Big challenges in TB drug resistance

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History of TB drug resistance

- UK MRC streptomycin trial 1947
- Resistance developed early with streptomycin monotherapy (median 45 days) and associated with poorer outcome
- Resistance developed less frequently if combined streptomycin with INH ± PAS
- Concept of combination anti-TB therapy born

UK MRC BMJ 1948
What do we need?

Person with TB symptoms → Clinic → Specimen → Rapid accurate test → Effective treatment

Ideally we want this to happen within a single clinical encounter
SA TB drug resistance survey 2012-2014
KwaZulu-Natal, new cases

Fully susceptible
INH mono
RIF mono
MDR
SA TB drug resistance survey
KwaZulu-Natal, previously treated cases

- Fully susceptible
- INH mono
- RIF mono
- MDR
Heterogeneity of drug-resistant TB epidemic
Proportion of positive Xpert tests with rifampicin resistance, 2014

District Health Barometer
What do we mean by TB drug resistance?

Clinical resistance: failure to respond to a particular drug

Phenotypic resistance: lack of inhibition of *M. tuberculosis* growth by a critical concentration of a specific drug

Genotypic resistance: presence of genetic mutation(s) known to be associated with drug resistance
Understanding genotypic-phenotypic correlation

- International collaboration (CRyPTIC)
- 10,209 isolates analysed (37% drug resistance)
- ~12% of isolates from South Africa or eSwatini
- Compared whole genome sequence data to phenotypic DST (MGIT, solid culture, or MODS)
Understanding genotypic-phenotypic correlation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prediction of resistance (sensitivity)</th>
<th>Prediction of susceptibility (specificity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>97.1%</td>
<td>99.0%</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>97.5%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>94.6%</td>
<td>93.6%</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>91.3%</td>
<td>96.8%</td>
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</tbody>
</table>
Do we have the tools we need to detect drug resistance?

- Xpert Ultra detects mutations in rifampicin resistance-determining region (RRDR) of \( rpoB \) gene

- Line probe assay (MTBDRplus) also targets same region of \( rpoB \) gene

Ng JCM 2018
Do we have the tools we need to detect drug resistance?

- Mutation outside RRDR first identified in eSwatini DRS 2009
- Screened 249 rifampicin-susceptible, isoniazid-resistant isolates from four provinces South Africa (GP, NW, LP, MP)
- 37/249 (15%) had Ile491Phe mutation
- Phylogenetic analysis suggested spread from eSwatini into South Africa
SA TB drug resistance survey 2012-2014
KwaZulu-Natal, new cases

- Fully susceptible
- INH mono
- RIF mono
- MDR
SA TB drug resistance survey 2012-2014
Resistance to other drugs amongst rifampicin-resistant isolates

Prevalence of resistance to individual drugs (with 95% CI) in RIF mono-resistant and MDR isolates
New DR-TB treatment regimen
Does our molecular diagnostic algorithm predict susceptibility/resistance to these drugs?


- Highlights need to better align diagnostic development with advances in treatment strategies
TB diagnostics pipeline

**Diversification of sputum-based testing and drug susceptibility testing (DST)**

**WHO-endorsed**

- RealTime MTB RIF/INH (Abbott)
- FluoroType MTBDR (Luminexpert)
- BD MAX MDR-TB (ED)
- GenoType MTBDR (Hain Lifescience)
- QMAC QDST (QuantaMatrix)
- Cobas MTD-RIF/INH (Roche)
- Hybridisation (TransGlobal, Scanogen)
- MDT (2017)
- Test: LAM ELISA kit (spumum for treatment monitoring and drug trials (Otsuka))
- TB MultiTest (Sartorius)
- TrueLab/Truenat MTB/DR (Molbio)
- Xpert Ultra (Cepheid)
- TB LAM ELISA kit (sputum) for treatment monitoring and drug trials (Otsuka)
- EasyNet MDR TB (Istar)
- Hydice-1K MDR TB (InSilica)

**Liquid cultures**

- TB modul (2018)
- BacT/ALERT (bioMérieux)
- Mycobacteria IT MDR (Capilia Ltd)
- GeneXpert (Cepheid)
- MGIT - Bedaquiline (BD)
- Xpert XDR (Cepheid)
- Genomica MDR-RIF (System)
- Aurolab MDR RIF/INH (Aurolab)
- Xpert MTB/RIF (Cepheid)
- TrueLab/Truenat MTB/DR (Molbio)
- Mycolab MDR (Zeebe Diagnostic)
- QPOC MDR TB (Quadax)

**Molecular methods**

- TruTrack MDR-TB / XDR-TB (Akonza)
- FluoroType XDR (Luminexpert)
- Omni Platform (Cepheid)
- First sequencing solutions (Genoscreen, BMS, Longhorn)
- Q-POC MDR TB (Quanta/MDRx)

**DISCLAIMER:** Images & time estimates are to be taken as indicative only.
Is whole genome sequencing the answer?

- Fast moving field – rapid developments in sequencing technology
- Major technical challenge for TB remains difficulty of sequencing directly from sputum
- Broader challenge is incomplete understanding of genotype-phenotype-outcome correlation
Is whole genome sequencing the answer?

(A) Reference mapping

(B) Variant detection & interpretation

(C) Timely, pathogen-tailored therapy

Groschel PLoS Pathogens 2018
Is whole genome sequencing the answer?

InDEXX trial (CAPRISA) – RCT comparing routine diagnostics plus whole genome sequencing to routine diagnostics alone for rifampicin-resistant TB in KwaZulu-Natal
Summary

• We currently lack effective tools to detect all forms of drug-resistant TB relevant to our context

• Diagnostic development needs to be better aligned with the advances in DR-TB treatment

• Whole genome sequencing may have a role but several challenges exist to bringing this into routine health care