

Resistance to first and second line anti-tuberculosis drugs among pulmonary tuberculosis patients in Southwestern Uganda

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Background

- Annual incidence of TB in Uganda 200/100,000 people .
- Uganda MDR-TB rates:
 - 1.4% in new cases,
 - 12.1% in Retreatment cases (Lukoye *et al.*, 2013)
- South Western Uganda MDR-TB rates:
 - 1.6% in new cases,
 - 4.8% in Retreatment cases (Bazira *et al.*, 2010)
- Limited data from SW Uganda to guide second or third line therapy regimens.

Objectives

- To estimate the regional levels of TB drug resistance
- To guide treatment of MDR-TB patients in the region.

Methods

Mbarara Study Site

- Mbarara Regional Referral Hospital is located in Mbarara Municipality, SW Uganda.
- Municipality is located 300 km south-west of Kampala capital city



Procedures

- Eligibility: clinical suspicion of PTB between February 2009 – February 2013.
- Ethical clearance from IRC and UNCST
- Isolation of TB strains from sputum of newly diagnosed patients at MRRH.
- 190 isolates were retrieved and sub-cultured on LJ
- MTBDR *plus* and Xpert were performed on all to detect INH- RIF and RIF resistance respectively.
- 92 randomly selected samples were tested for second-line drug using MTBDR*s/l* assay.
- Isolates with FQ mutation were confirmed by MGIT culture at the Ugandan National TB Reference Laboratory
- Isolates with discordant FQ results between MTBDR*s/l* and MGIT were sequenced at the Institute of Tropical Medicine in Antwerp, Belgium,
- Proportion of drug resistance for each assay was estimated and a confidence interval of 95% was calculated using STATA version 12 (Statacorp, College Station, Texas).

Results

Characteristics of Study participants

- (131/190, 69%) were male, median age 33 years (IQR 26-43), 42% (79/190) HIV-infected.

Resistance to first and second line drugs

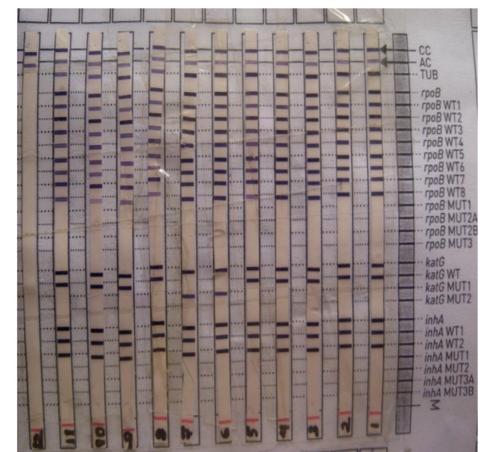
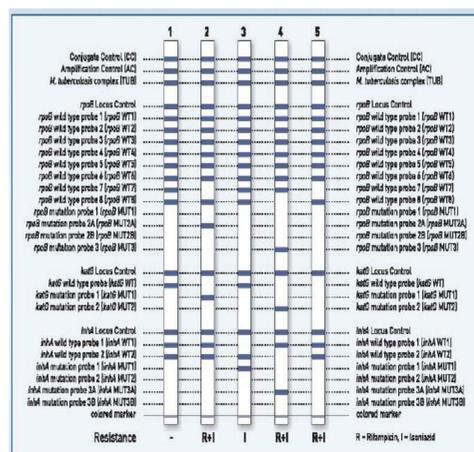
- (0/190, 0%, 95%CI 0.0 – 1.9%) rifampicin-resistance by MTBDR*plus* and Xpert MTB/RIF
- (1/190, 0.5%, 95%CI 0.0 – 2.9%) isoniazid-resistance by MTBDR*plus*
- 71 (77%) valid results with MTBDR*s/l*.
 - No detectable resistance to ethambutol or aminoglycosides/cyclic peptides,
 - 7 (9.8%, 95%CI 4.0 – 19.3%) resistant to FQ on initial testing.
 - MGIT found no FQ resistance
 - Sequencing of 7 found no FQ resistance genes
 - Repeated MTBDR*s/l* in another lab confirmed no resistance

Discussion

- FQ resistance was detected but culture and sequencing did not confirm these results.
- low MDR-TB resistance is consistent with prior studies in Uganda;
 - (1.4%, Lukoye *et al.*, 2013)
 - (1.6% Bazira *et al.*, 2010)
- This is the first study to report 1st and 2nd line drug susceptibility in SW Uganda
- The results support current MDR-TB treatment guidelines in Uganda:
 - (6KM+LFX+ETO+CS+Z) (MOH, 2010)
 - (18LFX+ETO+CS+Z)
- Despite high use of FQ [MoH, 2010], resistance among new TB patients appears rare.
- Although 10% resistance to FQ was detected initially by MTBDR*s/l*, the results were not confirmed with either culture or sequencing.
- The high false positive results could be attributed to the high sensitivity of the 2nd line assay. The poor specificity of the MTBDR*s/l* assay has also been reported previously at 57% [Kaswa *et al.*, 2014].
- This raises questions on the capacity of peripheral labs to detect true 2nd line resistance using molecular methods.
- Nevertheless the very low 2nd line resistance is similar to what was observed in a small sample of the Uganda national survey (n=31), [Lukoye *et al.*, 2013].
- Thus these results should promote caution in the use of the MTBDR*s/l* assay for detection of FQs resistance and suggest the confirmation of resistance by the use of culture method where possible.
- We also observed 23% invalid 2nd line results despite the high cost of the MTBDR*s/l* assay kit. This is more evidence for companies and individuals to develop more reliable tests for developing settings.

Conclusion

- There was no evidence of 1st or 2nd line anti TB drug resistance among PTB patients in Southwestern Uganda.
- These data support current national guidelines to include FQs, as empiric therapy for MDR-TB in the region.
- Molecular resistant testing should be routinely confirmed with culture based methods where possible.



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