

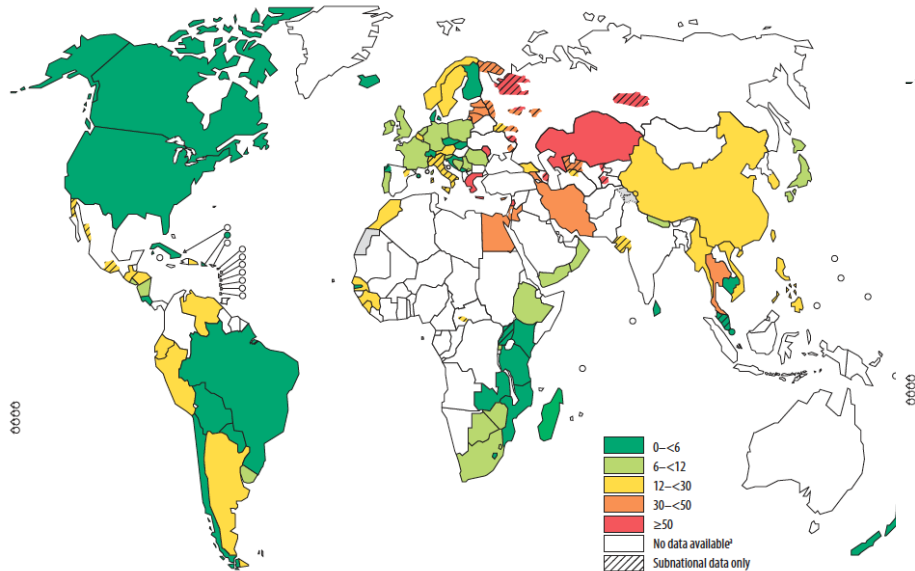
The Transmission Dynamics of MDR TB

Megan Murray, MD, ScD

Department of Global Health and Social Medicine
Harvard Medical School

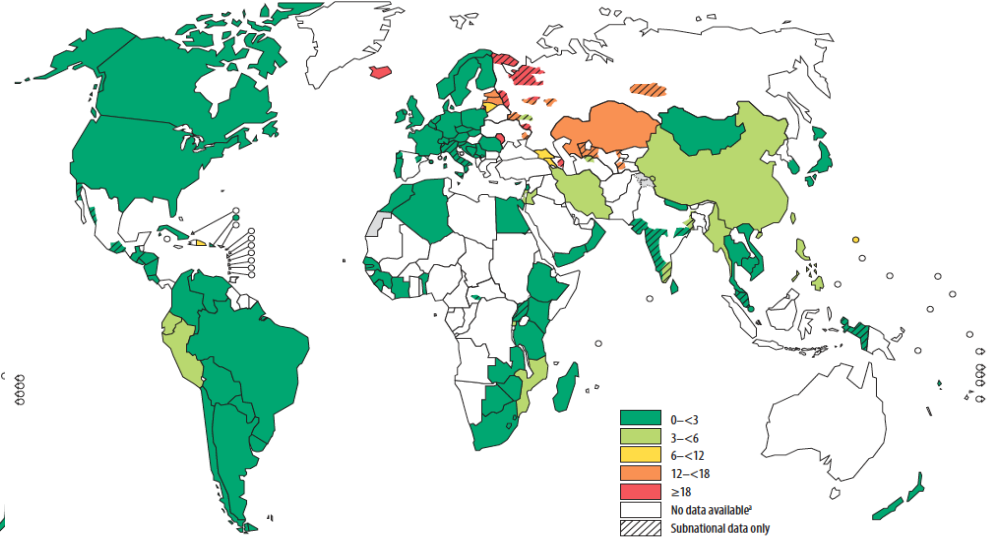
Department of Epidemiology
Harvard School of Public Health

MAP 4 Distribution of proportion of MDR-TB among previously treated TB cases, 1994–2009



^a Australia, Democratic Republic of the Congo, Fiji, Guam, New Caledonia, Solomon Islands and Qatar reported data on combined new and treated cases.

MAP 3 Distribution of proportion of MDR-TB among new TB cases, 1994–2009



^a Australia, Democratic Republic of the Congo, Fiji, Guam, New Caledonia, Solomon Islands and Qatar reported data on combined new and previously treated cases.

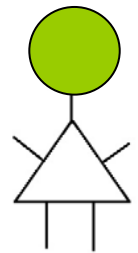
China (from WHO)

MDR-TB estimates of burden *

% of new TB cases with MDR-TB	5.7 (5.0–6.6)	[DRS 2007]
% of retreatment TB cases with MDR-TB	26 (23–28)	[DRS 2007]
MDR-TB cases among incident total TB cases in 2008	100 000 (79 000–120 000)	

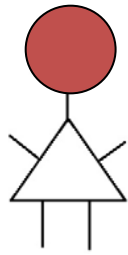
Drug sensitive TB

MDR



Acquisition of resistance

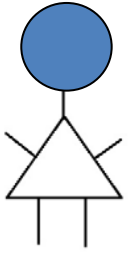
- Incorrect therapy
- Poor adherence
- Malabsorption
- Poor Drug Quality



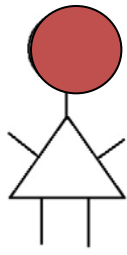
DOTS

Uninfected

Transmission of resistance



MDR

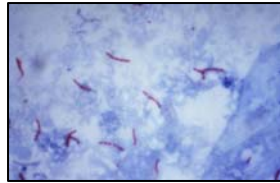


- Exposure in health care facility or community
- Delayed diagnosis and treatment
- Slow culture conversion
- Transmissibility of specific MDR strain

Routes to drug resistant TB

Gaps

Diagnosis

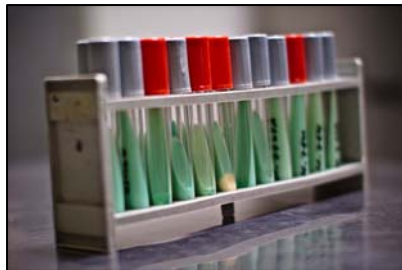


Smear Microscopy

Fast and Cheap

Misses 20-70% of cases

No DST



MTB Culture and DST

3-8 Week Delay

Better Sensitivity

Some DSTs Expensive and Difficult



Rapid Diagnostics

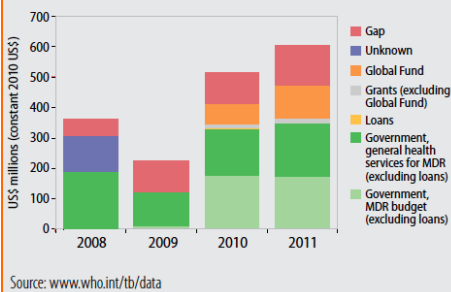
Fast but Expensive

Good Sensitivity

Incomplete DST

Treatment for MDR

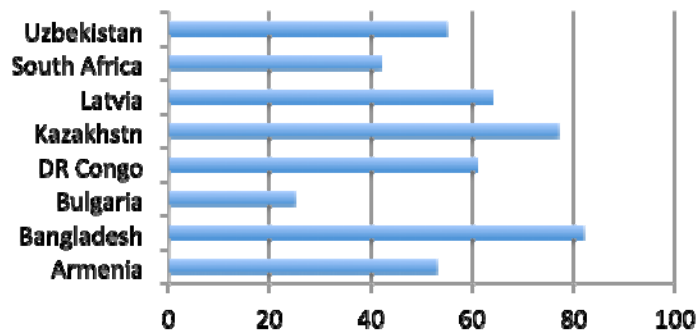
MDR-TB care and treatment costs by sources of funding. 23 high MDR-TB burden countries, 2008–2011*



Access

Funding and HR Gap
Increased access

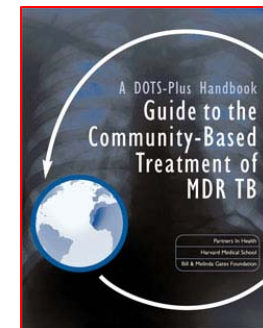
Rates of successful MDR treatment
By Country



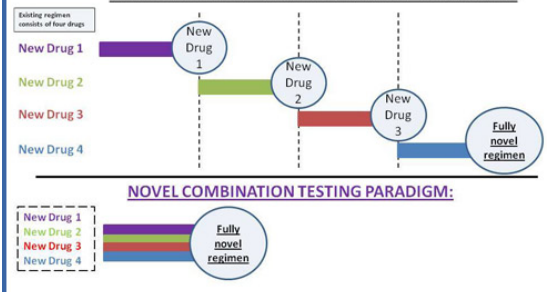
MDR Treatment Outcomes

Highly variable based on:

- Extent of DR (XDR)
- Political Will
- Treatment approach



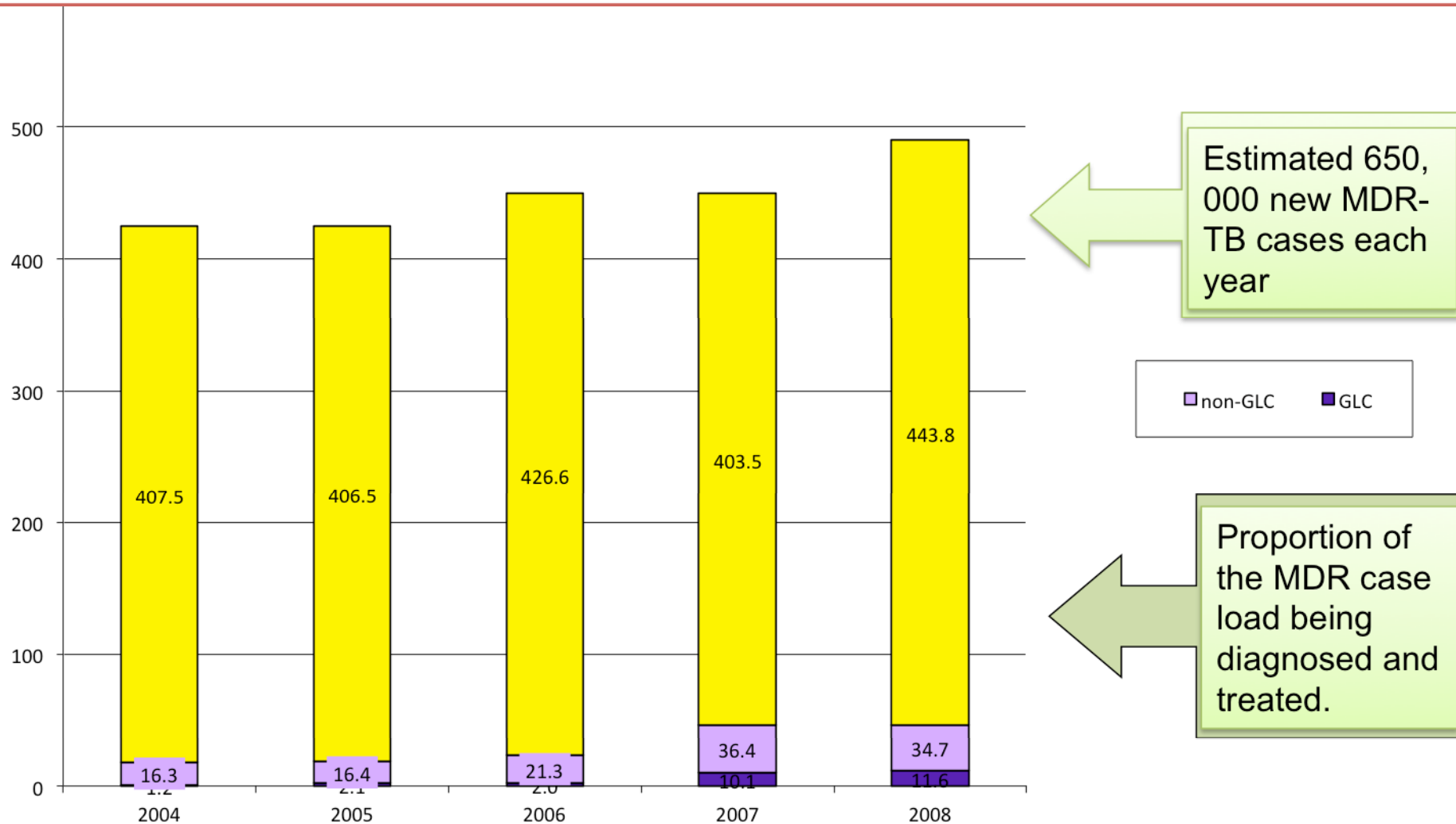
CURRENT REGIMEN DEVELOPMENT PARADIGM:



Need for New drugs

- Development
- Clinical Trials

Notified cases of MDR-TB (2004-2006) and projected patients to be treated (2007-2008) compared to estimated burden of MDR-TB

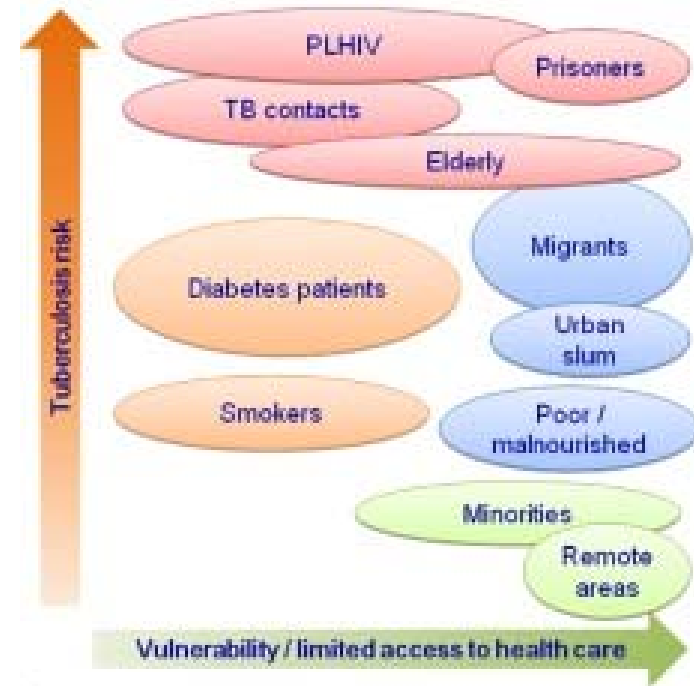
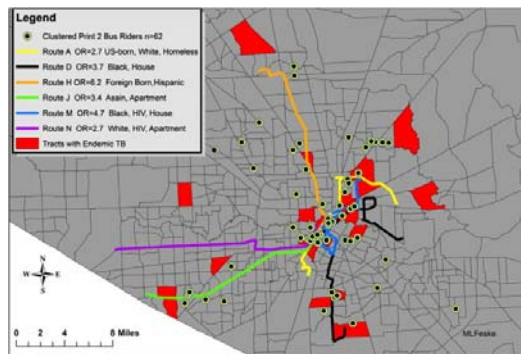


MDR Case Finding and Active Surveillance

Who?

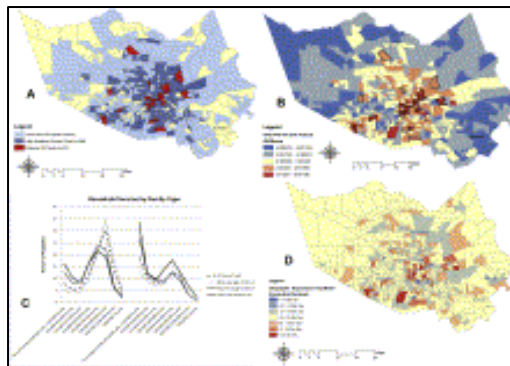
High risk groups

- TB Contacts
- HIV-infected
- Other risk factors



Where?

- Use of Molecular Epidemiology to identify transmission hot-spots
- Real time spatial mapping of MDR cases



Recent nosocomial transmission and genotypes of multidrug-resistant *Mycobacterium tuberculosis*

INT J TUBERC LUNG DIS 14(4):427-433

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A. Nodieva,^{*†} I. Jansone,[‡] L. Broka,[§] I. Pole,[§] G. Skenders,[§] V. Baumanis[‡]

1. MDR strains more likely to be transmitted. OR = 5.6
2. Beijing genotype more likely to be transmitted. OR = 12.1
3. Hospitalization associated with transmitted MDR strains compared to transmitted DS strains. OR = 18.3

Transmission of Drug-Resistant Tuberculosis among Treated Patients in Shanghai, China

JID 2007:195 (15 March)

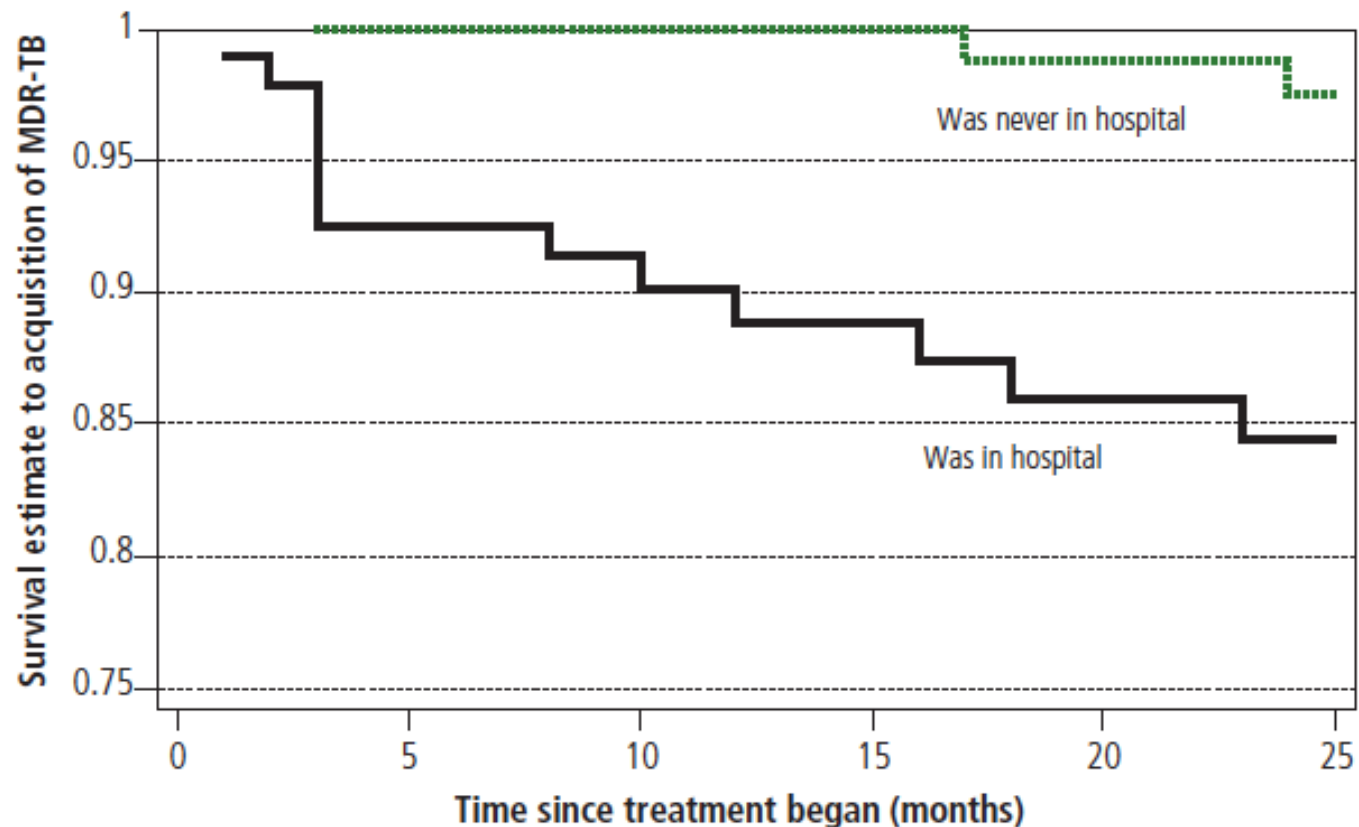
Xia Li,^{1,2,3} Ying Zhang,^{1,2,3} Xin Shen,⁴ Guomiao Shen,^{1,2,3} Xiaohong Gui,⁴
Bin Sun,⁴ Jian Mei,⁴ Kathryn DeRiemer,⁵ Peter M. Small,^{6,7}
and Qian Gao^{1,2,3}

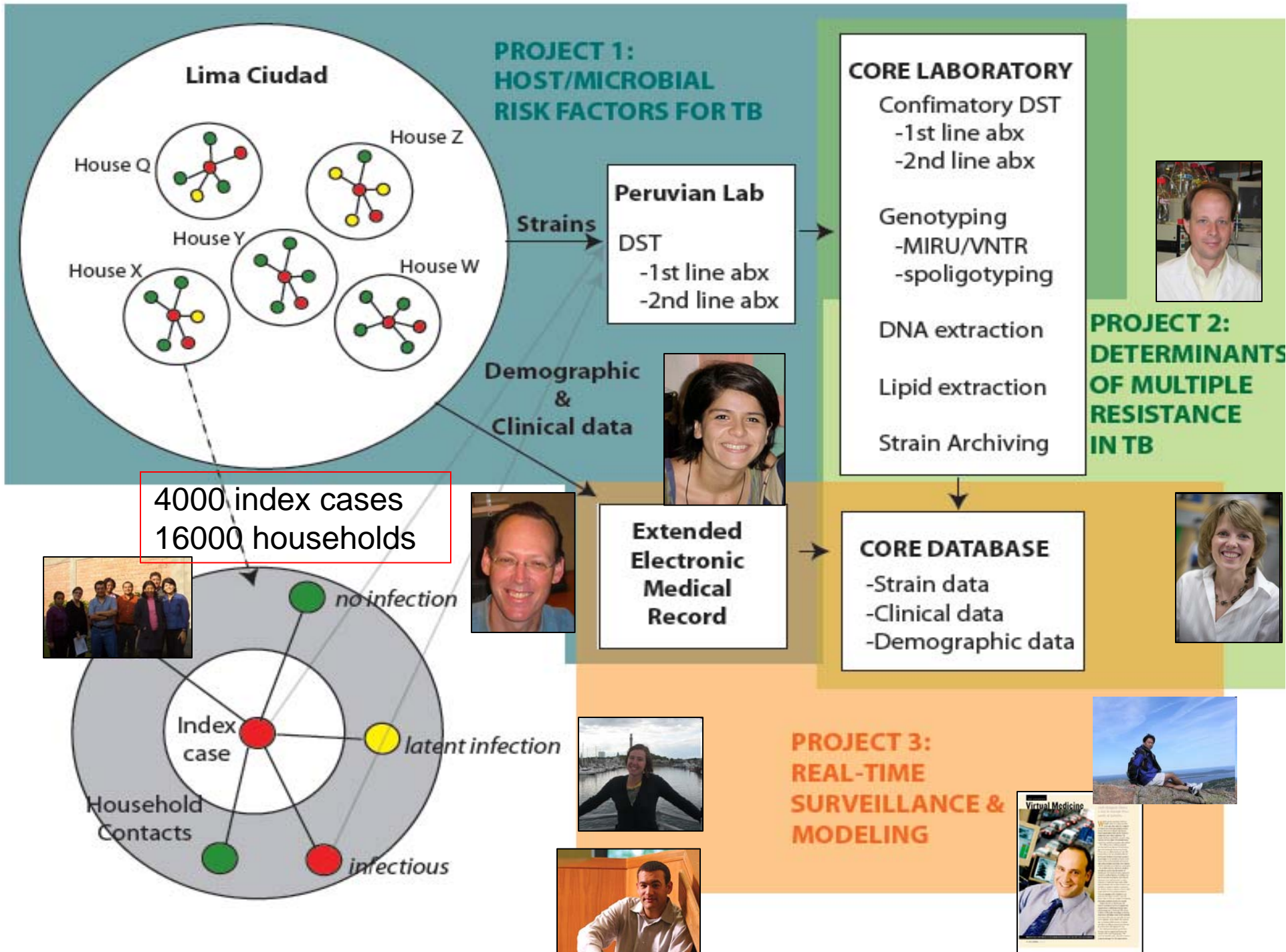
Among TB cases who failed therapy, 84% were infected with a new DR strain, suggesting ongoing transmission of MDR TB.

Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance

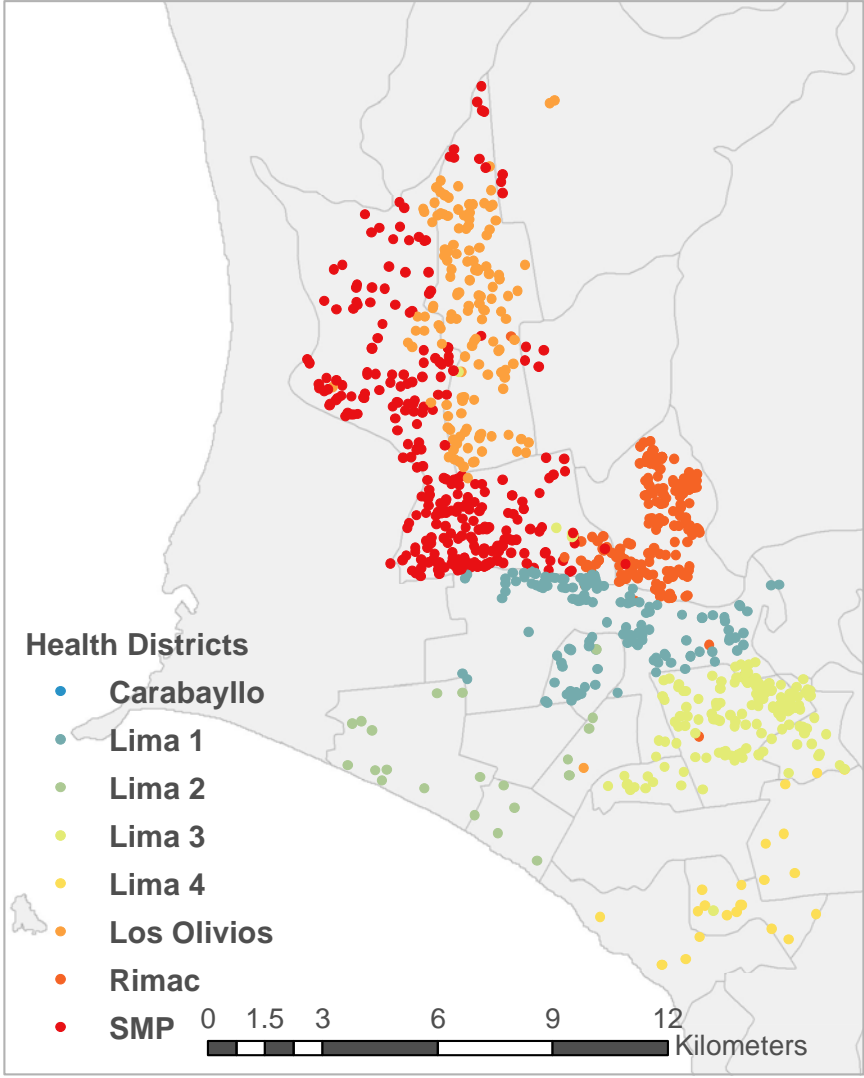
IY Gelmanova,^a S Keshavjee,^{b,c,d} VT Golubchikova,^e VI Berezina,^e AK Strelis,^{f,g} GV Yanova,^g S Atwood^d & M Murray^{b,h}

Fig. 3. Kaplan-Meier survival curves for hospitalization as a factor associated with time to acquisition of multidrug resistance

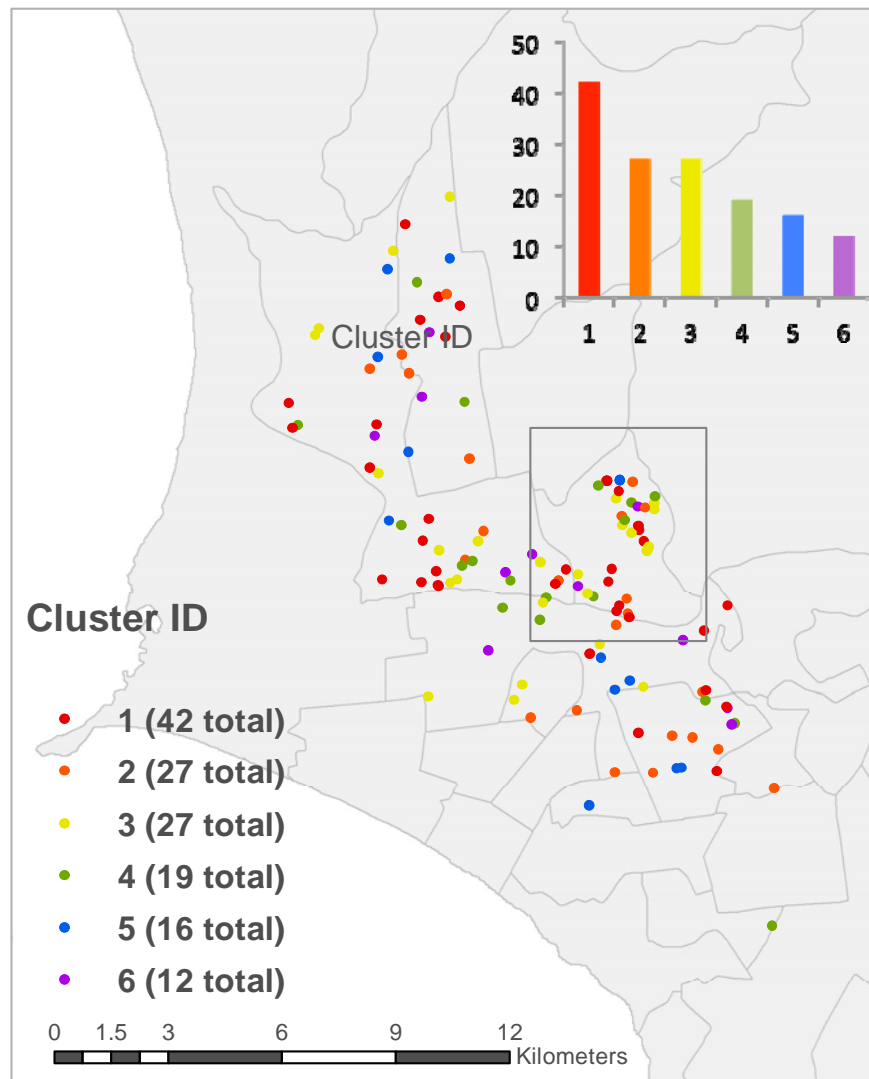




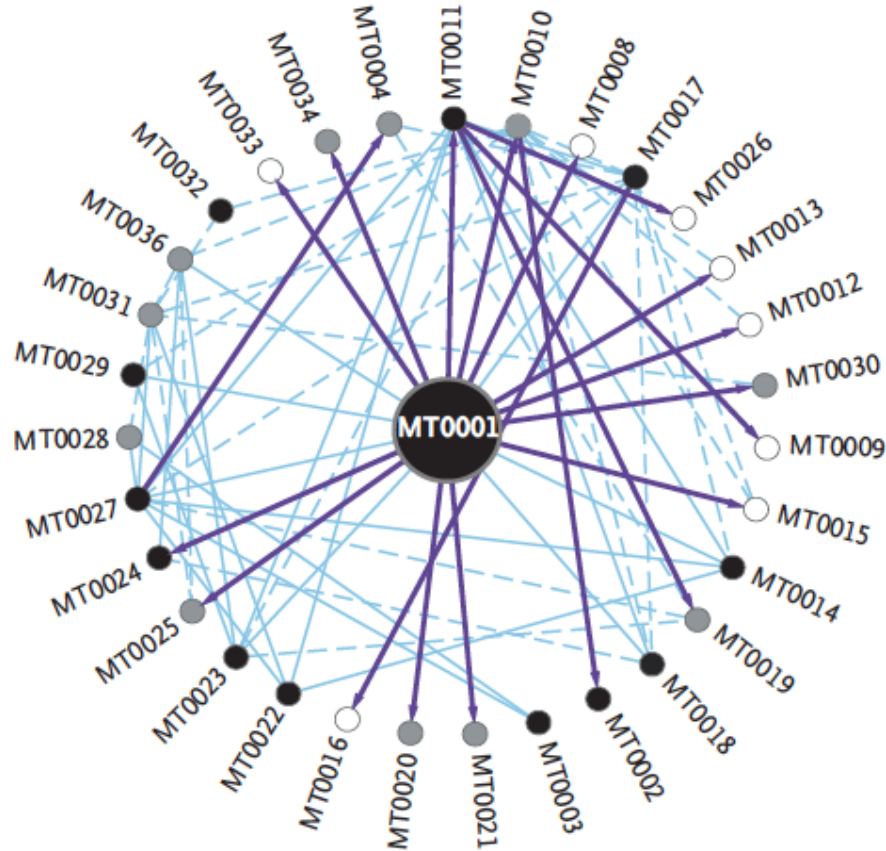
Lima, Peru: Study, Health District and Case Locations



Spatial Distribution of TB Clusters of Size 10 or More



A MIRU-VNTR and Social-Network Analysis



B Whole-Genome Sequencing and Social-Network Analysis

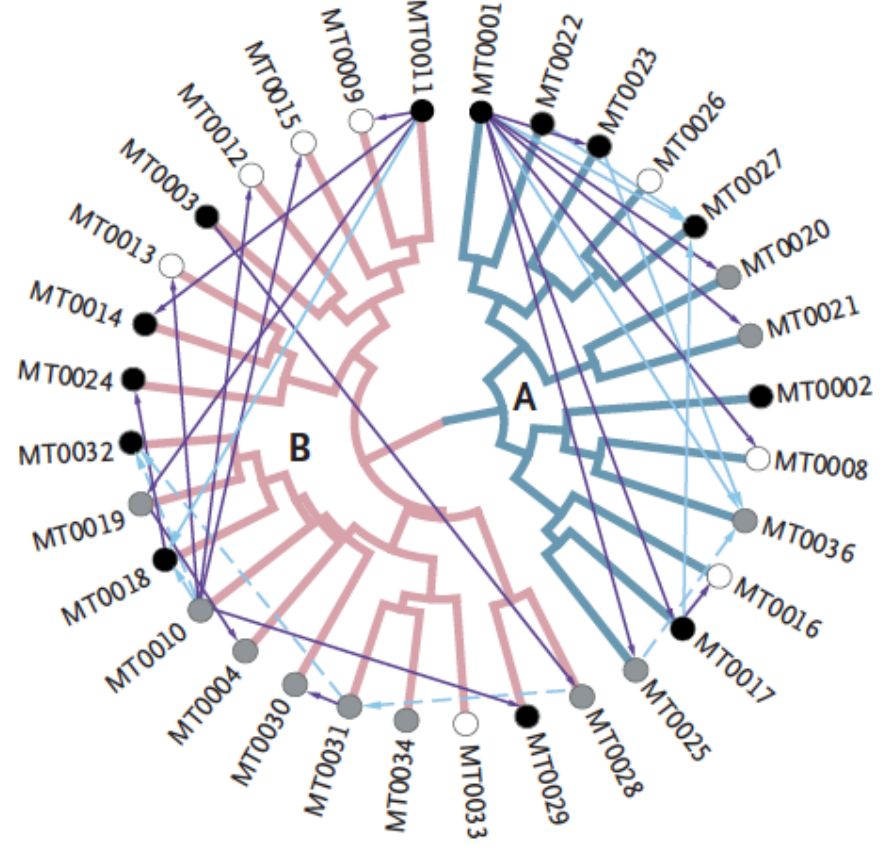


Figure 4. Putative Transmission Networks Constructed from Genotyping Data versus Whole-Genome Data for 32 Patients.

Whole-Genome Sequencing and Social-Network Analysis of a Tuberculosis Outbreak

N ENGL J MED 364;8 NEJM.ORG FEBRUARY 24, 2011

Epidemiologic studies

Epidemic modeling

Sequencing

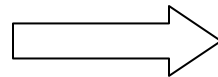
2000 Global Strains *M tb*

Drug Sensitive

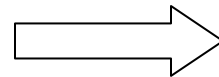
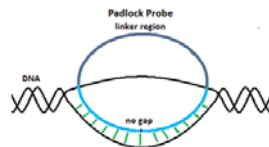
Mono-resistant

MDR

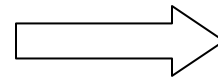
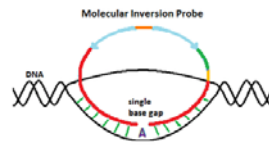
XDR



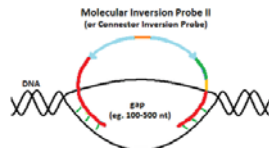
¶ Targeted Sequencing of 28 drug resistance genes



Link drug sensitivity profiles and clinical phenotypes to mutations



Retest those with discrepancies



Public database of TB resistance mutations and their frequency in clinical samples



Development for active surveillance and high throughput diagnostics

DR TB Priorities

- Early and accurate diagnosis of DR TB to improve clinical care.
 - Cheap molecular tools useable at local level
- Development of new drugs and protocols for testing of drugs in the pipeline.
 - Development and testing of new drugs in multiple populations
- Molecular and spatial surveillance to identify routes of transmission
 - Integration of new molecular tools with routine surveillance.