

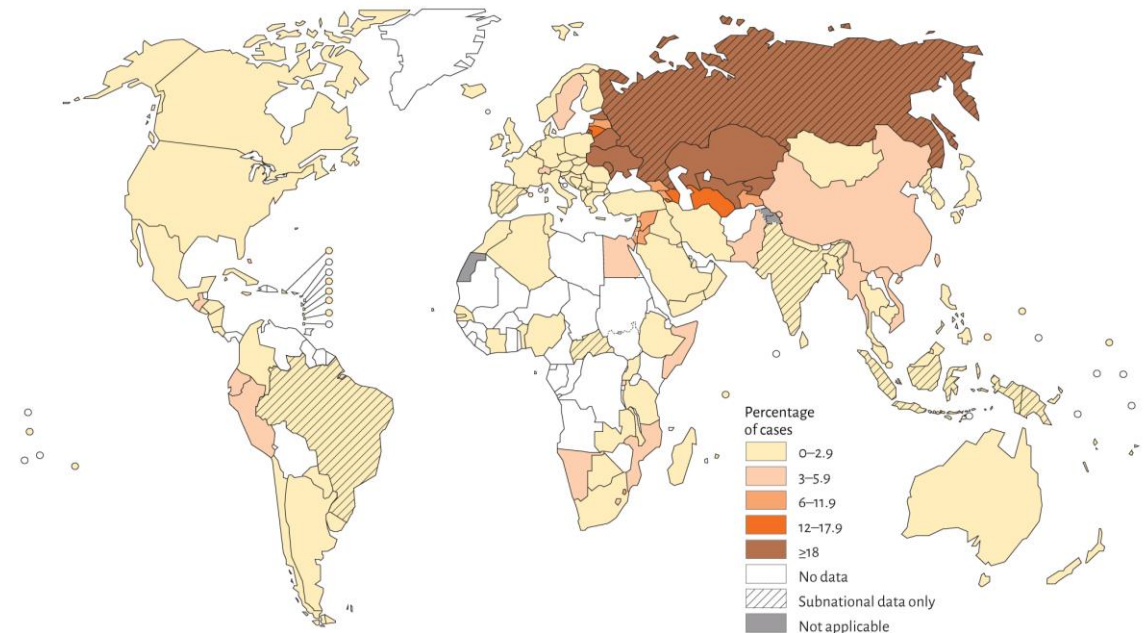
Ototoxicity is associated with exposure to Kanamycin & Capreomycin in the treatment of MDR TB

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Background

- MDR and XDR TB burden: cost & mortality
- Aminoglycosides are part of the treatment of drug-resistant tuberculosis
- Concentration-dependent killing
- Adversely affect auditory, vestibular, and renal function

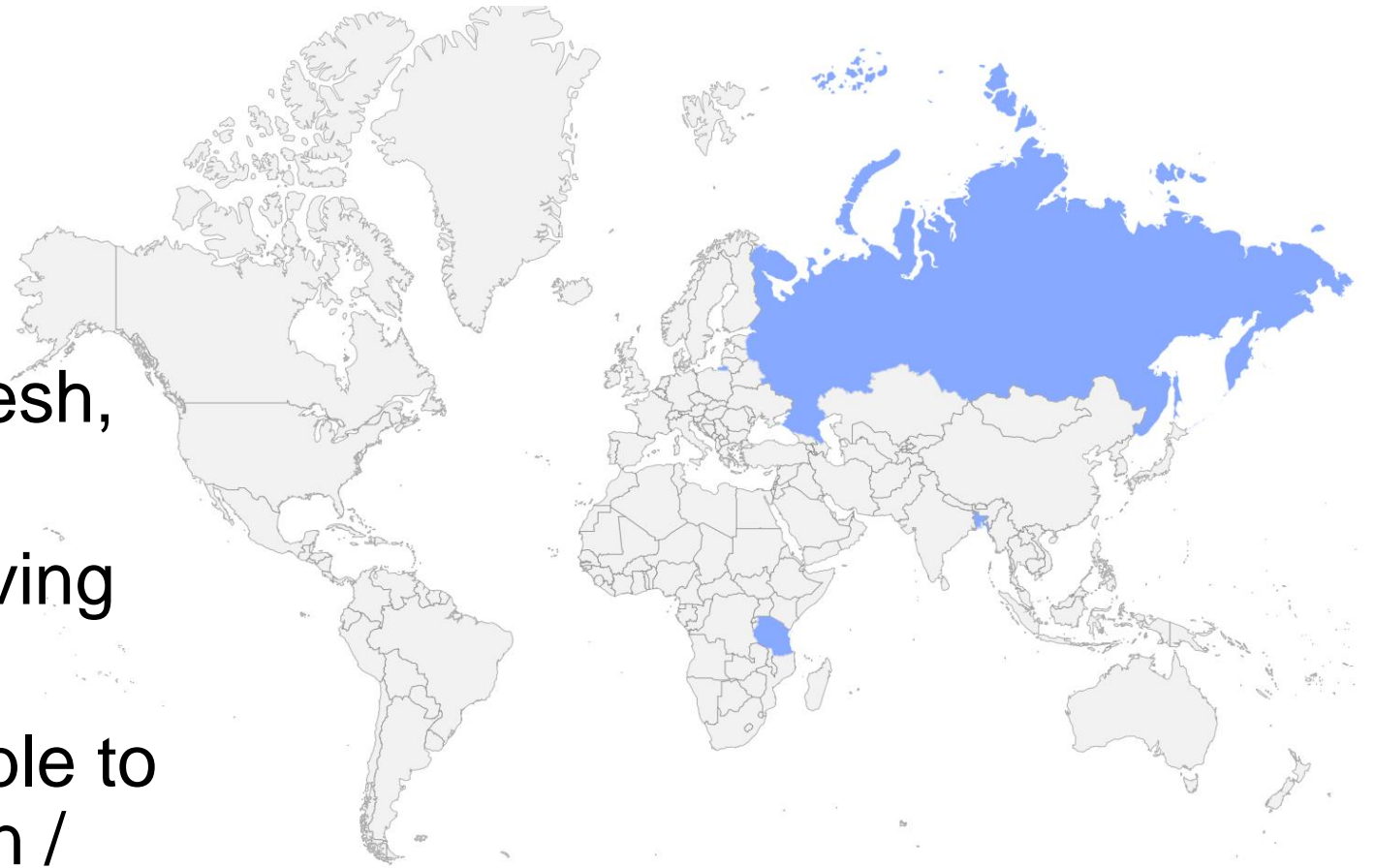


Background

- Risk of ototoxicity of *streptomycin*, *kanamycin*, and *amikacin* was associated with older age and larger cumulative dose received, but not the size of dose or the frequency.
- Cumulative days of therapy and AUC of *amikacin*: primary predictors of hearing loss.
- *Amikacin/kanamycin*: no correlation with dose (per kg / cumulative), duration, gender, age, BMI, weight, AUC₀₋₂₄, weighted C_{max}
 - At 8000 Hz: dose correlated with hearing loss

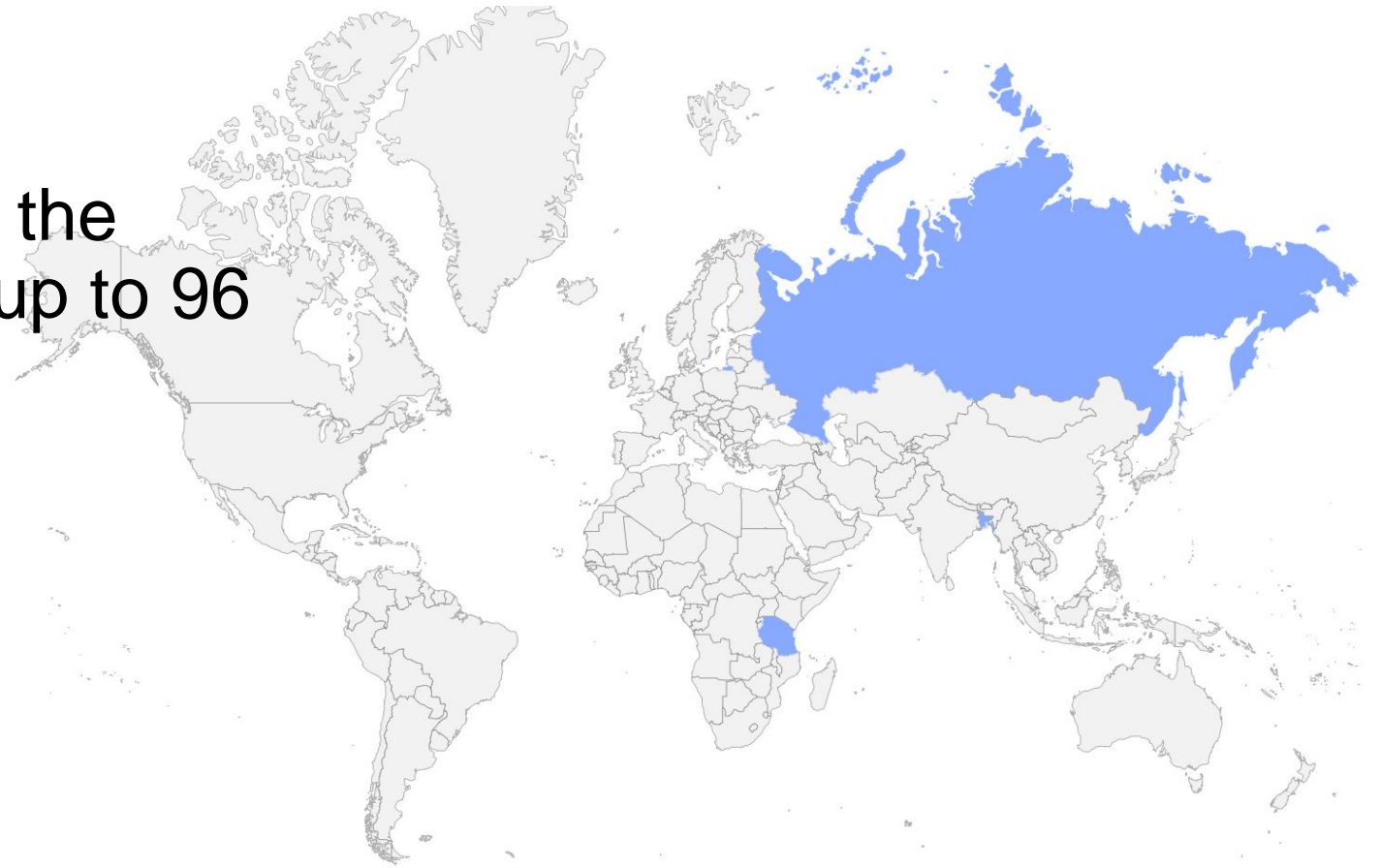
Methods

- Prospective cohort study (*ongoing*)
- Sites: Tanzania, Bangladesh, Russian Federation
- *Inclusion*: MDR TB, receiving capreomycin / kanamycin
- *Exclusion*: pregnant, unable to undergo sample collection / consent / return or contacted for follow up



Methods

- Subjects were enrolled in the hospital and followed for up to 96 weeks

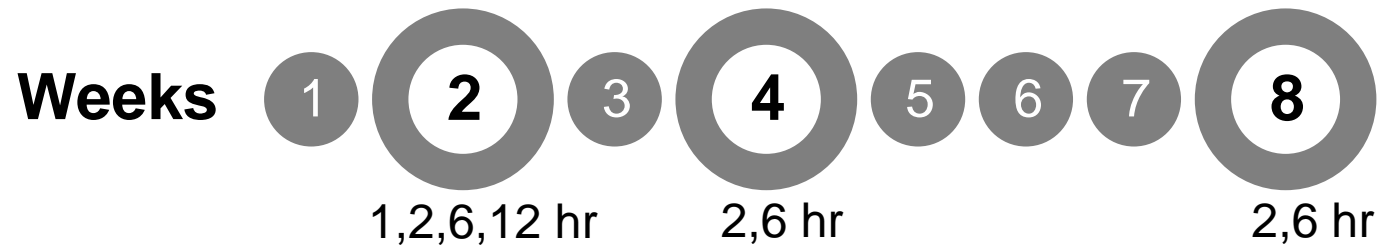


Methods

- Hearing testing:
 - Baseline, 1, 2, and 6 months after initiation of treatment
- Threshold measurements:
 - via air conduction at 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz.
 - via bone conduction at 500, 1000, 2000, and 4000 Hz.
- Ototoxicity: pure tone threshold change (loss) ≥ 20 dB compared to baseline at any frequency.

Methods

- PK samples:



- UF Infectious Disease Pharmacokinetics Lab
- Phoenix WinNonlin v7.0: NCA
highest AUC_{0-12} with corresponding C_{max} and $t_{1/2}$

Methods

- Pretreatment sputum samples:
 - MIC testing and culture
- Statistical analysis:
 - JMP v13

Results

- Tanzania data only

Baseline characteristics ^a	N=31 (225 serum samples)
Age, years	37.6 (20-68)
Males, n (%)	22 (71)
Weight, kg	52 (31-81)
Treatment received, n ^b	
Kanamycin	30
Capreomycin	10
Total duration of treatment prior to ototoxicity or audit, weeks	24 (2-32)
MIC, mcg/mL	
Kanamycin ^c	1.2 (0.3-10.0)
Capreomycin	0.6 (0.3-2.5)

a) data presented as medians and ranges unless specified; b) the total exceeds 31 as some patients were switched from one treatment to the other; c) two patients had MIC of 10 mcg/mL for kanamycin

Results

- **Gender vs. Ototoxicity**

2 females (22%) vs. 11 males (50%)

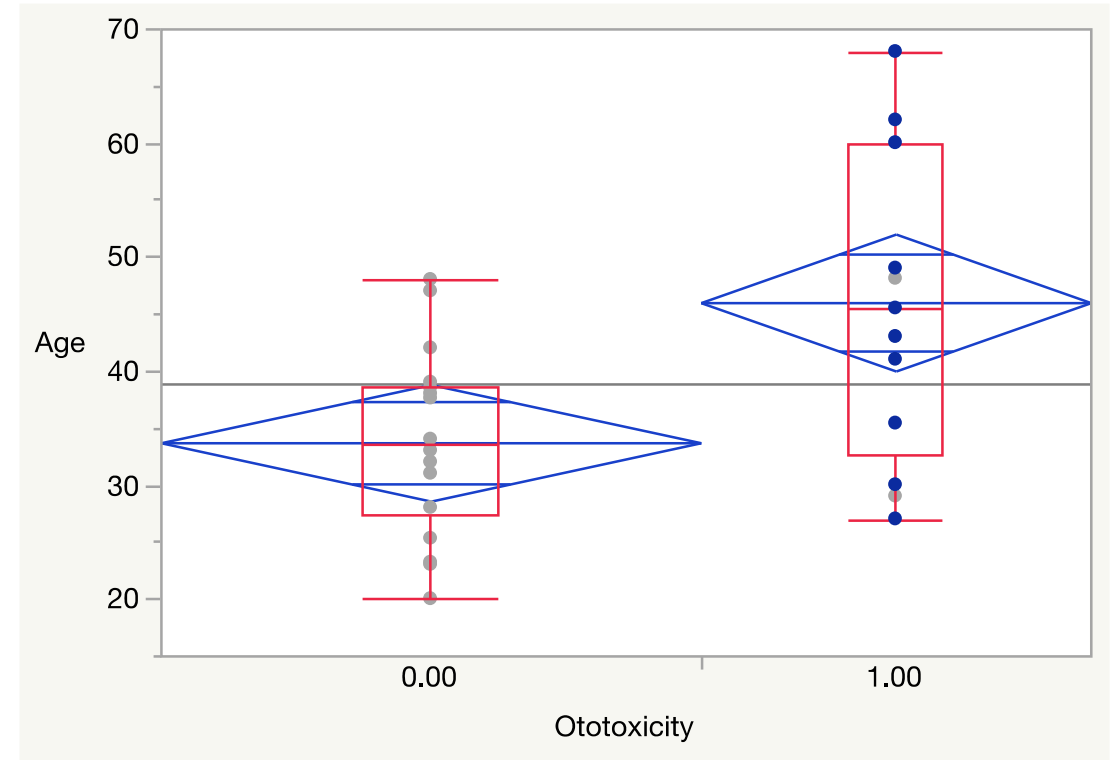
$p > 0.05$

Results

- **Age^a vs. Ototoxicity**

no ototoxicity: 33 years (20-48)

ototoxicity: 45 years (27-68)



$p = 0.01$

a) Data presented as median and range

Results

- **Weight^a vs. Ototoxicity**

no ototoxicity: 51 kg (36-81)

ototoxicity: 57.5 kg (31-73)

$p > 0.05$

a) Data presented as median and range

Results

- **Duration of therapy^a vs. Ototoxicity**

no ototoxicity: 24 weeks (2-32)

ototoxicity: 24 weeks (8-32)

$p > 0.05$

a) Data presented as median and range

Results

- **Capreomycin^a**

C_{max} (mcg/mL)

no ototoxicity: 24.9

ototoxicity: 25.7 (8.8-43.5)

t_{1/2} (hr)

no ototoxicity: 2.4

ototoxicity: 2.7 (2.5-4.2)

p>0.05

a) Data presented as median and range

Results

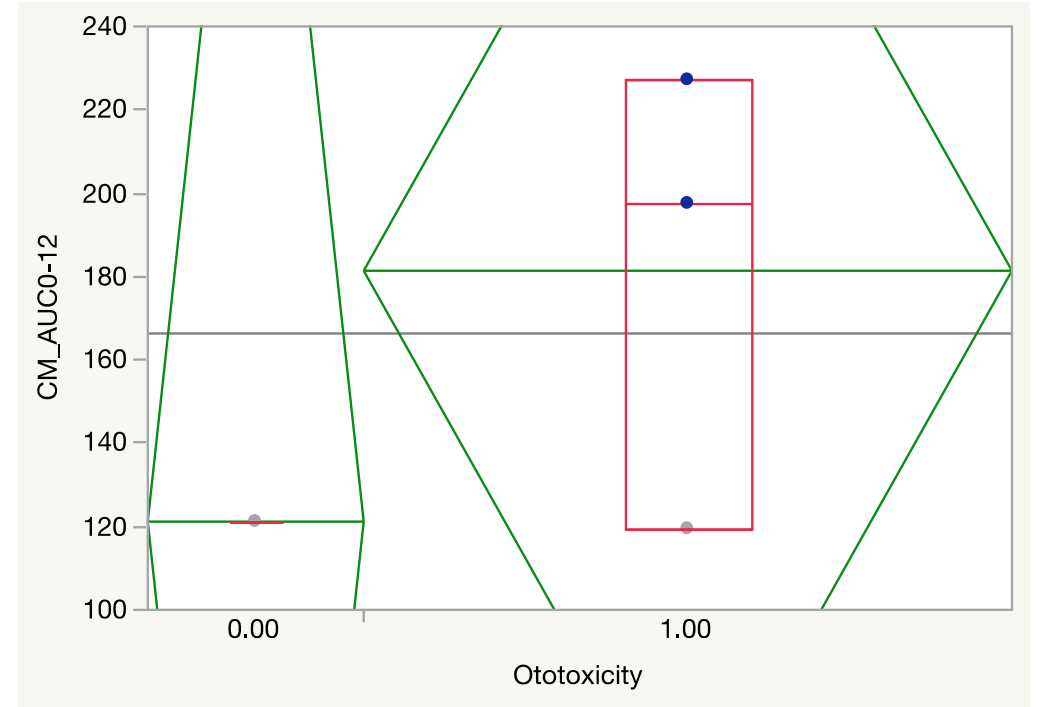
- **Capreomycin^a**

AUC₀₋₁₂ (hr.mcug/mL)

no ototoxicity: 121.2

ototoxicity: 197.5 (119.4-227.2)

$p > 0.05$ (*small N*)



a) Data presented as median and range

Results

- **Kanamycin^a**

C_{max} (mcg/mL)

no ototoxicity: 27.8 (15.7-65.1)
ototoxicity: 36.9 (23.9-50.5)

t_{1/2} (hr)

no ototoxicity: 2.4 (1.3-5.5)
ototoxicity: 2.4 (1.6-7.3)

p>0.05

a) Data presented as median and range

Results

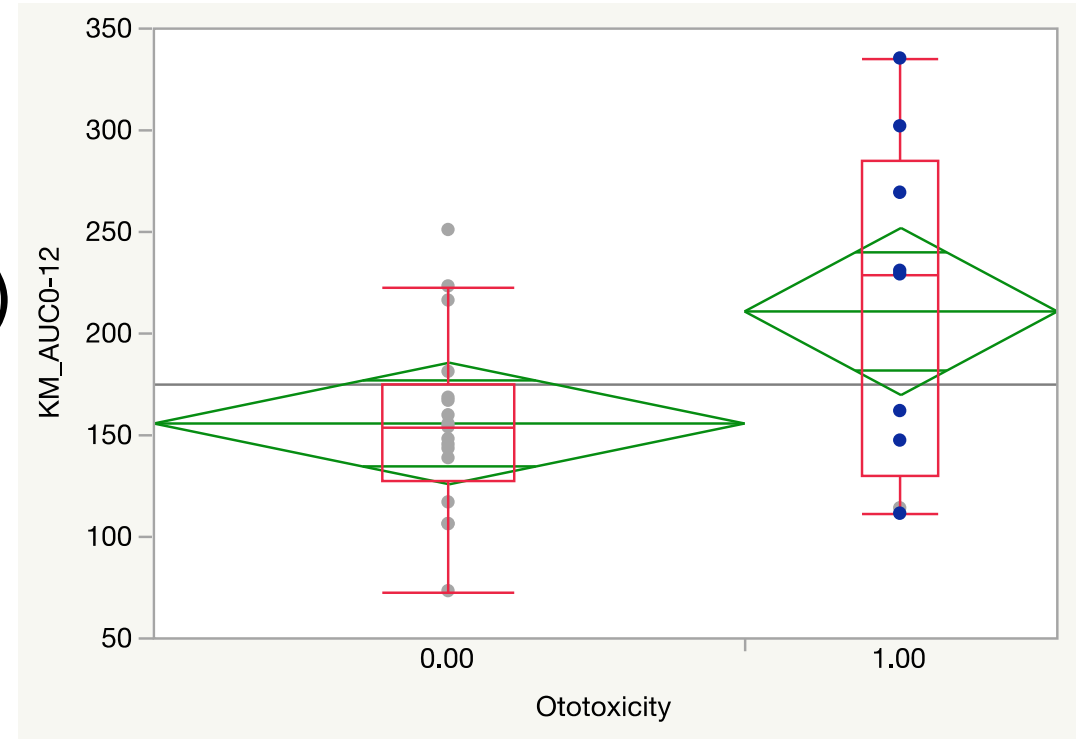
- Kanamycin^a

AUC₀₋₁₂ (hr.mcg/mL)

no ototoxicity: 153.5 (72.9-250.6)

ototoxicity: 228.8 (111-334.9)

p=0.03



a) Data presented as median and range

Conclusions

- KM and CM ototoxicity were associated with older age and higher AUC_{0-12}
- C_{max}/MIC and AUC/MIC : dosing with lower exposure and toxicity
- Ongoing study: target enrollment of 125 MDR each from Tanzania (current N=72), Bangladesh (current N=68), Russia (current N=51)
 - more exposure and toxicity data: better assess other determinants or confounders

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