Opportunities for Prevention of TB Drug Resistance

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Factors Contributing to Emergence of Drug Resistance

- Failure to recognize baseline resistance
- Limited understanding of how regimens can protect against emergence of resistance
- Inadequate adherence to the regimen
- Failure to diagnose TB

Barriers to Detecting Baseline Resistance

- Lack of genotypic resistance testing for the new agents
- Poor access to existing genotypic tests
- Costs of testing
- Timeliness of results

Table 1 Proportion of responses to the question: "The country currently has capacity for AST for which drugs (check all that apply)" ($n = 323$)

Drug	%
FQs (ofloxacin, levofloxacin or moxifloxacin)	94
BDQ	37
LZD	50
FQs + BDQ	37
FQs + LZD	50
FQs + BDQ + LZD	33
Clofazimine	41
Delamanid	21
Kanamycin* or amikacin	92
None of these	4

* No longer recommended.
FQ = fluoroquinolone; BDQ = bedaquiline; LZD = linezolid.

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Why do Regimens Fail to Protect Against Emergence of Resistance?

- PK imbalance of drugs in regimen
- Differential tissue penetration of drugs into caseum
- Limited activity of some agents against non-replicating organisms
- Frequency of resistance mutations may be greater than we think
- Antimycobacterial agents may increase mutation frequency

ACS Infect Dis 2016; 2:552–563
Mol Cell 2010;37:311-20
AAC 2018;62:e02266

Why is Adherence so Difficult?

- Adverse Drug Reactions (ADR) are a prime driver of nonadherence
- Patients report that 86% of missed doses result from ADR
- Of 373 patients treated for DS-TB with HRZE, 35% developed moderate/severe ADRs that required treatment interruption
- The goal should to be *less* toxic than HRZE, not just “non-inferior”

Br J Pharm 2024;90:313-320
CID 2023;76:1121-4

How can we Increase TB Diagnosis?

- Engage communities to address stigma
- Offer screening to a broad variety of audiences
- Provide support to ensure treatment success
- What it will take:

Country (years)	Initial TB Prevalence (per 100,000)	Post-Screening Prevalence (per 100,000)	Annual % with TB identified	Effect on Prevalence
Zimbabwe (2006-2008)	650	370	38%	-43%
Zambia/South Africa (2006-2009)	832	832	1.5%	0%
Vietnam (2014-2018)	389	126	64%	-68%
Uganda (2019-2021)	940	520	40%	-45%
Zambia/South Africa (2014-2017)	832	920	0.9%	+11%

Conclusions

- Molecular drug resistance testing for the new drugs needs to be developed and rolled out quickly
- Regimens for TB need to better protect against emergence of resistance
- Regimens for TB need to be easier for patients to tolerate
- Engagement of communities will be essential to convert new tools & strategies into prevention of DR-TB

To follow developments in MDR-TB diagnosis and treatment:

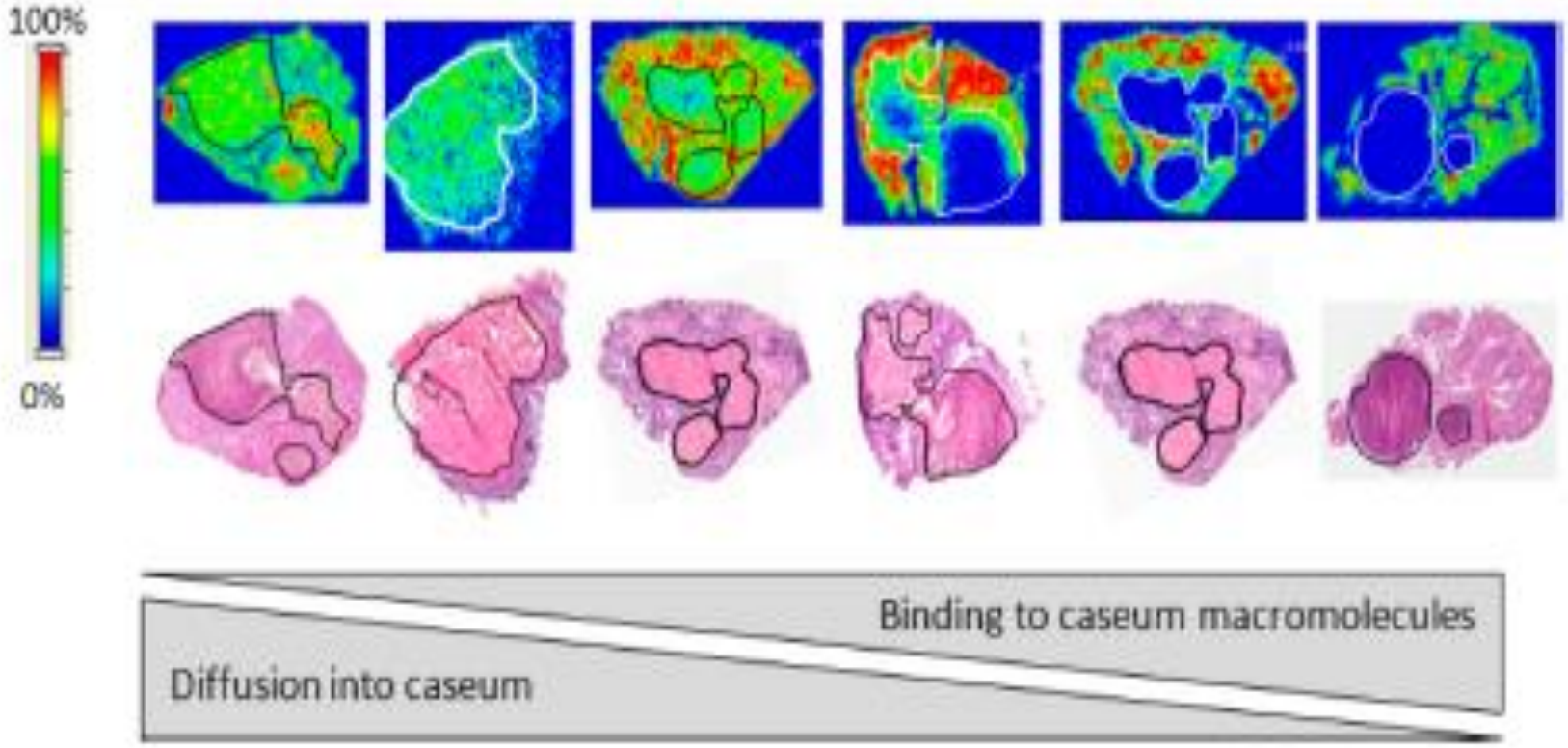
RESIST-TB Website

RESIST-TB Monthly Newsletter

www.resisttb.org

Penetration of TB drugs into Caseum

Drug	Pyrazinamide	Acetyl-isoniazid	Moxifloxacin	Rifampicin	Clofazimine	Bedaquiline
fu (%)	100	100	13.5	5.1	<0.01	<0.01



ACS ID 2016;2:552-63

Activity of TB drugs in Caseum

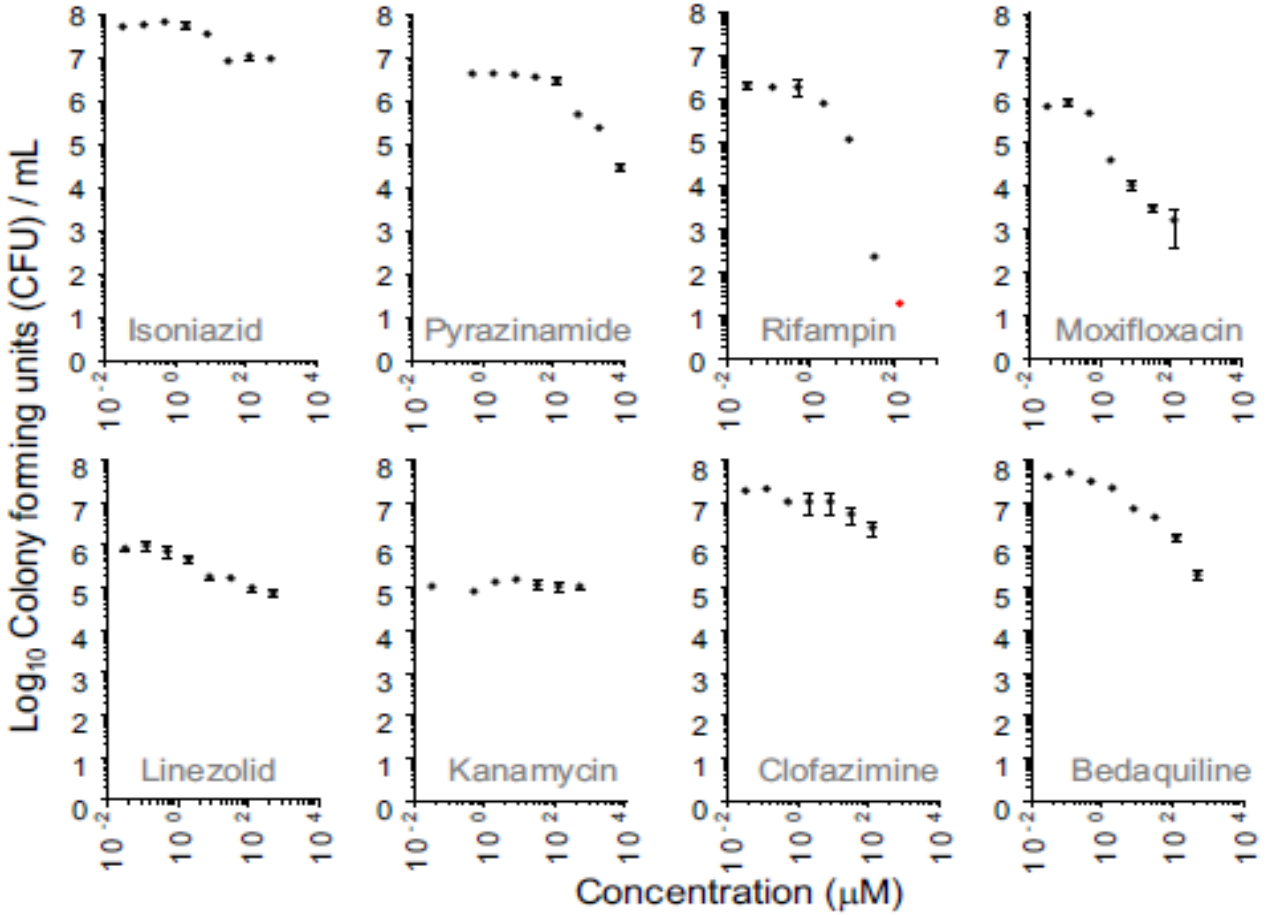


FIG 2 Bactericidal activity of eight standard TB treatment drugs in caseum. Data are expressed as $\log_{10}$ of average CFU per milliliter of homogenized caseum from three replicates. A red dot highlights data points below the limit of detection (LOD [approximately 20 CFU]); i.e., no CFU was recovered from the lowest dilution of caseum homogenate plated. Standard deviations are indicated by error bars.

AAC 2018;62:e02266