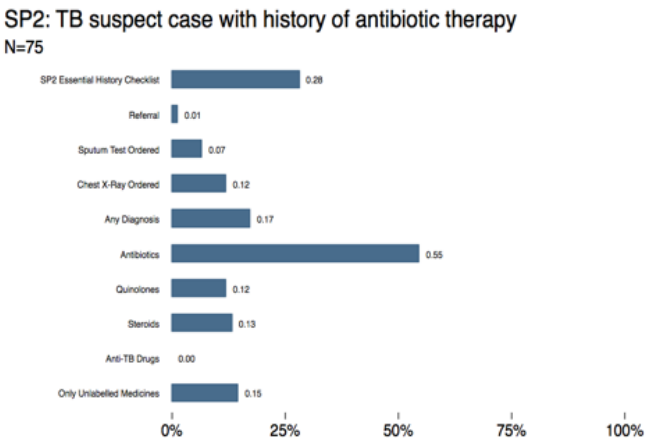


A NUMBER OF **KEY ISSUES** NEED TO BE ADDRESSED IN PARALLEL



THE ENEMY IS NOT YOUR COMPETITOR, IT IS RELUCTANCE TO ORDER SPUTUM TESTING

- Number of chest symptomatics who should get TB tests is enormous
- Providers demonstrate substantial reluctance to order sputum tests during initial visits
- Quality-assurance of sputum microscopy highly suspect
- Empiric treatment dominates



Only 7% asked for a sputum test for TB

Jishnu Das, Veena Das, Madhukar Pai et al. Unpublished data (Confidential)

ISSUE: THE “IMPORTED MODEL” DOES NOT FIT WELL WITH TB POLICY OR INDUSTRIAL SUPPORT SYSTEMS

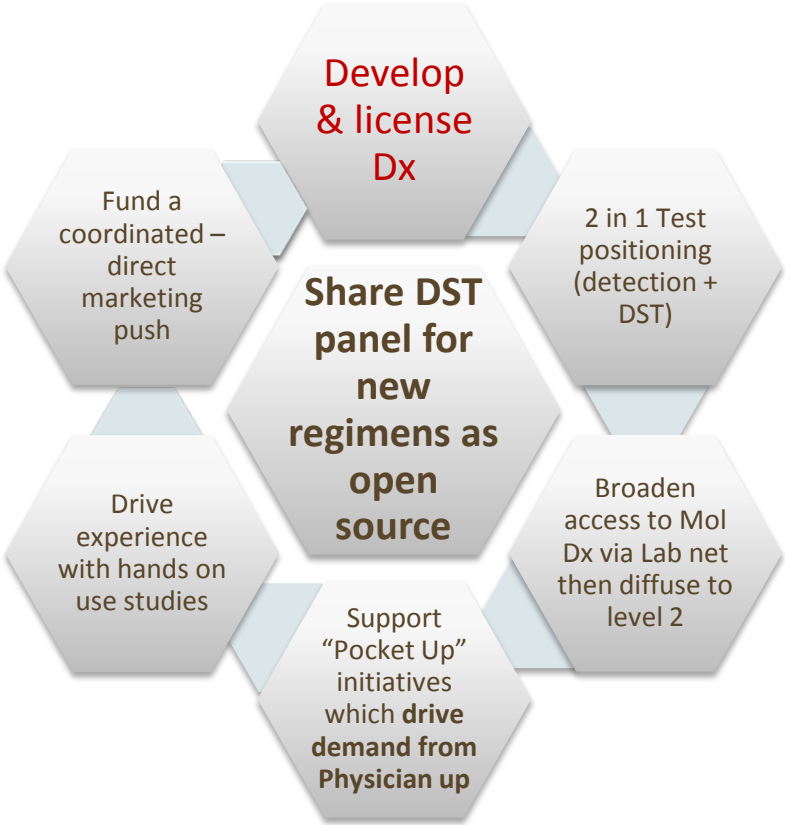
Ongoing delay and restrictions for import highly likely

IMPORT DUTY

Domestic procurement empowered by local product with multiple choices

DEVELOPMENT AND LICENSURE ARE ONLY BEGINNING OF ACTIVITIES TO DRIVE RAPID UPTAKE

Market shaping activities post-launch required for rapid uptake



SUMMARY

- Regimens are emerging, but will take years still
  - Next generation of regimens do not meet ideal TB treatment TPP
  - Not going to be ‘Universal treatment’ that is DST-free
- We need more than drugs, we need drugs and accompanying diagnostics.
- TPP for DST have been defined (WHO et al)
- Upcoming regimens (PaMZ) DST panel to be open sourcez

However…

- The enemy of the new TB diagnostic industries is not GX but empiric therapy
- Tests need to move up the access curve to face that enemy
- The path to selling any diagnostic test is getting users to use the current ones
- Pre- and Post-launch market preparation is essential for patient access & volumes of sales

Critical Path Institute Receives Third Grant to Accelerate Tuberculosis Diagnostics

Multi-year grant to fund innovative global data platform designed to streamline tuberculosis diagnosis and treatment

December 09, 2014 05:35 PM Eastern Standard Time

TUCSON, Ariz.--(BUSINESS WIRE)--Critical Path Institute (C-Path), an Arizona-based non-profit organization dedicated to fostering collaborative initiatives to improve the quality and efficiency of the drug development process, has received a new multi-year grant from the Bill & Melinda Gates Foundation. This grant will fund the creation and implementation of the Rapid Drug Susceptibility Test Data Platform. The platform will catalog a vast amount of tuberculosis genomic data of worldwide tuberculosis strains. Tuberculosis is the second leading cause of death (after HIV) from a single infectious agent.

The database will inform correlations between mutations and clinically relevant resistance. This will advance the development of rapid drug susceptibility tests for tuberculosis that can be used to speed up the selection of effective treatment. The longer-term vision of the database is to directly enable sequencing data interpretation and patient care.

"To create the kinds of tests essential to the effective deployment of novel tuberculosis treatments"

"To create the kinds of tests essential to the effective deployment of novel tuberculosis treatments," explains Martha Brumfield, Ph.D., President and CEO of C-Path, "we need a singular data resource that encompasses global resistance trends and markers for resistance that come directly from patients with tuberculosis and their caregivers."

C-Path's Critical Path to Drug TB Regimens (CPTR) program will partner with FIND, New Diagnostics Working Group (NDWG), the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) to compile the international tuberculosis data relevant to developing the ability to very rapidly diagnose the specific type of resistant TB present in a patient, and in turn, help define the most effective TB treatment regimen for each patient.

Release Summary

Critical Path Institute Receives Multi-Year Grant from the Bill & Melinda Gates Foundation to Accelerate Tuberculosis Diagnostics

Sharing

Company Information

CRITICAL PATH INSTITUTE

Release Versions

- **English**

http://www.businesswire.com/news/home/20141209006683/en/Critical-Path-Institute-Receives-Grant-Accelerate-Tuberculosis#.VJAEzV6EjBX

THANKS

Global TB Alliance
Jim Gallarda
Jan Gheuens
Peter Small
Madhu Pai
Diaceutics Ltd.

Month DD, YYYY