Study of PZA Resistance in China

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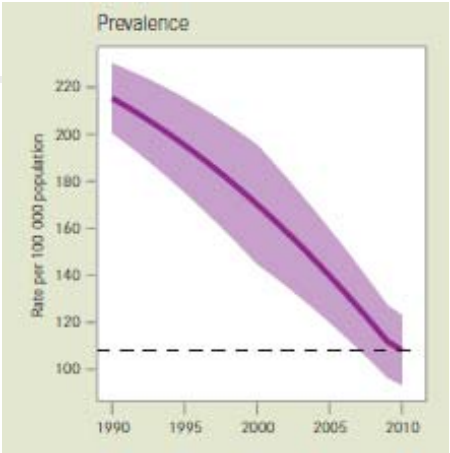
The Epidemic of TB in China

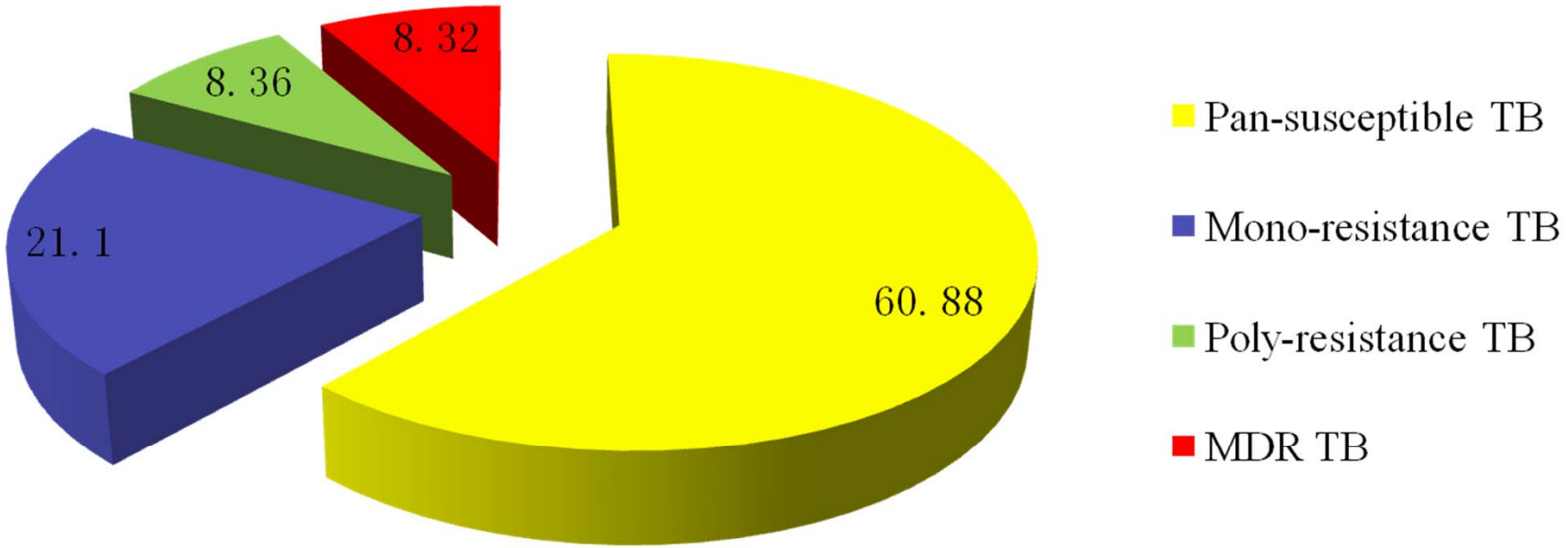
- >15 years old



	Prevalence rate(1/100,000)	No of cases(*10,000)
Active pulmonary TB	459	499
Smear positive pulmonary TB	66	72
Bacteria positive pulmonary TB	119	129

Data from the 5th national TB survey in China and WHO TB repoert in 2011)

Prevalence of Drug-resistance TB in China



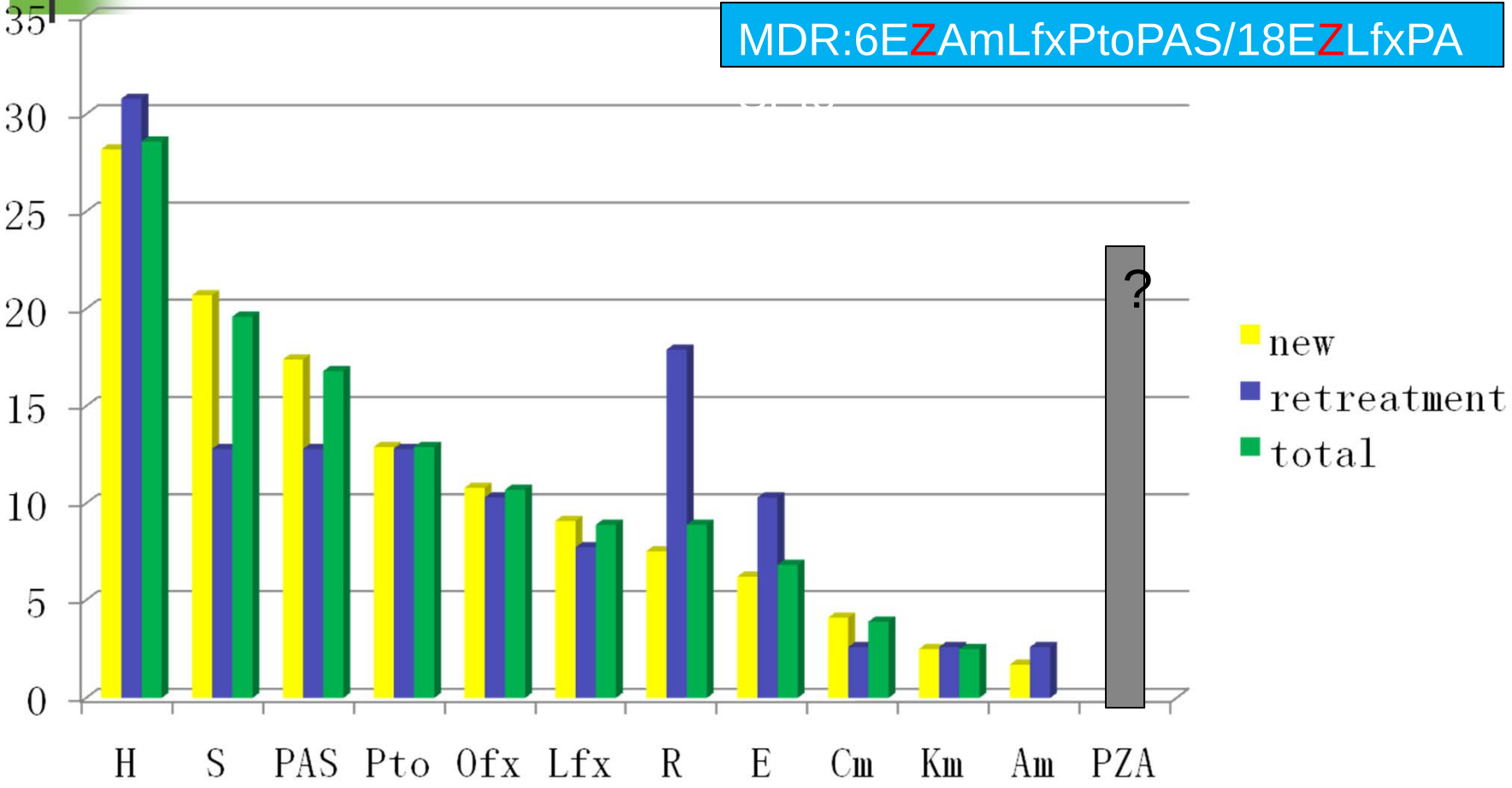
Data from National drug-resistance TB survey in 2007-2008

Resistance to anti-TB Drugs

New:2HREZ/4HR

Retreatment:2HREZS/6HRE

MDR:6EZAmLfxPtoPAS/18EZLfxPA



Data from 5th National TB survey in China（2007-2008）

Objectives of the Study

- **The Prevalence of PZA resistance in China**

- **Concordance between BACTEC MGIT 960 detection and *pnc*A mutation**

Geographic Sites for Sample Collection

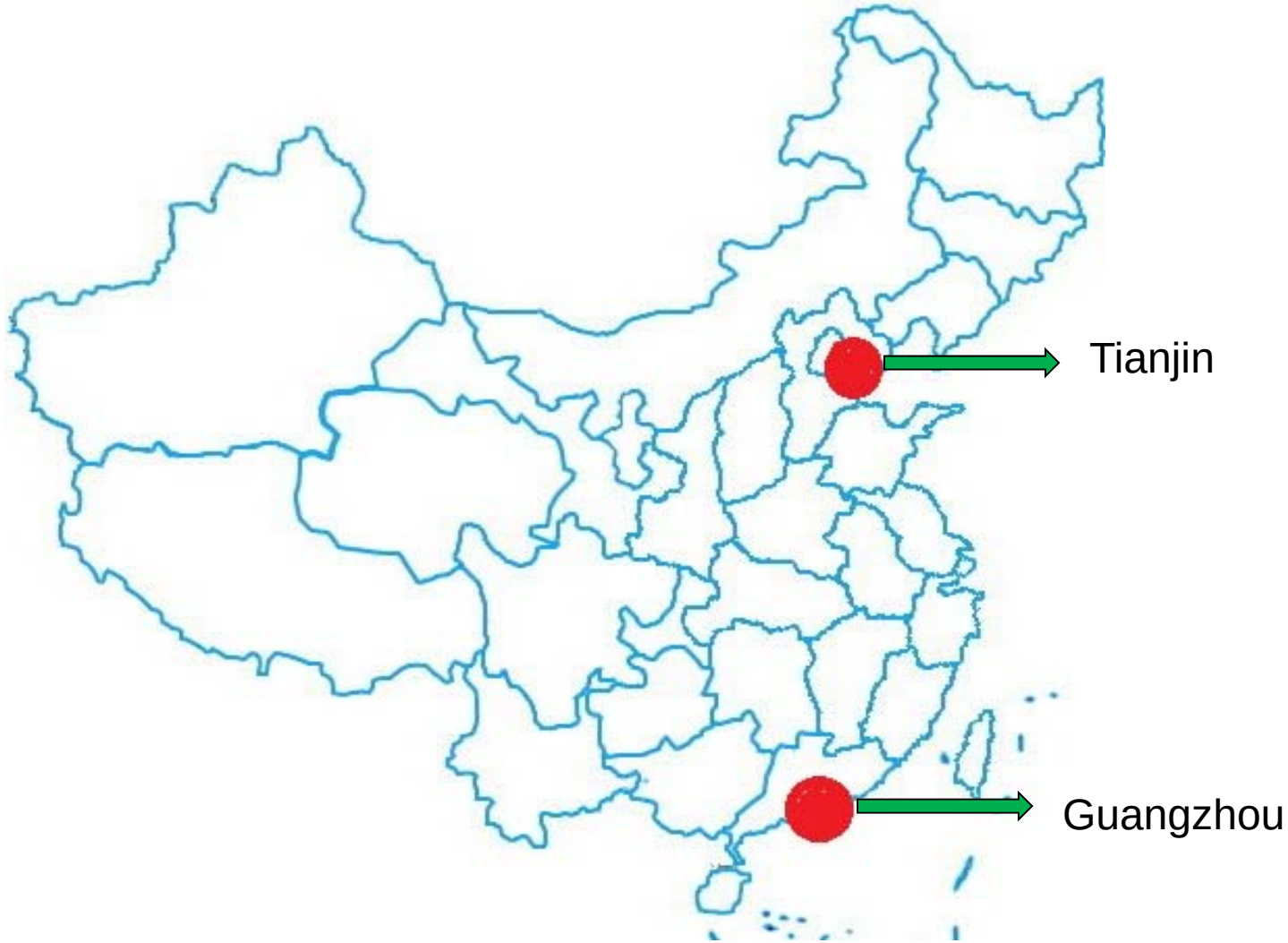
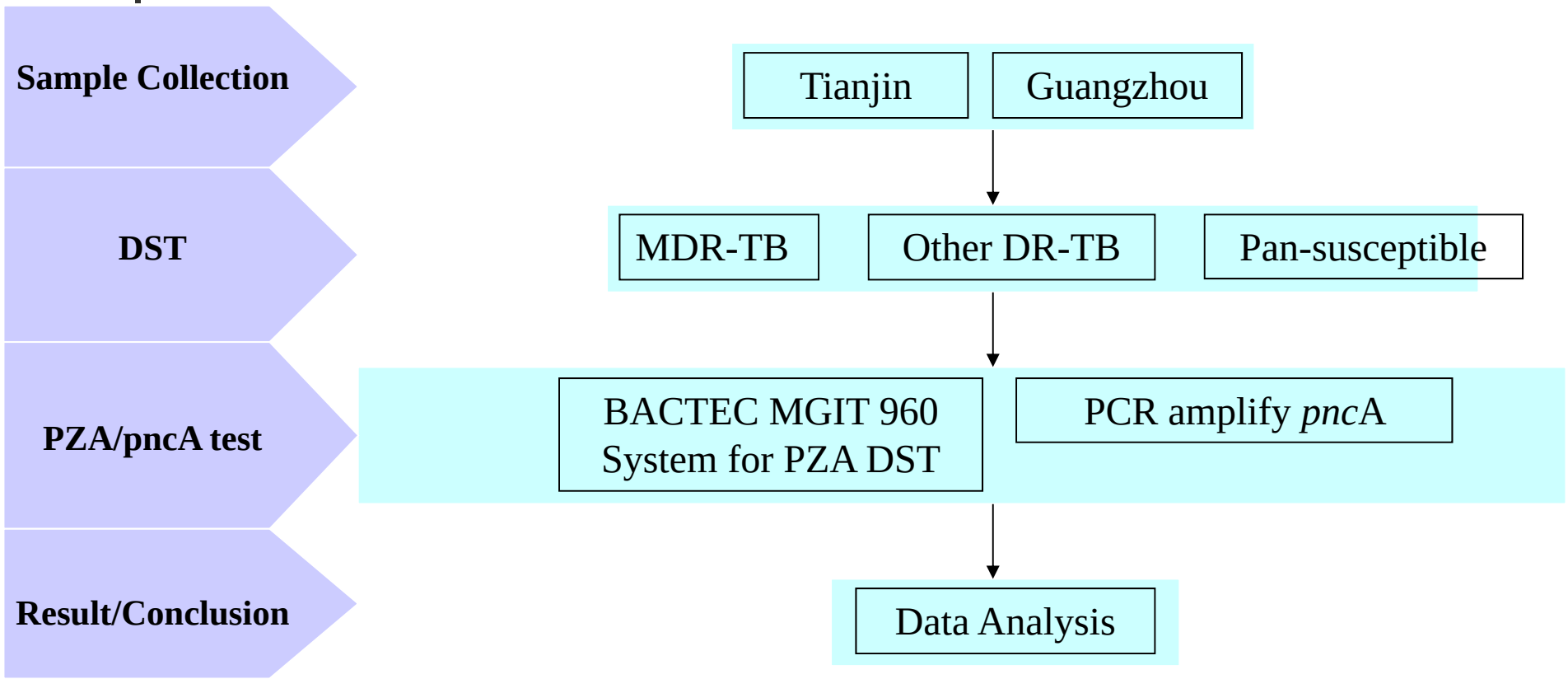


Diagram of Sample Collection & DST



I. Mutations of *pnc*A in MDR-TB (85 Clinical Strains)

Nucleotide Position	Nucleotide Change	Aa Replacement	No. of Strains
-11	A/G		1
8	GAC/GCC	Asp/Ala	1
10	CAG/CCG	Gln/Pro	2
12	GAC/GGC	Asp/Gly	1
13	TTC/CTC	Phe/Leu	1
18 和 54	TCG/CCG 和 CCG/CTG	Ser/Pro 和 Pro/Leu	1
24	GGC/GAC	Gly/Asp	1
26	**Insertion/G**	**Shift**	1
47	ACC/GCC	Thr/Ala	1
48	AAG/ACG	Lys/Thr	1
54	CCG/CTG	Pro/Leu	1
57	CAC/TAC	His/Tyr	1
58	TTC/TCC	Phe/Ser	1
62	CCG/CCC	Pro/Pro	1
66	TCG/CCG	Ser/Pro	1
67	**Delation/G**	**Shift**	1
69	CCA/CTA	Pro/Leu	2
76	ACT/CCT	Thr/Pro	1
81	TTC/GTC	Phe/Val	1
82	CAT/CGT	His/Arg	1
85	CTG/CAG	Leu/Gln	1
91	GAG/TAG	Glu/stop	1
94	TTC/CTC	Phe/Leu	1

96	AAG/GAG	Lys/Glu		1	
102	**Insertion/C**	**Shift**		3	
111	GAG/TAG	Glu/stop		1	
119	TGG/TGT	Trp/Cys		1	
122	CAA/TAA	Gln/stop		1	
135	ACC/CCC	Thr/Pro		1	
136	GAT/GGT	Asp/Gly		2	
139	GTG/GCG	Val/Ala	1		2
	GTG/GGG	Val/Gly	1		
142	ACG/GCG	Thr/Ala		1	
151	TTG/TCG	Leu/Ser		2	
	Insertion/CC	**Shift**	1		
159	CTG/CGG	Leu/Arg	1		3
	CTG/GTG	Leu/Val	1		
160	ACA/CCA	Thr/Pro		1	
166	**Insertion/C**	**Shift**		1	
167	ACC/ACT	Thr/Thr		1	
168	ACC/CCC	Thr/Pro		1	
170	**Deletion/C**	**Shift**		1	
174	**Insertion/GG**	**Shift**		1	
175	ATG/ACG	Met/Thr		1	
180	GTC/TTC	Val/Phe		2	
No. of Mutants		61.2% (52/85)			

备注：三线表中用黄色背景标记出的突变为天津和广东两地区菌株均出现的突变。

Concordance of *pncA* Mutation and PZA Resistance in MDR-TB (85 Clinical Strains)

	None Mutation	Mutant	Total
PZA Sensitive	31 (88.6%)	4 (11.4%)	35 (100.0%)
PZA Resistant	2 (4.0%)	48 (96.0%)	50 (100.0%)
Total	33 (38.8%)	52 (61.2%)	85 (100.0%)

Sensitivity=96.0%
Specificity=88.6%

Chi-square test，*p<0.001*

II. Mutations of *pncA* in other drug resistant (89 Clinical Strains)

Nucleotide Position	Nucleotide Change	Aa Replacement	No. of Strains
-11	A/G		2
85	CTG/CAG	Leu/Gln	1
91	**Insertion/**GAGG	**Shift**	1
129和130和131和132	**Deletion/**TGTGGTCGG	**Deletion**	1
139	GTG/GCG	Val/Ala	1
141	CAG/CCG	Gln/Pro	1
162	GGT/GAT	Gly/Asp	1
No. of Mutants		9.0% (8/89)	

备注：三线表格中用黄色背景标记出的突变为天津和广东两地区菌株均出现的突变。

Concordance of *pnc*A Mutation and PZA Resistance in other drug resistant TB (89 Clinical Strains)

	None Mutation	Mutant	Total
PZA Sensitive	77 (100.0%)	0 (0%)	77 (100.0%)
PZA Resistant	4 (33.3%)	8 (66.7%)	12 (100.0%)
Total	81(91.0%)	8 (9.0%)	89 (100.0%)

Sensitivity=66.7.0%
Specificity=100.0%

Chi-square test，*p<0.001*

III. Mutations of *pncA* in Pan-susceptible Strains (90 Clinical Strains)

Gene	Nucleotide Position	Nucleotide Change	Aa Replacement	No. of Strains
pncA	78	GGC/GGA	Gly/Gly	1
	No. of Mutants	1		
	Analyzed Strains	75		

Only one mutation was identified which didn't cause any amino acid change

IV. PZA Resistance and *pncA* Mutations in Bejing Genotype (From Tianjin)

	None Mutation	Mutant	Total
PZA Sensitive	111 (97.4%)	3 (2.6%)	114 (100.0%)
PZA Resistant	3 (14.3%)	18 (85.7%)	21 (100.0%)
Total	114 (84.4%)	21 (15.6%)	135(100.0%)

sensitivity=85.7%
specificity=97.4%

IV. PZA Resistance and *pncA* Mutations in non-Bejing Genotype (From Tianjin)

	None Mutation	Mutant	Total
PZA Sensitive	4 (80.0%)	1 (20.0%)	5 (100.0%)
PZA Resistant	0 (0%)	2 (100.0%)	2 (100.0%)
Total	4 (57.1%)	3 (42.9%)	7 (100.0%)

sensitivity=100.0%
specificity=80.0%

Conclusion

Method for	MDR-TB (N=85)		Other DR-TB (N=89)		Pan-TB (N=75)	
	Number of Strains (n)	Percentage (%)	Number of Strains (n)	Percentage (%)	Number of Strains (n)	Percentage (%)
MGIT 960	50	58.82	12	13.48	0	0
pncA	48	56.47	8	8.99	0	0

BACTEC MGIT960 and pncA Mutation Detection predict similar rate of PZA resistance in MDR-TB, other DR-TB and pan susceptible TB in Tianjin & Guangzhou, China

Among 89 MDR-TB strains, 58.82% were PZA resistant which is surprisingly high. So the PZA-including regimen for MDR-TB treatment is urgently need to be evaluated

Further Studies of PZA Resistance and *pncA* Mutations

- Multi-Center Study:

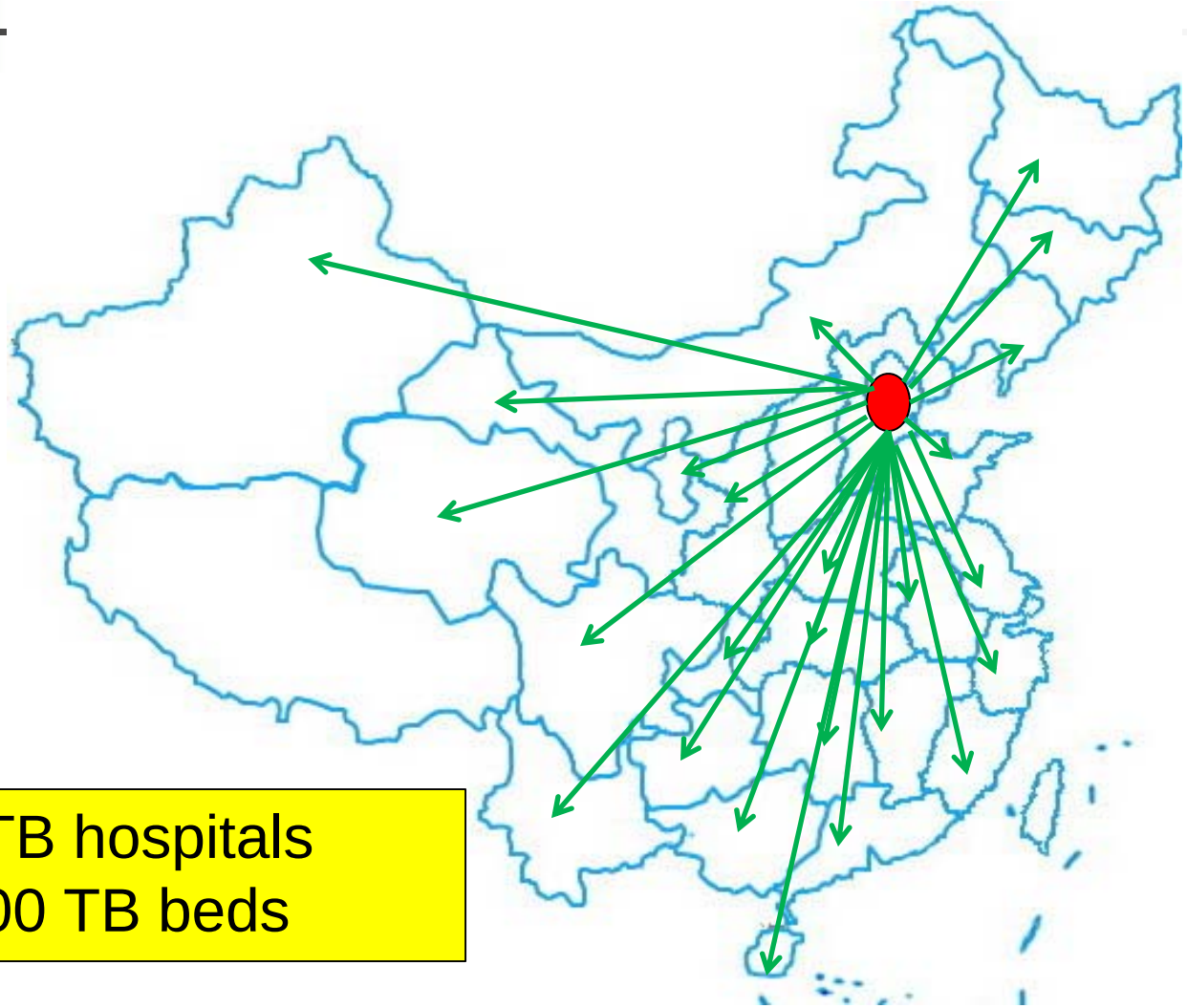
  22 TB hospitals will join the study

- Size of the Studied Population:

  2000 Clinical drug-resistance Strains

- Relation between PZA drug resistance and treatment outcome

TB Hospitals coalition in China



MDR-TB

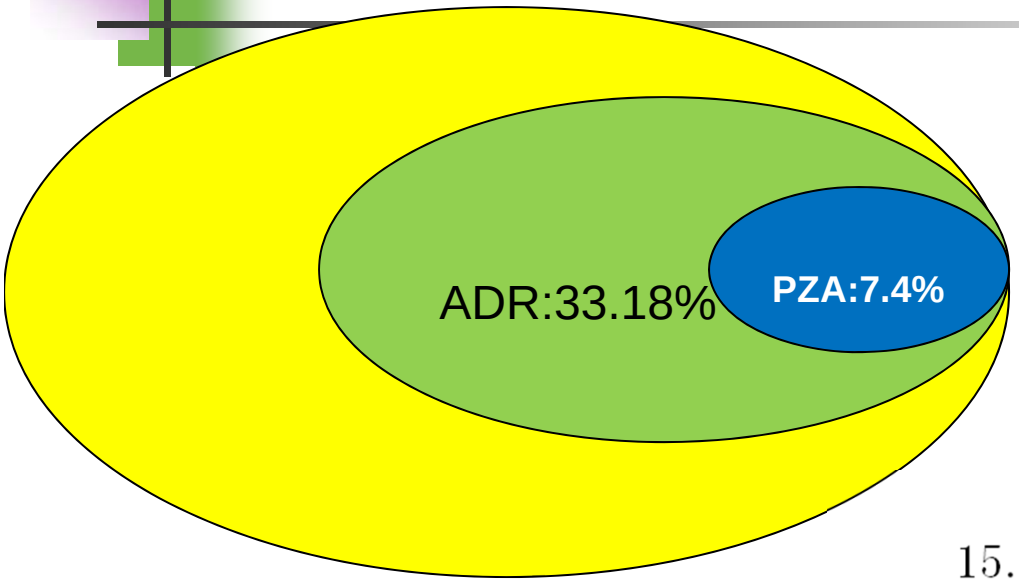
TB/HIV
TB/DM

Tele-Medicine system

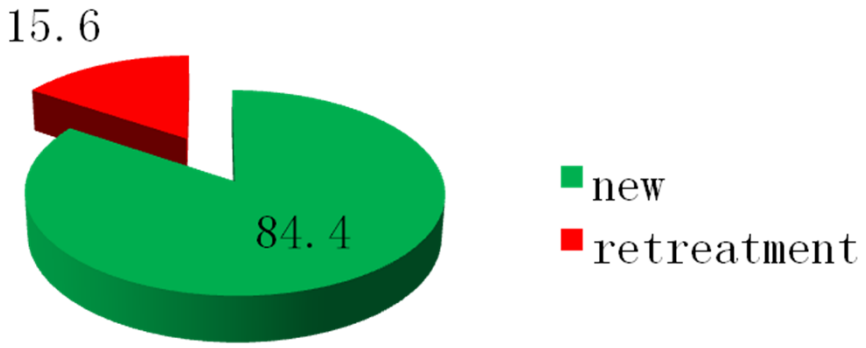
Clinical trials

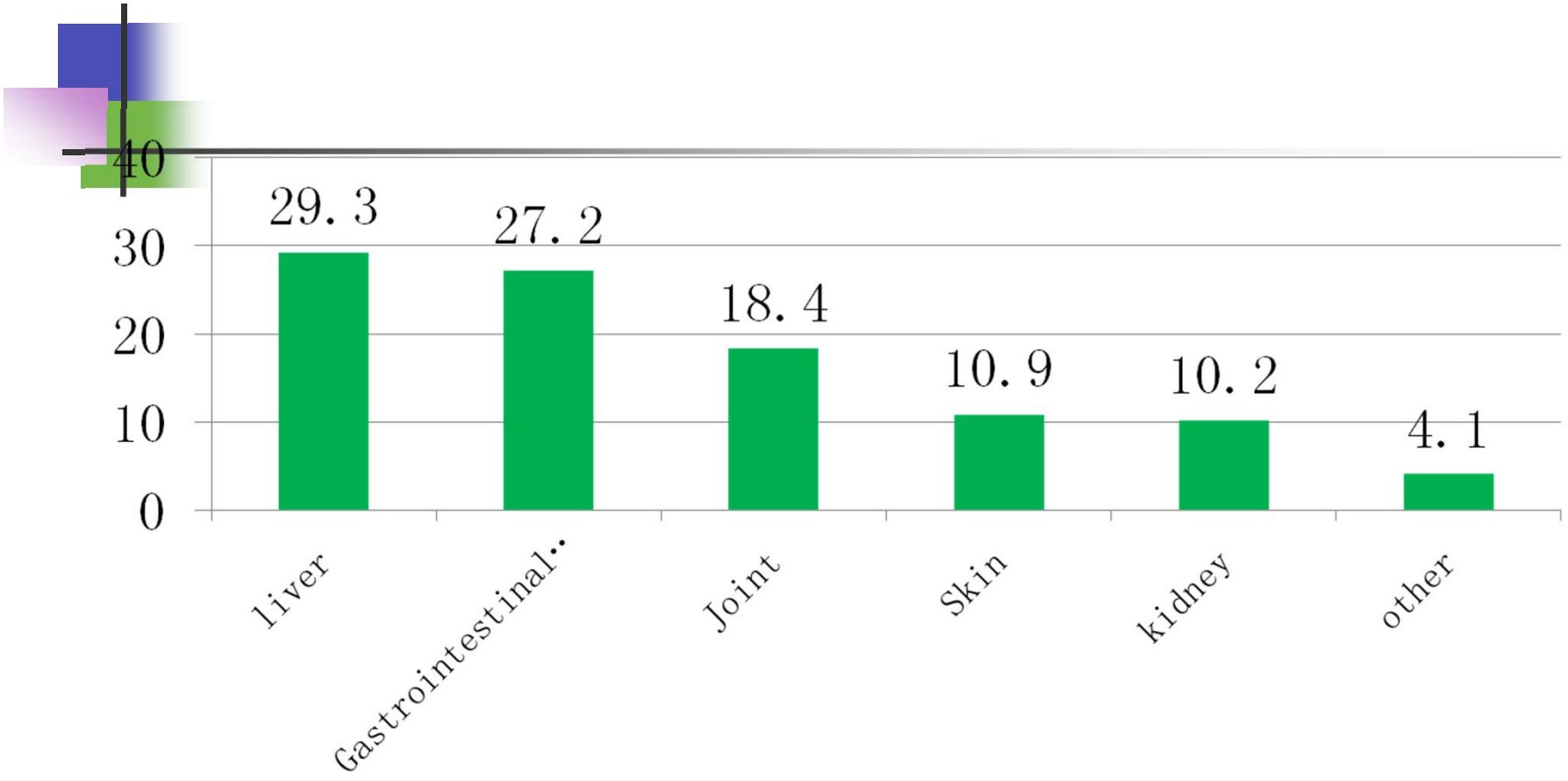
>100 TB hospitals
>20,000 TB beds

Adverse Drug Reaction(ADR) of PZA



1992 TB cases

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liver
Gastrointestinal..
Joint
Skin
kidney
other

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