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浙江省医学会结核病分会副会长

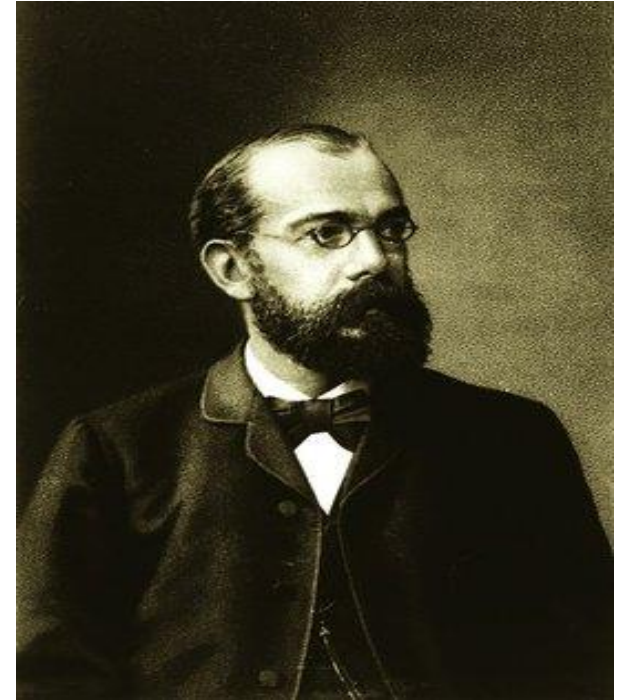
长期从事结核病流行病学、政策与技术研究。主持或参与完成多项省科技厅重大专项、科技部重大科技专项课题，获中国防痨协会科技创新二等奖1项，浙江省科技进步奖三等奖1项。在国内核心期刊上发表论文40余篇，SCI论文26篇，编写专著3部



结核病传播机制的探索研究

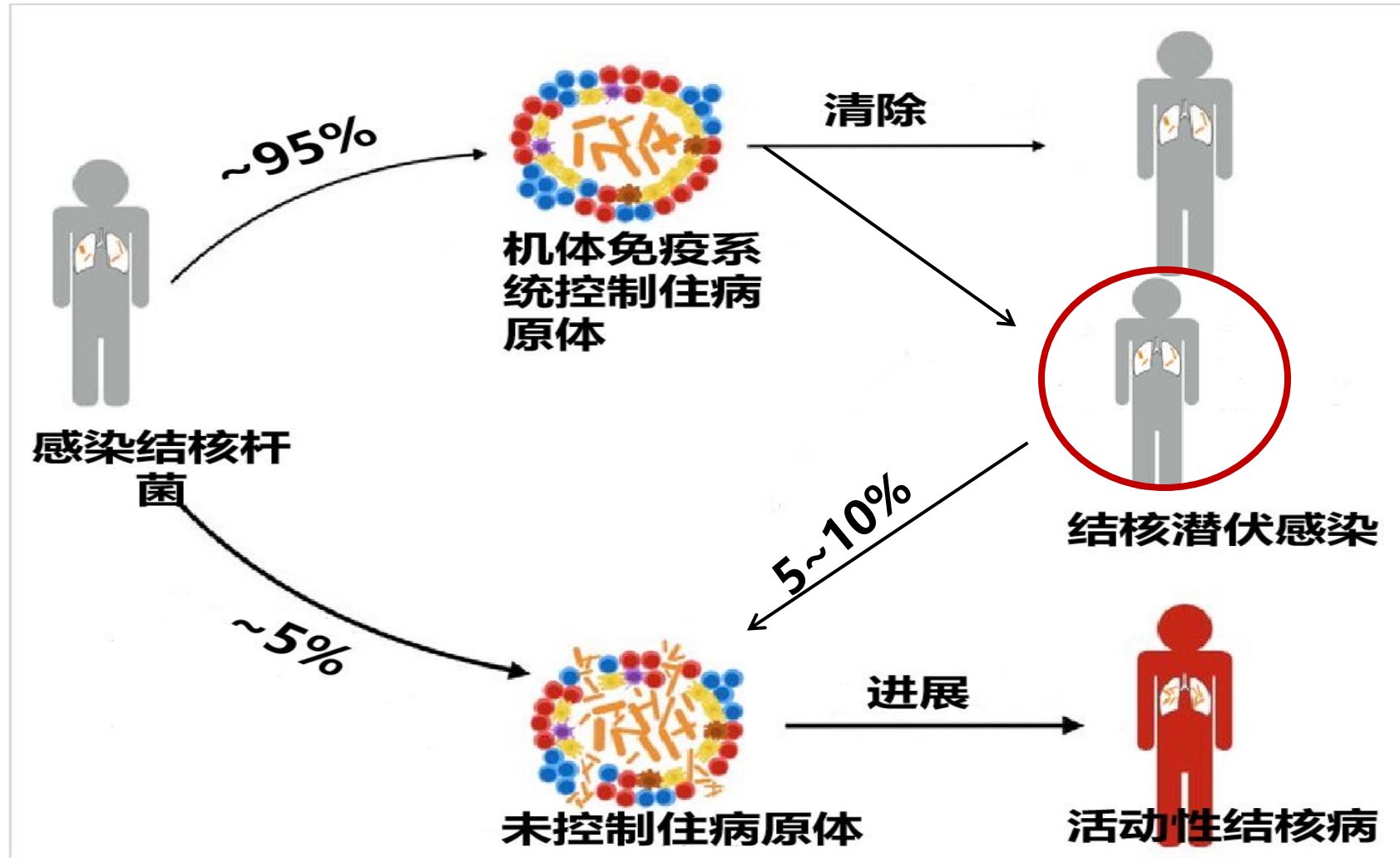
浙江省疾病预防控制中心
王晓萌

- 1882年，科赫发现结核杆菌时就指出“细菌不是结核病的全部病因”
- 感染结核菌后，宿主的最终结果—耐受、敏感乃至发病是结核分支杆菌和宿主之间一系列相互斗争过程的结果



罗伯特·科赫(1843-1910)
德国病理学家

结核病是结核分枝杆菌与宿主相互作用的结果



Global Burden of Tuberculosis Estimated Incidence, Prevalence, and Mortality by Country

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THE MOST RECENT PUBLISHED estimates of the global burden of tuberculosis (TB)¹⁻⁵ are based on data available up to 1990 and, with 1 exception,³ give figures for regions of the world rather than individual countries. The magnitude of the tuberculosis problem has changed since 1990, due to changing control practices, spread of human immunodeficiency virus (HIV), and population growth. As an interim measure, the World Health Organization (WHO)⁶ published a revised set of estimates for 1996, obtained by scaling earlier World Bank⁷ estimates to 1996 population sizes. A more thorough review is needed to take account of nearly a decade of change in TB epidemiology and to accommodate new data.

Our main aim was to estimate risk and prevalence of *Mycobacterium tuberculosis* (MTB) infection and TB incidence, prevalence, and mortality for 1997. The results are the fullest and most up-to-date assessment we can currently make of TB burden by country, by region, and globally. They define the magnitude of the global TB control problem for use in assessing present control efforts and

See also Patient Page.

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Objective To estimate the risk and prevalence of *Mycobacterium tuberculosis* (MTB) infection and tuberculosis (TB) incidence, prevalence, and mortality, including disease attributable to human immunodeficiency virus (HIV), for 212 countries in 1997.

Participants A panel of 96 TB experts and epidemiologists from more than 40 countries was chosen by the World Health Organization (WHO), with final agreement being reached between country experts and WHO staff.

Evidence Incidence of TB and mortality in each country was determined by (1) case notification to the WHO, (2) annual risk of infection data from tuberculin surveys, and (3) data on prevalence of smear-positive pulmonary disease from prevalence surveys. Estimates derived from relatively poor data were strongly influenced by panel member opinion. Objective estimates were derived from high-quality data collected recently by approved procedures.

Consensus Process Agreement was reached by (1) participants reviewing methods and data and making provisional estimates in closed workshops held at WHO's 6 regional offices, (2) principal authors refining estimates using standard methods and all available data, and (3) country experts reviewing and adjusting these estimates and reaching final agreement with WHO staff.

Conclusions In 1997, new cases of TB totaled an estimated 7.95 million (range, 6.3 million–11.1 million), including 3.52 million (2.8 million–4.9 million) cases (44%) of infectious pulmonary disease (smear-positive), and there were 16.2 million (12.1 million–22.5 million) existing cases of disease. An estimated 1.87 million (1.4 million–2.8 million) people died of TB and the global case fatality rate was 23%, but exceeded 50% in some African countries with high HIV rates. Global prevalence of MTB infection was 32% (1.86 billion people). Eighty percent of all incident TB cases were found in 22 countries, with more than half the cases occurring in 5 Southeast Asian countries. Nine of 10 countries with the highest incidence rates per capita were in Africa. Prevalence of MTB/HIV coinfection worldwide was 0.18%, and 640 000 incident TB cases (8%) had HIV infection. The global burden of tuberculosis remains enormous, mainly because of poor control in Southeast Asia, sub-Saharan Africa, and eastern Europe, and because of high rates of *M tuberculosis* and HIV coinfection in some African countries.

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provide a baseline from which to forecast and measure impact of control efforts.

METHODS

Data and Methods of Estimation

For all countries, participants reviewed available data on case notifications (all forms, pulmonary, smear-positive, extrapulmonary) and case detection rate, including evidence for overreporting and underreporting.

prevalence of infection (via tuberculin surveys), giving estimates of the annual risk of infection (ARI), and annual rate of decline in ARI.

Author Affiliations: Communicable Disease Prevention and Control, World Health Organization, Geneva, Switzerland.

A complete list of the panel members of the WHO Global Surveillance and Monitoring Project appears at the end of this article.

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RESEARCH ARTICLE

The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling

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Abstract

Background

The existing estimate of the global burden of latent TB infection (LTBI) as “one-third” of the world population is nearly 20 y old. Given the importance of controlling LTBI as part of the End TB Strategy for eliminating TB by 2050, changes in demography and scientific understanding, and progress in TB control, it is important to re-assess the global burden of LTBI.

Methods and Findings

We constructed trends in annual risk of infection (ARI) for countries between 1934 and 2014 using a combination of direct estimates of ARI from LTBI surveys (131 surveys from 1950 to 2011) and indirect estimates of ARI calculated from World Health Organization (WHO) estimates of smear-positive TB prevalence from 1990 to 2014. Gaussian process regression was used to generate ARIs for country-years without data and to represent uncertainty. Estimated ARI time-series were applied to the demography in each country to calculate the number and proportions of individuals infected, recently infected (infected within 2 y), and recently infected with isoniazid (INH)-resistant strains. Resulting estimates were aggregated by WHO region. We estimated the contribution of existing infections to TB incidence in 2035 and 2050.

In 2014, the global burden of LTBI was 23.0% (95% uncertainty interval [UI] 20.4%–26.4%), amounting to approximately 1.7 billion people. WHO South-East Asia, Western-Pacific, and Africa regions had the highest prevalence and accounted for around 80% of those with LTBI. Prevalence of recent infection was 0.8% (95% UI: 0.7%–0.9%) of the global population, amounting to 55.6 (95% UI: 48.2–63.8) million individuals currently at high risk of TB disease, of which 10.9% (95% UI: 10.2%–11.8%) was isoniazid-resistant. Current LTBI alone, assuming no additional infections from 2015 onwards, would be expected to generate TB incidences in the region of 16.5 per 100,000 per year in 2035 and 8.3 per 100,000 per year in 2050.

OPEN ACCESS

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

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Competing Interests: The authors have declared that no competing interests exist.

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1997 感染率

- 全球 : 32%
- 中国 : 36%

2014 潜伏感染率

- 全球 : 23%
- 中国 : 26%

人群感染负担计算参数：年新发感染率 (ARI)
ARI升高 1%，涂阳肺结核患者的发病率升高 49/10万

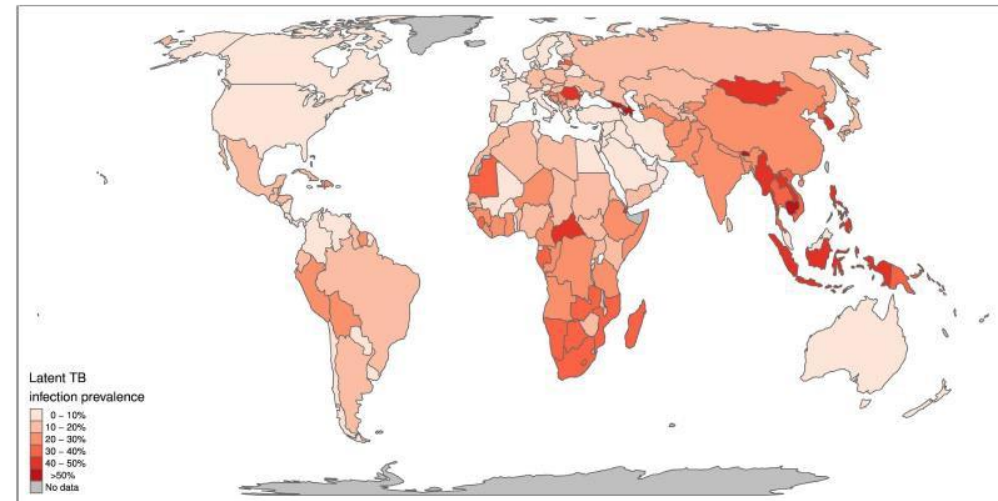
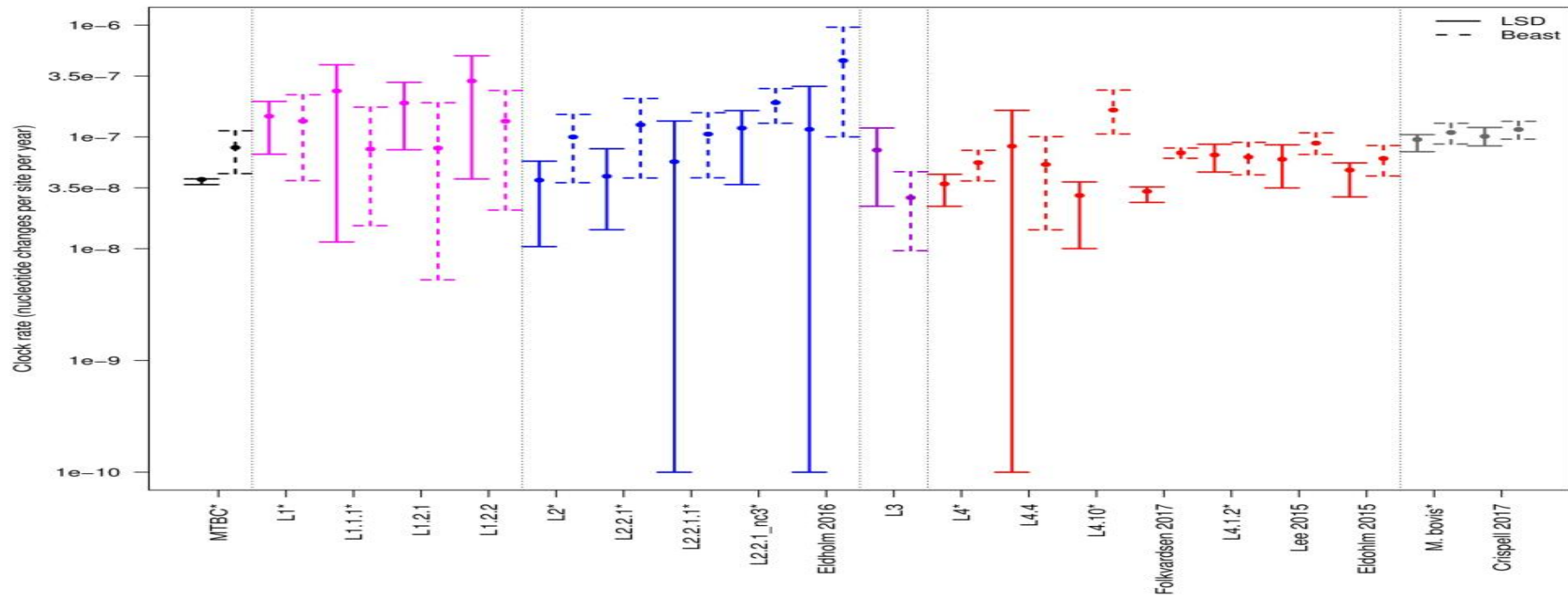


Fig 2. Global map of prevalence of latent TB infection. Median estimated population prevalence of latent *Mycobacterium tuberculosis* infection by country, 2014.

结核分枝杆菌在宿主体内进化的分子特征

- MTB基因组的单克隆性，高度保守，并且不同菌株间很难发生重组或者基因水平转移
- 对临床菌株测序与H37Rv基因组比较发现多种SNP和插入缺失片段，表明MTB菌株的存在较广多态性
- MTB的突变速率约为0.3~0.5突变/基因组/年（2017年）
- 近期一项发表在《PLoS Pathogens》杂志上的研究对全球各地的6285株结核分枝杆菌的分子进化进行了系统研究MTB的分子钟速率约为0.04~2.2 突变/基因组/年（2019年）
- 不同的MTB谱系的分子钟速率存在本质上的不同

- 按照分子钟速率进行排序，进化最快的是第1谱系（0.91突变/基因组/年）其次是第2谱系（0.54突变/基因组/年）、第3谱系菌株（0.14突变/基因组/年）和第4谱系菌株的进化相对较慢（0.25突变/基因组/年）
- 亚谱系L2.2.1（即“现代北京家族”）的进化速率（0.89突变/基因组/年）相较于整个第2谱系菌株更高
- 之前一些研究表明，L2.2.1在流行病学上具有快速增长的传播速率、致病性和耐药性，这些特征也与其相对与第4谱系菌株进化速率更快



江山、常山两县基于社区长达7年的结核分支杆菌传播机制研究

江山、常山两县结核病的基本情况

	2015报告发病率 (/10万)	2016报告发病率 (/10万)	2017报告发病率 (/10万)	2018报告发病率 (/10万)
江山	67.83	60.83	61.28	66.10
常山	86.02	101.03	95.20	100.44
浙江				45.26
全国				59.27

研究对象的人口学特征：男性(74.4%)、老年人(55.6%)、汉族(99.3%)、**本地居民(94.4%)**、农民(79.4%)、低学历(85.6%)

研究背景

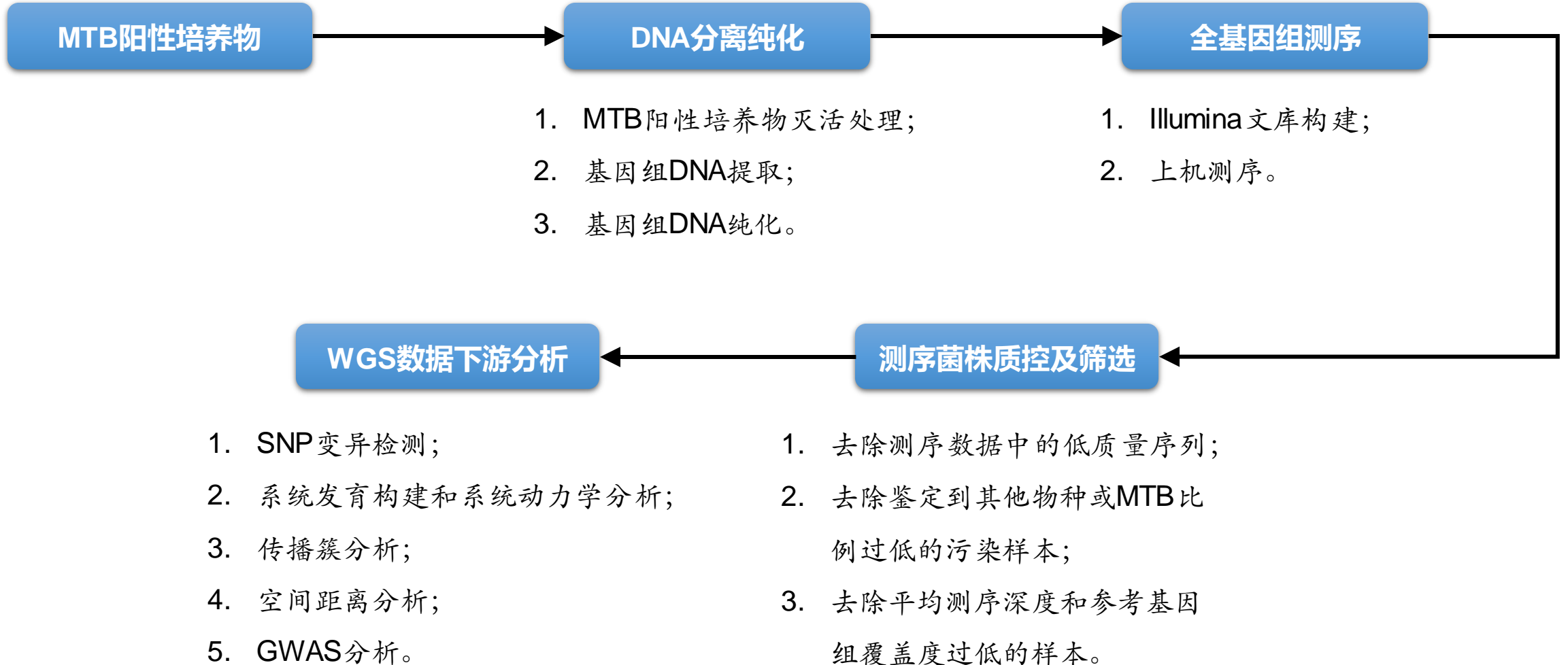
浙江省衢州市辖的常山县和江山市西部与江西省接壤、南部与福建省接壤，省内与杭州市和丽水市毗邻，属于浙江省西部结核病高疫情地区



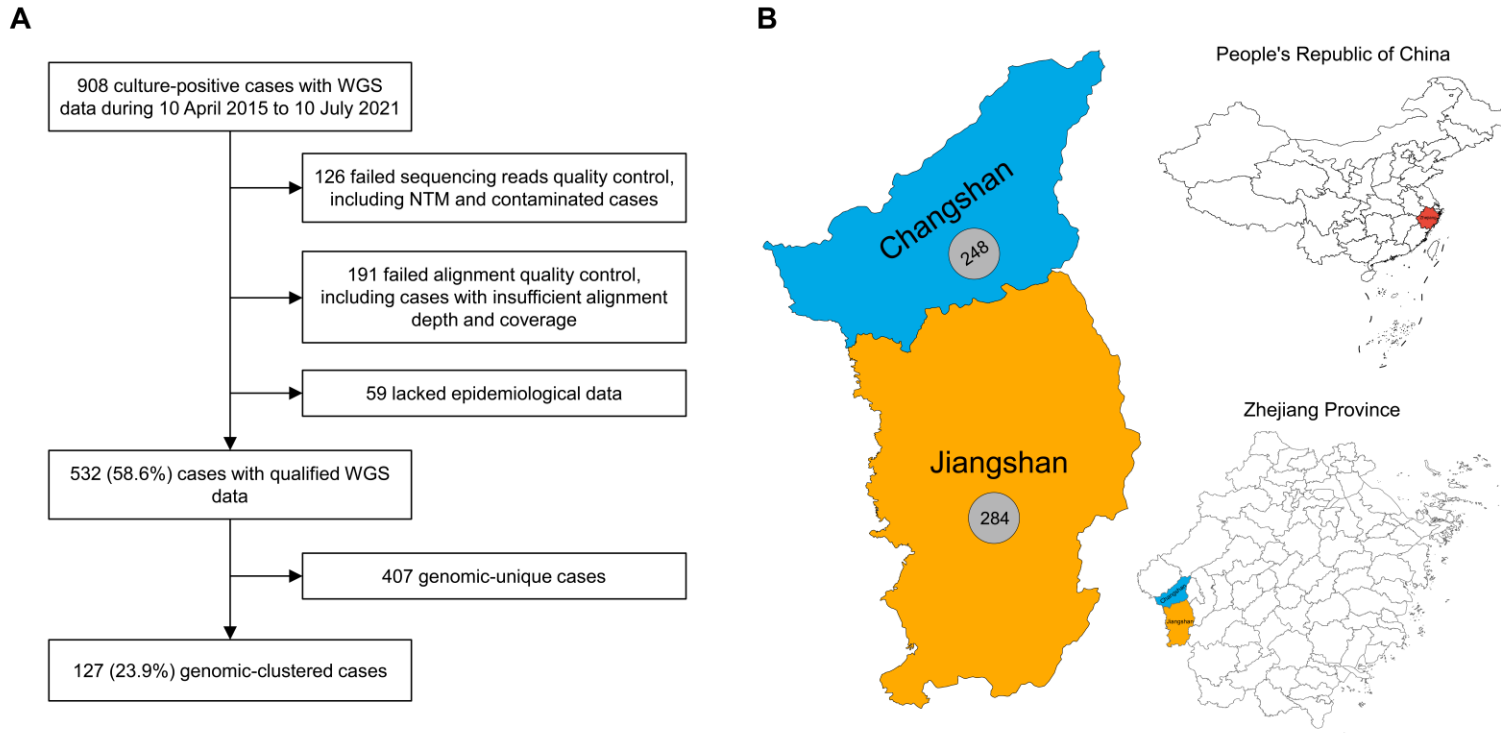
研究设计

- 研究人群包括2015年至2021年期间在中国浙江省西部的江山市（JS）和常山县（CS）当年所有的TB患者并进行培养
- 在流行病学调查之前，所有患者接受了标准化的访谈。患者的人口统计学和临床特征信息从国家结核病登记系统和江山常山地区医院的临床系统中收集
- 综合利用基于WGS的分子流行病学、传统流行病学和空间流行病学，评估研究地区结核病的传播水平和特征，分析传播的风险因素与高危场所

WGS和数据分析



研究结果 —— 江山常山MTB样本的人口特征



- 从2015年4月10日到2021年7月10日，对江山常山收集的共**908**株MTB临床菌株进行全基因组测序
- 经过数据质量控制筛选，最终纳入研究的病例为**532**例（其中常山地区**248**例，江山地区**284**例）
- 剔除了**317**例未通过数据质量控制和**59**例缺乏流行病学数据的病例

Figure 1. (A) 研究样本招募和流程图。 (B) 研究地点地图，江山常山位于中国浙江省南部，属于中国东南部地区。

研究结果 —— 江山常山MTB样本的人口特征

□ 纳入研究的患者中，76%（403/532）为男性，患者的中位年龄为66岁（四分位数范围为53-74岁）

□ 在江山常山地区的患者中，职业分布相对简单，农民占比较高（80%，424/532）

	N	Region		p-value ²
		Overall, N = 532 ¹	CS, N = 248 ¹	
Age	532			<0.001
≤25		30 (5.6%)	8 (3.2%)	22 (7.7%)
25~		57 (11%)	20 (8.1%)	37 (13%)
45~		176 (33%)	71 (29%)	105 (37%)
65~		269 (51%)	149 (60%)	120 (42%)
Gender	532			0.2
Female		129 (24%)	54 (22%)	75 (26%)
Male		403 (76%)	194 (78%)	209 (74%)
Profession	532			<0.001
Catering/Servant		19 (3.6%)	2 (0.8%)	17 (6.0%)
Farmer		424 (80%)	207 (83%)	217 (76%)
Officer/Retiree		35 (6.6%)	23 (9.3%)	12 (4.2%)
Student/Teacher/Doctor		16 (3.0%)	5 (2.0%)	11 (3.9%)
Worker		24 (4.5%)	8 (3.2%)	16 (5.6%)
Other/Unknown		14 (2.6%)	3 (1.2%)	11 (3.9%)
Lineage	532			0.3
Lineage 1		3 (0.6%)	2 (0.8%)	1 (0.4%)
Lineage 2		426 (80%)	192 (77%)	234 (82%)
Lineage 4		103 (19%)	54 (22%)	49 (17%)
Drug resistance	532			0.2
Sensitive		429 (81%)	210 (85%)	219 (77%)
Pre-MDR		43 (8.1%)	17 (6.9%)	26 (9.2%)
MDR		6 (1.1%)	3 (1.2%)	3 (1.1%)
Pre-XDR		5 (0.9%)	1 (0.4%)	4 (1.4%)
Other		49 (9.2%)	17 (6.9%)	32 (11%)

¹ n (%)

² Pearson's Chi-squared test; Fisher's exact test

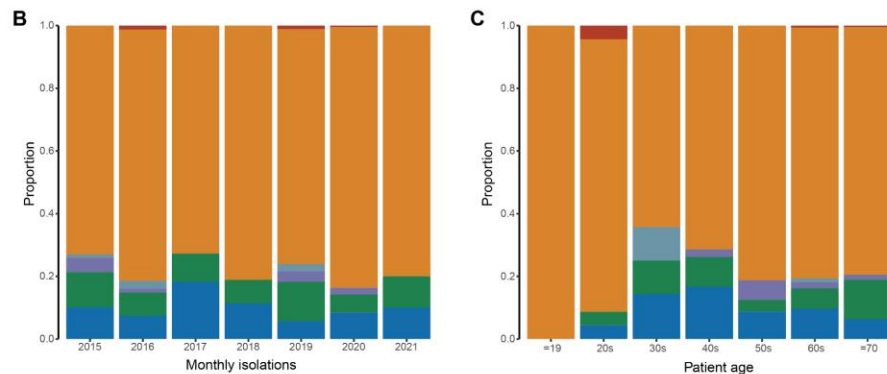
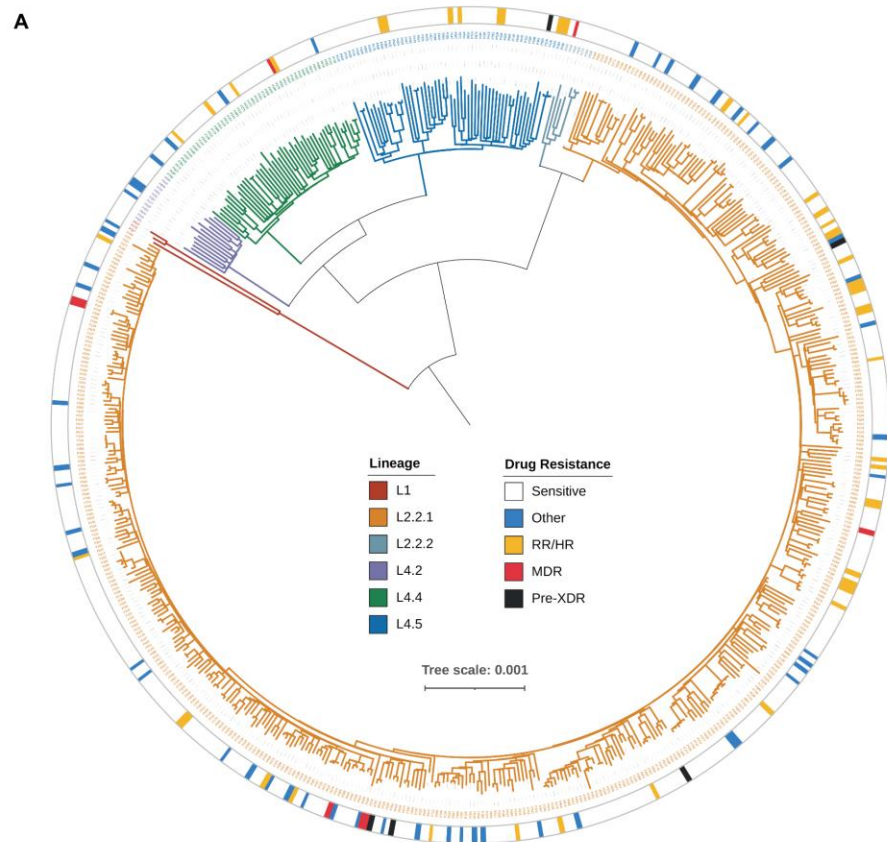
研究结果 —— 基于WGS的基因型分型

在江山常山MTB菌株可分为多个不同谱系

□ 469株 (79.4%) 属于Lineage2, 119株 (20.1%) 属于Lineage4, 3株 (0.5%) 属于Lineage1

□ 按年份分布的谱系频率分布。在研究的7年期间，谱系的分布未发生较大变化

□ 北京型亚谱系 **Lineage2.2.1** 明显与年龄较年轻的人相关联

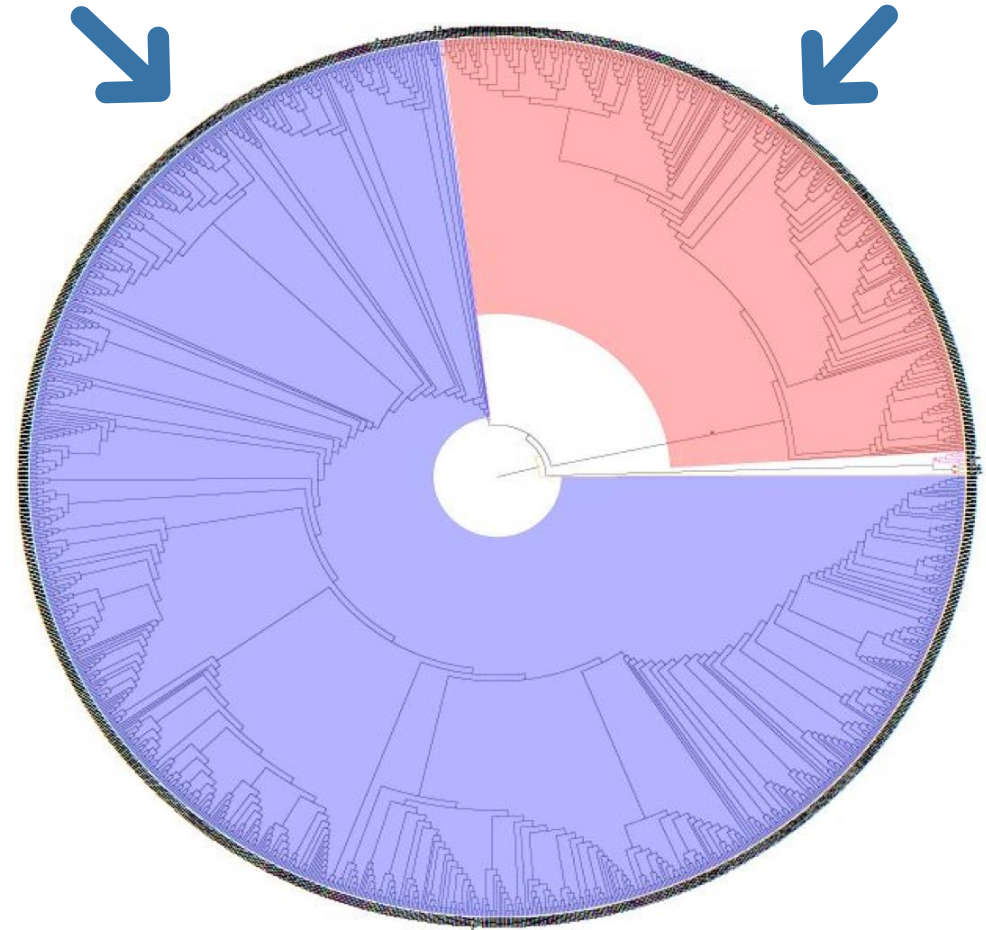


浙江省结核分枝杆菌第二谱系占73.96%

- 1198株结核分枝杆菌仅来自两个 lineage，分别为lineage2和 lineage4
- 1198株结核分枝杆菌中886株属于 lineage2，占有菌株的73.96%，312株属于lineage4，占26.04%
- 886株lineage2的菌株中，40.1%属于 lineage2.3
- **浙江省优势菌群为lineage2.3**

Lineage 2

Lineage 4



浙江省结核分枝杆菌SNP系统发育树图

研究结果 —— 基于WGS的基因型分型

Area	Strains tested	Beijing family strains	Proportion (%)	Location
Beijing	108	100	92.59	north
Gansu	224	196	87.50	north
Heilongjiang	200	179	89.50	north
Henan	95	76	80.00	north
Jilin	326	293	89.88	north
Ningxia	72	49	67.12	north
Shandong	135	116	85.93	north
Shanxi	115	92	80.00	north
Tianjin	112	102	91.07	north
Xinjiang	205	139	67.80	north
Anhui	157	134	85.35	south
Fujian	433	236	54.50	south
Hong Kong	355	243	68.45	south
Hunan	100	66	66.00	south
Jiangsu and Zhejiang	351	243	69.23	south
Zhejiang	1296	964	74.38	south
Shanghai	175	135	77.14	south
Guangxi	208	115	55.29	south
Taipei	356	187	52.53	south
Sichuan	76	44	57.89	south
Jiangsu	260	209	80.38	south

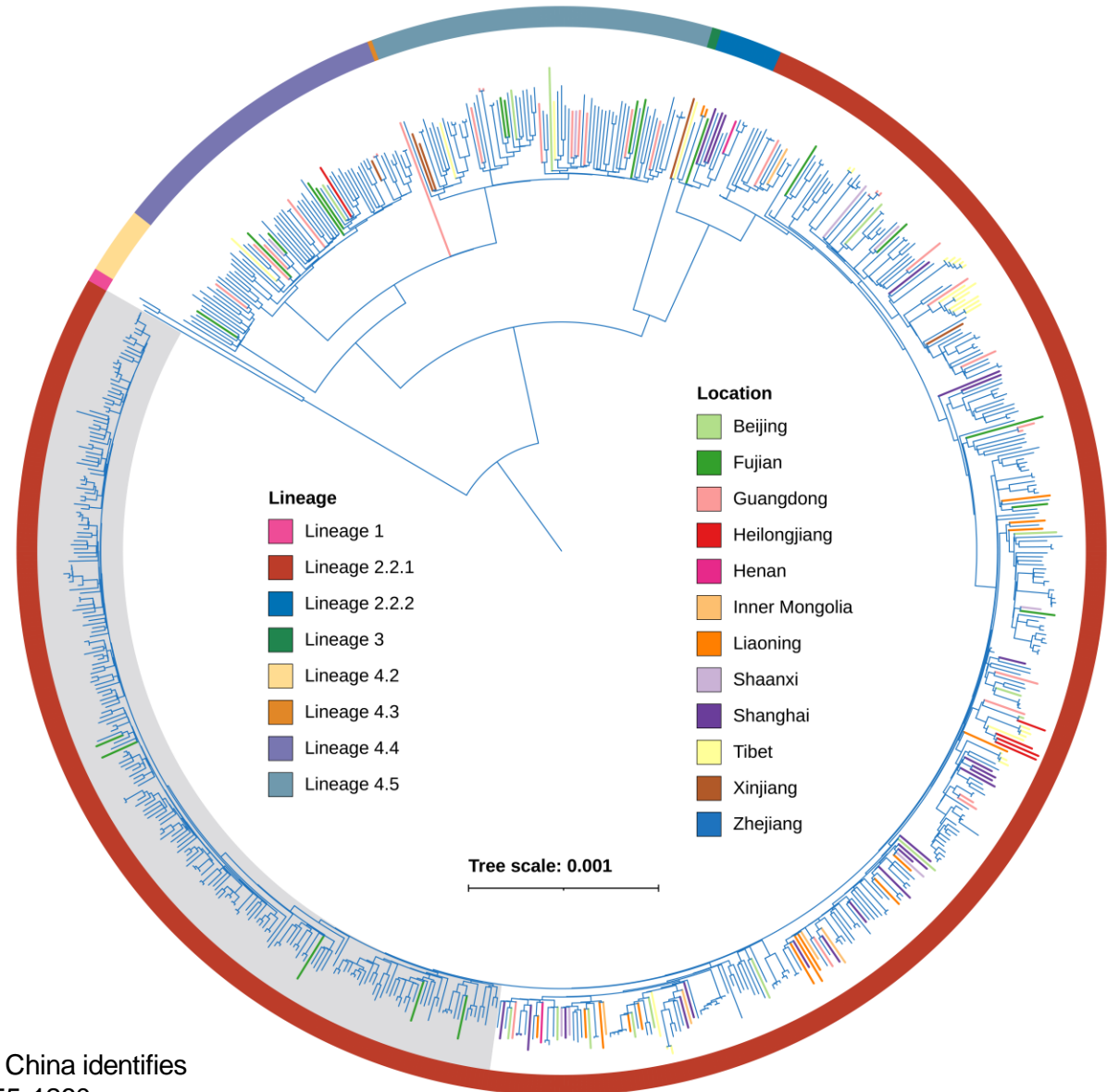
比较江山常山地区与中国其他省份北京型MTB菌株的流行率

- 江山常山地区北京型菌株的流行率 (79.4%) 低于中国北方地区 (例如北京为92.6%，吉林为89.9%)
- 高于西南地区或中部地区 (例如四川为57.9%，湖南为66.0%)
- 与周边地区相似，包括上海为77.14%，江苏为80.38%

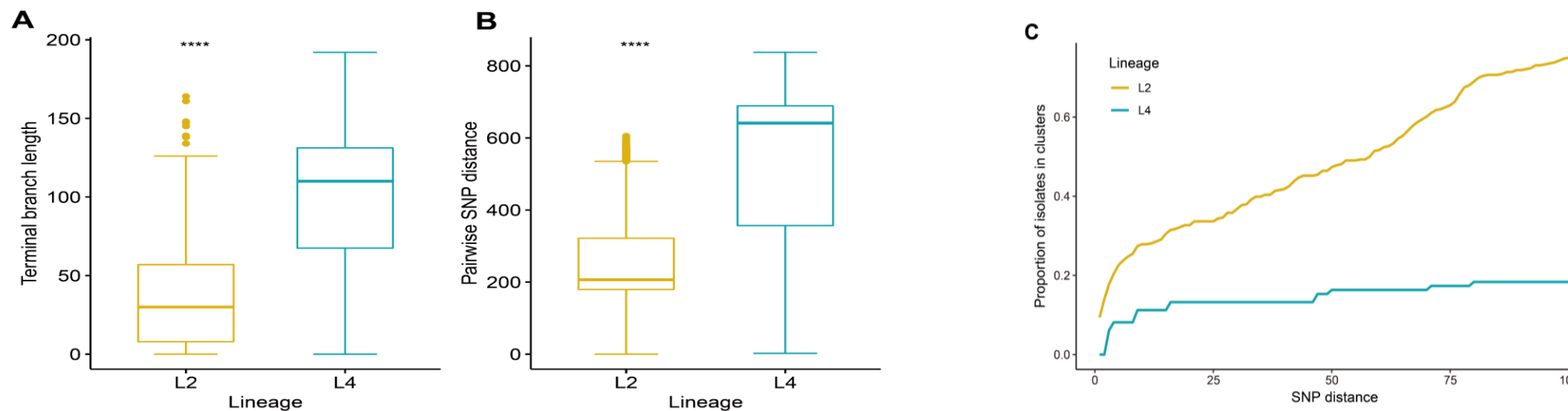
研究结果 —— 基于WGS的基因型分型

江山常山的591株MTB菌株和其他中国地区的161株菌株构建系统发育树。：

- 蓝色线条代表在江山常山地区收集到的菌株，而其他颜色代表在之前研究中，中国其他地区获得的菌株。
- 江山常山地区的大部分菌株与其他地区的菌株混合存在。然而，在现代北京型（**Morden Beijing**）分支中，存在一个亚谱系（属于**L2.2.1**），包含了来自中国东南部的233株菌株，其中228株来自江山常山地区，5株来自福建。
- 此亚谱系中的菌株之间的遗传距离非常小，这表明近十年来江山常山地区可能存在潜在的扩张。



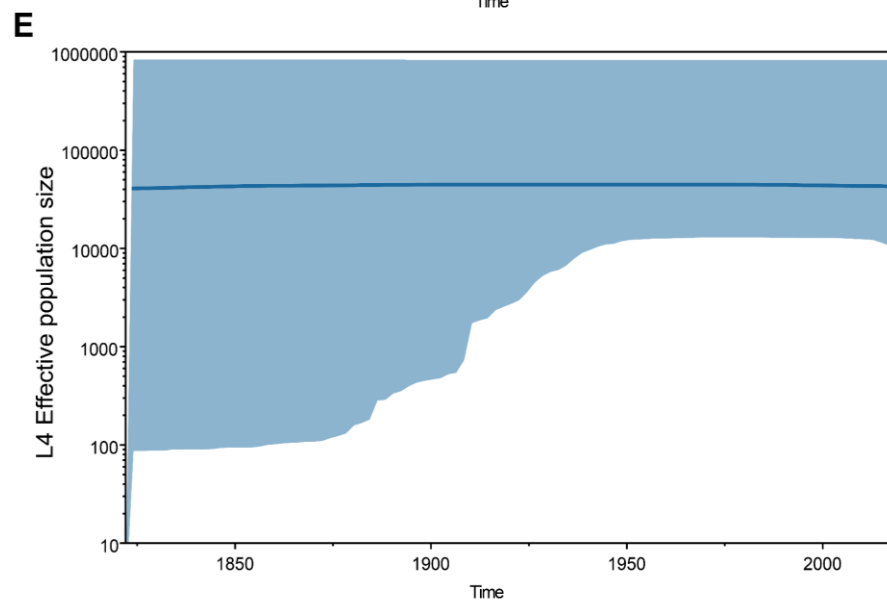
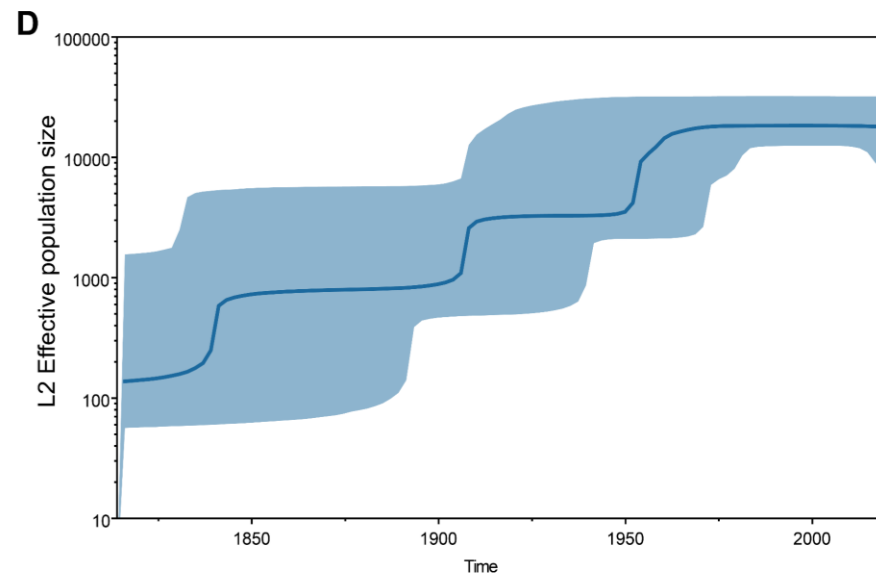
研究结果 —— 江山常山MTB L2和L4菌株基因组特征



- 与L4相比，L2的系统发育树末端支长度显著较短（图A，Wilcoxon检验 $P < 0.001$ ）
- 属于L2的分离株在遗传上更相似，这表现为更小的中位数成对SNP距离（图B，Wilcoxon检验 $P < 0.001$ ）
- 我们使用1-100个SNP的最大成对SNP距离阈值范围来定义传播簇的分布（图C）。与L4菌株相比，L2菌株中属于传播簇的比例显著更高

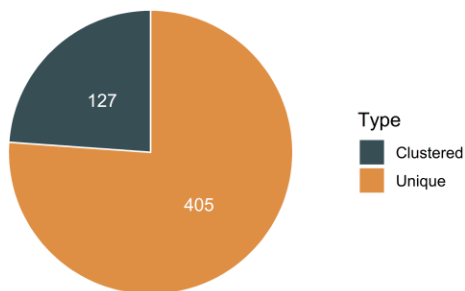
使用Bayesian skyline分析来估计江山常山地区L2和L4菌株种群的历史规模，L2北京菌株有效种群规模扩大

- L2菌株的最近共同祖先 (tMRCA) 估计约为1800年左右。与tMRCA起源相比，显示在1850年代、1910年代和1960年代分别至少有100倍的细菌有效种群规模增长
- L4菌株的细菌有效种群规模保持不变

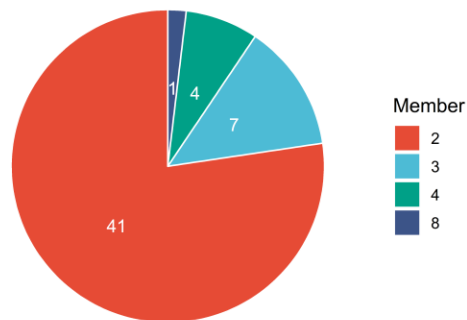


研究结果 —— 基于TransFlow泛基因组学的传播簇的识别

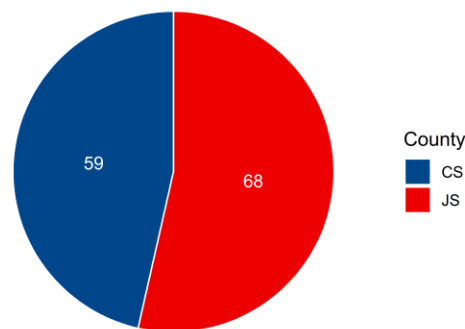
A



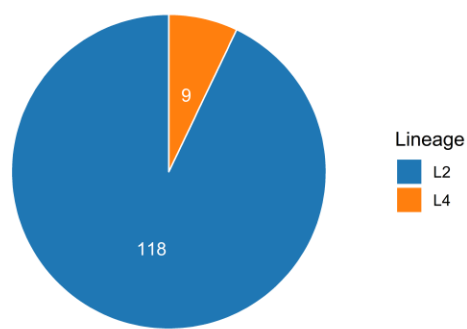
B



C



D



- 共有127株（23.9%，127/532）菌株分为53个传播簇，每个簇含有2至8株菌株，**结果表明近期传播贡献了近四分之一的江山常山地区结核病负担。**
- 常山（23.89%，59/247）和江山（23.94%，68/284）的成簇率几乎相同。
- 北京型和非北京型之间的成簇率存在显著差异（北京型27.7% [118/426] vs 非北京型8.5% [9/106]，Fisher确切性检验 $P < 0.001$ ）。

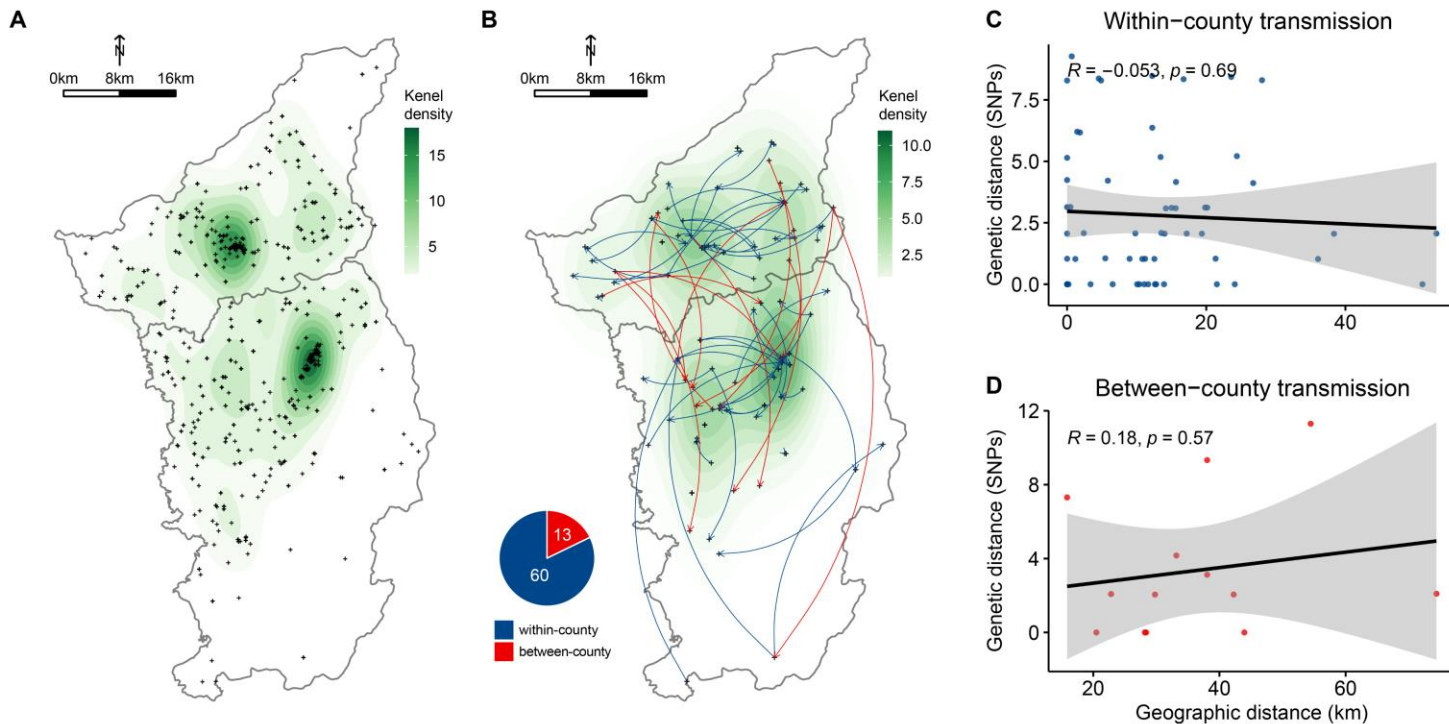
研究结果 —— 传播簇的识别及其风险因素的确定

- 单变量逻辑回归表明 **L2菌株感染**和 **治疗后复发**与成簇存在显著关联。多变量回归证实这两个因素与成簇独立相关
- 与其他患者相比，L2菌株感染病例的传播风险是**12.7**（OR, 12.7; 95% CI, 2.33-241），而治疗后复发病例的传播风险是**7.70**（OR, 7.7; 95% CI, 2.53-25.1）。

	Univariable				Multivariable		
	N	OR [†]	95% CI [†]	p-value	OR [†]	95% CI [†]	p-value
Age	532						
≤25		—	—				
>25		0.52	0.24, 1.16	0.10			
Gender	532						
Female		—	—				
Male		1.41	0.87, 2.34	0.17			
Lineage	529						
Lineage 4		—	—		—	—	
Lineage 2		4.00	2.06, 8.76	<0.001	12.7	2.33, 241	0.018
Drug resistance	532						
Sensitive		—	—				
Drug-resistant		0.73	0.42, 1.22	0.24			
Smoking	168						
No		—	—				
Yes		1.64	0.72, 3.70	0.23			
Treatment history	168						
Treat-naive		—	—		—	—	
Retreatment		5.80	2.08, 16.2	<0.001	7.70	2.53, 25.1	<0.001

[†]OR = Odds Ratio, CI = Confidence Interval

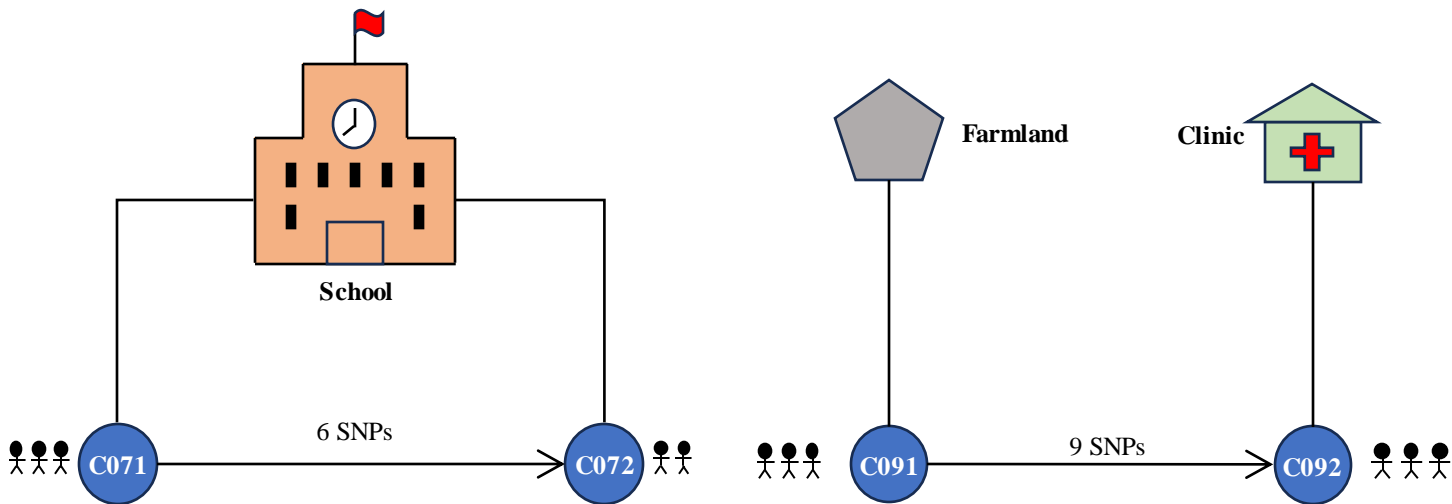
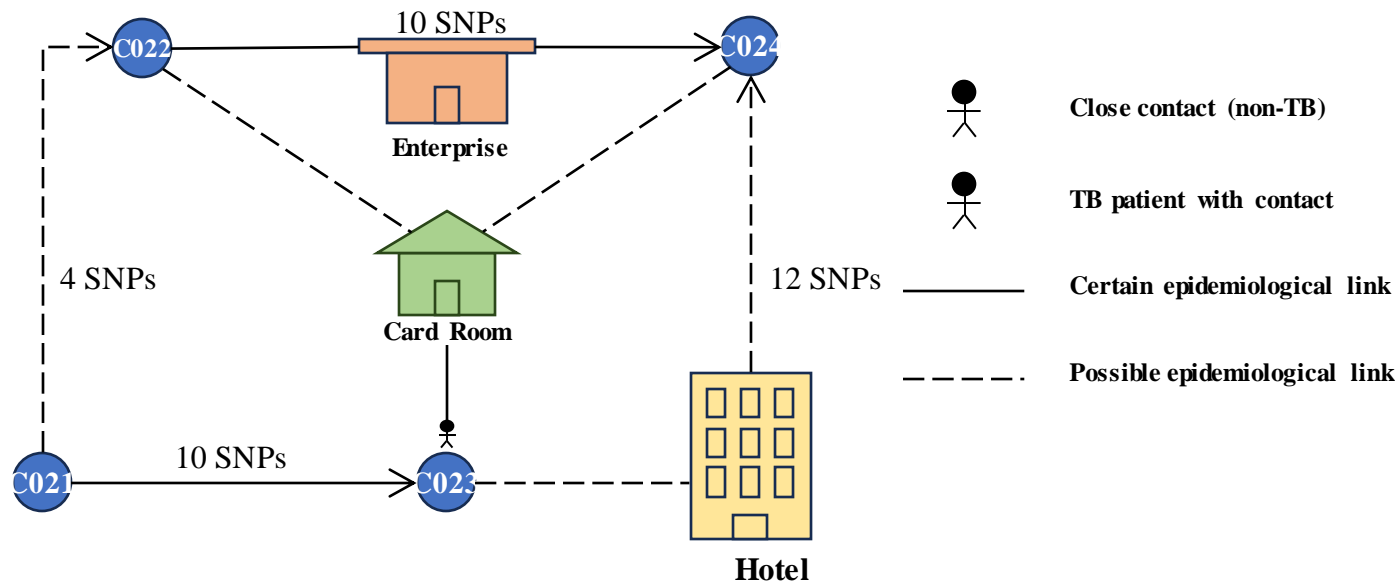
研究结果——江山常山地区结核病病例的空间分析



- 在所有病例和成簇病例的地图中，出现了两个热点区域，分别位于常山（天马街道）和江山（双塔街道）人口密集的中心地带。通过比较每个传播群集中病例的居住区域，发现仅有13例（17.8%，13/73）传播发生在两个县之间，而大多数传播簇（82.2%，60/73）中的患者居住在同一个县。
- 地理距离和基于SNP的遗传距离在县内和县间链路之间都没有相关性。

对江山常山地区结核病病例的空间分布进行表征，使用病人的住址信息绘制了核密度地图，包括所有病例（图A）和成簇病例（图B）

研究结果 —— 基因组成簇患者流行病学调查



- 基于分子结果鉴定的53个传播簇，有8个簇存在确定的流行病学联系，3个簇可能存在流行病学联系。提示现场的TB主要为偶然传播，并没有类似TB低负担国家疫情中超级传播者的存在
- 成簇患者主要为其配偶、子女、孙辈等，部分来自同学或同事的接触
- 棋牌室、室内集市（小超市）、企业、学校、医院等机构是发生TB传播的主要场所

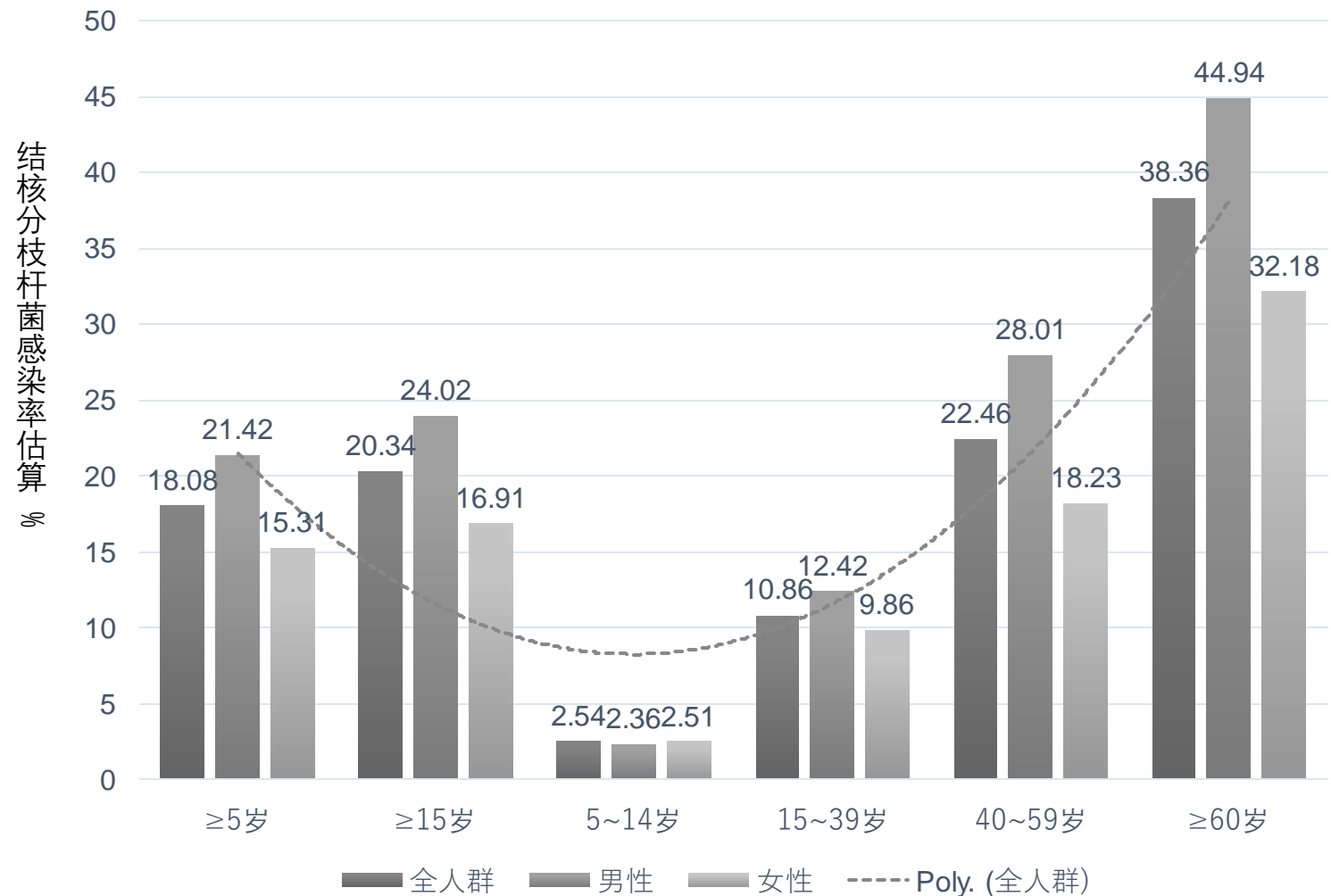
常山、江山的65岁以上老年人群潜伏感染率很高

- 江山市坛石镇、常山县招贤镇、兰溪市女埠镇、海宁市丁桥镇、普陀区六横镇5个县区社区，共调查农村65岁及以上老年人4342人，总体结核分枝杆菌感染率为28.24%
- **常山招贤镇37.1%、江山坛石镇37.4%**、兰溪女埠镇28.4%、海宁丁桥村14.2%、普陀区六横镇22.2%

地区	人数	结核分枝杆菌感染检测结果值					
		阴性		阳性		不确定	
		人数	比例	人数	比例	人数	比例
常山	1000	616	61.60%	371	37.10%	13	1.30%
海宁	1049	890	84.84%	149	14.20%	10	0.95%
江山	884	553	62.56%	331	37.44%	0	0.00%
兰溪	1004	700	69.72%	285	28.39%	19	1.89%
普陀	405	307	75.80%	90	22.22%	8	1.98%
合计	4342	3066	70.61%	1226	28.24%	50	1.15%

$$\chi^2 = 201.9, P < 0.001$$

我国潜伏感染人群的估算，60岁以上人群最高，32.18%



根据B-SHADE模型估算结果显示:

- 2013年我国**5岁及以上人群**结核分枝杆菌潜伏感染率为**18.08%**(95%CI: 13.73% ~ 22.42%);
- **15岁及以上人群**结核分枝杆菌潜伏感染率为**20.34%**(95%CI: 15.63% ~ 25.06%)。
- **5~14岁人群**的结核分枝杆菌潜伏**感染率**较低;
- **15岁以后**呈现**随着年龄增长而升高**的趋势,并且同年龄段男性的潜伏感染率高于女性。

- 随着年龄增加，结核分枝杆菌感染率整体呈现上升趋势
- 同一年龄组，在各地区间的感染率均存在统计学差异，疫情高发地区高于低疫情地区

年龄 分组	调查 人数	结核分枝杆菌感染检测结果值					
		阴性		阳性		不确定	
		人数	比例	人数	比例	人数	比例
65-	1482	1097	74.02%	368	24.83%	17	1.15%
70-	1397	978	70.01%	399	28.56%	20	1.43%
75-	890	604	67.87%	274	30.79%	12	1.35%
80-	347	237	68.30%	109	31.41%	1	0.29%
85-	226	150	66.37%	76	33.63%	0	0.00%
合计	4342	3066	70.61%	1226	28.24%	50	1.15%

$\chi^2=22.16$, $P=0.005$

结核病发病率与结核分枝杆菌感染率关系

son相关分析评
系 (r=0.919,
析显示, 结核
CI: 1.28/10万-

调查地区	常驻人口	发病数	乡镇报告发病 率 (1/10万)	感染阳性比 例 (%)
江山坛石镇	15604	19	121.76	37.44
常山招贤镇	22090	26	117.7	37.10
兰溪女埠镇	28463	26	91.35	28.39
海宁丁桥镇	43738	10	22.86	14.20
舟山六横镇	87043	13	14.94	22.22

结核分枝杆菌感染者发病风险

- 江山、常山两地调查对象中，潜伏感染阳性者在一年内的累积发病率为1200/10万，阴性者为100/10万，平均为491/10万
- 调整相关因素后，潜伏感染阳性者发病风险约为阴性者的9倍左右

The cumulative tuberculosis incidence of participant during the one-year observation period

	No TB (%)	TB (%)	Incidence Rate (per 100,000)	OR (95%CI)	AOR (95%CI)
LTBI results					
Negative	1197 (99.9%)	1 (0.1%)	100	1	1
Positive	635 (98.8%)	8 (1.2%)	1200	15.08 (1.88-120.84)	9.59 (1.07-86.20)

OR, Odds Ratio; AOR, Adjusted Odds Ratio; CI, confidence interval; LBTI, latent tuberculosis infection; TB, tuberculosis; The AOR was adjusted for sex, age, education, marital status, body mass index, smoking status, alcohol consumption, habit of opening windows frequently for ventilation, and the chest radiograph result.

The total is less than 1856 due to missing values.

小结

- 本研究基于泛基因组学的分子传播探测分析，江山、常山菌株成簇率为23.9%，近期传播只贡献了近25%的结核病负担。老年人群潜伏感染率为37%，表明高疫情地区TB传播模式主要为远期感染的内源性复燃，防控机制需要考虑传染源控制与潜伏感染高危人群干预并举，持续每年开展发病高危人群的主动筛查
- 系统发育动力学显示本地区MTB以第2.2.1谱系北京型为主且历史上有多次种群扩大的时期，已演化出本地区特有的种群并在年青人中传播，提示需加强对北京型MTB亚群的监测与研究
- 加强对聚集成簇场所的干预，棋牌室、室内集市（小超市）

谢谢!