

# 全球结核病流行和控制研究进展

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## 肺结核病

慢性感染性疾病  
由结核分枝杆菌感染所致  
肺结核为主要类型 TB  
潜伏感染和发病

When?  
Who?



### MDGs 联合国千年发展目标

-  **Goal 6: Combat HIV/AIDS, malaria and other diseases**  
抗击HIV/AIDS, 疟疾和其他疾病
-  **Goal 1: Eradicate extreme poverty and hunger**  
消除极端贫困
-  **Goal 3: Promote gender equality and empower women**  
促进性别平等, 提升妇女权力
-  **Goal 8: Develop a Global Partnership for Development**  
发展全球伙伴关系

## In 1993, WHO declared TB a global emergency

全球结核病紧急状态



### 全球采取的行动

- ◆ 建立和开展国家结核病控制项目
- ◆ 成立全球抗击结核病联盟: 1998-
- ◆ 实施DOTS 策略
- ◆ 目标: 涂阳结核病治愈率 85%, 发现率 70%

**THE TB TARGETS FOR 2015**  
UN Millennium Development Goals: Do have halved and begun to reverse incidence  
Current assessment: On target in all regions except E. Europe

**The Stop TB Partnership targets:** halving prevalence and deaths by 2015 in comparison with 1990  
Current assessment: Not on target in Africa and Europe



### DOTS 策略及其发展 (Directly Observed Treatment, Short-Course)

- 政府承诺持续开展结核病控制项目
- 对应该就诊病人进行痰涂片检查
- 在病例统一管理的基础上实行标准化疗, 并采用直接观察下的治疗方法
- 有效的药物供应体系
- 建立可用于治疗效果评价的结核病记录和报告系统

**扩大DOTS策略, 遏制结核病策略**



### 逃跑的新郎: XDR-TB Comes (Back) to America

CDC公开警告: 与该患者搭乘同一航班的美国居民(估计有292人)曾长时间与XDR-TB患者共处同一密闭机舱, 虽然受感染的几率不低, 但是他们仍有被传染结核的可能

July 2007. CDC officials confirmed this patient, who was previously diagnosed with XDR-TB (extensively drug resistant tuberculosis), has in fact, MDR-TB

### 高负担国家M/XDR-TB部长会议

WHO calls drug-resistant TB a time bomb as the Gates Foundation and Chinese government announce a \$33 million initiative to fight it

1 April 2009 - Beijing

### 耐药结核病和广泛耐药结核病(M/XDR-TB)

- ❖ 耐药性结核病 (MDR-TB) 是指同时对异烟肼和利福平这两种最重要的抗结核药耐药
- ❖ 耐药结核病更难治疗且费用更高, 更可能导致发展中国家病死率上升
- ❖ XDR-TB是在MDR-TB耐药的基础上, 还对任何氟喹诺酮类药物以及三种二线注射药物(硫酸卷曲霉素、卡那霉素和阿米卡星)中至少一种具有耐药性的结核

### Estimated TB incidence rates, 2010

- 8.7 million new cases in 2011, 13% HIV/TB co-morbidity
- 1.4 million TB deaths in 2011, 1 million HIV (-)
- one of the top killers of women, with 500 000 deaths
- 12.0 million prevalent cases in 2010

WHO 2012 report

Table 2.2 Estimated burden of disease caused by TB, 2011. Numbers in thousands.

Region	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	Estimated burden of disease caused by TB, 2011	
Algeria	33 358	13	7.3	23	130	55	1300	411	33	0.3	0.4
Algeria	134 814	84	2.9	140	420	200	1 000	400	800	0.4	1.2
Algeria	14 505	9.1	4.3	16	120	90	140	43	53	7.0	3.5
Algeria	1 327 000	47	12	48	1 200	1 200	1 000	1 000	1 000	1.2	1.7
Algeria	87 739	16	16	62	250	180	120	220	220	34	27
Algeria	84 224	14	11	120	200	200	200	200	200	24	24
Algeria	1 241 869	100	100	420	1 000	1 000	2 000	2 000	2 000	53	77
Algeria	242 230	62	7.9	120	620	250	1 200	600	600	10	11
Algeria	31 810	6	4.7	15	120	84	200	130	130	120	85
Algeria	24 810	11	4.6	22	120	84	200	130	130	84	84
Algeria	136 152	12	11	120	240	180	1 000	100	100	92	12
Algeria	162 471	37	6.1	64	240	21	620	190	300	50	23
Algeria	86 810	29	2.7	21	440	400	200	200	200	11	24
Algeria	162 480	22	2.2	44	380	22	200	200	200	3.4	1.4
Algeria	59 810	25	11	44	380	22	200	200	200	3.8	2.0
Algeria	69 810	9.8	4.2	18	110	61	200	80	71	100	13
Algeria	59 810	9.8	4.2	18	110	61	200	80	71	100	13
Algeria	49 810	6.4	3.1	11	82	43	130	78	73	83	28
Algeria	89 810	8.1	1.2	8.9	270	130	1000	100	100	220	11
Algeria	12 718	6.1	2.4	11	77	110	77	50	50	66	66
Algeria	4 270 774	820	820	820	8 200	8 200	11 000	7 200	8 200	820	820
Algeria	819 269	720	180	270	1 000	1 000	2 000	2 000	2 000	820	820
Algeria	184 810	21	1.8	24	330	250	420	260	240	32	40
Algeria	608 810	98	31	150	650	650	650	650	650	97	89
Algeria	809 810	45	4.4	44	500	370	1 050	350	350	400	23
Algeria	809 810	160	350	620	1 600	1 600	1 600	1 600	1 600	1 600	170
Algeria	809 810	130	1 000	1 100	2 000	2 000	2 000	2 000	2 000	100	81
Algeria	809 810	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000

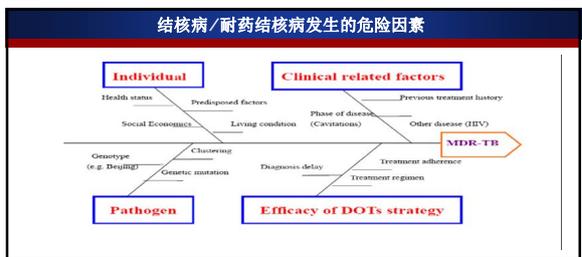
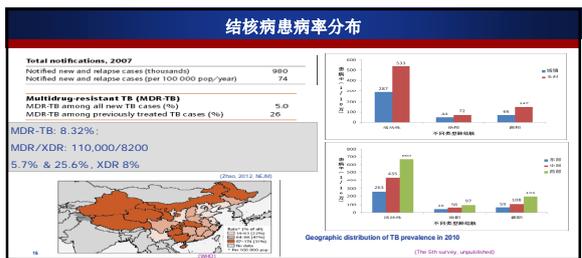
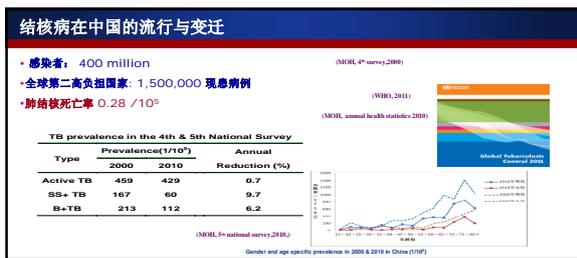
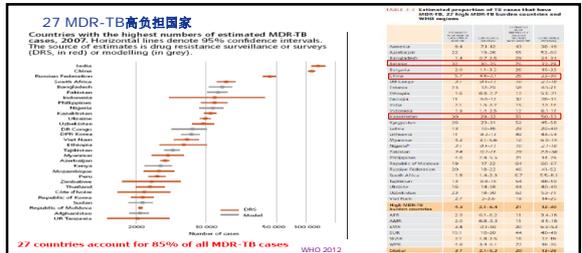
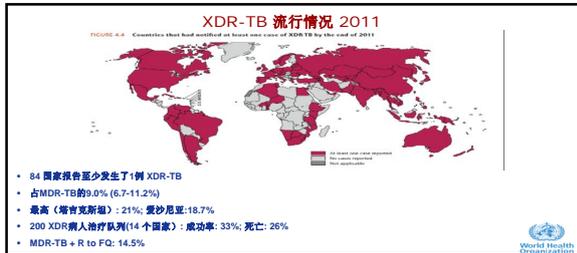
WHO 2012 report

### MDR-TB 流行情况 2011

估计病例数: 310 000 (220000-400000)  
 报告数: 60 000, Detection: 19%  
 新病人中的MDR-TB: 3.7% (2.1-5.2)  
 既往病人中的MDR-TB: 20% (13-26)  
 50% 病例中国和印度, 3% 和 6% 发现

治疗成功率: 48% (目标: 75%);  
 失访: 28%  
 治疗成本: 50-200 倍

WHO 2012 global report



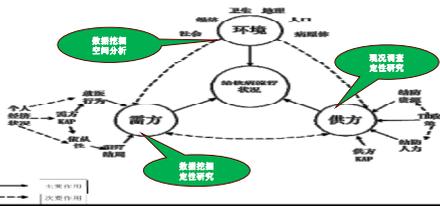
### 结核病流行和控制研究进展

- ✓ 结核病和耐药结核病流行危险因素研究
- ✓ 结核病和耐药结核病控制策略研究
- ✓ 结核杆菌潜隐感染研究
- ✓ 结核病流行和传播的分子流行病学研究

### 社会经济发展和结核病流行

- ✧ 结合社会经济发展指标
- ✧ 结合地理环境信息
- ✧ 综合发病率、患病率和死亡率指标

### 结核病高疫情社会经济影响因素的研究



### Area-based socio-economic disadvantage and tuberculosis incidence

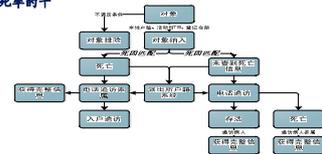
DESIGN: All incident TB cases in Washington State, United States ( $n = 2161$ ), reported between 1 January 2000 and 31 December 2008 were identified. Multivariate Poisson analysis was used at the ZIP Code™ tabulation area (ZCTA) level, which allowed for further exploration of area-specific influences on TB incidence.

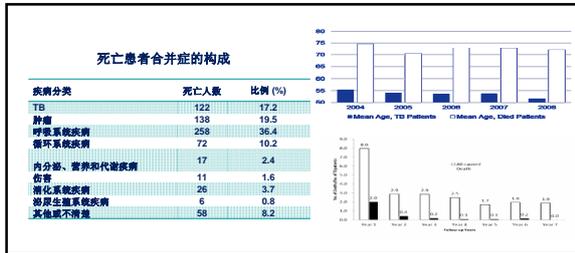
### Area-based socio-economic disadvantage and tuberculosis incidence

ZIP Code	Population	Incidence Rate	Relative Risk	P-value
98001	10,000	1.0	1.0	>0.05
98002	15,000	1.2	1.2	<0.001
98003	20,000	1.5	1.5	<0.001
98004	25,000	1.8	1.8	<0.001
98005	30,000	2.0	2.0	<0.001
98006	35,000	2.2	2.2	<0.001
98007	40,000	2.5	2.5	<0.001
98008	45,000	2.8	2.8	<0.001
98009	50,000	3.0	3.0	<0.001
98010	55,000	3.2	3.2	<0.001
98011	60,000	3.5	3.5	<0.001
98012	65,000	3.8	3.8	<0.001
98013	70,000	4.0	4.0	<0.001
98014	75,000	4.2	4.2	<0.001
98015	80,000	4.5	4.5	<0.001
98016	85,000	4.8	4.8	<0.001
98017	90,000	5.0	5.0	<0.001
98018	95,000	5.2	5.2	<0.001
98019	100,000	5.5	5.5	<0.001

### 控制和降低死亡率研究

- ✧ 城市结核病患者死因归类及降低病死率的干预措施研究
- ✧ 设计: 历史性队列研究
- ✧ 方法: Cox比例风险模型





### 结核病患者诊断后因结核病死亡的Cox回归分析

特征	N % total	Crude HR 95% CI	Adjusted HR 95% CI
性别			
男	1595 23.6	1	1
女	976 26.7	0.9 0.7-1.1	1.0 0.8-2.3
年龄	1377 20.2	0.9 0.8-1.1	1.0 1.1-1.0 †
死亡	702 16.5	0.9 0.8-1.2	1.0 1.0-1.2 †
民族	1213 21.7	1	1
汉	3508 74.3	0.6 0.2-0.7 †	0.5 0.3-0.8 †
维吾尔族	4234 89.7	1	1
哈萨克族	16 0.3	0.8 0.1-5.5	1.0 0.2-11.3
蒙古族	51 1.1	2.0 0.4-20.9	1.5 0.3-11.1
藏族	391 8.3	0.8 0.4-1.6	1.1 0.5-2.3
其他民族	29 0.6	1.4 0.2-10.1	1.4 0.3-17.4
其他	2369 45.1	4.2 2.7-6.5 †	3.1 1.9-5.0 †
其他	2715 56.6	1	1
其他	172 3.3	1.3 0.5-3.4	1.2 0.5-3.3

### 结核病患者诊断后因结核病死亡的Cox分析-续

特征	N % total	Crude HR 95% CI	Adjusted HR 95% CI
教育			
有	1401 26.7	1.0 0.7-1.5	0.9 0.5-1.4
无	3776 71.9	1	1
不确定或不清楚	74 1.4	2.9 1.1-8.0 †	2.3 0.8-6.6
职业			
有	43 0.9	3.4 1.2-9.4 †	3.1 0.7-6.1
无	1679 31.3	1	1
有职业但不清楚	1322 25.2	0.9 0.5-1.1	1.3 0.8-1.9
肺结核治疗史			
有	899 17.4	1	1
无	822 17.4	1.5 1.0-2.3 †	1.6 1.0-2.5

### 耐药结核病流行病学调查-中国

Table 1. Drug Susceptibility and Resistance to First-Line and Second-Line Antituberculous Drugs.<sup>10</sup>

Susceptibility or Resistance	Patients with New Cases of Tuberculosis (N=3037)		Patients with Previously Treated Tuberculosis (N=497)	
	no.	% (95% CI)†	no.	% (95% CI)†
Susceptibility to all four first-line drugs‡	2009	65.8 (62.4-69.1)	417	45.5 (40.6-50.4)
Resistance to first-line drugs				
Any first-line drug	1028	34.2 (30.8-37.6)	475	54.5 (49.6-59.4)
Isoniazid	486	16.0 (13.9-18.1)	315	38.5 (33.7-43.3)
Rifampin	202	6.7 (5.3-8.0)	258	28.4 (24.8-34.0)
Ethambutol	153	4.9 (3.7-6.1)	157	17.2 (13.7-20.7)
Streptomycin	814	27.7 (24.4-31.0)	200	27.2 (22.5-42.0)
Fluoroquinolone or rifampin (but not both)	318	11.2 (8.4-14.2)	141	16.1 (8.0-24.7)
Multidrug resistance§	175	5.7 (4.5-7.0)	236	25.6 (21.2-29.8)
Susceptibility to rifampicin and kanamycin	2006	95.8 (94.7-96.9)	797	88.6 (85.3-91.8)
Resistance to rifampicin and kanamycin				
Ofloxacin or kanamycin	131	4.2 (3.1-5.3)	95	11.4 (8.2-14.7)
Ofloxacin	88	2.7 (1.8-3.6)	76	9.7 (6.1-11.2)
Kanamycin	59	2.0 (1.4-2.6)	21	4.8 (2.5-7.2)
Multidrug resistance plus resistance to ofloxacin or kanamycin	58	1.8 (1.0-2.6)	73	9.5 (6.4-10.6)
Extensive drug resistance¶	15	0.5 (0.2-0.8)	14	2.1 (0.6-3.5)

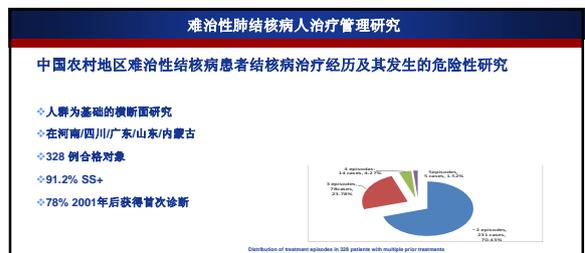
Zhao Y et al., 2012 NEJM

### 耐药相关危险因素分析

Table 2. Multivariate Analysis of Risk Factors for Drug-Resistant TB in New and Previously Treated Cases of TB.<sup>10</sup>

Risk Factor	New Cases of TB		Previously Treated TB	
	Drug-Resistant, Non-Multidrug-Resistant TB	Multidrug-Resistant TB	Drug-Resistant, Non-Multidrug-Resistant TB	Multidrug-Resistant TB
	adjusted odds ratio (95% CI)†			
Female sex	0.9 (0.7-1.1)	1.3 (1.0-2.1)	1.7 (1.1-2.7)	2.2 (1.4-3.5)
Age >60 yr	0.9 (0.7-1.1)	NA‡	0.8 (0.5-1.2)	0.4 (0.1-0.7)
Occupation as construction	1.2 (1.0-1.4)	1.4 (1.0-2.0)	NA‡	NA‡
Residence in area with DOTS implementation in 2000 or after	0.8 (0.7-1.0)	NA‡	1.4 (1.0-2.0)	1.7 (1.2-2.4)
History of treatment with TB drugs and prior TB diagnosis	reference	reference	reference	reference
No treatment, with or without a prior TB diagnosis	reference	reference	reference	reference
Treatment of <1 mo and a prior TB diagnosis	1.6 (1.1-2.1)	1.2 (0.7-2.4)	NA	NA
Treatment of any duration and/or prior TB diagnosis	1.2 (0.9-1.5)	2.4 (1.5-3.8)	NA	NA
No. of prior TB treatment episodes and medical facility providing last TB treatment				
One prior course of treatment, at medical facility other than TB hospital	NA	NA	reference	reference
One prior course of treatment, at TB hospital	NA	NA	1.6 (0.7-3.5)	1.5 (0.6-4.4)
≥2 prior courses of treatment, with last treatment at medical facility other than TB hospital	NA	NA	1.5 (0.8-2.3)	3.3 (0.1-9.2)
≥2 prior courses of treatment, with last treatment at TB hospital	NA	NA	4.0 (1.2-14.0)	13.3 (3.9-46.0)

† NA denotes not applicable.  
‡ These variables were not included in the final logit-regression models.



### 患者既往治疗中二线药使用情况

Episode	No. of patients	total	Using of 2 <sup>nd</sup> -line drugs			Health facilities		
			No. of drugs (%)	1 drug	>1 drug	CTD	Hospital	Others
1	228	18(5.9)	9(5.0)	3(5.0)	14 (77.8)	4(22.2)	-	-
2	338	48(14.6)	25(52.1)	23(47.9)	19 (39.6)	28(58.4)	1(2.1)	-
3	97	44(45.4)	12(27.3)	32(72.7)	4 (9.1)	36(81.8)	4(9.1)	-
4	19	9(47.7)	1(11.3)	8(88.9)	-	6(66.7)	3(33.3)	-
5	5	2(40.0)	-	2(100.0)	-	2(100.0)	-	-

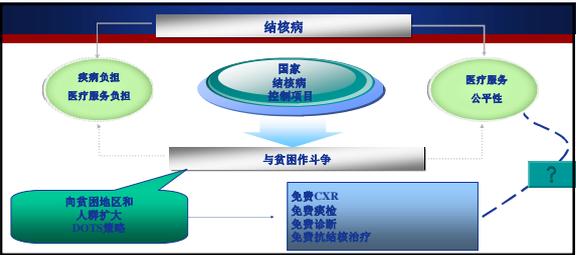
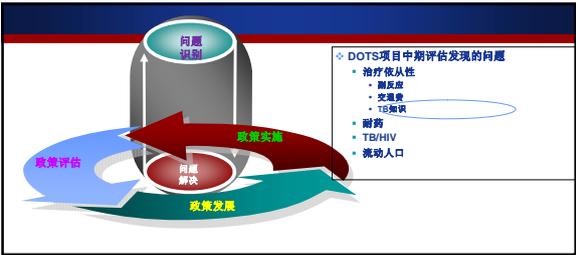
Using of 2nd line drugs in patients with different 1<sup>st</sup>-line drug resistant patterns

Susceptibility/resistance	2nd-line drug used		2nd-line drug not used	
	No.	%	No.	%
Susceptible	40	85.1	7	14.9
MDR-TB	120	89.5	29	19.5
Other resistance	52	86.7	8	13.3
Total	212	82.8	44	17.2

Chi square: 1.342, p=0.311  
\* Missing value: 21

### 二线抗结核药物使用影响因素的多因素分析

Factors	β	p	OR	95.0% CI	
				Lower	Upper
Gender(M vs. F)	-.619	.160	.539	.227	1.276
Age (yrs.)	-.023	.145	.977	.946	1.008
Average annual income (CNY)	-.197	.001	1.170	.741	1.848
No. of treatment episode		0.000			
3 vs. 2	1.529	.001	4.615	1.860	11.446
4 vs. 2	2.814	.000	16.683	3.510	79.302
Education years (>6vs. <=6)	-.897	.071	.408	.154	1.079
Medical insurance		.012			
NCMS vs. none	-.987	.188	.420	.116	1.526
Others vs. none	.746	.263	2.109	.571	7.790
smear microscopy (+ vs. -)	.276	.763	1.318	.219	7.932
DST of 1st-line drugs		.347			
MDR vs. Susceptible	-0.222	.879	.905	.273	2.997
Other DR vs. Susceptible	-0.123	.752	.801	.201	3.187

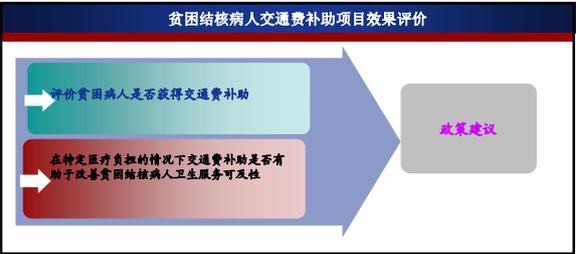


### 贫困结核病人交通费补助项目-实施原则

- 针对贫困的肺结核患者实施交通补助费
- 交通补助费的发放由县级防结核机构具体负责实施
- 要在配套经费及时足额到位的基础上, 开展此项工作
- 在国家测算补助对象人数的基础上, 各省要结合实际对补助人数进行测算

额度: 10CNY/次, 6-8 次  
范围: 当地所有结核病人的30%

(贫困肺结核病人交通费补助项目实施原则)





### 研究结果

单次交通费 (CNY)

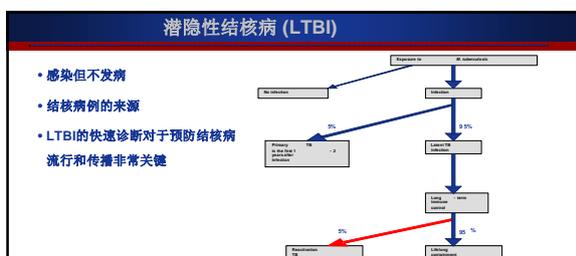
Sites	Mean	Median	P25-P75
Shapingba	7.36	3.5	2-10
Wanzhou	19.18	16	5-30
Xianyou	17.19	15	10-20
Datian	23.08	20	6.5-40
Total	15.92	12	4-20

Sites	Before				On and after			
	Mean	Median	Min	Max	Mean	Median	Min	Max
Shapingba	27.19	0	0	10	5.5	27.5	0	350
Wanzhou	34.38	0	0	6.5	79	64	0	400
Xianyou	42.27	0	0	0	121	105	0	490
Datian	135.7	30	0	200	162	140	0	700

- ### 结论
- ◆ 贫困病人交通费补助项目得到了患者和医务人员的认可，尤其是对贫困病人的倾斜和扶助得到了肯定
  - ◆ 交通费补助对于贫困病人坚持随访完成治疗发挥了非常重要的作用
  - ◆ 现有的补助额度可以满足城区、交通便利地区结核病人的交通费用，但对于偏远山区的结核病人而言补助额度偏低，作用微小
  - ◆ 项目的实施在一定程度上受制于有限的经费、有限的补助范围、缺乏贫困病人的筛选工具和政策与经费的可持续性等因素

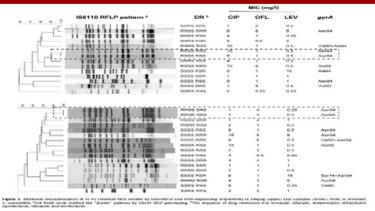
- ### 政策建议
- ◆ 评价标准合理化，操作流程简单化
  - ◆ 补助范围扩大化、补助额度弹性化
  - ◆ 确保政策的可持续性发展
  - ◆ 加大健康教育，提高结核病患者卫生服务可及性
  - ◆ 充分发挥新农合的作用，进一步减轻结核病人的经济负担



- ### 上海市结核病密接和学生人群LTBI研究
- #### 研究问题
- ◆ 发达城市儿童结核感染负担和年感染风险?
  - ◆ 普通城市居民结核感染负担及发病风险?
  - ◆ 结核病人密切接触者结核感染危险?



### 耐喹诺酮菌株成簇性分析



### 政策建议

- ✓ 慎用二线药物
- ✓ 治疗前药敏实验 (尤其是异烟肼和利福平)
- ✓ 干预高危人群
- ✓ 关注优势菌株

### 正在或急需开展的重要研究

- ◇ MDR-TB 诊断及可及性及其影响因素-前方供方
- ◇ 贫困与结核病发病
- ◇ 以细菌学为依据的耐药结核病诊断和新诊断技术评价
- ◇ MDR-TB 治疗可及性及其影响因素
- ◇ MDR-TB 治疗方法、管理和成本效果
- ◇ 二线药物的使用、管理和耐药监测
- ◇ 结核病治疗 DOT 新方法
- ◇ 结核病综合防治模式
- ◇ 将(耐药)结核病治疗纳入新农合
- ◇ 结核感染控制



### 合作伙伴

- > NCTB, 上海市CDC, 山东省TB控制中心, 上海市肺(TB)重点实验室, 上海市肺科医院;
- > 浙江省德清县、湖北当阳市、江苏省建湖、阜宁、灌云县和扬州市CDC, 重庆市结核病所, 福建省CDC, etc.
- > 上海市CDC, 长宁、普陀、松江、嘉定、徐汇、闵行、杨浦区 and 浦东新区CDC等
- > 美国公共卫生研究所, 林斯顿结核病控制项目
- > 瑞典Karolinska Institutet
- > 德国Heidelberg University

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**TB ANYWHERE IS EVERYWHERE**

THE CALL TO STOP TB

Actions for Life

Invest

Research

Act

now to Stop TB

**Thank you**

For sharing  
time, talent  
& Knowledge