Introduction to Molecular Epidemiology of Tuberculosis

Qian Gao
Fudan University, Shanghai
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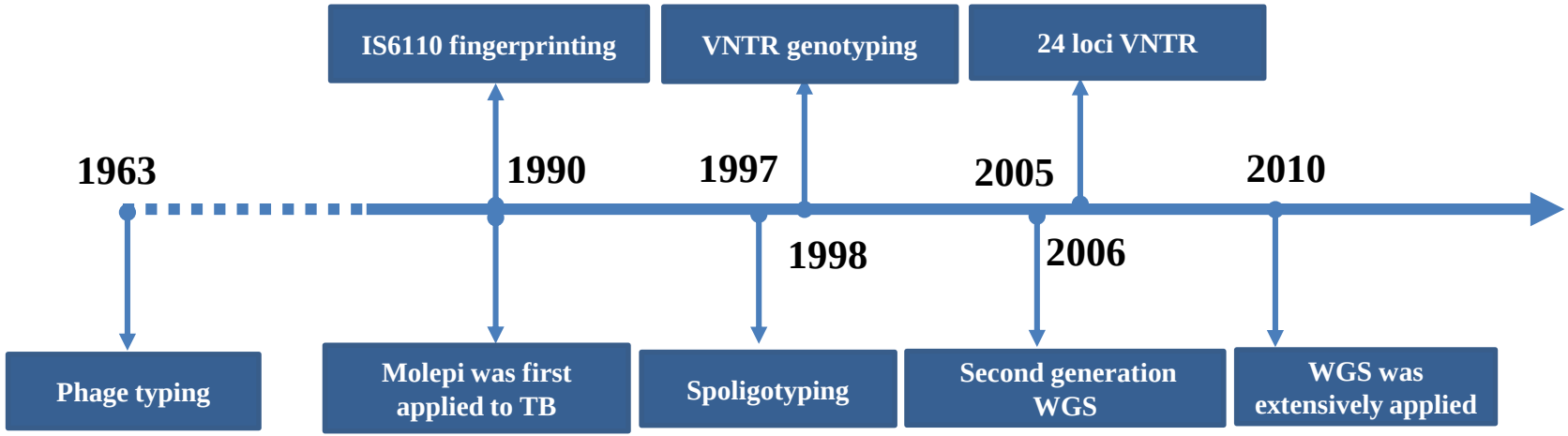
Outline

- Introduction of MolEpi of tuberculosis
- Genotyping methods of *M. tuberculosis*
- Key points should be paid attention to in Molepi Study
- Several examples of Molepi study

The History of MolEpi of Tuberculosis

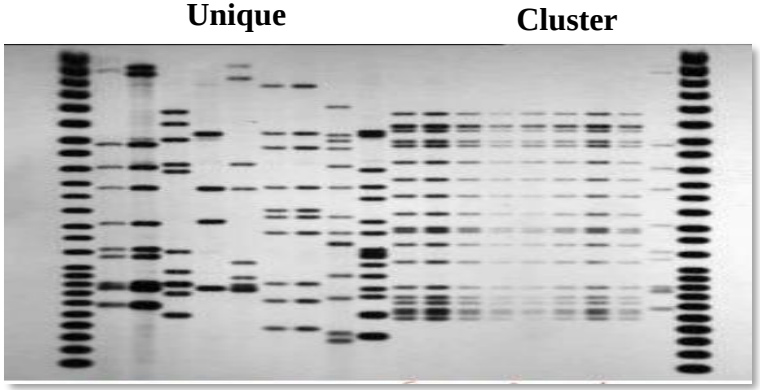
Genotyping methods + Epidemiological methods = Molepi



Infect Genet Evol. 2012 Jun;12(4):602-9

Molecular Epidemiology Assumption

- How to differentiate different strain?
  - Colony morphology and Phage typing: Impossible
  - Molecular genotyping: Possible
- Based on genotyping method
  - Identical genotype = same strain: outbreak, recent transmission
  - Unique genotype = different stains, reactivation, reinfection

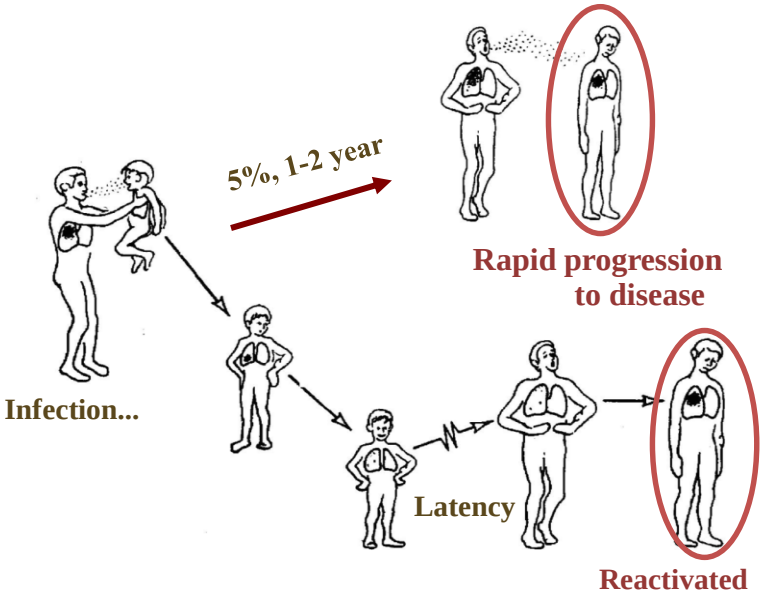


The Significance of MolEpi

- Insights into the transmission of tuberculosis
  - Dogma: more then 90% of TB patient were caused by reaction
  - Molepi studies showed 30-70% patient caused by recent transmission
- Genotyping for tuberculosis control programs
  - Identification of risk factor for transmission
  - Improving investigations of contacts
  - Evaluation of tuberculosis programs (recent transmission rate)
- Genotyping for clinical management
  - Confirm the cross-contamination in lab
  - Identify the relapse or reinfection
  - Identify the acquired drug resistant of reinfection

Recent transmission or Reactivation?

Dogma:90% of patient were coursed by reactivation.



Nature History of TB

Settings	Duration of Study	Genotyping Methods	Recent Transmission Rate	Risk Factor for Recent Transmission
New York	1989-1992	IS6110-RFLP	38%	HIV(+), Hispanic patients, DR-TB, younger age, *et al.*
San Francisco	1991-1992	IS6110-RFLP	40%	Younger age, black race, AIDS, TB control clinic, *et al.*
Malawi	1995-2003	IS6110-RFLP	72%	HIV(+), younger age, *et al.*

Small P., *et al.*, N Engl J Med. 1994,
Alland D., *et al.*, N Engl J Med. 1994,
J Infect Dis. 2005

Risk Factor for Recent Transmission

Homeless people

Prison

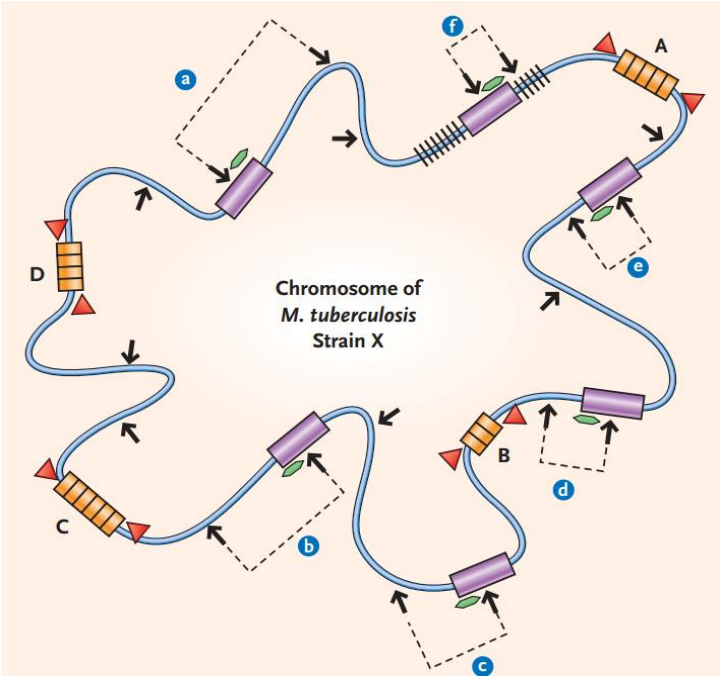
School and Kindergarten

Nursing home

Genotyping Methods

Traditional Genotyping Methods

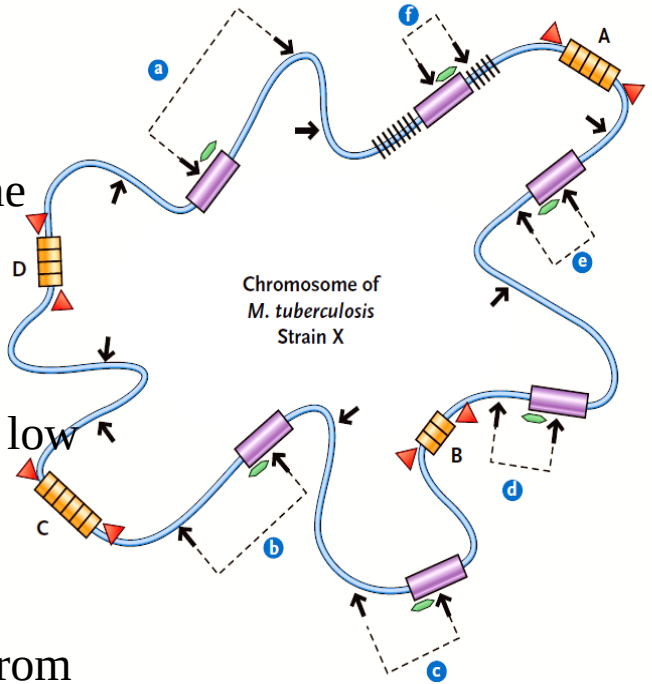
- IS611-RFLP (Restriction – fragment-length polymorphism)
- Spoligotyping
- MIRU-VNTR (Mycobacterial interspersed repeat units-Variable Number Tandem Repeat)

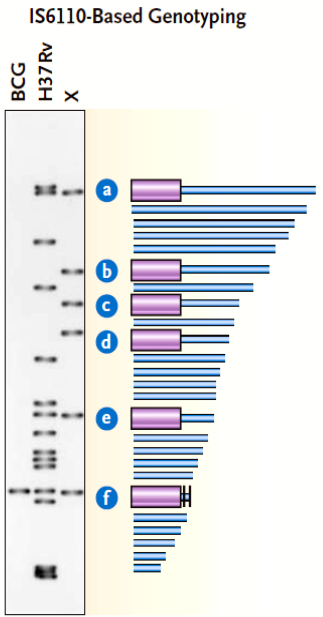


Barnes P. & Cave D., N Engl J Med. 2003

IS*6110*-RFLP

- Differentiate the Strains based on
  - IS6110 copies
  - Positions of IS*6110* in the genome
- Characteristic of IS6110-RFLP genotyping
  - High discriminatory power
  - But not for the strains with no or low copy number of IS6110
  - Needs more DNA sample and complicated operation
  - Difficult to compare the results from different lab

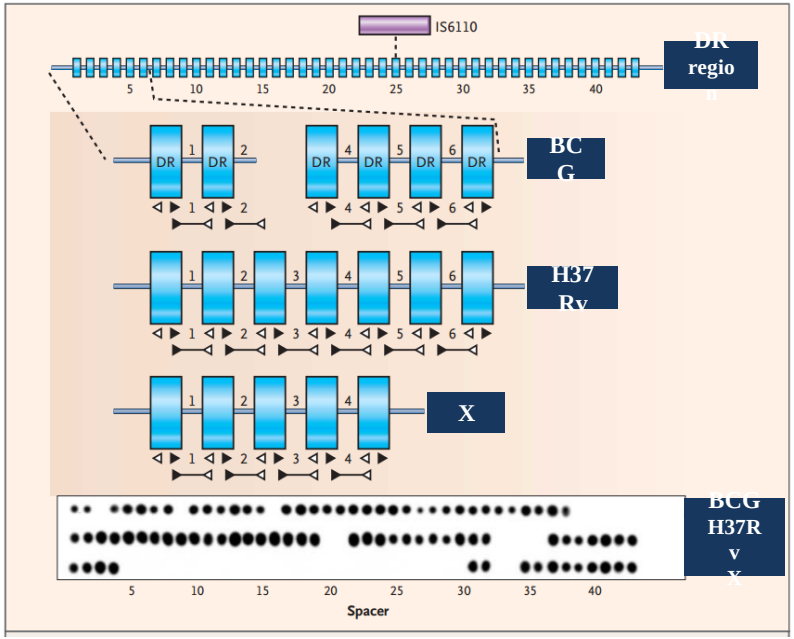




Barnes P. & Cave D., N Engl J Med. 2003

Spoligotyping

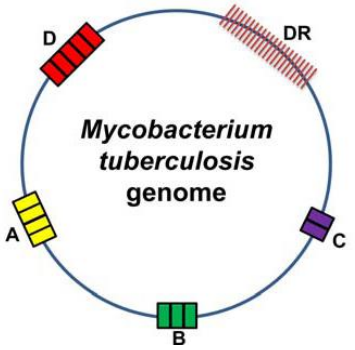
- Differentiate the Strains based on
  - 43 of DR(direct-repeat) present or absent
- Characteristic of spoligotyping
  - Easier and faster
  - Digitalized results and easy for inter-laboratory comparison
  - low discriminatory power

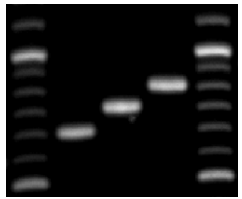


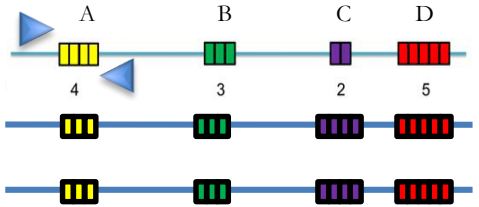
Barnes P. & Cave D., N Engl J Med. 2003

MIRU-VNTR

- Differentiate the Strains based on
  - Copies of the tandem repeated
- Characteristic of MIRU-VNTR
  - High discriminatory power based on locus used (12, 16, 24 loci)
  - Easier and faster
  - Digitalized results and easy for inter-laboratory comparison
  - VNTR-24 is recommended by USA CDC







	A	B	C	D
Strain 1	4	3	2	5
Strain 2	3	3	4	5
Strain 3	3	3	4	5

Whole Genome Sequencing (WGS)

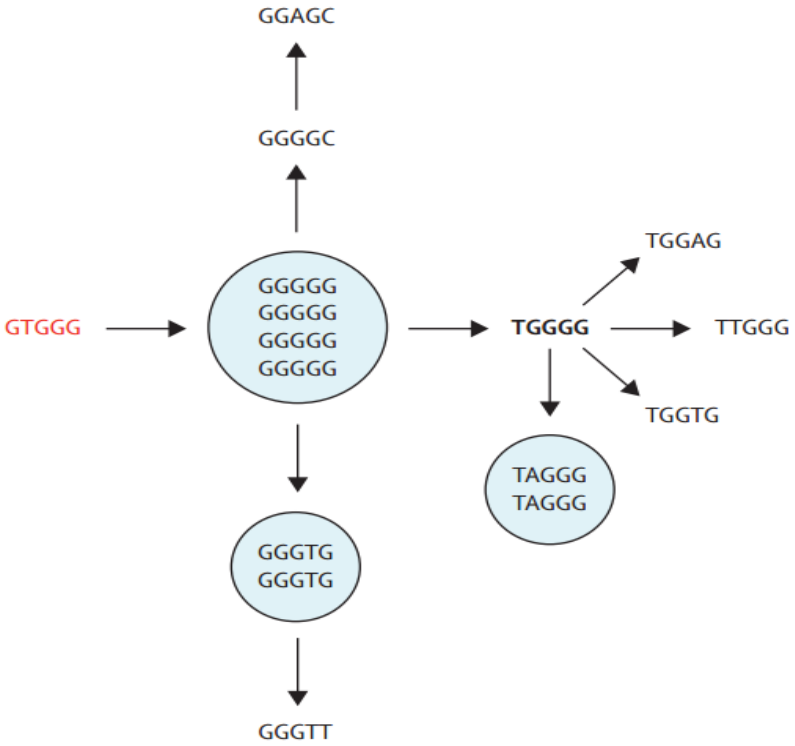
- WGS is an increasingly accessible and affordable for *M. tuberculosis* typing
  - The cost is getting cheaper
  - Differentiate the Strains based on the SNP (single nucleotide polymorphism) on entire genome, the mutation rate about 0.3-0.5 SNP per year per genome
- Characteristic of WGS
  - The highest of discriminatory power
  - Great increased the precision of genotyping and contact tracing
  - Elucidated the Mutation rate, drug resistance and phylogeny and evolution of *M. tuberculosis*

WGS's Two Characteristics

- Traditional genotyping methods: inaccurate when tracing transmission routs
- WGS: tracing transmission routs by delineating the order of nucleotide changes

  - The reverse mutation of M. tuberculosis rarely happens

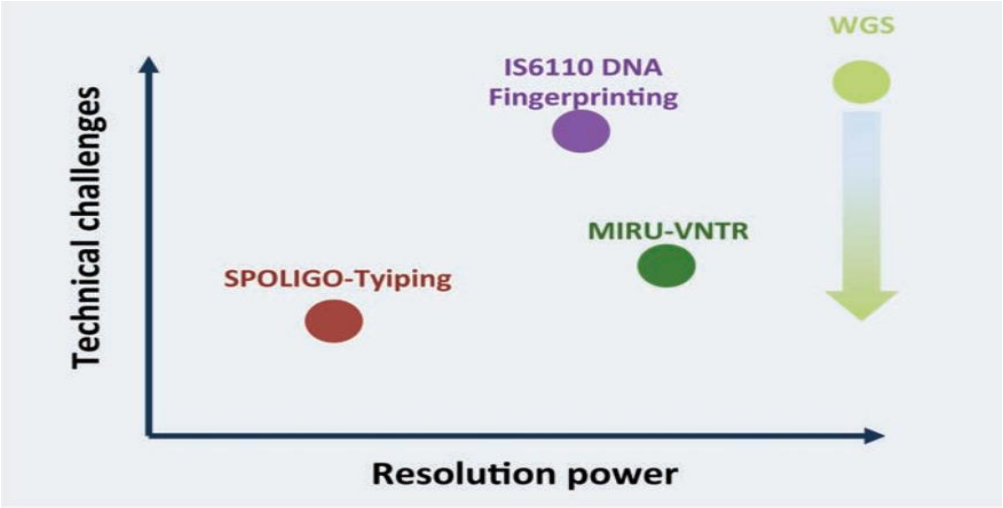
  - It is not common that different strains of *M. tuberculosis* have same mutations



Takiff H.& Feo O., Lancet Infect Dis 2015

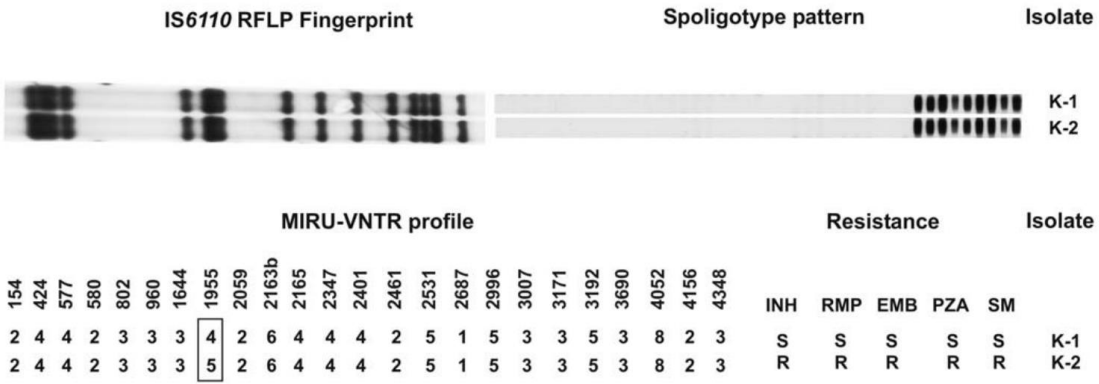
WGS Vs Traditional Genotyping

- Traditional genotyping methods: including less than 1% of the genome
- WGS: including about 90-95% of the genome

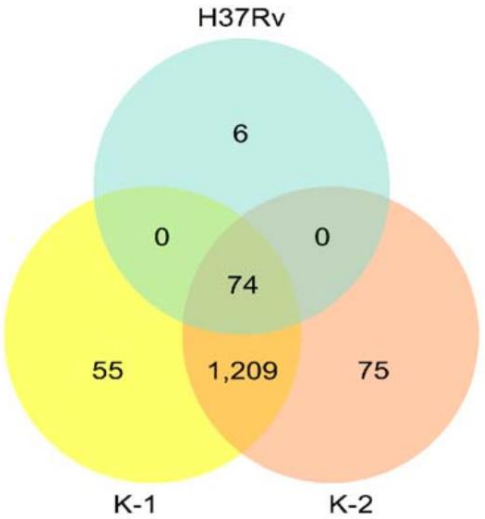


Cannas A., et al., Infect Dis Rep. 2016

WGS Vs Traditional Genotyping



All traditional DNA fingerprints for both isolates were isogenic, with the exception of the MIRU-VNTR locus 1955

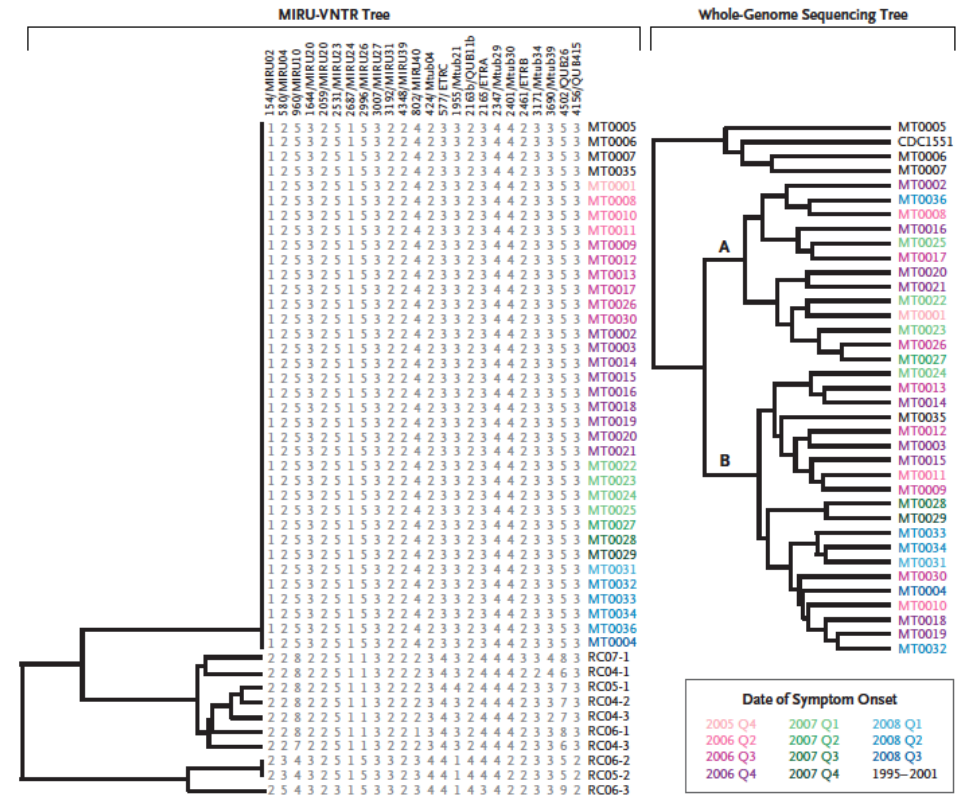


WGS shows substantial genomic diversity

- K-1 and K-2 are two clinical isolates, belong to Beijing K-family
- Both isolates were part of a large cluster of closely related organisms

Niemann S., *et al.*, PLoS One. 2009

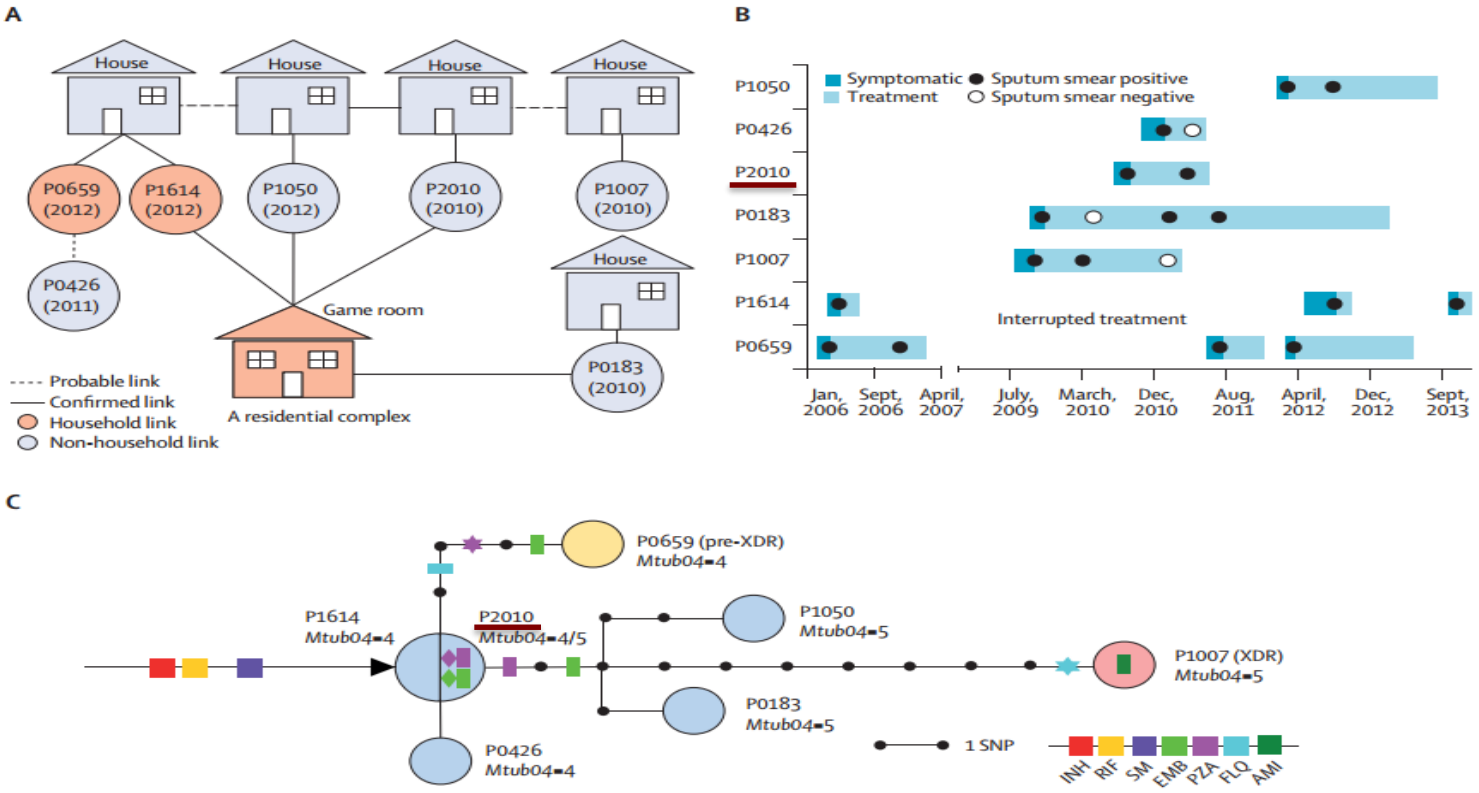
Describes Outbreaks More Accurately



- An outbreak of TB occurred over 3 year in Canada
  - MIRU-VNTR genotyping suggested the outbreak was clonal
  - WGS data revealed two genetically distinct lineages and suggesting two concomitant outbreaks

Gardy J., et al., N Engl J Med. 2011

Disclose Transmission More Precisely



Yang C., et al., Lancet Infect Dis 2017

Estimate the Mutation Rate

MTBC markers	Mutation rate estimates	Homoplasy index	Applications
Spoligotype	2.0×10^{-2}–9.0×10^{-2} per year[a]	Yes/relatively high	Preliminary screen of genetic diversity, excluding possible laboratory contaminations
Regions of difference/targeted interrogation of phylogenetic SNPs	Not determined	No	(Sub-)lineage classification
IS*6110* sequence	0.0135 changes per copy per year[b]	Yes/low to moderate (genotypes with low numbers of IS6110 copies)	(Local) molecular epidemiological investigations, differentiation between relapse/re-infection
	0.0161 changes per copy per year[c]		
MIRU-VNTR loci	7.0×10^{-4}–1.5×10^{-2} per locus per year[a]	Yes/moderate	(Global) molecular epidemiological investigations, differentiation between relapse/re-infection, screening for potential TB transmission clusters, screening for lineage identification
	3.3×10^{-4}–9.8×10^{-3} per locus per year[d]		
	10^{-4} per locus per year[e]		
	2.5×10^{-3}–2.6×10^{-2} per locus per year[f]		
	1.2×10^{-3}–2.6×10^{-3} per locus per year[g]		

Estimate the Mutation Rate

WGS/genome wide SNP analysis	0.24–0.34 SNPs per genome per year[h]	No/very low	Molecular epidemiological investigations, differentiation between relapse/re-infection, high resolution outbreak investigation, drug resistance prediction, robust phylogenetic analysis
	0.26–0.66 SNPs per genome per year[i]		
	0.3–0.5 SNPs per genome per year[j,k]		
	0.3–0.7 SNPs per genome per year[l]		
	0.93–1.56 SNPs per genome per year[g]		
	0.13–0.27 SNPs per genome per year[m]		
	0.0073–0.013 SNPs per genome per year[n] (long-term rate)		

References are as follows: [a]Reyes and Tanaka (2010), [b]Tanaka and Rosenberg (2001), [c]Rosenberg et al. (2003), [d]Ragheb et al. (2013), [e]Wirth et al. (2008), [f]Aandahl et al. (2012), [g]Eldholm et al. (2016), [h]Eldholm et al. (2015), [i]Roetzer et al. (2013), [j]Ford et al. (2011), [k]Ford et al. (2013), [l]Walker et al. (2013a),[m]Bos et al. (2014), and [n]Comas et al. (2013)

Gagneux S., Advances in Experimental Medicine and Biology, Vol. 1019

Key points should be paid attention

Two Caveats to MolEpi

- Require the population based study

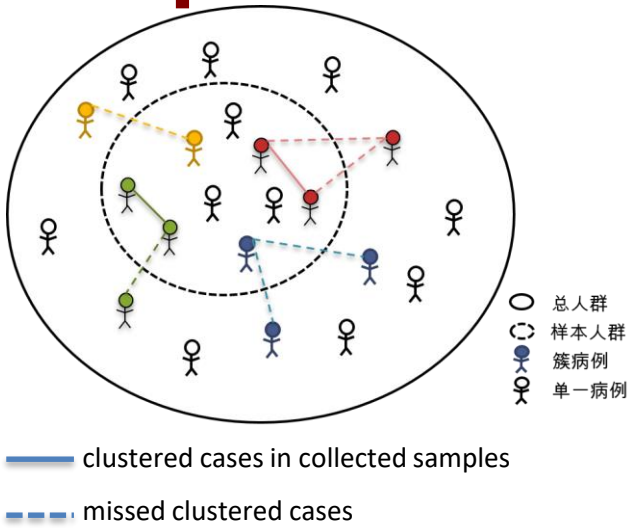
  - To get accurate clustered rate requires the evaluation of a large percentage of TB cases in the population and over a long period.

- Require the epidemiologic information

  - Careful to interpreter the genotyping data

  - Same genotyping may not reflect recent transmission

  - Is WGS data better?



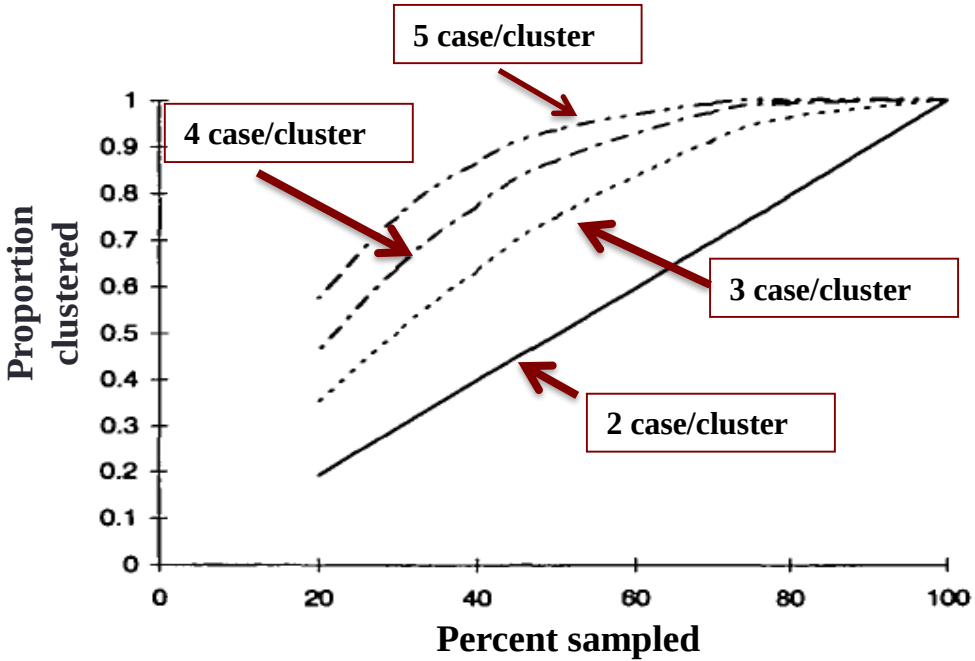
$$\text{Cluster Rate} = \frac{n}{N} \text{ or } \frac{n-1}{N}$$

n = No. of clustered isolates

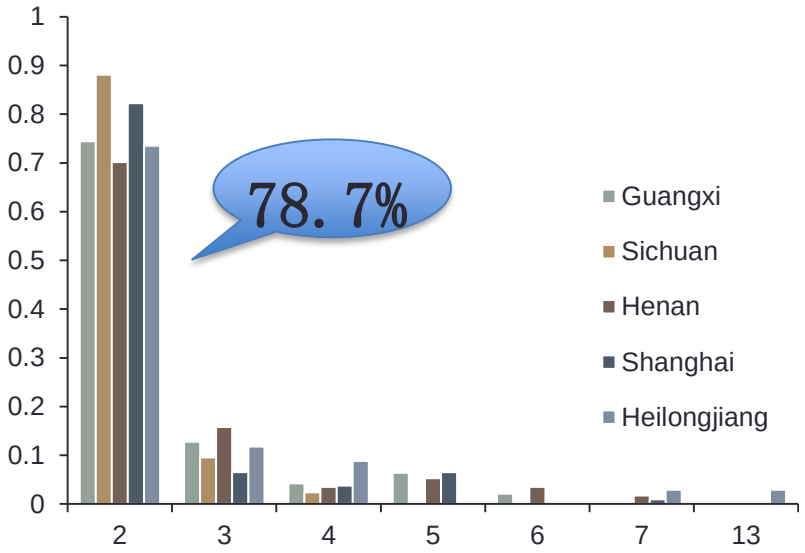
N = No. of total of isolates

1 = No. of cluster

Estimates of Recent Transmission Rate



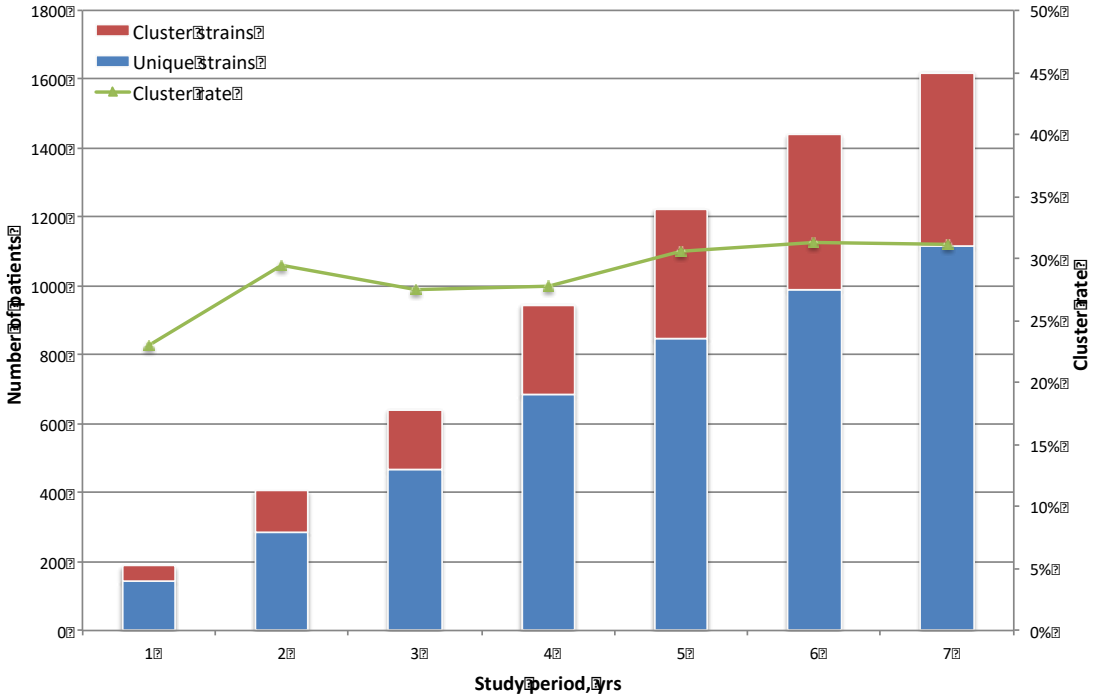
Simulation model estimates of the influence of sampling proportion, “n” method, 100 samples



Glynn JR, et al *Am J Epidemiol* 1999

Estimates of Recent Transmission Rate

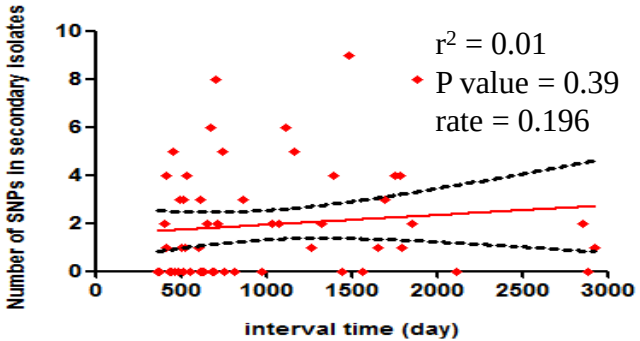
- The longer time leads to increased cluster rate



Unpublished data

How to Define the Identical Genotype?

- Depends on genotyping methods, WGS might be the “gold standard”
  - An artificial concept and not absolute, 5 SNP Or more SNP?
  - SNPs accumulation was not linearly correlated with time in short time interval
- The change of molecular markers significantly affect the threshold
  - IS6110-RFLP half life 3.2 years; VNTR mutation rate:$10^{-2.06}$ per locus per year
  - SNP mutation rate: 0.3-0.5 SNP per year per genome



Accumulated SNP Vs. Time

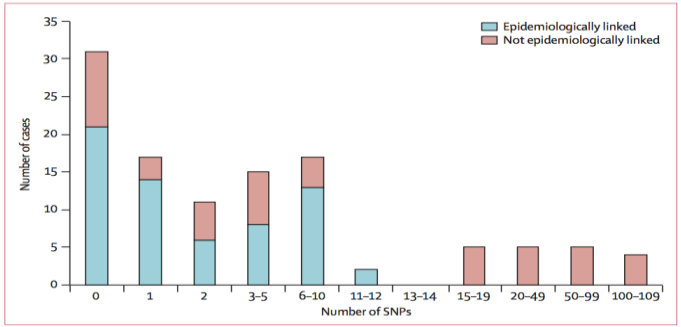


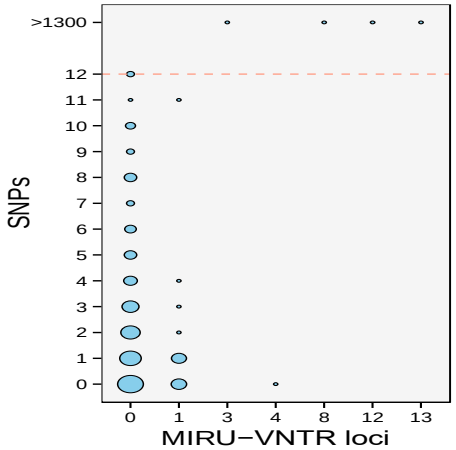
Figure 2: **Distribution of the number of SNPs in isolates from the closest multidrug-resistant tuberculosis cases within a cluster**
SNP=single nucleotide polymorphism.

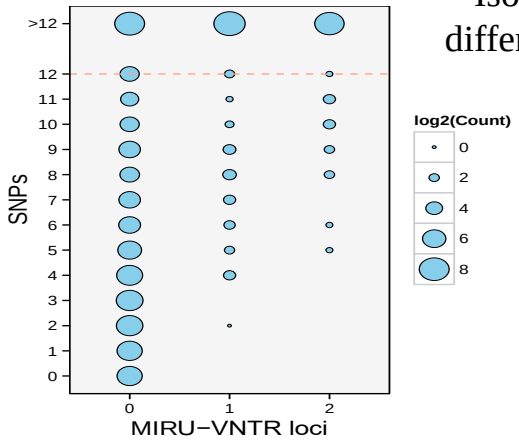
Yang C., et al. Lancet Infect Dis. 2017

How to Define the Identical Genotype

- VNTR genotype define: 1 locus different is same or not?
  - Isolates from the same patient: might be the same
  - Isolates from different patient: might be different

Isolates from same patient



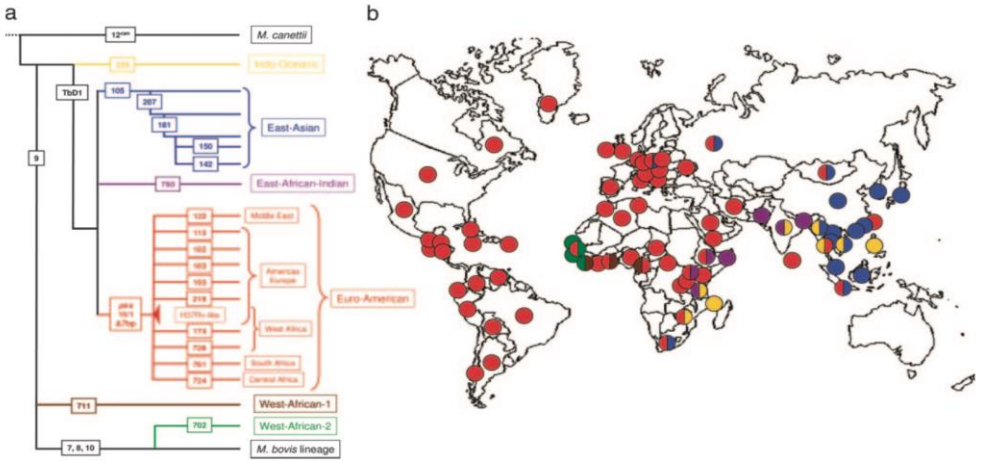


Isolates from different patients

SNP distance	Within patient	Between patients	
		United Kindom*	Songjiang,Shanghai
SNP distance <= 12	20(100%)	46(11.3%)	13(15.1%)
SNP distance > 12	0(0%)	360(88.7%)	73(84.9%)

Unpublished data

Why Need to Develop an Optimal VNTR Set for Local?

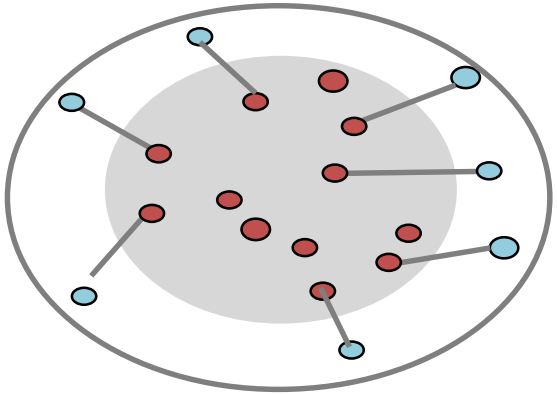


Method	Clusters	HGI
VNTR-15	6	0.99
VNTR-24	6	0.992
IS6110-RFLP	3	0.999

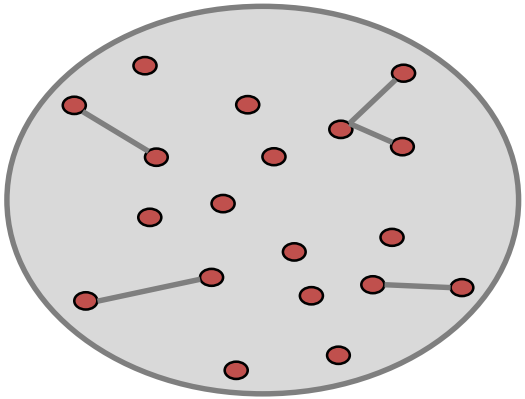
- The population structure of *Mycobacterium tuberculosis* varies in different regions
- Beijing strains are genetically highly similar, which leads to limited discriminatory power of VNTR-15/24
- Reducing the number of loci tested is good for application

Sebastian et al. Proc Natl Acad Sci USA. 2006
A Dong Shen et al. J Clin Microbiol. 2008

How to Develop an Optimal VNTR Set



Collected strains
Missed strains
Clustered



Hospital based study
MIRU-12 HGI=0.99

$$\mathbf{HGI} = 1 - \frac{1}{N(N-1)} \sum_{j=1}^{s} n_j(n_j - 1)$$

Population based study
MIRU-12 HGI=0.87

- Population based sample collection reflect the true HGI value
- Hospital based or random selected isolates will missed clustered isolates, which result in overestimate of discriminatory power

Several Examples of MolEpi

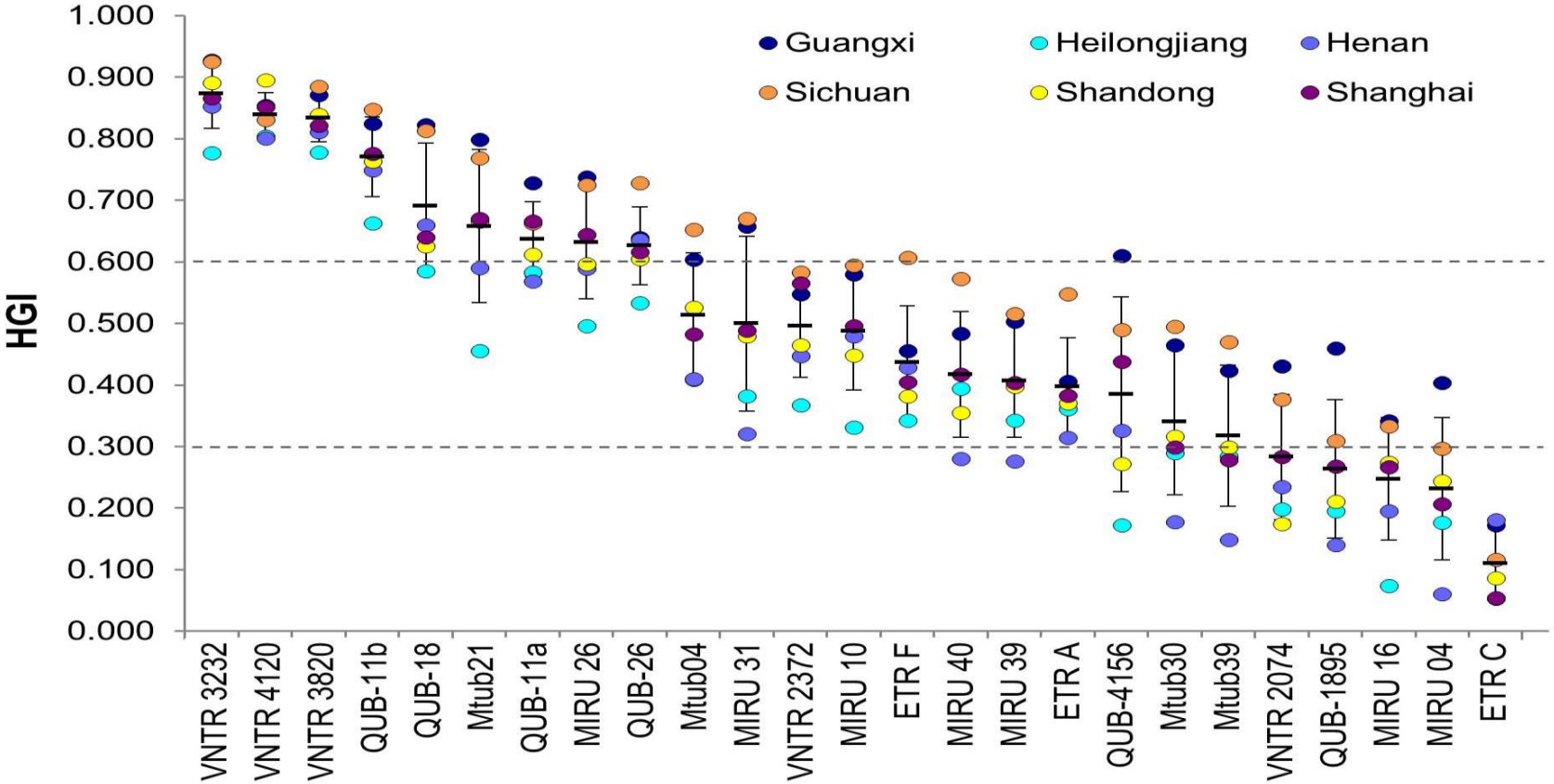
Development of VNTR Set in China

- VNTR Genotyping
  - MIRU12
  - VNTR15
  - VNTR24，VNTR 24+4
- VNTR in China
  - not standardized, many different methods were used,MIRU 12, VNTR15, VNTR24 et al.
- Objective: to develop a VNTR typing method that can achieve high resolution with a small number of loci

Population-based Collections of the Isolates

Study fields	Total	Beijing genotype	%
Sichun	216	115	53
Guangxi	176	109	62
Shanghai	396	314	79
Shandong	206	160	78
Henan	197	177	90
Heilongjiang	184	159	86
Total	1375	1034	75

Discriminatory Powers of 25 VNTR Loci



Optimal VNTR Combinations

No. of loci (no. of possible combinations)	No. of combinations with HGI higher than VNTR-15	Optimal combinations with highest the HGI[a]	HGI (mean ± STDEV)		
			All strains	Non-Beijing strains	Beijing strains
2 (190)	0	1-5	0.900±0.041	0.852±0.044	0.951±0.015
3 (1140)	0	1-2-5	0.948±0.027	0.917±0.030	0.973±0.014
4 (4845)	0	1-2-4-5	0.966±0.025	0.947±0.031	0.980±0.014
5 (15504)	0	1-2-3-4-5	0.974±0.022	0.961±0.027	0.984±0.012
6 (38760)	0	1-2-3-4-5-8	0.980±0.020	0.970±0.025	0.988±0.010
7 (77520)	0	1-2-3-4-5-6-8	0.984±0.017	0.977±0.022	0.991±0.005
8 (125970)	0	1-2-3-4-5-6-8-12	0.987±0.013	0.981±0.016	0.992±0.006
9 (167960)	8	**1-2-3-4-5-6-7-8-10**	0.989±0.011	0.985±0.014	0.993±0.005
10 (184756)	219	1-2-3-4-5-6-7-8-10-12	0.991±0.008	0.988±0.010	0.993±0.005
11 (167960)	1506	1-2-3-4-5-6-7-8-10-12-17	0.992±0.008	0.989±0.010	0.993±0.005
12 (125970)	4864	1-2-3-4-5-6-7-8-10-12-14-17	0.993±0.006	0.990±0.008	0.993±0.005
13 (77520)	8836	1-2-3-4-5-6-7-8-10-12-14-15-17	0.994±0.006	0.991±0.008	0.993±0.005
14 (38760)	9513	1-2-3-4-5-6-7-8-9-10-12-14-15-17	0.994±0.006	0.991±0.008	0.993±0.005
15 (15504)	6599	1-2-3-4-5-6-7-8-9-10-12-14-15-17-18	0.994±0.006	0.992±0.007	0.994±0.005
16 (4845)	3081	1-2-3-4-5-6-7-8-9-10-12-14-15-16-17-18	0.994±0.006	0.992±0.008	0.994±0.006
17 (1140)	941	1-2-3-4-5-6-7-8-9-10-12-14-15-16-17-18-20	0.995±0.006	0.992±0.008	0.994±0.006
18 (190)	181	1-2-3-4-5-6-7-8-9-10-11-12-14-15-16-17-18-20	0.995±0.006	0.992±0.008	0.994±0.006
19 (20)	20	1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18-20	0.995±0.006	0.992±0.008	0.994±0.006
20 (1)	1	1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18-19-20	0.995±0.006	0.993±0.008	0.994±0.006

VNTR (9+3) Genotyping for China

- Optimized 9-locus (VNTR-9) plus 3 hypervariable loci (HV-3) as standard for nationwide genotyping of MTB in China
  - VNTR-9 can be used as the first-line method for large-scale genotyping
  - HV-3 can be used to subtype the VNTR-9 clustered strains to identify the transmission in local

簇(成簇菌株数)	河南	黑龙江	广西	上海	四川
VNTR “24 +4”	10(21)	9(20)	5(10)	23(49)	5(10)
VNTR “9 +3”	11(23)	14(33)	6(12)	23(49)	5(10)
VNTR-24	23(68)	21(73)	15(37)	30(77)	14(30)
VNTR-15	25(76)	26(93)	16(44)	31(86)	23(50)
VNTR-9	25(78)	23(87)	18(50)	32(93)	23(50)
VNTR-L15	27(107)	22(103)	21(69)	35(117)	28(83)
MIRU-12	25(142)	22(123)	21(96)	34(154)	28(125)

VNTR (9+3) Vs. VNTR (24+4)

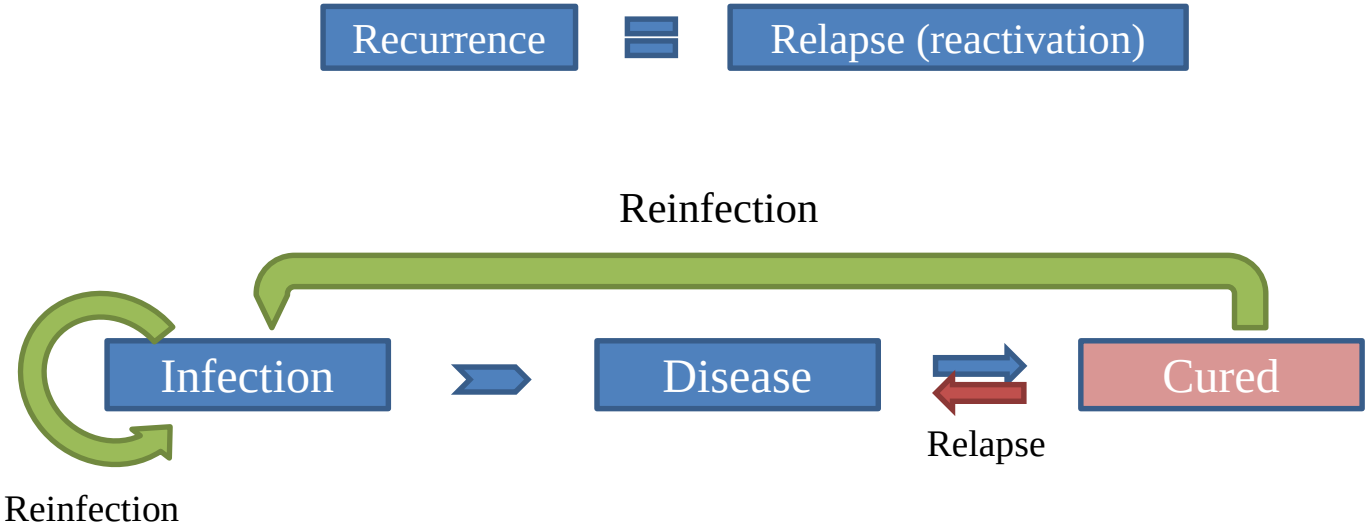
株数	黑龙江	广西	上海	四川	河南	总数
菌株总数	163	137	202	188	161	851
成簇菌株数[a]	18	10	47	8	21	104
单基因型菌株数[a]	128	125	151	176	138	718
一致菌株数	146	135	198	184	159	822
一致率(%)	89.6	98.5	98.0	97.8	98.8	96.6

Luo T., *et al.*, PLoS One. 2009
Liu M., et al., Chin J Tuberc Respir Dis,2015

Recurrent Tuberculosis

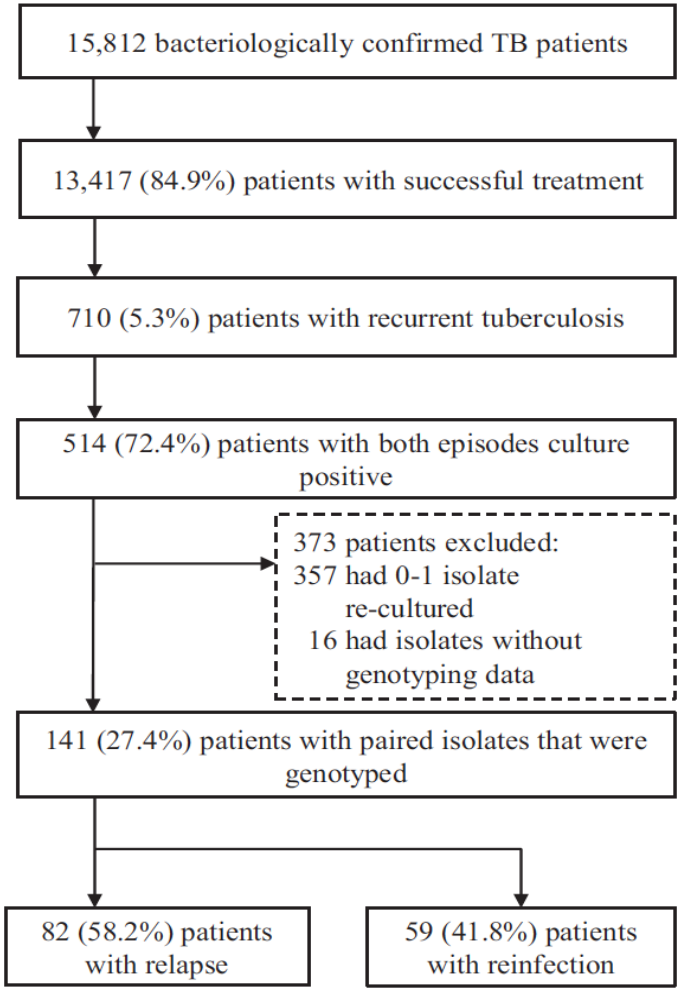
-reinfection or relapse ?

- 5-20% cases are expected to be recurrent even cured by DOTS
- Dogma:



Recurrent Tuberculosis in Shanghai:
-reinfection or relapse ?

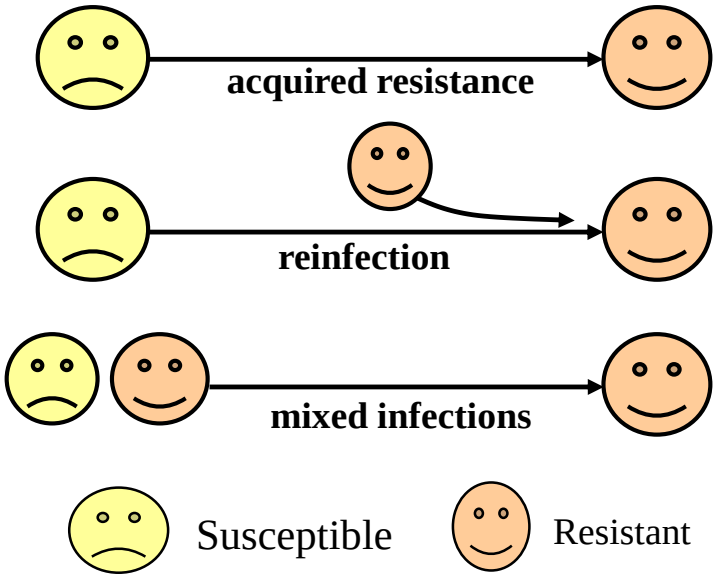
- Retrospective, population-based analysis of recurrent tuberculosis from 2000 to 2012 in Shanghai city, China
- HIV Prevalence in Shanghai is low
- Compared the DNA genotypes between isolates of initial episode with those of subsequent episode.
- **42%** patients with paired isolates had unmatched genotype patterns (re-infection)



Shen X., et al., Tuberculosis,2017

Transmitted or Acquired DR among Treated Patients?

- Dogma: Treated patients have acquired drug resistance
- Real acquired resistance：
  Resistance mutations in bacterial genome result in acquired resistance
- Resistant patients with TB history may come from：
  - Real acquired resistance
  - Exogenous reinfection
  - Mixed infection



Are Resistant Patients with TB History Really Acquired Resistance?

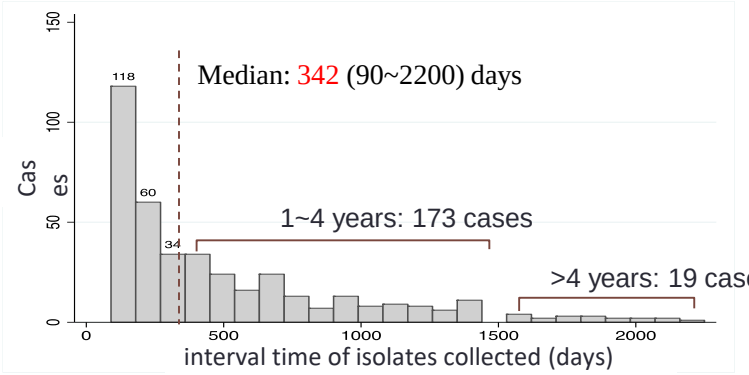
TB cases during 2009~2015 in Shanghai

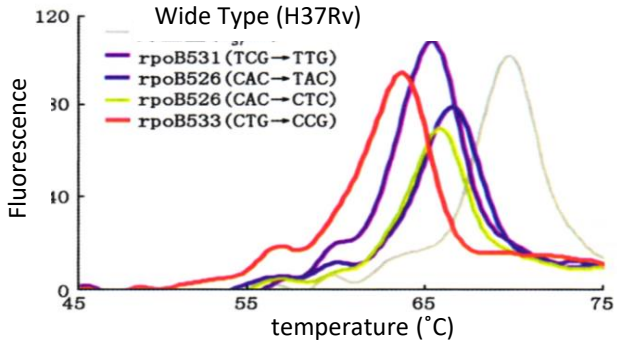
Sample duration of paired sputum from individual case ≥ 90 ds: 390 cases (780 isolates)

molecular DST

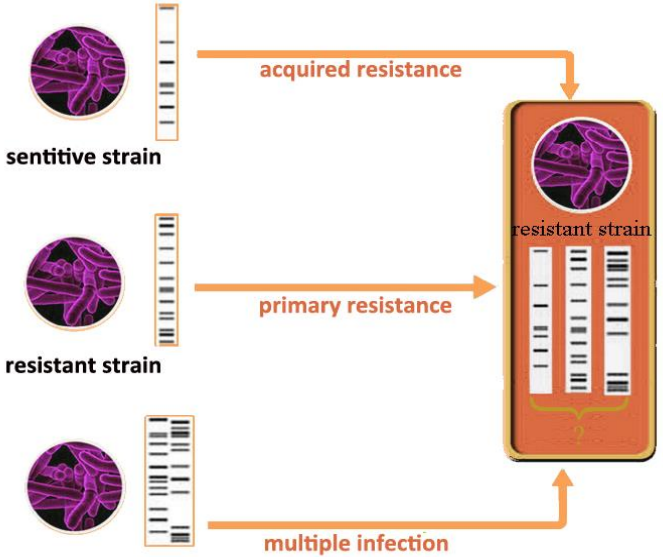
decreased resistance	increased resistance	identical resistance
N= 39 (10%)	N= 81 (20.8%)	N= 270 (69.2%)

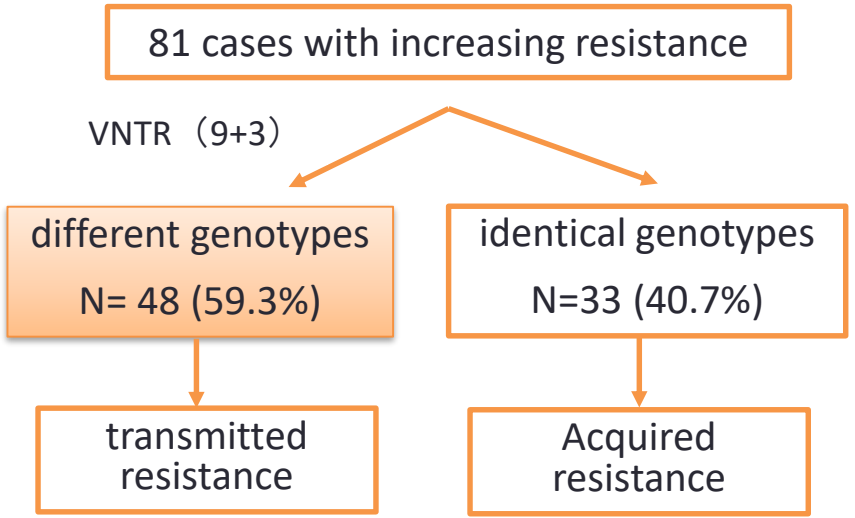
VNTR(9+3) genotyping, WGS
Identical genotypes –acquired resistance
Different genotypes – reinfection/mixed infections





60% Treated Resistant Patients were Transmitted Resistance



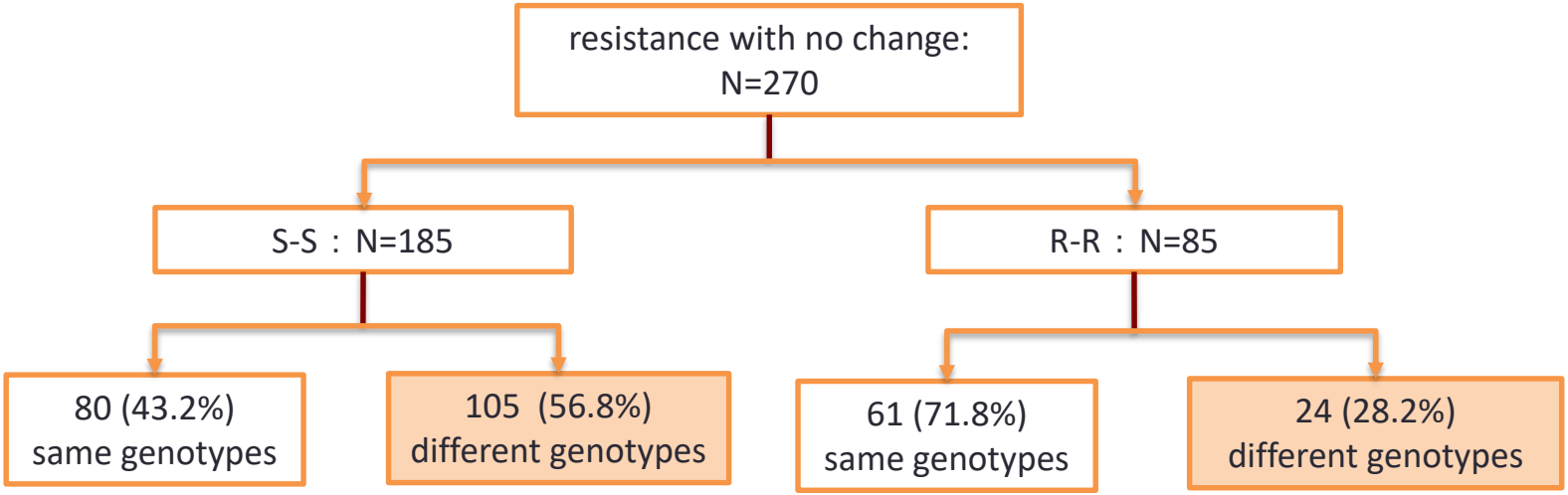


- Increasing resistance among treated mostly (~60%) caused by transmission
- 84% (27/32) resistance was transmitted resistance

To be published

Li X., et al. Journal of Infect Dis, 2007

50% Treated Patients were Reinfection

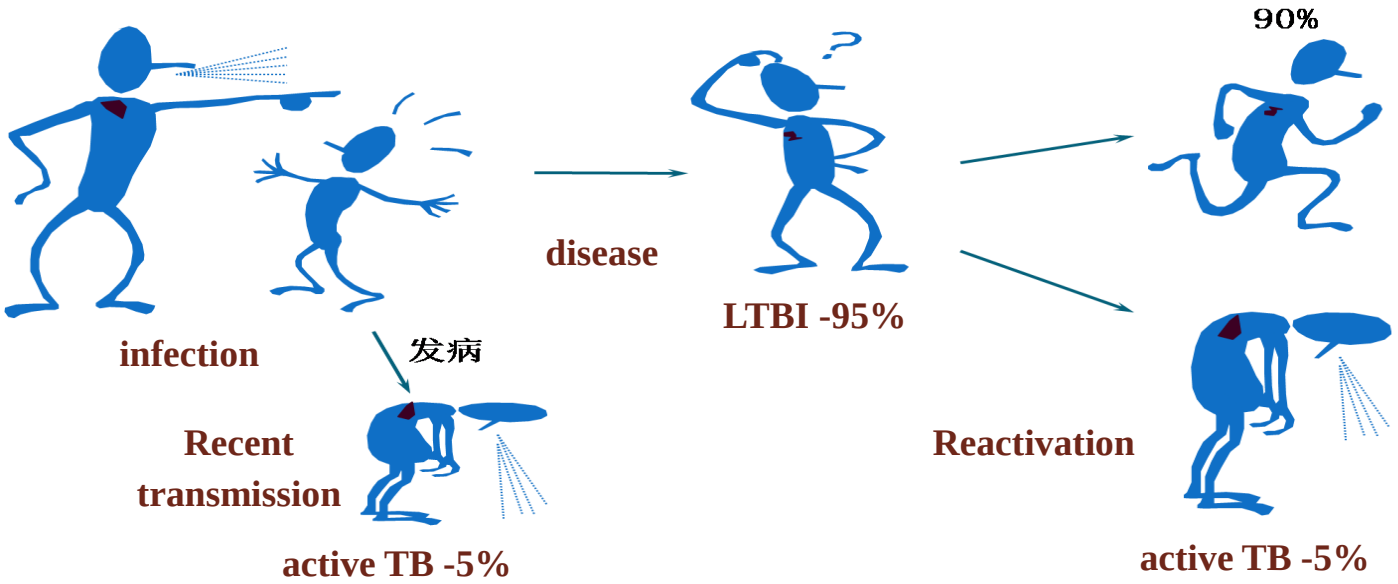


- Among patients whose resistance didn't change during treatment, 50% were reinfected with another strains, indicating serious transmission.

to be published

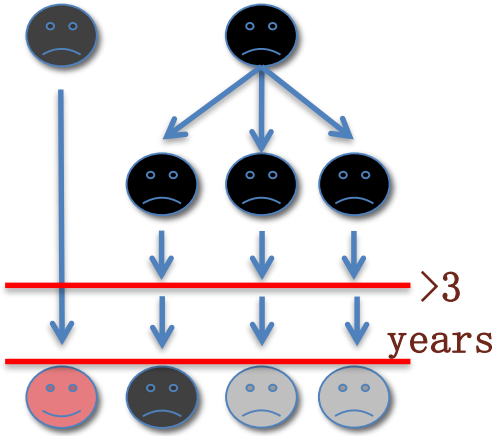
Recent Transmission of TB

- Recent transmission: develop disease shortly (1-2ys) after infection
- Reactivation: develop disease far from infection

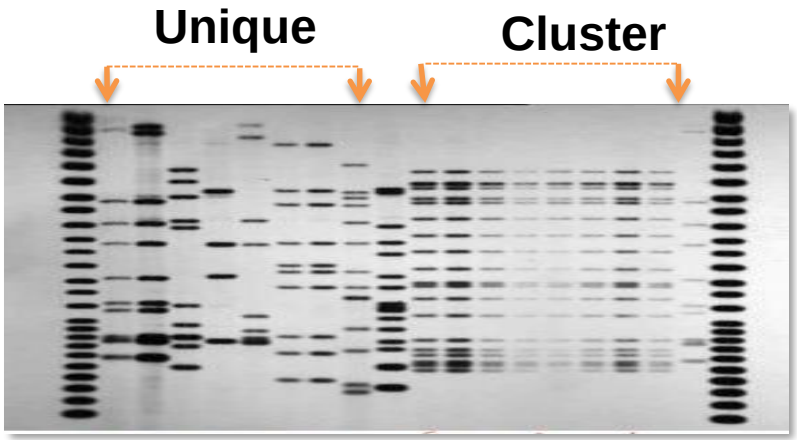


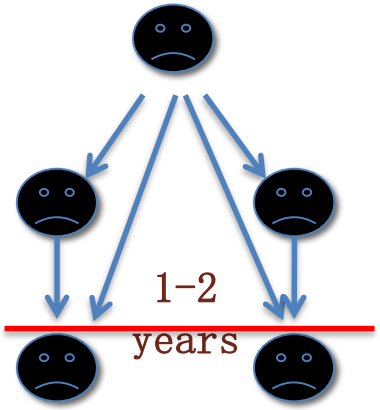
How to Differentiate Recent Transmission?

- Molecular Epidemiology assumption
  - Identical genotype (Cluster strains) - recent transmission
  - Unique genotype – reactivation
  - Genotyping: IS6110-RFLP, VNTR, Whole Genome Sequence



remote transmission
different resources



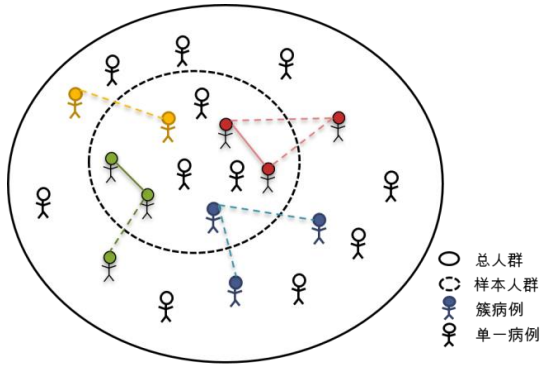


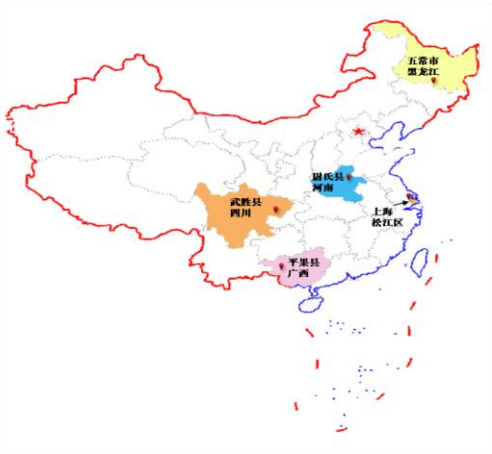
recent
transmission

Study Design

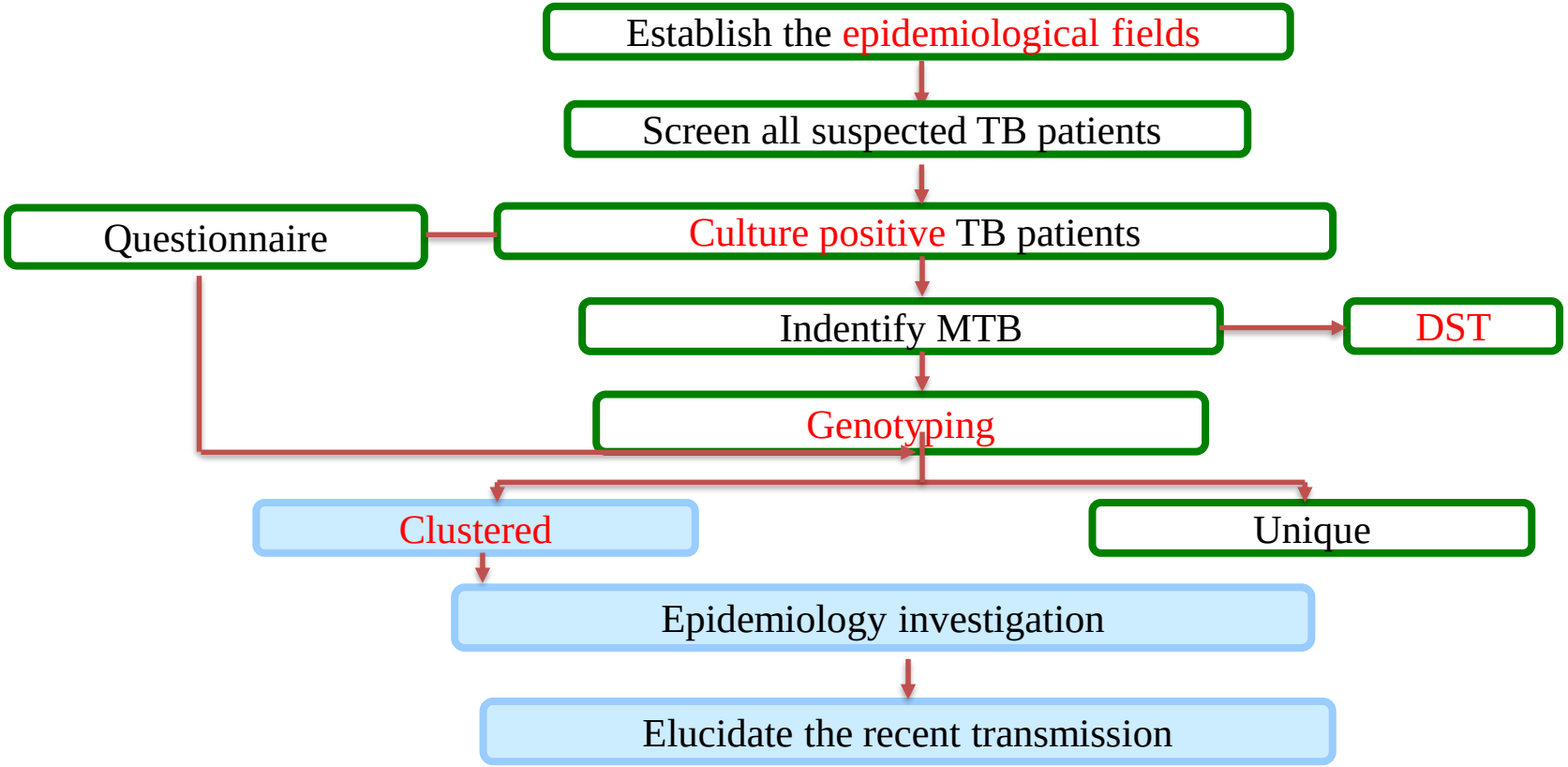
- Population-based prospective study, small scale, full coverage
- 5 sites covering 4 million population
- Represent different location, economic and TB epidemic in China

sites	area (km^2)	population(000)	prevalence (/100 000)
Wuchang, HLJ	**3,756**	**520**	**512**
Weishi, HN	**1,307**	**868**	**497**
Songjiang, SH	**604**	**1 634**	**96**
Wusheng, SC	**966**	**838**	**544**
Pingguo, GX	**2,473**	**457**	**477**





Study Strategy



Established of Field Sites

Sputum microscopy

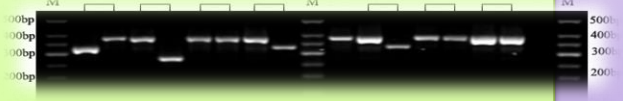
Epidemiologic investigation

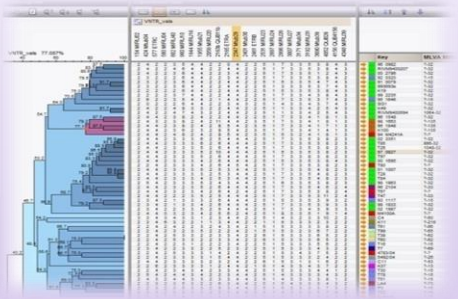
Sputum culture

DST

Internet-based database

VNTR genotyping





Data analysis

Staff management

Quality control

County-level lab

Provincial lab

Fudan University

Sample Collection

- From June 2009 to June 2012, 17,905 suspects people were screened for tuberculosis,
- 2274 (12.7%) culture-confirmed patients were diagnosed, most (71.3%) of them were male, with median age of 41 yrs (range 15-93)

Fields	No. of Cases	Male (%)	Median Age, yrs	DR(%)	INH(%)	RIF(%)	MDR(%)
Guangxi	324	78.1	44	14.3%	11.5%	8.1%	5.3%
Sichuan	414	77.2	44	17.0%	14.6%	11.7%	9.2%
Henan	481	76.3	52	11.3%	10.0%	7.3%	6.1%
Shanghai	797	64.0	32	12.1%	11.5%	6.0%	5.1%
Heilongjiang	258	67.8	48	14.0%	10.6%	7.9%	4.4%
Total	2274	71.3	41	13.3%	11.6%	7.8%	6.0%

1/3 TB was Caused by Recent Transmission

- During June 2009 to June 2012, 2238 culture (+) patients were enrolled, most (71.3%) were male, median age 41 ys (15~93)
- Cluster rate = 31%, indicating 31% cases were resulted from recent transmission

Sites	total strains	clustered strains	clusters	cluster rate (%)	cluster size	max cluster size
Wusheng, SC	414	90	42	21.7	2.1	4
Pingguo, GX	324	117	47	36.1	2.6	6
Weishi, HN	481	149	57	30.9	2.6	7
Songjiang, SH	797	255	107	32.0	2.5	7
Wuchang, HLJ	258	94	34	36.0	3.0	13
total	2274	705	287	31.0	2.5	13

Distribution of Cluster Size

- Most (78.7%) of the clusters were comprised of two patients

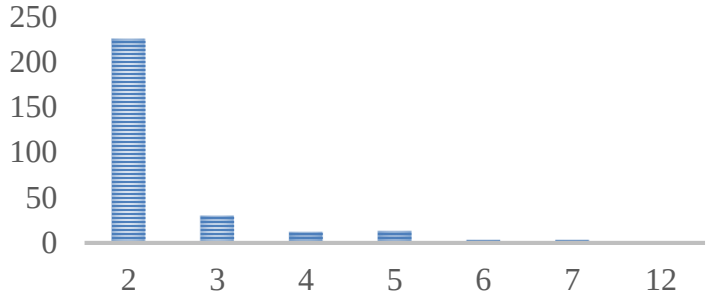
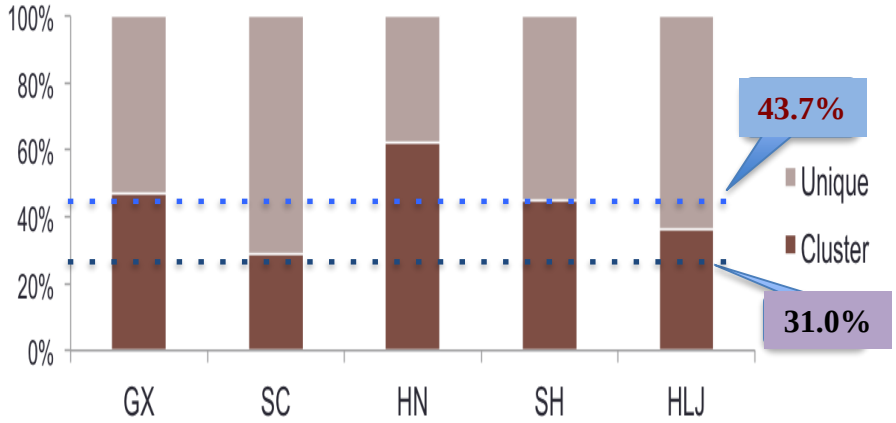


Table 2. Distribution of Genotype Clusters in 5 Study Sites—China, 2009–2012

Study Sites (Province)	Total Cases, No.	Clusters, No.	Clustered Cases[a], No. (%)	Maximum Patients in a Cluster, No.	Clustered Cases With Questionnaire, No.	Clustered Case With Epidemiological Link[b], No. (%)
Guangxi	324	47	117 (36.1)	6	113	46 (40.7)
Sichuan	414	42	90 (21.7)[c]	4	82	14 (17.0)
Henan	481	57	149 (30.9)	7	127	35 (27.6)
Shanghai	797	107	255 (32.0)	7	205	41 (20.0)
Heilongjiang	258	34	94 (36.0)	13	87	28 (32.2)
Total	2274	287	705 (31.0)	13	614	164 (26.7)

MDR-TB is More likely to Transmit

- Cluster rate of MDR-TB is much higher than DS-TB (43.7% vs 31.0%, p=0.005)
- MDR strains transmit easier than susceptible strains (aOR=1.86, 95%CI 1.25-2.63)



Risk factor	Adjusted OR	95%CI	*P* value
MDR-TB	**1.86**	**1.25-2.63**	**0.001**
Beijing Strains	**1.56**	**1.23-2.96**	**<0.001**

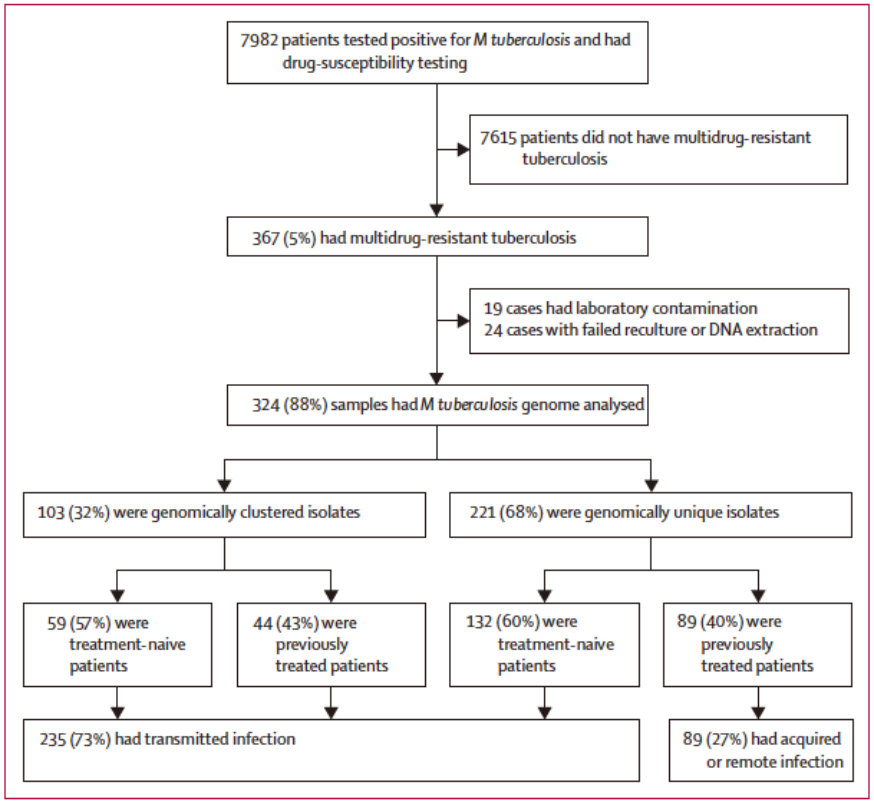
Yang C, et al. Clin Infect Dis 2015

WGS to Analysis the Recent Transmission of MDR-TB

- 2009-2012, all culture (+) TB patients from 31 designated hospitals in Shanghai
- DST: L-J proportion method (RIF & INH)
- Genotyping
  - VNTR (9+3)：differentiate recent transmission except for resistant strains
  - WGS of clustered isolates explains recent transmission in detail

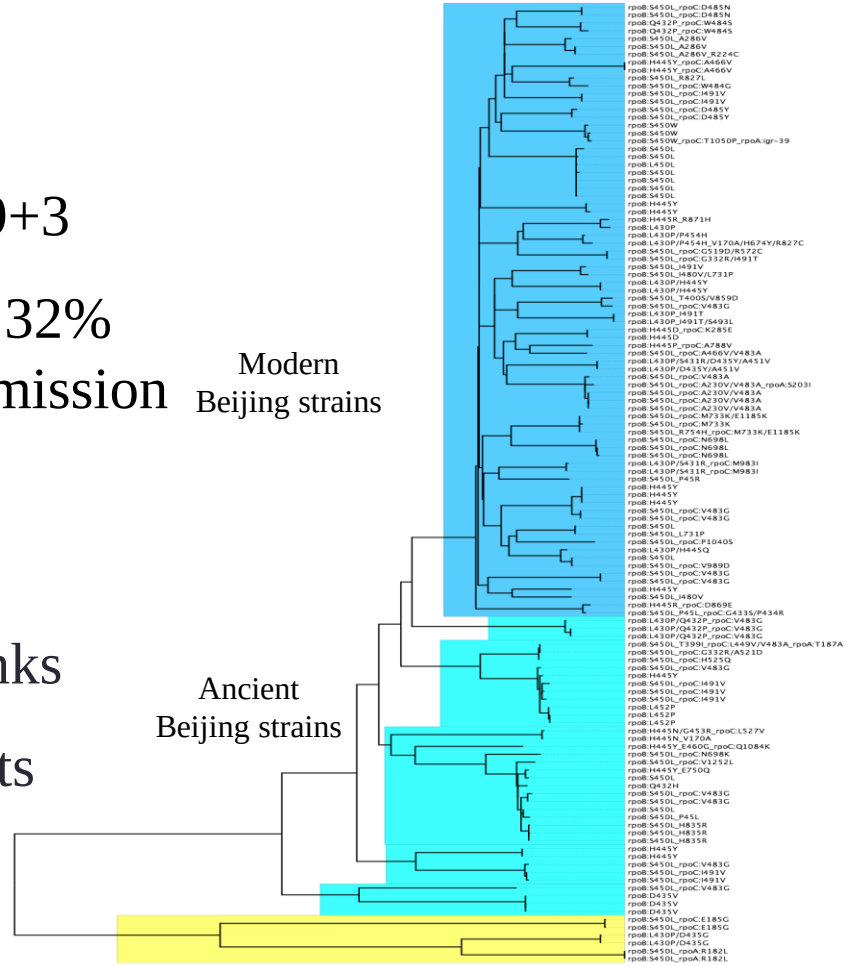
Primary Outcomes

- During 2009-2012, 7982 isolates collected
- 367 (4.6%, 95%CI 4.1-5.1) were MDR-TB
- 60% were new cases
- 73% male, median age 39 ys (16-88 ys)



WGS Analysis

- 125 (38.6%) were clustered by VNTR9+3
- WGS of 122 VNTR-clustered isolates, 32% (103/324) were confirmed recent transmission with a cutpoint of 12 SNPs
- 38 clusters with 2-8 cases
- 69% (64/93) clustered cases had epi-links
- 43% (44/103) retreated resistant patients resulted from transmission

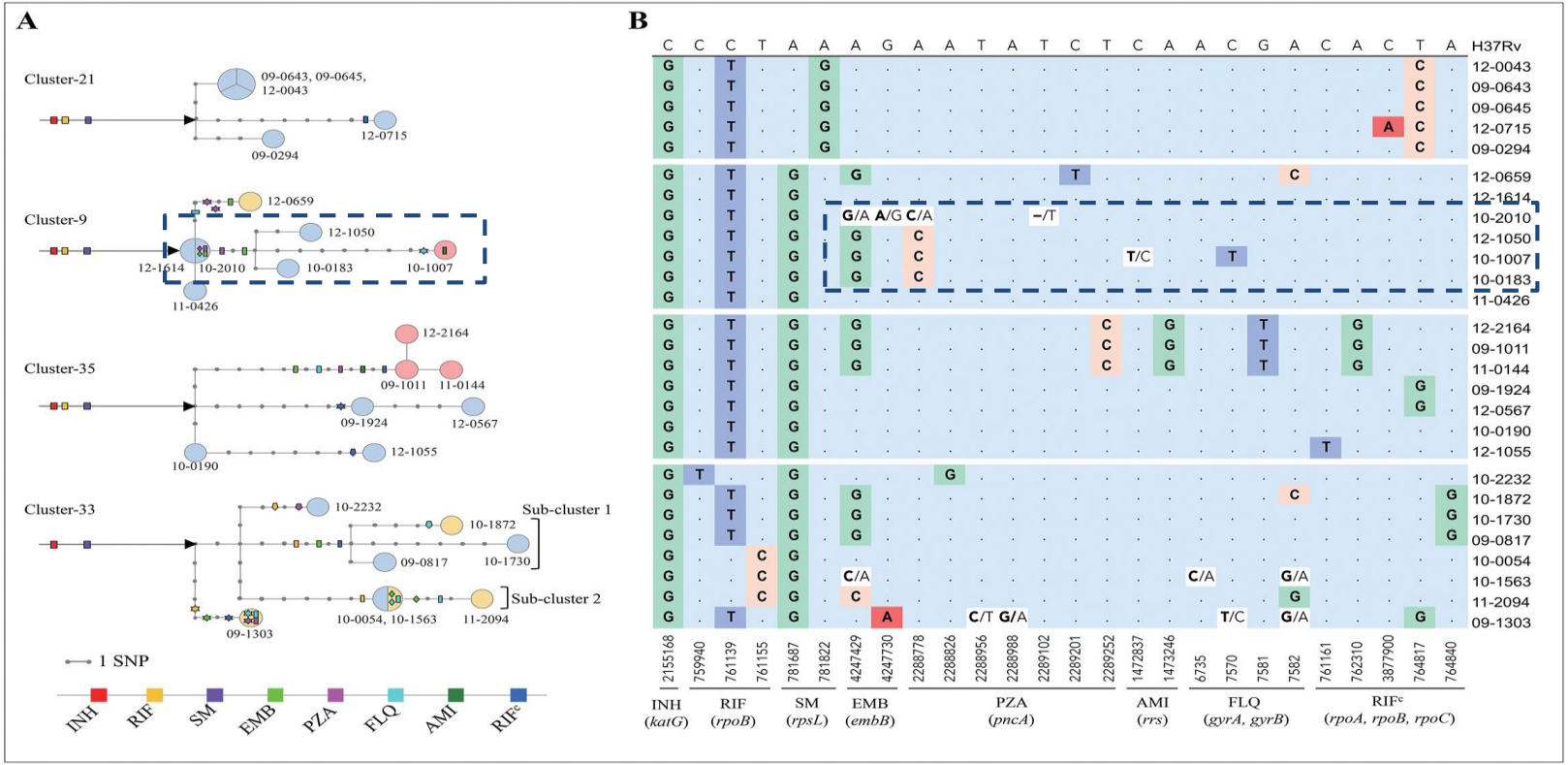


Risk Factors of Recent Transmission

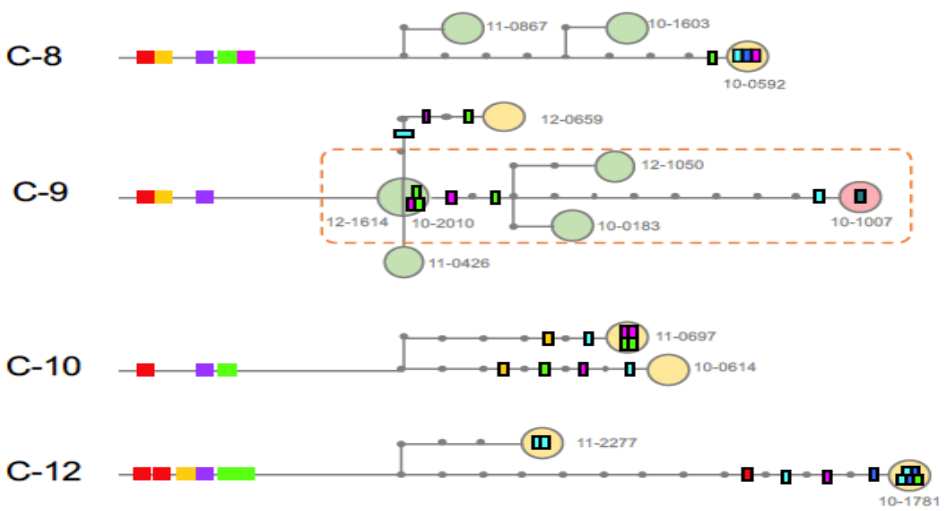
- Diagnosis delay (>2 months), elderly
- No related to gender, TB history, smear(+)
- Public entertainment or consumer places like card rooms, community markets were hotspots for transmission

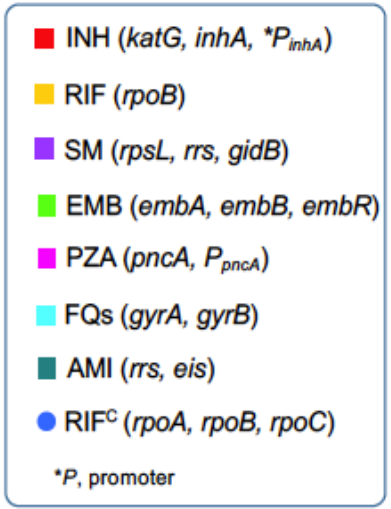
Factors	aOR*	95%CI	p value
diagnosis delay (≥2 ms)	2.29	1.19-4.07	0.005
45-64 ys	2.15	1.18-3.90	0.009
≥65 ys	3.18	1.36-7.41	0.004

Tracking the Transmission of MDR



Accumulation of New Mutations during Transmission

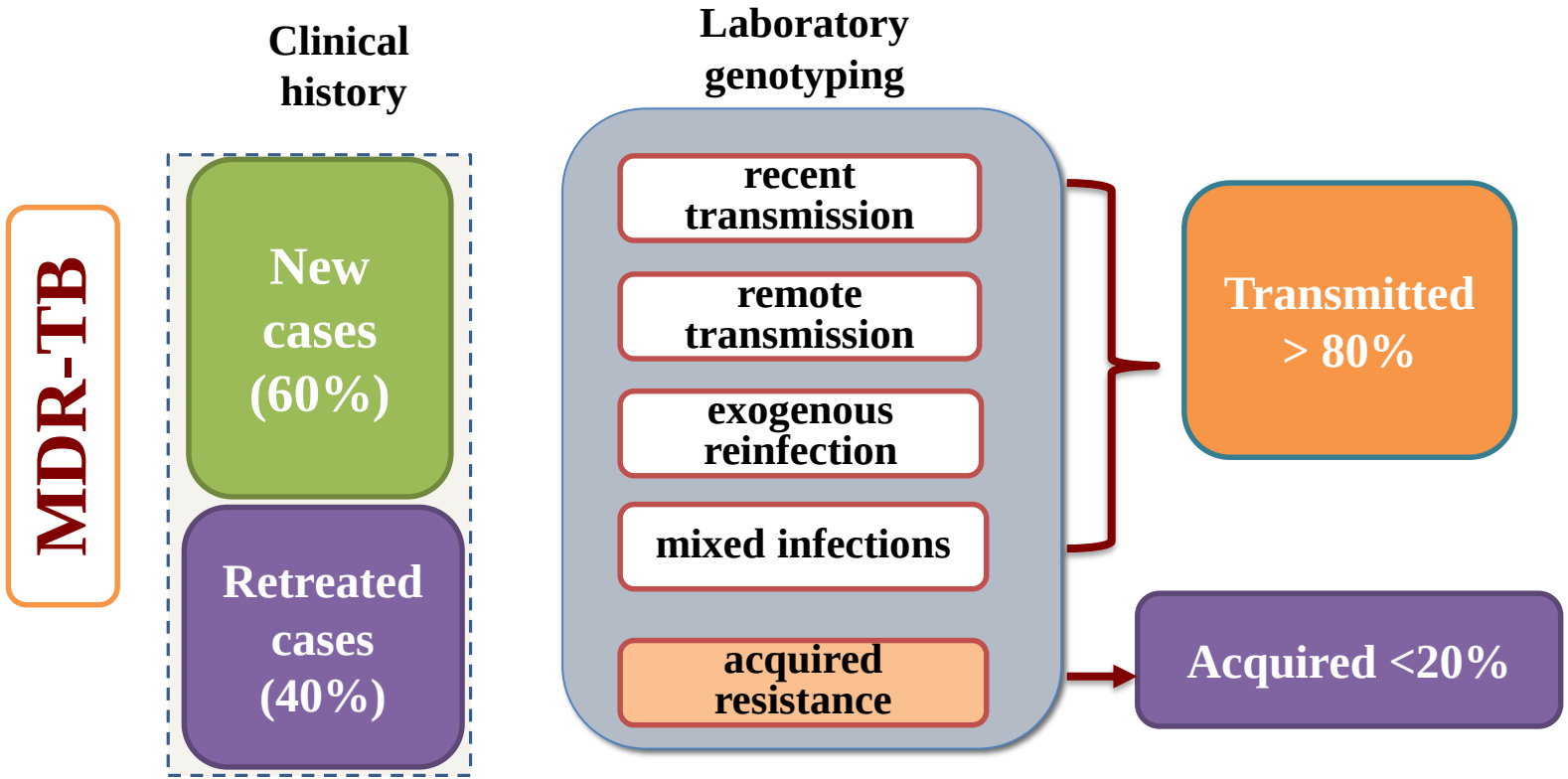




- 36% (37/103) clustered isolates obtained non-fixed mutations, being selected in vivo
- 87% (33/38) clusters accumulated new resistance-conferring mutations in transmission: 42% developed to pre-XDR, 11% to XDR-TB

Yang C., et al., Lancet Infect Dis 2017

Transmission is the major Reason for Epidemic MDR-TB



Transmission Modelling Analysis

	Bangladesh	Ethiopia	Malawi	Peru	Philippines	Uzbekistan
Features of notification data	High TB, moderate MDR, very high ratio	Moderate TB, moderate MDR, moderate ratio	Moderate TB, low MDR, high ratio	Moderate TB, high MDR, moderate ratio	High TB, moderate MDR, moderate ratio	Low TB, very high MDR, low ratio
TB prevalence, per 100 000						
WHO	402 (210–656)	211 (170–257)	135 (67–226)	124 (110–142)	438 (385–495)	120 (61–199)
Model	355 (259–467)	227 (194–268)	207 (168–246)	179 (138–234)	441 (383–487)	120 (89–150)
TB incidence, per 100 000 per year						
WHO	224 (119–253)	224 (188–276)	156 (152–168)	164 (77–283)	292 (261–331)	80 (68–97)
Model	222 (198–249)	201 (164–238)	157 (148–165)	121 (108–139)	289 (261–319)	80 (66–93)
MDR in new TB cases, %						
WHO	1·4% (0·7–2·5)	1·6% (0·9–2·8)	0·4% (0·1–1·0)	3·9% (3·6–4·2)	2·0% (1·4–2·7)	23% (18–29)
Model	1·2% (0·3–2·1)	1·5% (0·5–2·4)	0·3% (0·1–0·8)	3·9% (3·6–4·2)	2·0% (1·3–2·6)	27% (23–31)
MDR ratio: % among re-treatment cases to % among new cases						
WHO	20·7% (17·1–24·3)	7·5% (3·5–13·1)	12·0% (8·0–17·3)	9·0% (8·5–9·5)	10·5% (8·0–14·5)	2·7% (2·3–3·1)
Model	20·5% (17·4–24·4)	8·1% (5·2–13·7)	12·1% (8·7–17·4)	9·0% (8·5–9·5)	10·1% (7·7–13·4)	3·0% (2·7–3·4)
Model estimate of transmitted MDR (% of incident MDR cases [95% UR])	48% (30–75)	92% (58–99)	82% (56–97)	95% (79–100)	76% (51–98)	99% (91–100)

WHO estimates are shown as a reported point estimate (reported uncertainty interval); model estimates are shown as the weighted median (95% uncertainty range). TB=tuberculosis. MDR=multidrug-resistant or multidrug resistance. UR=uncertainty range.

Table 2: **Model calibration and estimates of transmitted MDR tuberculosis for six representative countries with disparate MDR tuberculosis notification data**

"More then 80%of incident MDR tuberculosis cases in most present-day epidemic settings result from transmission of MDR tuberculosis rather than selection of de-nove resistance during previous treatment of the index case".

Kendall E., *et.al.*, Lancet Respir Med. 2015

Summary

- Molepi has revolutionized our understanding of the transmission of tuberculosis
- WGS has great increased the precision of genotyping and contact tracing
- Prospective, population-based Molepi still limited, especially in the TB high burden countries.
- Hope more Molepi research to discover the new pattern of TB transmission and promote the TB control program in the TB high burden countries

Thank you!