Global Perspective on Transmission: Value in Genotype Mapping of Disease Transmission Dynamics

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Emergence of TB Drug Resistance

• Streptomycin: first drug active against
  – Developed in 1945
  – Despite initial response, resistance emerged in 85% of participants
    • Median time to resistance 45 days
  – Monotherapy conferred no survival benefit
Spontaneous mutations

• Drug resistance occurs as a result of spontaneous mutation, which occurs at a predictable rate for each drug
  – Streptomycin: 1 in $10^6$
  – Isoniazid: 1 in $10^6$
  – Rifampin: 1 in $10^8$
  – Ethambutol: 1 in $10^7$
  – Pyrazinamide: 1 in $10^6$
  – Fluoroquinolones: 1 in $10^6$-$10^8$
Drug-resistant mutants in large bacterial population

Multidrug therapy: No bacteria resistant to all 3 drugs

INH
RIF
PZA

INH

Monotherapy: INH-resistant bacteria proliferate

Albino & Reichman. Respiration. 1998
Spontaneous mutations develop as bacilli proliferate to $>10^8$.

INH resistant bacteria multiply to large numbers.

INH mono-resist. mutants killed, RIF-resist. mutants proliferate → MDR TB

INH RIF

INH

Albino & Reichman. Respiration. 1998
Fig 1. Resistance development in the KZN family of strains of *Mycobacterium tuberculosis* from 1994 till 2006

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Resistance found for the first time in: Pillay & Sturm CID 2007
Acquired resistance:
Patient develops resistance
due to incomplete or
inappropriate treatment

Slide courtesy of Dr. Sarita Shah
Primary (Transmitted) Resistance

Acquired resistance: Patient develops resistance due to incomplete or inappropriate treatment

Primary Resistance: Patient develops resistance due to transmission of drug-resistant strain

Slide courtesy of Dr. Sarita Shah
Primary (Transmitted) Resistance

**Primary Resistance:**
Patient develops resistance due to transmission of drug-resistant strain

**Acquired resistance:**
Patient develops resistance due to incomplete or inappropriate treatment

*Strengthen TB program*

*Infection control programs*

Slide courtesy of Dr. Sarita Shah
Initial Approach to Drug-Resistant TB

- Initial belief: Drug-resistant strains would not propagate
  - Mutations conferring resistance believed to exert fitness cost
  - Thus, no intervention necessary…It would just die out
Outbreaks of MDR TB 1990s


An Outbreak of Multidrug-Resistant Tuberculosis involving HIV-Infected Patients in Two Hospitals in Milan, Italy

An Outbreak of Multidrug-Resistant Tuberculosis among Hospitalized Patients with the Acquired Immunodeficiency Syndrome

BR Edlin, et al. NEJM 1992

ML Moro et al. AIDS 1998
Genotyping to Identify Transmission

- Genotyping provided methodology for determining role of transmission of TB strains
  - MDR TB outbreaks in 1990’s due to hospital transmission
  - Drug-resistant TB transmission is widespread

Daley NEJM 1994
Characteristics of 1990s Outbreaks

• Delayed Diagnosis: 6 weeks – 6 months
  – Reliance on smear microscopy
  – Delays in completing culture and drug susceptibility testing

• Infection Control precautions inadequate
  – Patients not isolated based on suspicion
  – Isolation rooms poorly maintained
    • Air flow studies showed positive pressure

• Transmission to Health Care Workers
  – TST conversion in 30-60%
Lessons Not Learned Globally

TB Ward, Tugela Ferry, South Africa, 2003
Transmission of XDR TB in 2000s

- Largest XDR TB cluster reported worldwide from Tugela Ferry, South Africa
- Total of 516 XDR TB cases culture confirmed from 2005-2009
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  - Incidence: 52 XDR TB / 100,000

Gandhi et al. J Inf Dis 2013
Transmission of XDR TB in 2000s

- Largest XDR TB cluster reported worldwide from Tugela Ferry, South Africa
- Total of 516 XDR TB cases culture confirmed from 2005-2009
- Genotyping revealed that >85% of cases with single predominant fingerprint

KZN-1 M. tuberculosis IS6110–based Restriction Fragment Length Polymorphism profile

Gandhi et al. J Inf Dis 2013
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Gandhi et al. J Inf Dis 2013
Rapid Rise in MDR TB cases

![Bar chart showing the increase in MDR TB cases from 2001 to 2007. The chart indicates a significant rise, with the number of cases increasing from 210 in 2001 to 3040 in 2007.](Wallengren K et al Emerg Inf Dis 2011)
Widespread Transmission

• Pooling of genotyping data allows identification of transmission across large geographic areas

• Epidemiology investigation and network analysis allows better characterization of transmission relationships between clustered cases

• Analysis of genotyping data in US revealed multi-state clusters of MDR TB
  – New York, Georgia, Florida, Colorado, Nevada

Clusters of Multidrug-Resistant *Mycobacterium tuberculosis* Cases, Europe

- 54% MDR & XDR TB cases clustered within country
- 43% clustered across European borders
- Clusters with drug-resistant cases originating in Asia & Africa

Devaux Emerg Inf Dis 2009
Household Transmission of DR TB

THE LANCET

Tuberculosis Burden in Households of Patients with MDR and XDR TB

Household Contact Investigation of MDR and XDR TB In High HIV Prevalence Settings

• Incidence of MDR and XDR TB in household contacts 1500-4000 case per 100,000 patient-years
Reinfection with MDR & XDR TB

- Patients who develop drug resistance while on treatment or as a relapse
  - Previously presumed to be due to acquired resistance

- Genotyping of baseline isolate and follow-up isolate demonstrate exogenous reinfection
  - San Francisco 1993: 45% reinfection
  - China 2007: 84% reinfection
  - South Africa 2008: 100% reinfection

Genotypes of Patients with XDR TB Relapse

Initial Isolate

Follow-up Isolate

Andrews JR et al. JID 2008
Estimating Global Role of Transmission

Revised estimation of proportion of cases due to transmission: new cases + relapse after cure/completion

- WHO: 74% of MDR TB cases globally arise from transmission rather than acquired resistance
- China: 78% of MDR TB due to transmission
- Meta-analysis of 31 cohorts: 90% of XDR TB cases with no prior history of MDR TB treatment

Conclusions

• Genotyping enables the measurement of transmission among cases of drug-resistant TB

• Two decades of experience now definitively demonstrate the significant role of transmission in development of MDR and XDR TB cases

• Estimates suggest that transmission is now the predominante source of drug-resistant cases globally
  – Accounting for nearly 75% of drug-resistant TB cases
Implications

• Efforts to control the drug-resistant TB epidemic must focus on halting transmission
  – Infection Control efforts have been largely neglected as TB control strategy

• Comprehensive strategy, including redesign of healthcare facilities, early diagnosis and early treatment of drug-resistant TB cases needed
Thank you