

Transmission of Multidrug Resistance Tuberculosis in China

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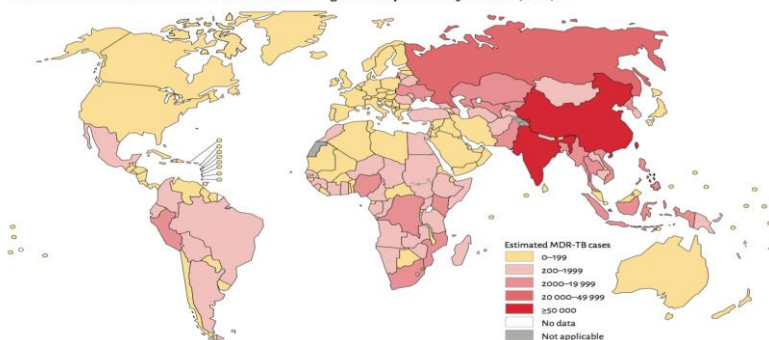
2018.09.13, Suzhou

Outline

- Transmission of MDR Tuberculosis
 - MDR-TB in new cases
 - Resistance in treated cases
 - Recent transmission of MDR-TB

MDR-TB around the World & China

Number of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2014



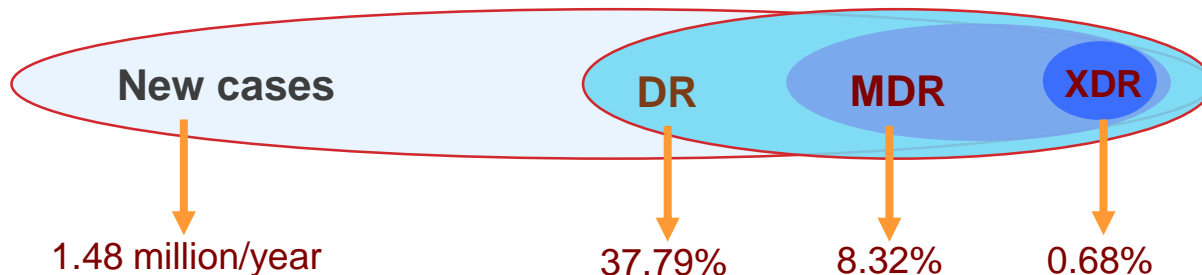
- Globally in 2014, an estimated **480 000** cases & **190 000** people died of MDR-TB.

DR-TB: resistant to any first line anti-TB drug

MDR-TB: resistant to at least **INH & RIF**

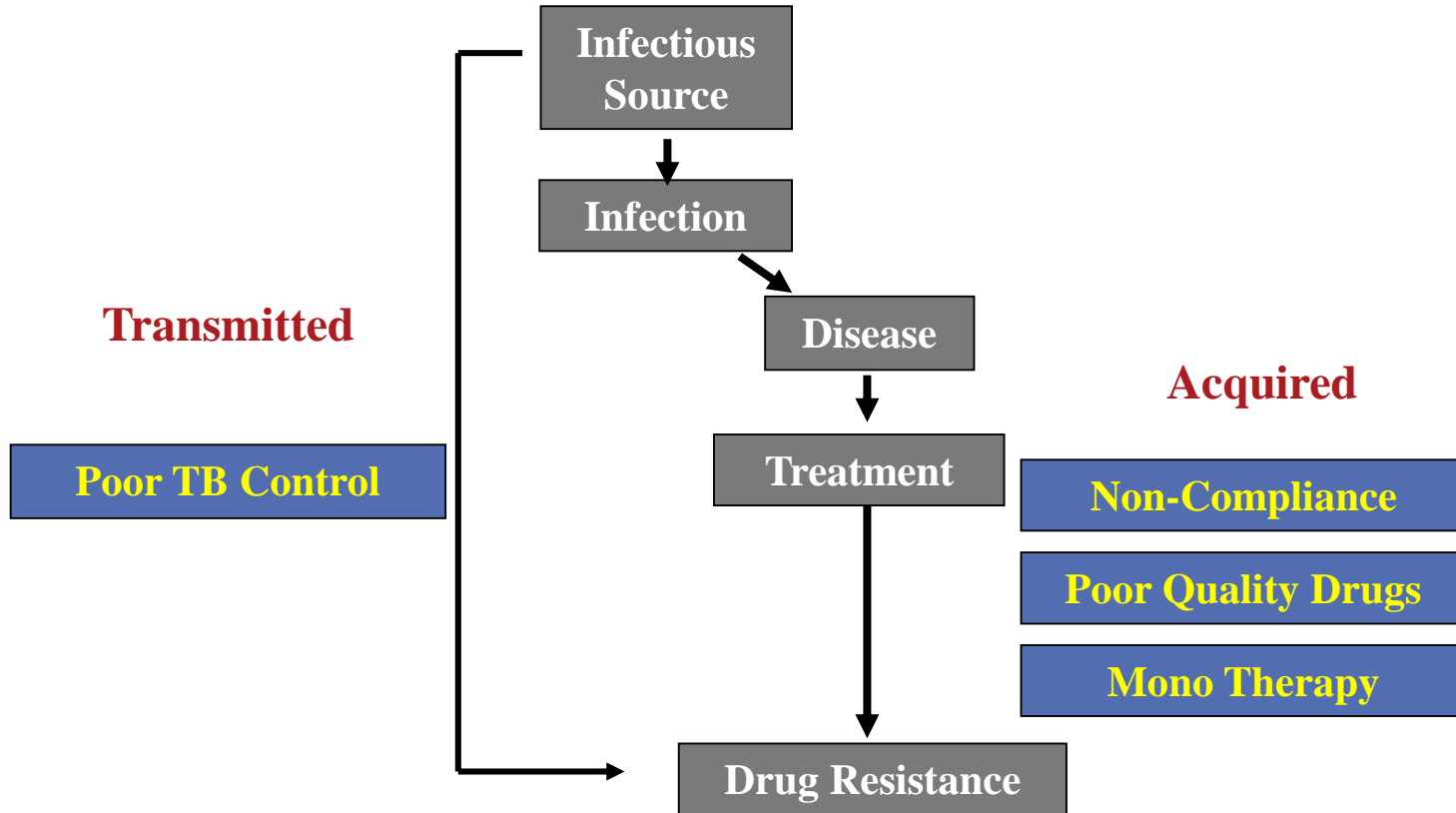
XDR-TB: **MDR+** FQs /any injectable drug

Global Tuberculosis report 2015, WHO



2007-2008 China National Survey

How DR Developed



About 60% of MDR-TB were New Cases

MDR Rate = MDR in New cases / Total of New cases

	% of new cases	95%CI	% of re-treated cases	95%CI
China	5.7	4.5-7.0	26	22-30
India	2.2	1.9-2.6	15	11-19
Indonesia	1.9	1.4-2.5	12	8.1-17
South Africa	1.8	1.4-2.3	6.7	5.4-8.2
HIGH BURDEN	3.8	2.2-5.4	22	13-31

Global Tuberculosis report 2015, WHO

Proportion = MDR in New Cases / Total of MDR

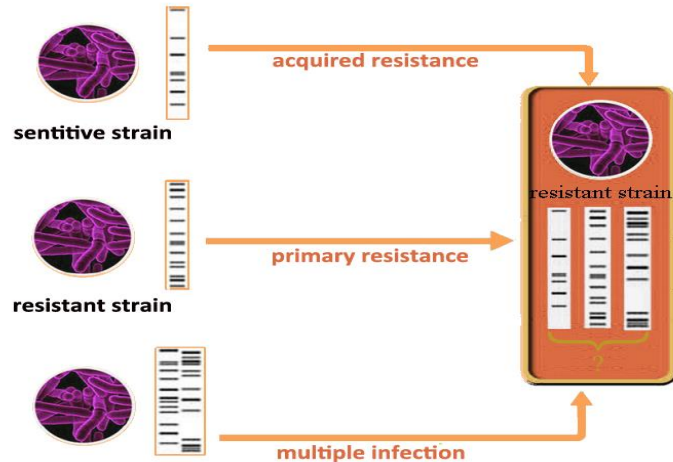
Settings	No. of cases	DR		MDR	
		No.	%	No.	%
Shanghai	New	7035	1016 (14.4)	199	(2.8)
	Re-treated	1380	385 (27.9)	134	(9.7)
	Rate of new case	-	1016/1401 (72.5)	199/333	(59.8)
National (Five fields)	New	1867	352 (18.8)	74	(4.0)
	Re-treated	239	101 (42.3)	51	(21.3)
	Rate of new case	-	352/453 (77.7)	74/125	(59.2)

- More than 70% of DR were new cases
- About 60% MDR/XDR-TB were new cases, caused by transmission

Shen X, et al. Int J Tuberc Lung Dis, 2009, Zhao M., et al., Plos ONE. 2009, Yang C, et al., Clin Infect Dis., 2015

About 60% Treated DR-TB were Transmitted

Dogma: Treated patients were acquired DR



84% (27/32) is transmitted resistance

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

Resistance increased: 81 cases

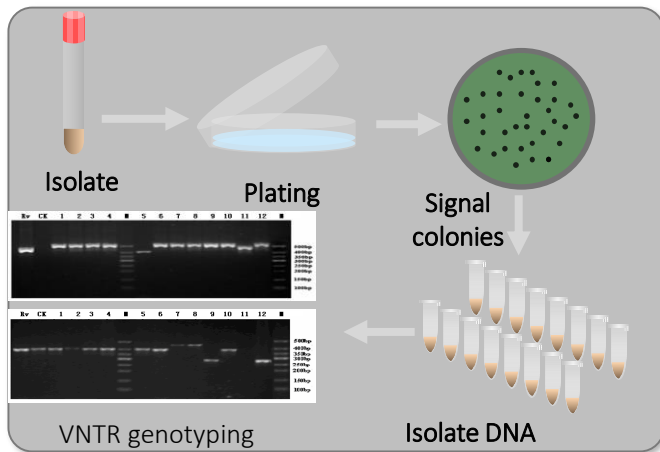
different
genotypes:
48 cases (59%)

identical
genotypes:
33 cases (41%)

- Patients during treatment or re-treatment, **59%** of the increased resistance is due to transmitted

Nsofor C., et al., *Sci Rep*, 2017

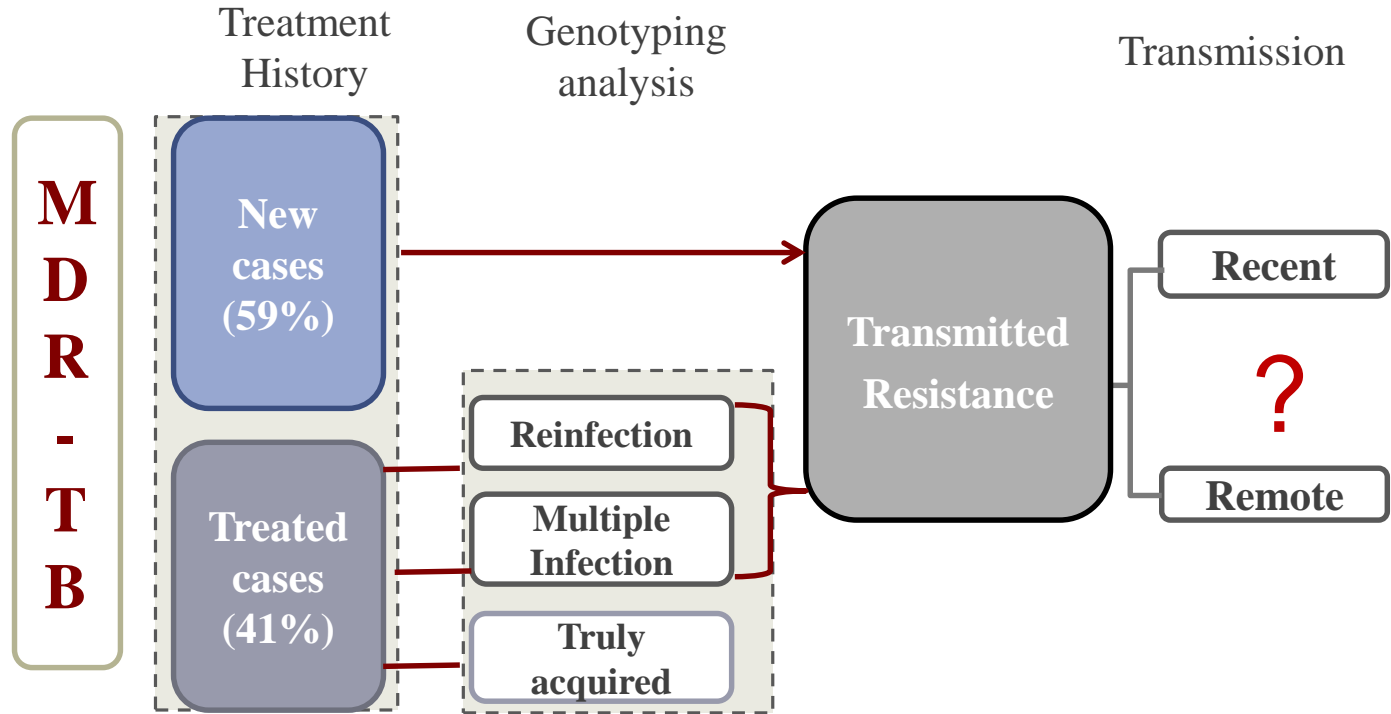
Multiple Infections among Patients



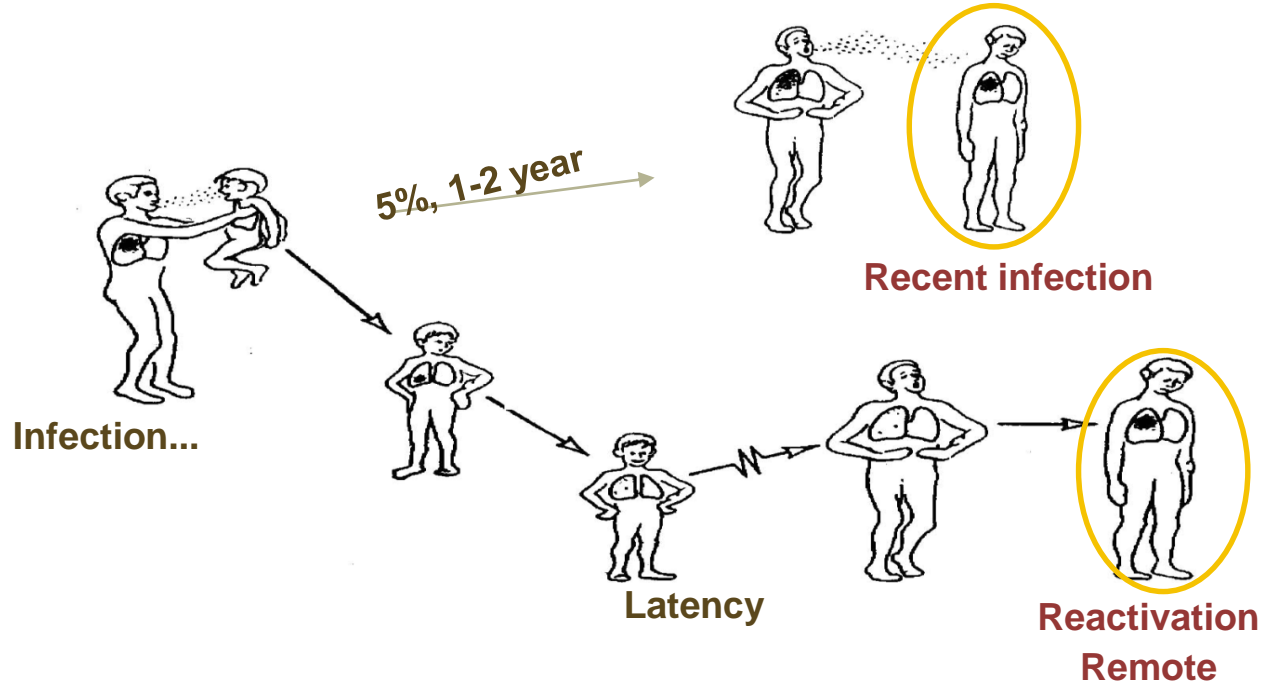
- Among TB patients in Shanghai, the estimated rate of mixed infections was 5.6%.
- Mixed infections were detected in 11.2% of TB cases in Heilongjiang.

Case	collection time	isolates	DST					VNTR genotypes				
			INH	RFP	Miru31	Etr-F	Mtub04	Miru39	Mtub21	Miru26	Qub26	Qub11a
2-2	11/12/09	66-1	S	S	5	2	4	3	5	7	8	5
	11/12/09	66-2	R	S	5/3	2/1	4/2	3/2	5	7	8	5
2-11	10/12/09	58-1	S	S	5	1	4	3	5	6	9	5
	10/12/09	58-2	R	S	5	2	4	3	7	7	8	8

Time of Transmission: Recent or Remote?

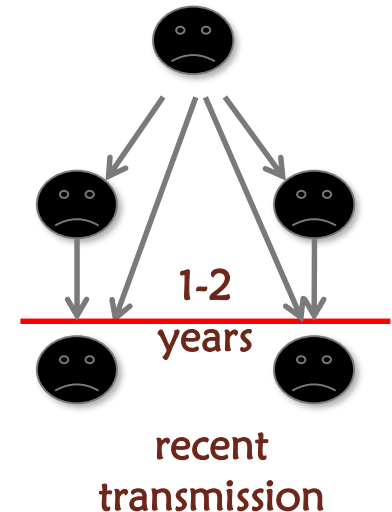
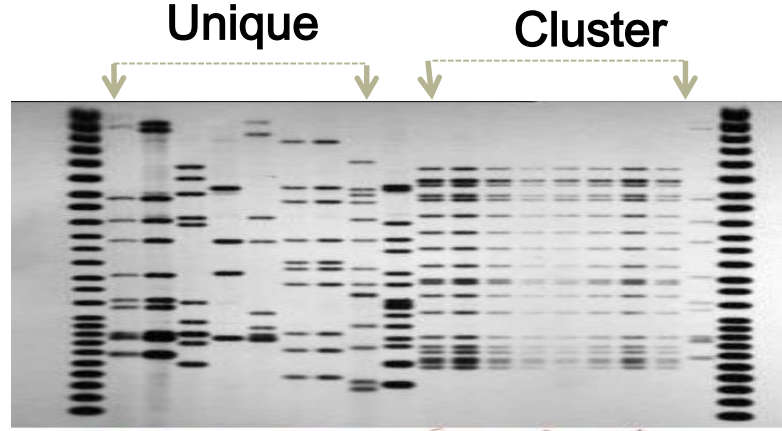
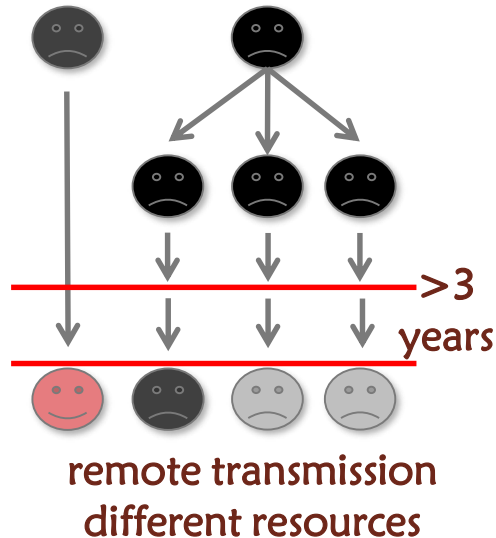


Time of Transmission: Recent or Remote?



How to Differentiate Recent Transmission?

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



Population-based Molecular Epidemiology

- From 2009 to 2012, still ongoing
- Selection of five field sites
- Covering ~5.8 million inhabitants
- Including all culture-positive TB

Fields	Areas(km ²)	Population	Prevalence of TB (/100,000)
Heilongjiang	3,756	520,000	512
Henan	1,307	868,000	497
Shanghai	604	1,634,000	96
Sichuan	966	838,000	544
Guangxi	2,473	456,500	477



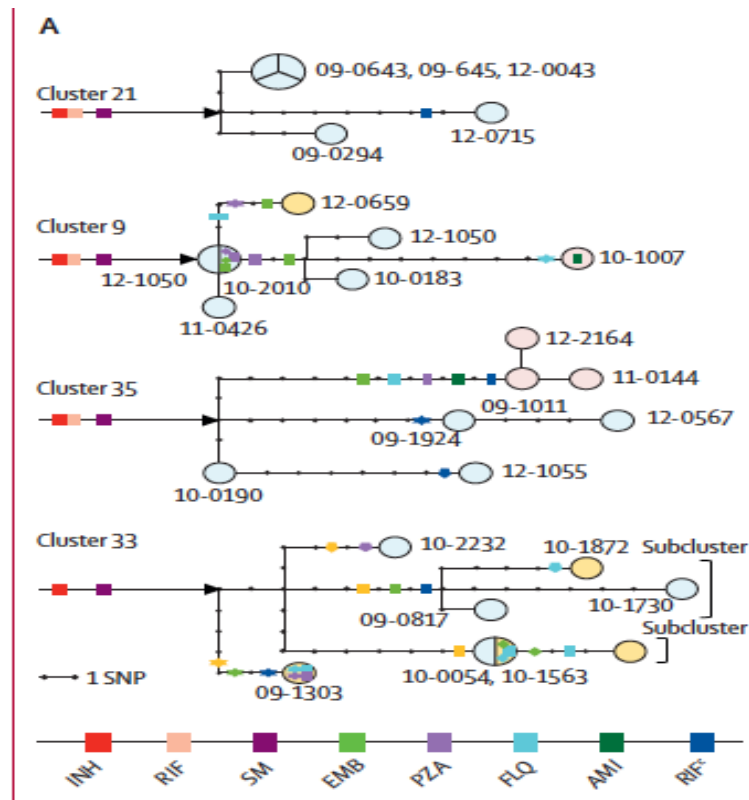
Population-based Molecular Epidemiology

Fields	No. of isolates	No. of clustered	cluster rate (%)	average cluster size
Wusheng, SC	414	90	21.7	2.1
Pingguo, GX	324	117	36.1	2.6
Weishi, HN	481	149	30.9	2.6
Songjiang, SH	797	255	32.0	2.5
Wuchang, HLJ	258	94	36.0	3.0
Total	2274	705	31.0	2.5

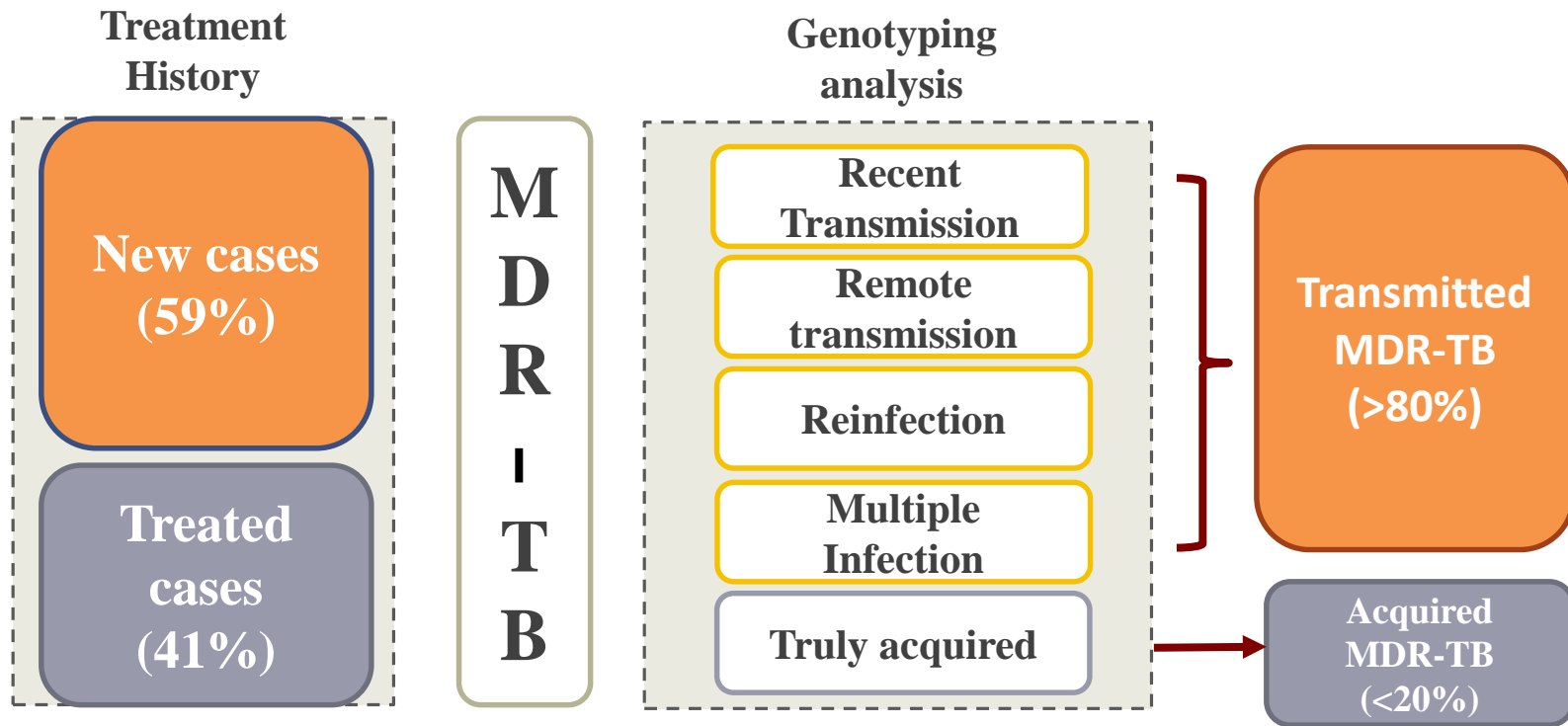
- 2009 to 2012, **all** culture-positive TB were enrolled in five fields across China
- **41%** MDR-TB were clustered and indicates recent transmission
- MDR-TB were more likely to be clustered than susceptible cases (**41% vs 31%**), suggesting a risk factor of recent transmission, **aOR=1.86 (95% CI 1.25-2.63)**

Genomic Cluster Analysis in Shanghai

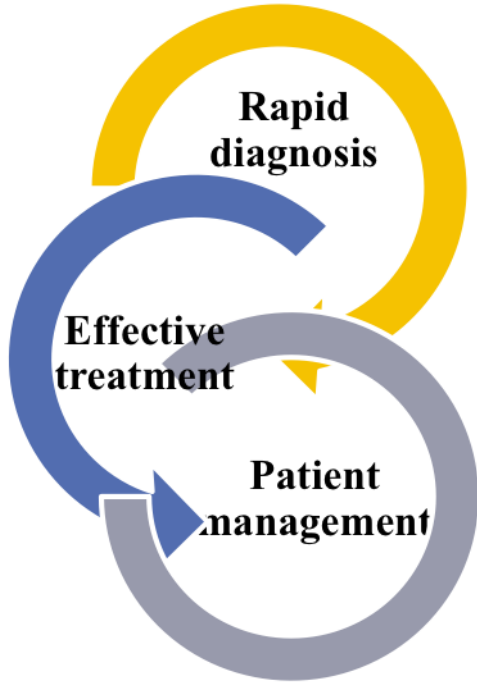
- 2009-2012, **4.6%** (367/7978) were MDR cases 60% were new cases
 - **38.6%** (125/324) were VNTR-clustered
- Risk factor for recent transmission
 - diagnosis delay (≥ 2 ms): aOR=2.3 (1.2-4.1)
 - elderly (≥ 65 ys): aOR=3.2 (1.4-7.4)
- MDR-TB in **91.9%** (34/37) clusters were transmitted
- **86.8%** (33/38) clustered cases accumulated additional resistance mutations, developed to pre-XDR & XDR cases



Most MDR-TB were Caused by Transmission



Tremendous Challenges



- **Case Detection: lacking human & financial resource**
 - less than **15%** were diagnosed and treated
 - Backward technology, diagnosis delay (2~3 months)
 - **> 80%** of the county TB lab **did not perform culture**
- **MDR Treatment: lacking drugs & financial support**
 - Insufficient treatment (not based on DST regimen)
 - Low success rate (<40%)
- **Transmission Control: NO any laws or regulations**
 - Almost no infection control
 - No restriction on MDR-TB patients

Take Home Messages

- **MDR-TB transmission is serious in China**
 - About 60% of MDR-TB were new cases
 - About 60% of DR in retreated cases caused by transmission
 - At least 1/3 of MDR-TB cases were due to recent transmission
 - Totally, more than 80% of MDR-TB cases were due to transmission
- **Timely DST is urgently needed for all bacteria positive patients!**



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