Preserving Effective TB Treatment Study (PETTS)

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Presentation Overview

- Background
- Baseline drug resistance and risk factors
- Acquired resistance to second-line drugs
- Effect of acquired drug resistance on outcomes

GLC was established in 2000 to promote access to high quality 2nd-line drugs while preventing increasing resistance to 2nd-line drugs

PETTS Study Objectives

- To determine the frequency, timing, and risk factors for acquired resistance to second-line drugs (SLD) in diverse MDRTB control programs, including
  - Program characteristics
  - Patient characteristics
  - Mycobacterial characteristics
  - Treatment
- To determine the effect of acquired SLD resistance on patient outcomes

PETTS Study Overview

- Prospective cohort study
- 9 countries, 26 sites
- MDRTB patients treated with SLD drugs
- Consecutive enrollment
- Prisoners, pregnant women, and persons <18 years of age were excluded
- Follow-up to end of treatment (or 2 years)
- Baseline and monthly clinical data and sputum cultures
- Cultures shipped to CDC for centralized testing
  - BL and Final isolates for DST and genotyping
  - Intermediate isolates cultured and stored
- Data sent to DTBE, merged for analysis

PETTS Network

PETTS Chronology

- 2005: Enrollment started
- 2008: Enrollment ended
- 2010: Follow-up ended
- 2012: First PETTS report published
  - Dalton et al., "Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study,", Lancet, Oct 20;380(9851):1406-17.

Drug Susceptibility Testing

- DST for all sites performed at CDC using Middlebrook agar 7H10 proportion method
- First-line drugs: INH, RIF, EMB, PZA, SM
- Second-line drugs
  - RBT
  - CIP
  - OFL

    Fluoroquinolones (FQ)
  - KM
  - AMK
  - CAP

    Second-line injectable drugs (SL-INJ)
  - ETA
  - PAS

    Group 4 drugs (GRP4)

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Baseline PETTS isolates

Country	n Baselines Tested	n Usable Baselines	n included: MDR confirmed Clinical data
Estonia	50	46	46 (92%)
Latvia	106	103	100 (94%)
Peru	213	202	177 (83%)
Philippines	456	414	397 (87%)
South Africa	425	348	293 (69%)
South Korea	119	105	99 (91%)
Russia	132	119	115 (87%)
Thailand	63	60	51 (81%)
Total	1564	1397 (89%)	1278 (82%)

Potential Risk Factors

- 94% of patients had at least 1 previous TB episode
- 47% reported previous contact with any TB patient
  - Of those, 15% had contact with known MDR TB (34% unknown if MDR or not)
- 7% had history of imprisonment and 2.8% were homeless at some point
- 17% currently abuse alcohol and 24% smoked tobacco
- 13 % known HIV-infected
- 13% with diabetes
- 15% previously received at least 1 SLD for >1 month

Prevalence of drug resistance in MDR baseline isolates, 8 countries, 2005–2008 (n=1278)

DRUG	n RESISTANT	% RESISTANT	Range across sites (% RES)
RBT	875	68.5	56.0-82.6
EMB	826	64.6	47.1-89.1
SM	881	69.0	46.5-100
KM	237	18.5	1.8-42.0
AMK	205	16.0	1.8-35.0
CAP*	152	12.0	0.3-27.7
1 SL-INJ	255	20.0	2.0-47.0
3 SL-INJ*	134	10.5	0.3-25.6
FQ	165	12.9	7.1-32.3
THA	249	19.5	7.3-30.5
PAS	137	10.7	2.0-34.3
XDR	86	6.7	0.8-15.2

* n=1270

Risk Factor Analysis

- 28 risk factors analyzed for association with resistance to 4 drug combinations
  - Any FQ, ≥1 SL-INJ, XDR-TB, and any GRP4 drug
- Prevalence of resistance to FQ and SL-INJ is higher in non-GLC sites than in GLC sites
  - FQ resistance: 11% GLC and 17 % in non-GLC
  - SL-INJ resistance: 17% in GLC and 25% in non-GLC
- 11% of PETTS patients from non-GLC sites had XDR-TB as compared to 5% from GLC sites
- In addition, patients with previous treatment with SLDs were at greater risk for resistance to FQ and SL-INJ

Risk Factors

- Risk of XDR more than quadrupled in previously treated patients
- Previous treatment with SLDs was consistently the strongest risk factor for resistance to these drugs
- Resistance to SL-INJ drugs was associated with social factors (i.e. unemployment, alcohol, smoking, and imprisonment)
- Hospitalization at enrollment also associated with SLD resistance
- Other risk factors differed by drug and country

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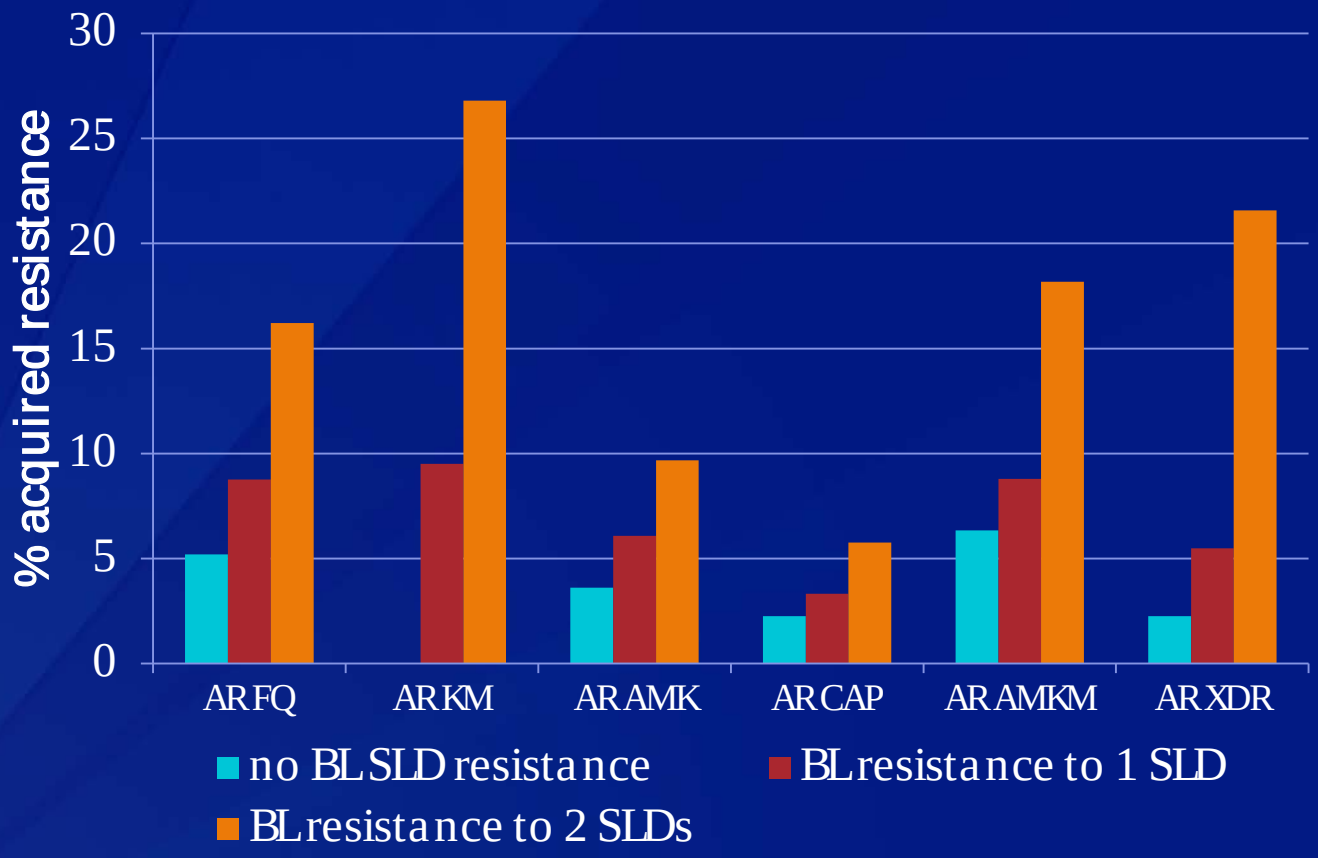
Acquired Drug Resistance

- 825 paired isolates (442 GLC and 383 non-GLC)
- 249/825 (30%) had a DST change for RIF, INH, FQ, SL-INJ, or any combination of these drugs
- 164/249 (66%) pairs matched MIRU24 for BL and final isolate and were considered to have acquired resistance
- Overall, 15% of MDRTB patients starting treatment with SLDs acquired resistance to a FQ, SL-INJ, or both during treatment

Acquired SLD resistance stratified by GLC

GLC	Acquired Resistance	%	RR	CL
N	FQ	18.7	3.7	2.2, 6.1
Y	FQ	5.0		
N	1 SL INJ	10.9	2.0	1.2, 3.3
Y	1 SL INJ	5.5		
N	XDR	14.8	3.8	2.2, 6.7
Y	XDR	3.9		

Baseline drug resistance is a risk factor for acquired drug resistance



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Treatment outcomes in relation to baseline SLD resistance (%)

Baseline SLD resistance	Success n=724	Poor outcome (Failure+Death) n=240	Unknown (includes default) n=264
No	67	11	22
INJ only	57	19	24
FQ only	56	25	19
XDR	26	56	18

Treatment outcomes in relation to acquired SLD resistance (%)

Baseline SLD resistance	Acquired SLD resistance	Success n=724	Poor outcome (Failure+Death) n=240	Unknown (includes default) n=264
No	No	67	11	22
No	INJ-R only	39	46	15
No	FQ-R only	26	63	11
No	INJ+FQ (XDR)	14	50	36

Treatment outcomes in relation to baseline and acquired SLD resistance (%)

Baseline SLD resistance	Acquired SLD resistance	Success n=724	Poor outcome (Failure+Death) n=240	Unknown (includes default) n=264
No	No	67	11	22
INJ only	No	57	19	24
No	INJ-R only	39	46	15
FQ only	No	56	25	19
No	FQ-R only	26	63	11
XDR	N/A	26	56	18
No	INJ+FQ (XDR)	14	50	36
INJ only	FQ (XDR)	11	69	20
FQ only	INJ (XDR)	11	78	11

Discussion

- 44% of patients had resistance to ≥1 SLD upon initiation of MDRTB treatment
- 9% of MDR patients acquired XDRTB during treatment
- It is not enough to detect mutations associated with rifampicin resistance. Introduction of tools such as GeneXpert requires clear algorithms for reflex testing
- The availability of rapid, reliable SL DST is essential to MDRTB patient management
- Patients that acquire resistance face worse outcomes than those with baseline SLD resistance indicating the necessity for routine repeat DST during therapy
- MDRTB scale up must also include the careful introduction of new anti-TB drugs

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