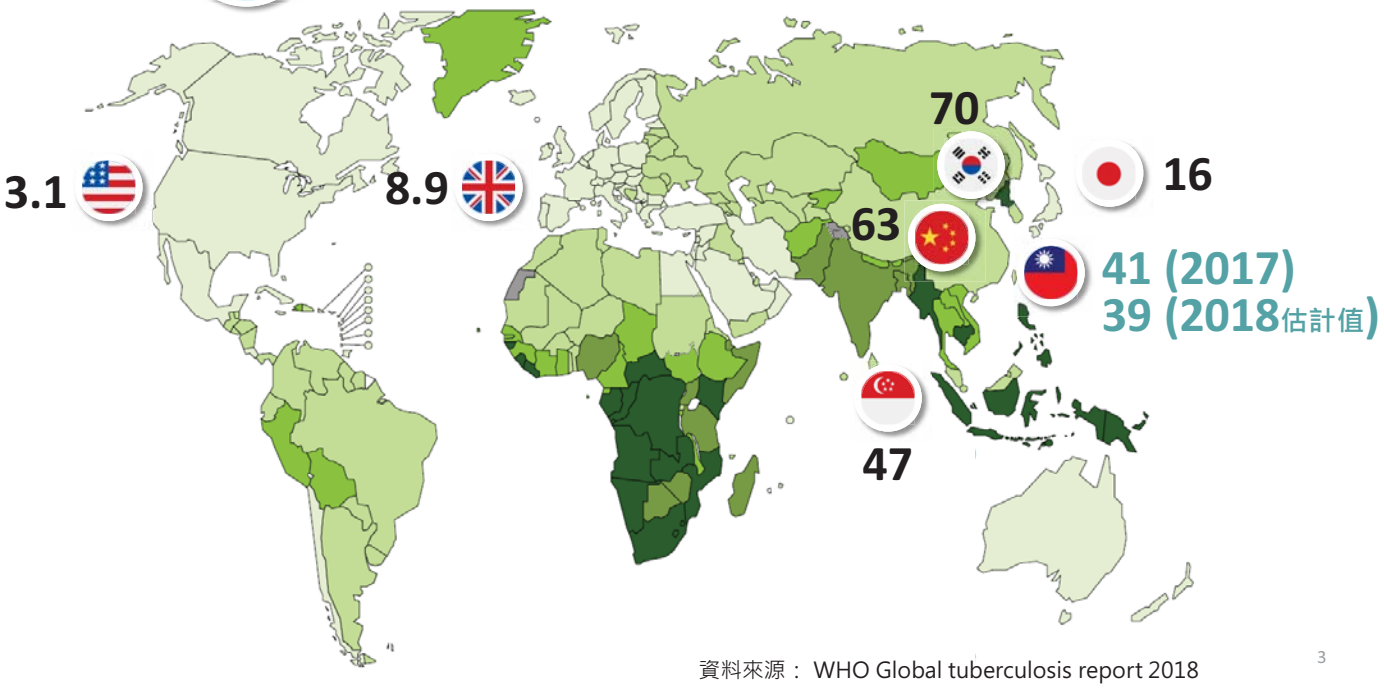
被結核菌感染了，怎麼辦？

台大內科莊祐中醫師

被結核菌感染了，怎麼辦？

2017年各國結核病流行情形



資料來源： WHO Global tuberculosis report 2018

全球結核病負擔

960萬	150萬	120萬	48萬
新發結核病人	死於結核病	HIV感染者發生結核病，其中40萬死亡	多重抗藥性結核病人，其中19萬死亡

WHO: The End TB Strategy 2015

目前進展

2000年~2014年間透過有效診斷與治療使**430萬**結核病人存活

自1990年起，死亡率降低**47%**，盛行率降低42%

過去十年來，HIV感染者因TB死亡已下降**32%**

2014年幾乎所有確診為**MDR-TB**的病人皆開始二線藥物治療

未來挑戰

結核病防治每年仍有**14億**美元之**資金短缺**

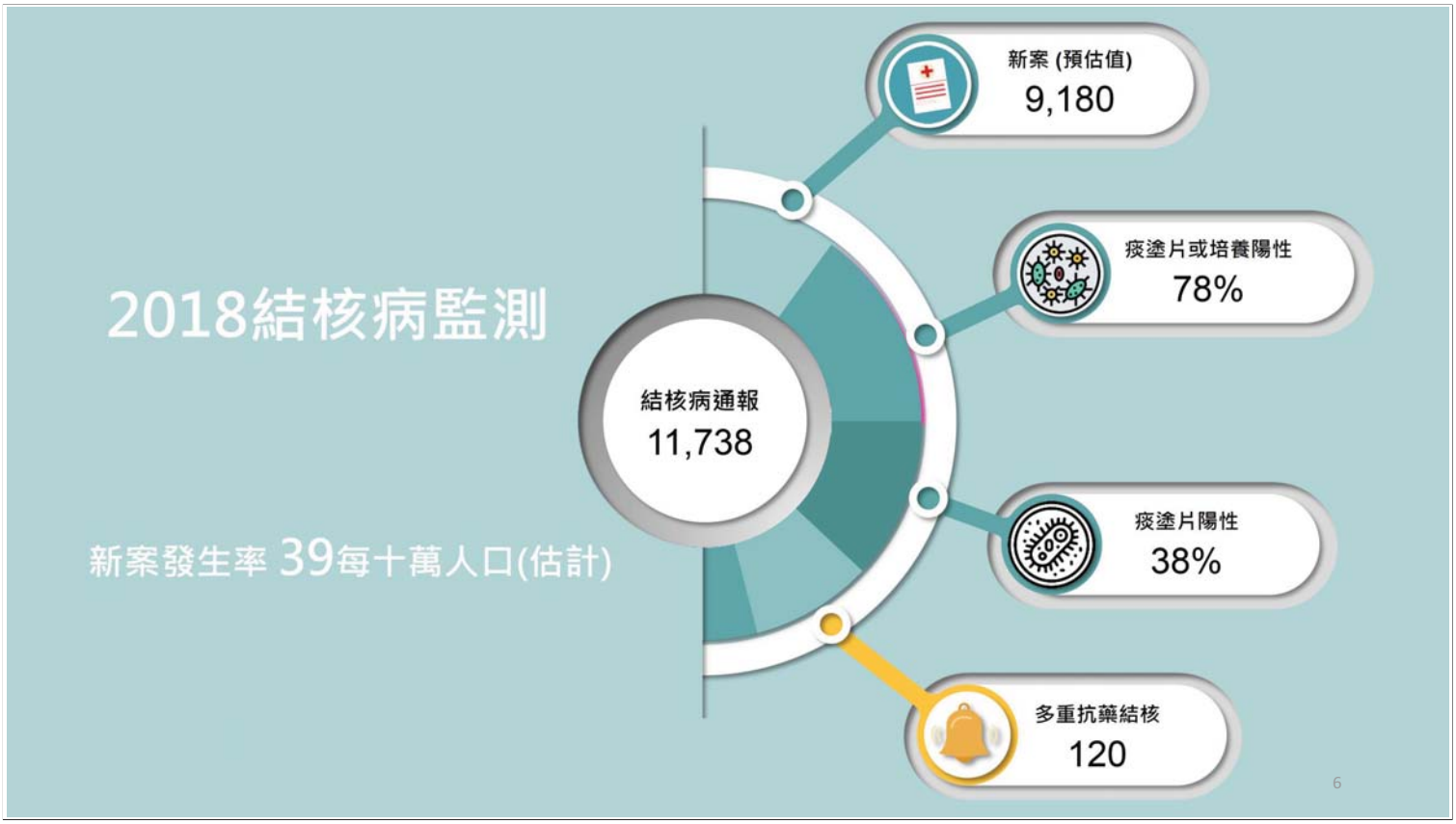
每年有**360萬**結核病人**未能進入醫療體系**接受照護

TB/HIV共病管理需要加速

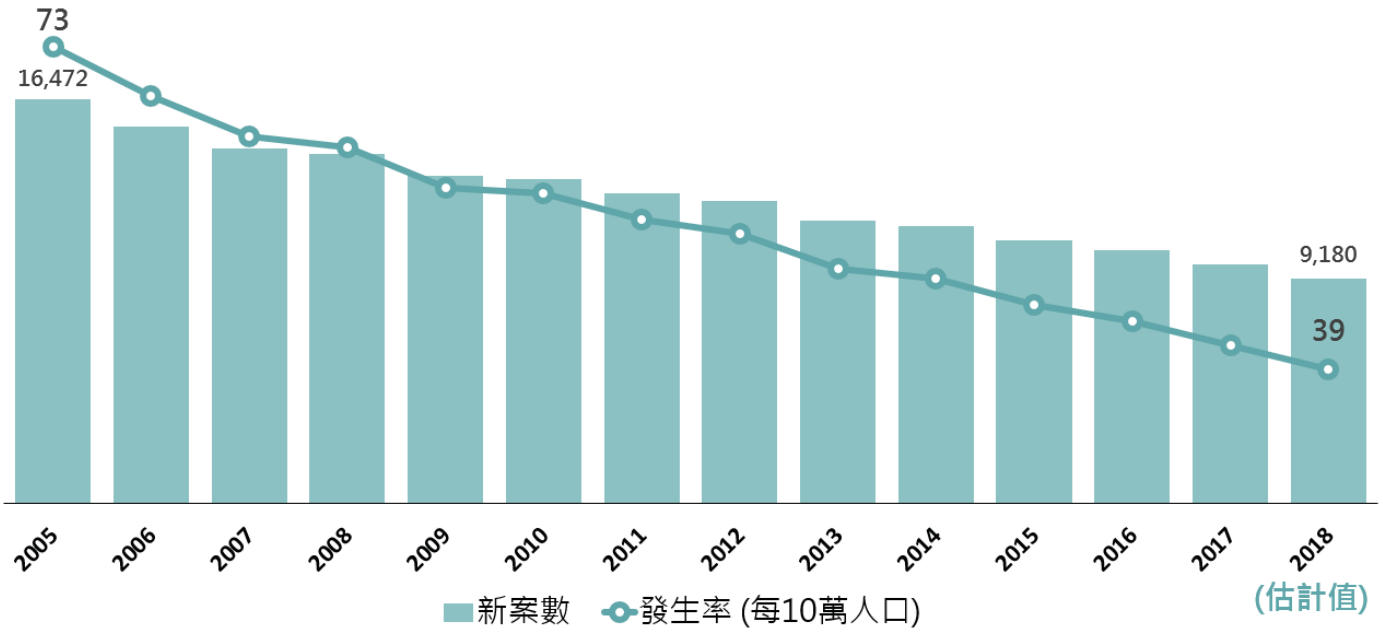
MDR-TB危機

每4名MDR-TB病人只有1人被確診，每2人中只有1人被治療。

WHO: The End TB Strategy 2015



全國結核病發生率

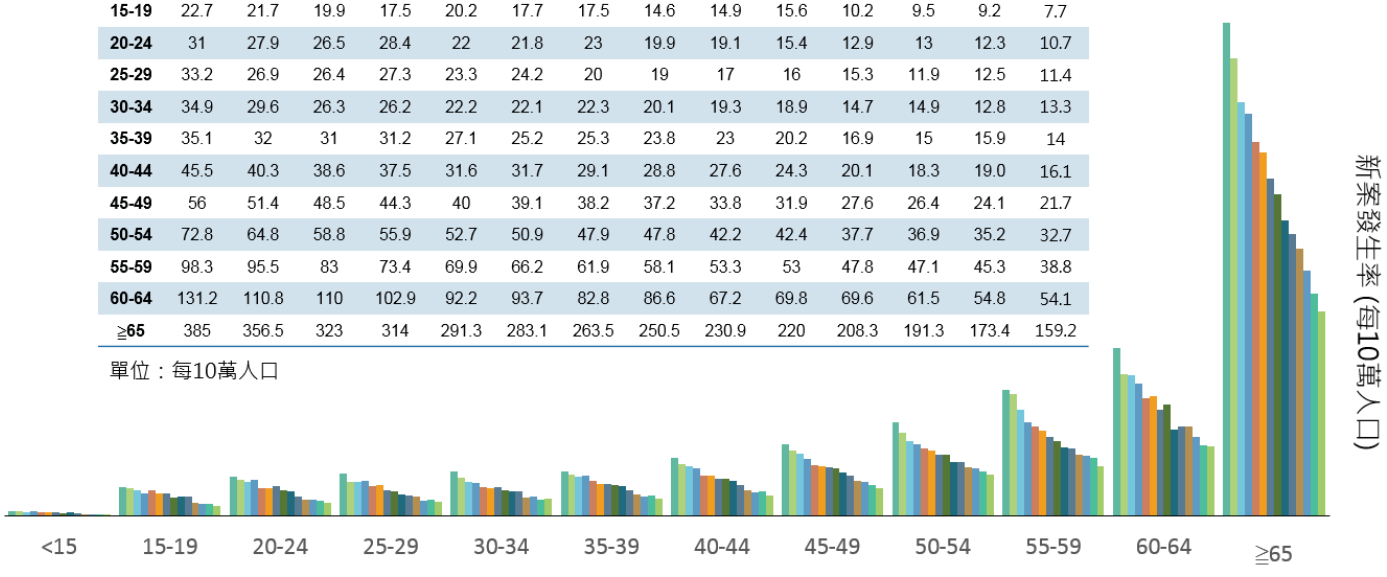


結核病年齡別發生率(2005-2018)

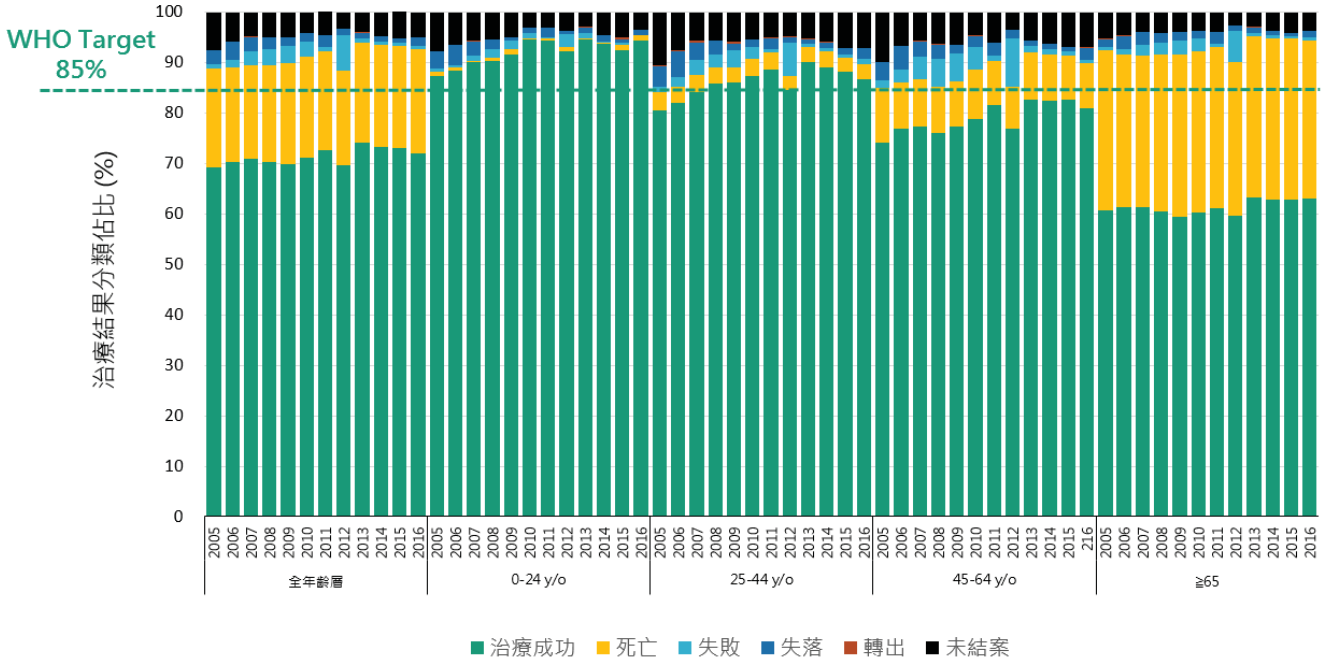
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
<15	3.5	3.5	3.3	4	3.2	2.6	3.3	2.2	2.7	2.2	1.5	1.7	1.6	1.2
15-19	22.7	21.7	19.9	17.5	20.2	17.7	17.5	14.6	14.9	15.6	10.2	9.5	9.2	7.7
20-24	31	27.9	26.5	28.4	22	21.8	23	19.9	19.1	15.4	12.9	13	12.3	10.7
25-29	33.2	26.9	26.4	27.3	23.3	24.2	20	19	17	16	15.3	11.9	12.5	11.4
30-34	34.9	29.6	26.3	26.2	22.2	22.1	22.3	20.1	19.3	18.9	14.7	14.9	12.8	13.3
35-39	35.1	32	31	31.2	27.1	25.2	25.3	23.8	23	20.2	16.9	15	15.9	14
40-44	45.5	40.3	38.6	37.5	31.6	31.7	29.1	28.8	27.6	24.3	20.1	18.3	19.0	16.1
45-49	56	51.4	48.5	44.3	40	39.1	38.2	37.2	33.8	31.9	27.6	26.4	24.1	21.7
50-54	72.8	64.8	58.8	55.9	52.7	50.9	47.9	47.8	42.2	42.4	37.7	36.9	35.2	32.7
55-59	98.3	95.5	83	73.4	69.9	66.2	61.9	58.1	53.3	53	47.8	47.1	45.3	38.8
60-64	131.2	110.8	110	102.9	92.2	93.7	82.8	86.6	67.2	69.8	69.6	61.5	54.8	54.1
≧65	385	356.5	323	314	291.3	283.1	263.5	250.5	230.9	220	208.3	191.3	173.4	159.2

(估計值)

單位：每10萬人口



結核病12個月治療追蹤結果



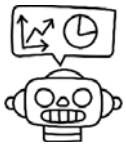
2035消除結核

A WORLD FREE OF TB
ZERO deaths, disease, and suffering due to TB
END THE GLOBAL TB EPIDEMIC

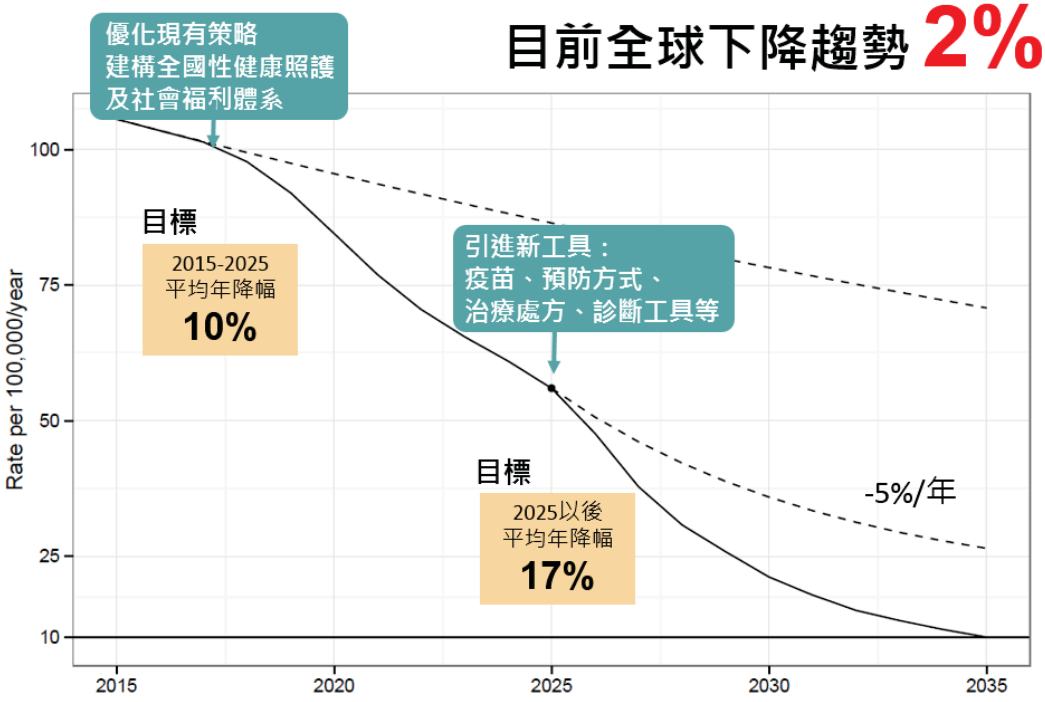
目標

	里程碑		聯合國永續發展目標 (SDGs)	WHO終結TB策略
	2020	2025	2030	2035
TB死亡數 相較2015年下降比率	35%	75%	90%	95%
TB發生率 相較2015年下降比率	20%	50%	80%	90%
因TB導致重大經濟困難之家庭比率	0%	0%	0%	0%

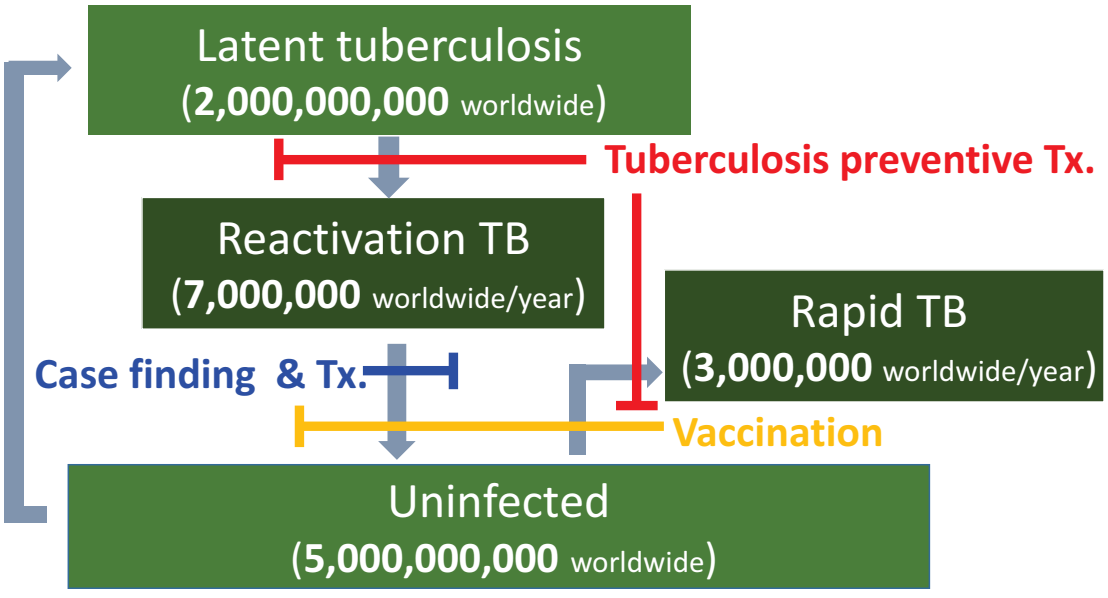
全球消除結核目標與趨勢



目前全球下降趨勢 2%

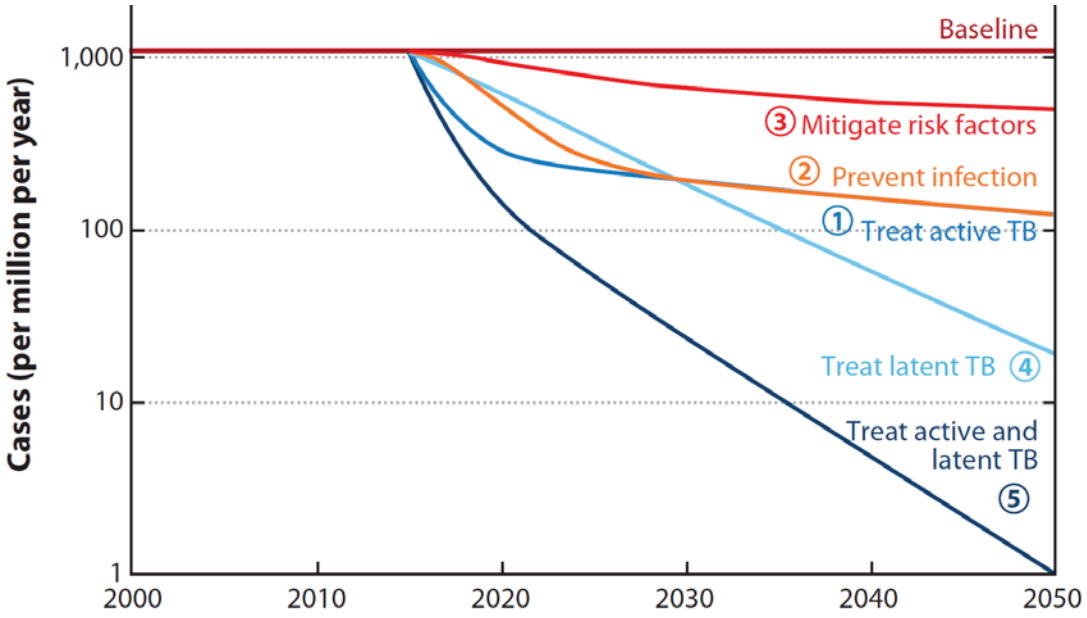


How to Eliminate TB?
-Eliminate the reservoir-

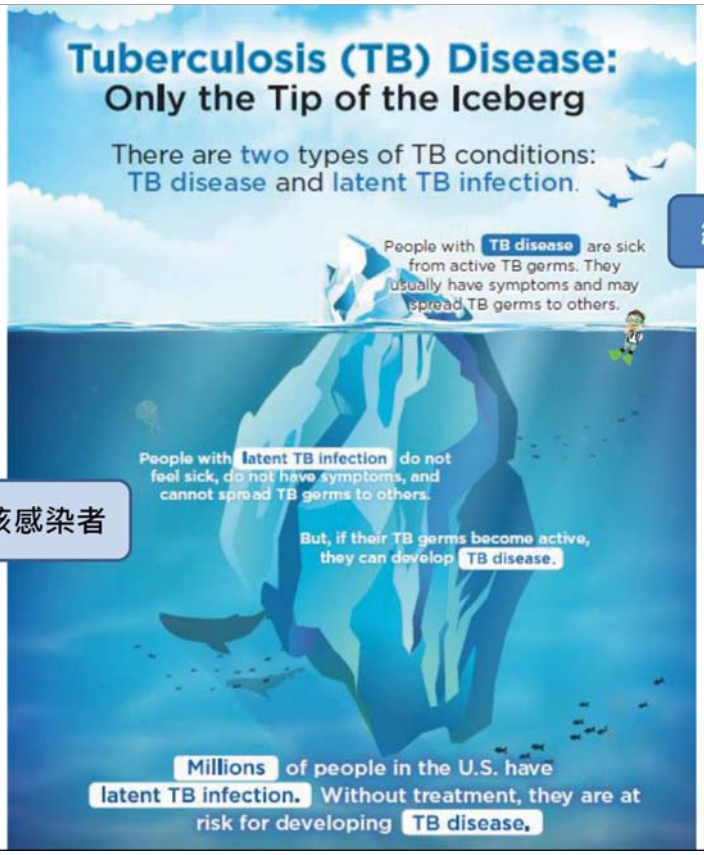


Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet 2015; 386: 2344–53*

終結結核：終結起源



Dye C. ***Annu Rev Public Health*** 2013;34:271-86.



結核病人

潛伏結核感染者

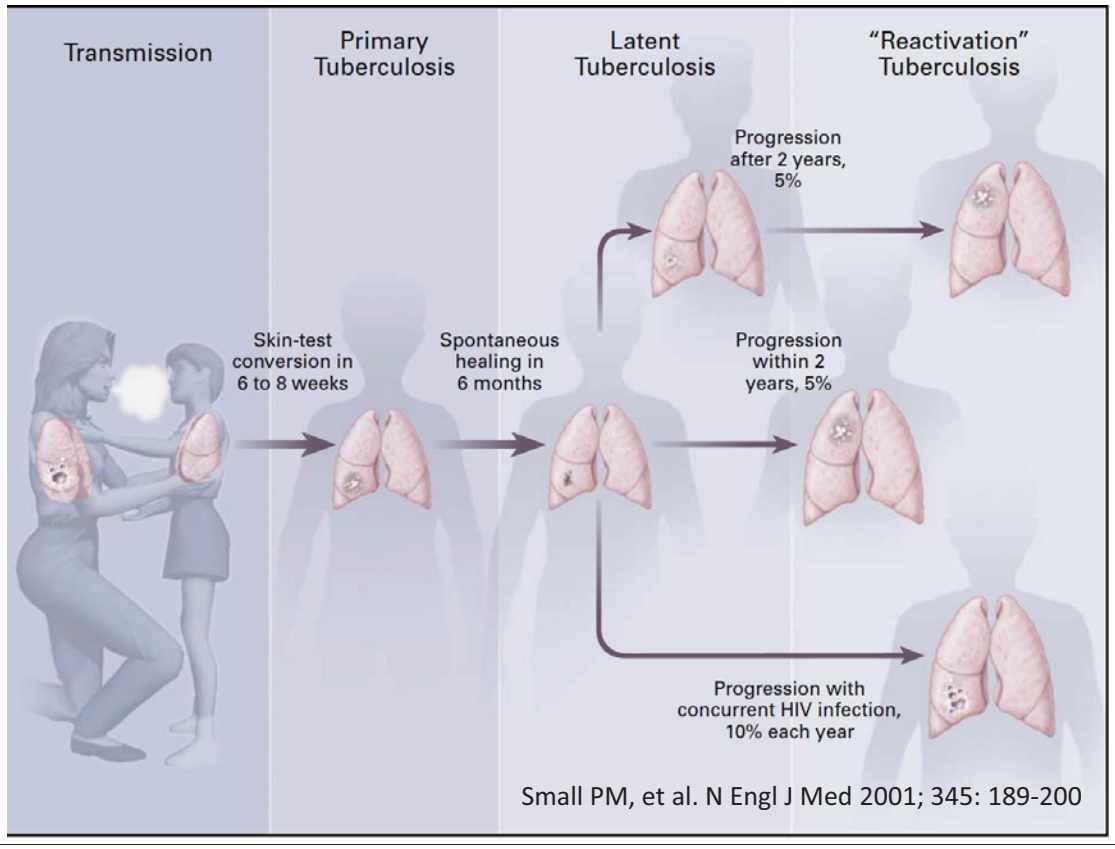
2 billion people
are infected with TB

10% life-time risk
progression into TB disease

One active TB case infect
10 - 15 individuals in a year

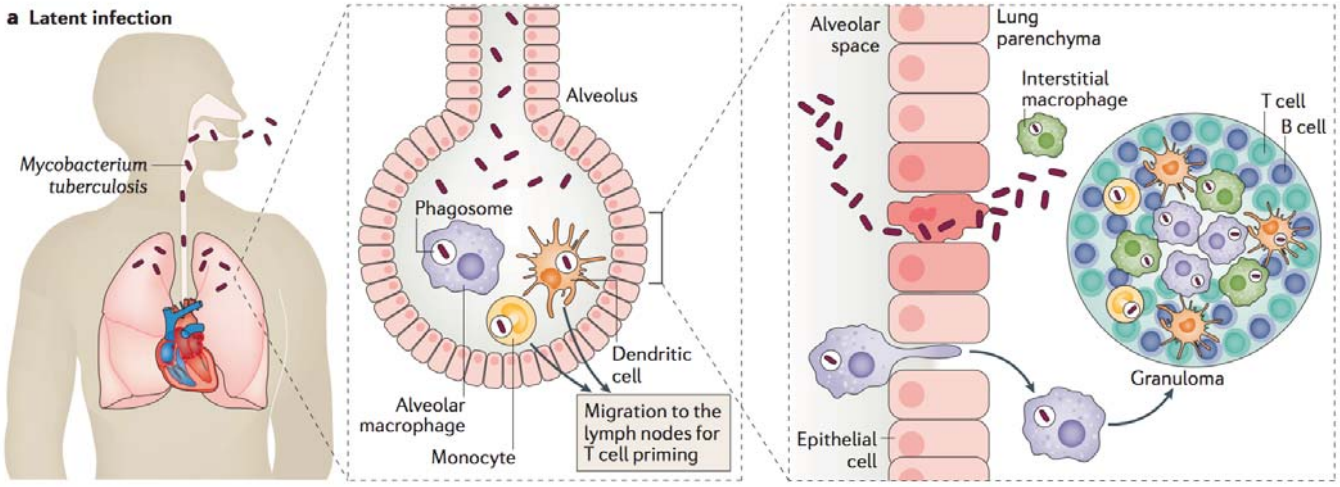
17

被結核菌感染了，怎麼辦？

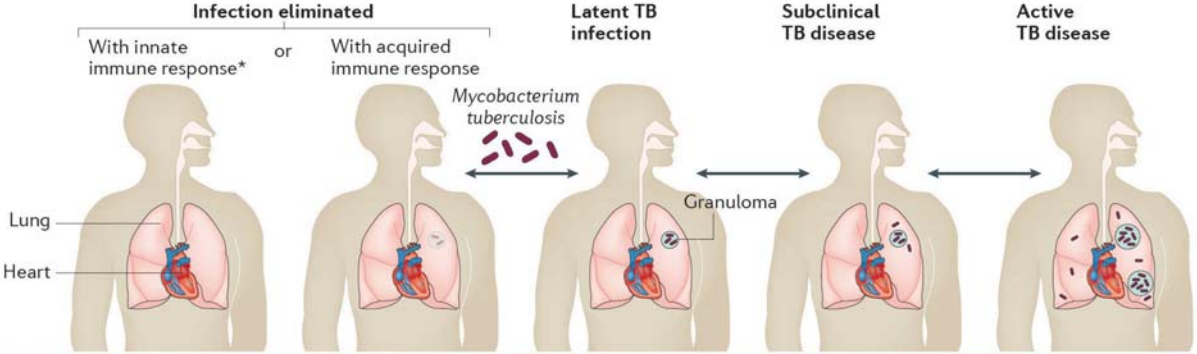


Small PM, et al. N Engl J Med 2001; 345: 189-200

潛伏結核感染



Pai M, et al., *Nat Rev Dis Primers*, 2016. **2**: p. 16076.



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai M, et al., *Nat Rev Dis Primers*, 2016. **2**: p. 16076.

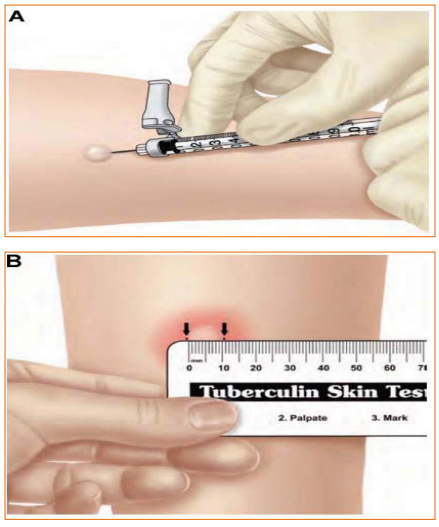
Latent TB Infection
- Definition -

"A state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifested active TB."

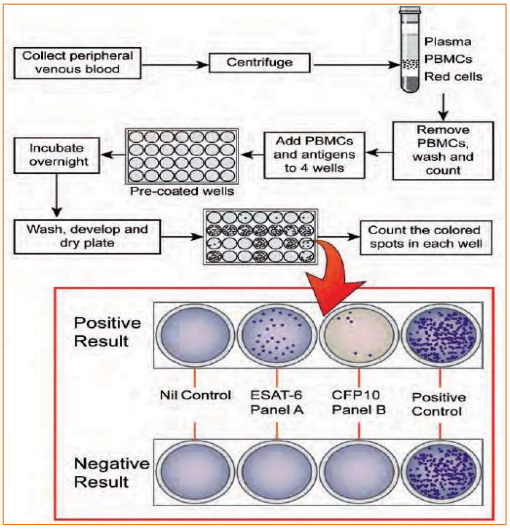
Latent tuberculosis infection - Updated and consolidated guidelines for programmatic management (WHO 2018)

Latent TB Infection
– Testing Method –

- PPD - Based Test



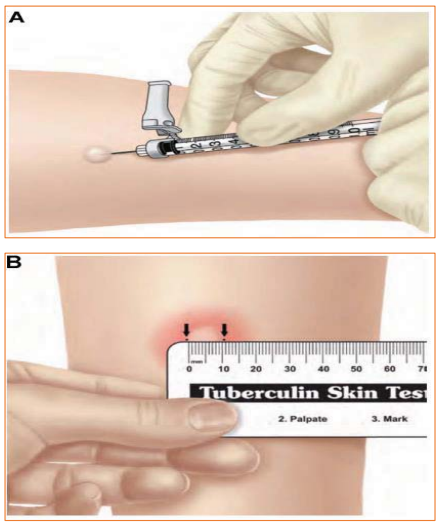
- IGRAs (ELISPOT)



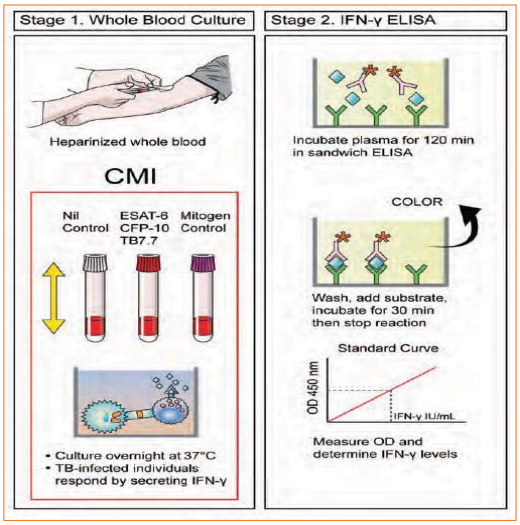
Moon HW, et al. Ann Clin Lab Sci 2013 Spring;43(2): 221-9

Latent TB Infection
– Testing Method –

- PPD - Based Test



- IGRAs (ELISA)



Moon HW, et al. Ann Clin Lab Sci 2013 Spring;43(2): 221-9

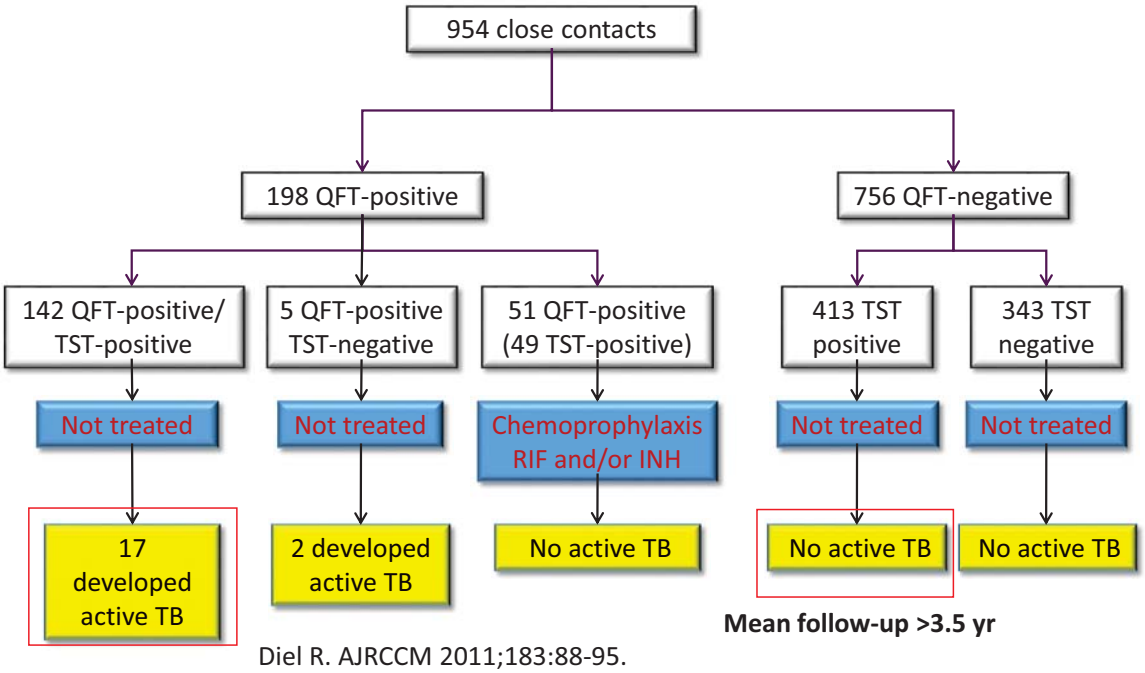
IGRA的特異性

Tuberculosis Complex	ESAT-6	CFP-10	TB7.7
M tuberculosis	+	+	+
M africanum	+	+	+
M bovis	+	+	+
BCG substrain			
gothenburg	-	-	-
moreau	-	-	-
tice	-	-	-
tokyo	-	-	-
danish	-	-	-
glaxo	-	-	-
montreal	-	-	-
pasteur	-	-	-

Environmental Strains	ESAT-6	CFP-10	TB7.7
M abcessus	-	-	-
M avium	-	-	-
M branderi	-	-	-
M celatum	-	-	-
M chelonae	-	-	-
M fortuitum	-	-	-
M gordonii	-	-	-
M intracellulare	-	-	-
M kansasii	+	+	-
M malmoense	-	-	-
M marinum	+	+	-
M oenavense	-	-	-
M scrofulaceum	-	-	-
M smegmatis	-	-	-
M szulgai	+	+	-
M terrae	-	-	-
M vaccae	-	-	-
M xenopi	-	-	-

IGRA不會對BCG及大部分的NTM有反應，但對未滿5歲兒童是否適用，全世界仍待蒐集研究證據評估，故本階段選擇5歲以上之接觸者進行IGRA 檢查

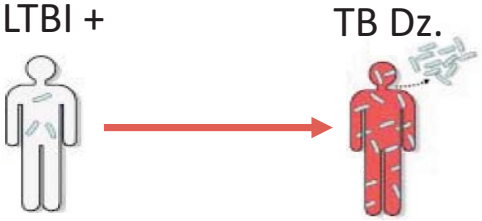
使用QFT對於日後發生活動性結核病的陰性與陽性預測值



Diel R. AJRCCM 2011;183:88-95.

Latent TB Infection – Testing Prognostication –

	TST	IGRAs
	Progression to active TB	
PPV[1]	LTBI + → TB Dz.	
NPV[1]		
Risk Ratio[2]		
Incidence Rate Ratio[2]		



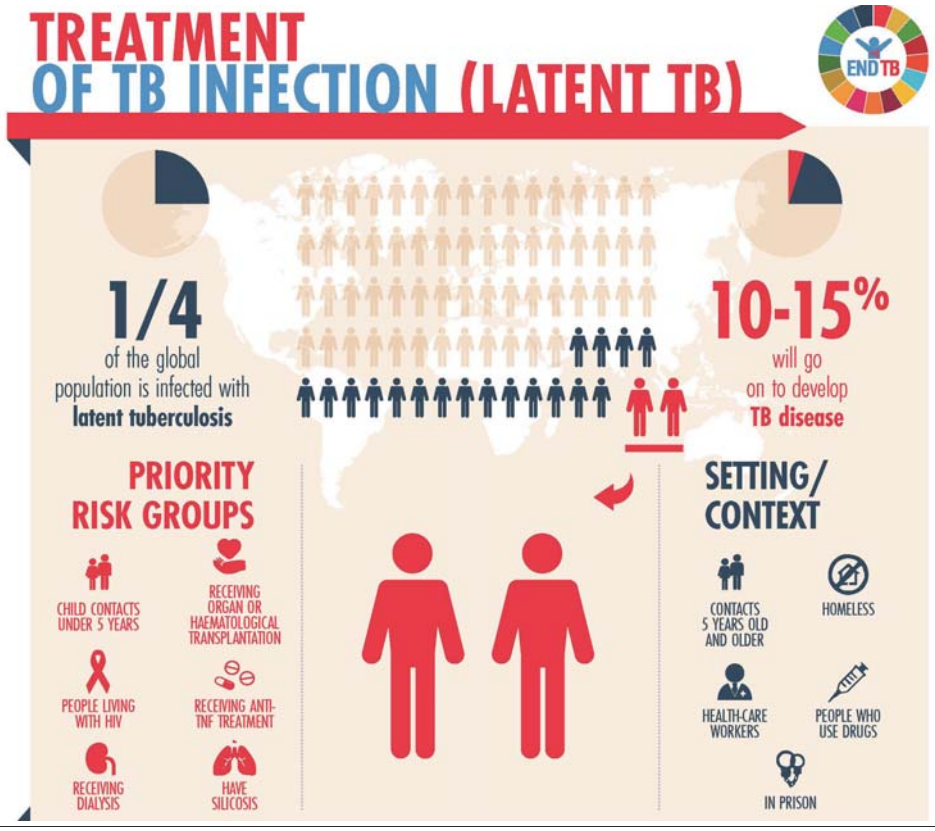
Positive & Negative predict value
Risk Ratio & Incidence rate ratio

1 Diel R., et el. Chest 2012 142(1) 63-75
2 Guidelines on the Management of Latent Tuberculosis Infection (WHO 2015)

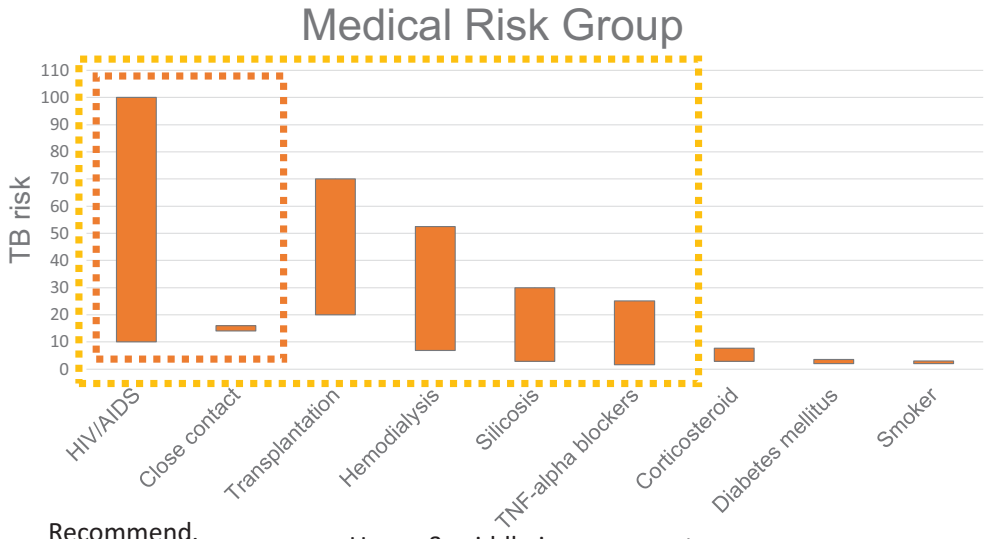
Latent TB Infection
– Testing Prognostication –

	TST	IGRAs
	Progression to active TB	
PPV[1]	1.5% (1.2%-2.7%)	2.7% (2.3%-3.2%)
	2.4% (1.9%-2.9%)[High Risk]	6.8% (5.6%-8.3%)[High Risk]
NPV[1]	99.4% (99.2% - 99.5%)	99.7% (99.5%-99.8%)
Risk Ratio[2]	2.58 (1.72-3.88)	4.94 (1.79-13.65)
Incidence Rate Ratio[2]	2.07 (1.38-3.11)	2.40 (1.26-4.60)

1 Diel R, et el. Chest 2012 142(1) 63-75
2 Guidelines on the Management of Latent Tuberculosis Infection (WHO 2015)



Latent TB Infection
– Priority for treatment–



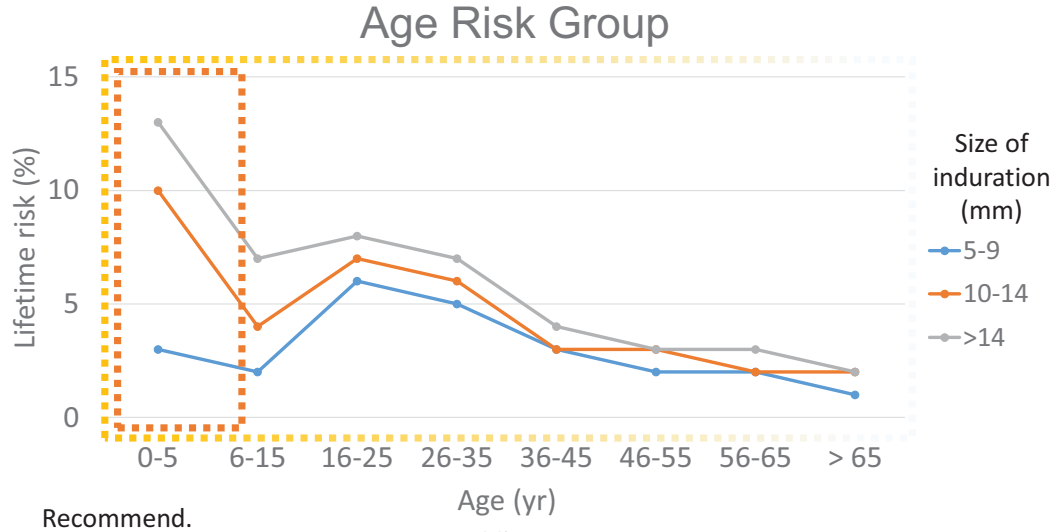
Recommend. Screen and Tx (WHO)

Upper & middle income country TB incidence < 100/100,000

All countries

Jing-Wen Ai, et al. Emerging Microbes and Infections (2016) 5, e10

Latent TB Infection
– Priority for treatment–



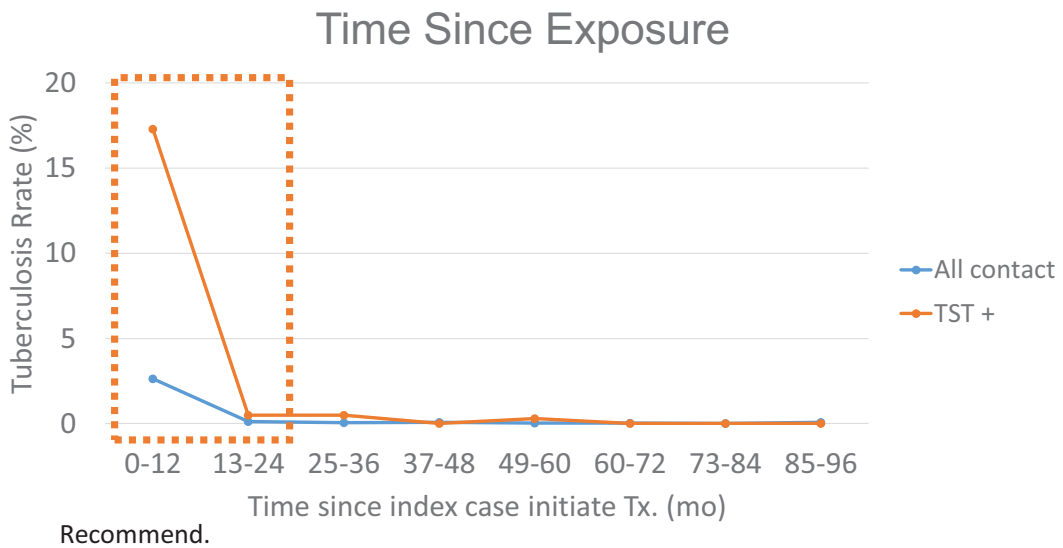
Recommend. Screen and Tx (WHO)

Upper & middle income country TB incidence < 100/100,000

All countries

Horsburgh, et el. NEJM 2004; 350; 20 2060-7

Latent TB Infection
– Priority for treatment –



Recommend. Screen and Tx (WHO)

All countries (Except high burden countries or MDR-TB)

Reichler MR et al. J Infect Dis 2018 Aug 14; 218:1000

被結核菌感染了，怎麼辦？

TB接觸者就醫轉介單

- ✓作為臨床評估依據及接觸者檢查免部分負擔之憑證
- ✓診斷碼ICD-10
  - 接觸者檢查Z20.1
  - 潛伏結核感染治療評估 R76.1

附件 10-10

TB 接觸者就醫轉介單

請協助事項：☐接觸者檢查[1](ICD10：Z20.1)：○胸部 X 光檢查 ○IGRA ○TST
☐潛伏結核感染治療評估(ICD10：R76.1)

一、接觸者資料

基本資料
姓名：_____ 管理單位：_____縣/市_____鄉鎮市區
性別：☐男☐女 身分證字號：_____ 出生：____年____月____日
卡介苗疤痕：☐無 ☐有 免疫不全狀況：☐無 ☐有 肝毒性風險族群[2]：☐否 ☐是：_____
結核病症狀：○無 ○咳嗽 ○咳血 ○咳痰 ○發燒 ○胸痛 ○食慾差 ○體重減輕
接觸者風險評估得分：_____分（未滿 5 歲接觸者適用，衛教內容請參考手機 APP 內容）

接觸者檢查結果
1. 胸部 X 光檢查檢查結果：檢查日期____年____月____日
☐正常[3]
☐異常無關結核，註：_____
☐疑似肺結核(請依傳染病防治法第 39 條進行通報)：☐異常，無空洞 ☐異常，有空洞
☐異常，肺浸潤(請繼續追蹤至排除結核病)
2. IGRA 日期____年____月____日，結果：☐陽性 ☐陰性 ☐不確定 ☐不確定(mitogen< 0.5)
試劑：☐QFT ☐T-SPOT
3. TST 第 1 次：____年____月____日，結果：_____mm（免疫不全時，TST 判讀標準為 5mm）
第 2 次：____年____月____日，結果：_____mm
5 歲(含)以上接觸者，請進行 IGRA；未滿 5 歲接觸者，請進行 TST。
第 1 次 TST 請於接觸起始日起 1 個月內完成；IGRA 或第 2 次 TST 請於終止有效暴露 8 週後完成。

臨床建議
1. 接觸者檢查結果建議：☐繼續追蹤 ☐TB 治療 ☐其他建議：_____
2. 潛伏結核感染治療評估建議：
※請確認接觸者最近 1 個月內胸部 X 光已排除活動性結核病
☐需進行潛伏結核感染治療(Treatment of LTBI)：
☐ 3HP ☐ 9H ☐ 4R (限 INH 抗藥但 RMP 敏感指標之接觸者使用)
☐需進行預防性投藥(prophylaxis)，並於 8 週後完成 TST
☐家屬（本人）拒絕
☐暫不需進行治療：☐肝功能檢查值過高 ☐擔心藥物交互作用 ☐指標個案為 MDR-TB
☐其他：_____
醫院名稱：_____ 回復醫師簽章：_____ 連絡電話：_____

二、指標個案資料（提供接觸者風險評估參考）

TB 總編號：_____ 性別：☐男 ☐女 來自 TB 高盛行區：☐是 ☐否

採檢日期	痰塗片（NAA 檢驗）	痰培養（鑑定）
第一套____年____月____日	☐陰性☐陽性(_____)☐已驗未出	☐陰性☐陽性(_____)☐已驗未出
第二套____年____月____日	☐陰性☐陽性(_____)☐已驗未出	☐陰性☐陽性(_____)☐已驗未出
第三套____年____月____日	☐陰性☐陽性(_____)☐已驗未出	☐陰性☐陽性(_____)☐已驗未出

胸部 X 光檢查結果：____年____月____日 ☐有空洞☐無空洞； 單純肺外：☐是☐否
抗結核藥物 ☐已用：____年____月____日 ☐未用 抗藥性：☐無☐INH☐RMP☐未知

開立單位：_____縣（市）_____衛生所 日期：____年____月____日
連絡人：_____ 連絡電話：_____

備註：
1. 接觸者檢查(胸部 X 光檢查、IGRA 抽血檢查、TST 施打)及後續回診者報告(胸部 X 光報告、IGRA 檢查報告、TST 判讀結果)，均可使用本轉介單以減免部分負擔，故本轉介單最多可使用 2 次。
2. 35 歲以上成人、肝硬化、慢性肝炎或肝病變、酒癮、注射藥癮者、HIV 感染者、孕婦及產後 3 個月婦女即為肝毒性風險族群，須於治療前先檢查肝功能。
3. 檢查結果正常者，倘日後出現異常呼吸道症狀或咳嗽超過 2 週，應儘速就醫檢查，並告知醫師接觸史。

第一聯：醫療院所轉介個案檢查結果黏貼於個案病歷上，若倘您於接檢過程中，遭遇任何問題或有不公平待遇，請聯絡衛生所或撥打免付費電話：0212。

31

Recommended drugs

Table 2 Recommended dosages of drugs for the treatment of LTBI

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7–15 mg)	300 mg
Daily rifampicin alone for 3–4 months	Adults, 10 mg Children, 15 mg (range, 10–20 mg)	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid: Adults, 5 mg Children, 10 mg (range, 7–15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10–20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥ 12 years: Isoniazid: 15 mg Individuals aged 2–11 years: isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg > 50 kg = 900 mg	Isoniazid, 900 mg Rifapentine, 900 mg

Guidelines on the Management of Latent Tuberculosis Infection (WHO 2018)

Comparison of Efficacy and Hepatotoxicity among LTBI Regimens

TABLE 3 Standard random effects meta-analysis comparison of efficacy and hepatotoxicity among various treatment regimens for treatment of latent tuberculosis (TB) infection

每種LTBI治療都可以有效降低TB發病

Comparator	Intervention	Development of incident TB	Hepatotoxicity
Placebo	Isoniazid 6 months	0.61 (0.48–0.77)	0.99 (0.42–2.32)
Placebo	Isoniazid 12–72 months	0.53 (0.41–0.69)	0.59 (0.23–1.55)
Placebo	Rifampicin 3–4 months	0.48 (0.26–0.87)	
Placebo	Rifampicin and isoniazid 3–4 months	0.52 (0.33–0.84)	
Isoniazid 6 month	Rifampicin 3–4 months	0.78 (0.41–1.46)	0.03 (0.00–0.48)
Isoniazid 6 month	Rifampicin and isoniazid 3–4 months	0.89 (0.65–1.23)	0.89 (0.52–1.55)
Isoniazid 6 month	3 month weekly rifapentine plus isoniazid#	1.09 (0.60–1.99)	1.00 (0.50–1.99)
Isoniazid 9 month	3 month weekly rifapentine plus isoniazid	0.44 (0.18–1.07)	0.16 (0.10–0.27)

VS

Data are presented as odds ratios with 95% confidence intervals. #: exclusively among people living with HIV.

但不同處方肝毒性的確有差異

ERJ 2015 Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries

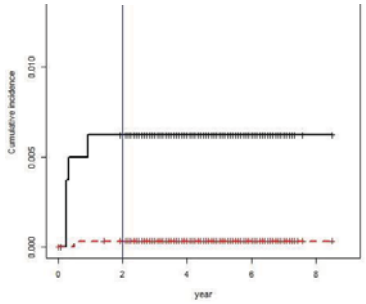
台灣地區使用9個月INH預防性治療的效果

MOHW104-CDC-C-315-000203

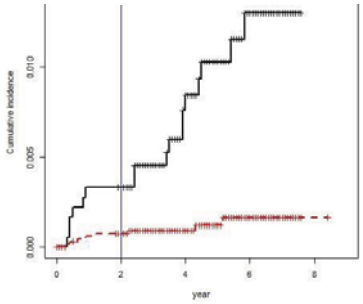
接觸者：2008/4 ~ 2013/9
追蹤期限：2015/8/31

預防治療	<5Y			5-12Y			13-17Y		
	No.	TB No.	Incidence	No.	TB No.	Incidence	No.	TB No.	Incidence
是	2550	1	**35**	6703	8	**75**	2395	5	**125**
否	804	5	**600**	1812	17	**332**	1257	14	**1118**

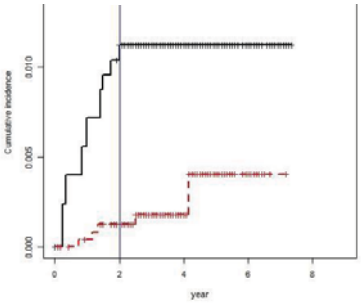
RR: 0.06 (<0.01 ~ 0.34)
94% protection



RR: 0.22 (0.06 ~ 0.74)
78% protection



RR: 0.11 (0.02 ~ 0.34)
89% protection

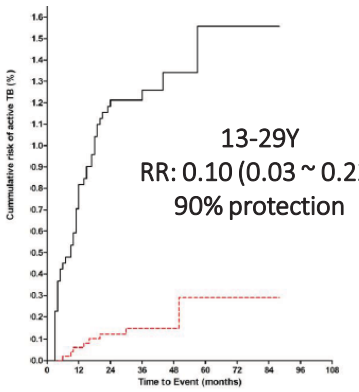


台灣地區使用9個月INH預防性治療的效果

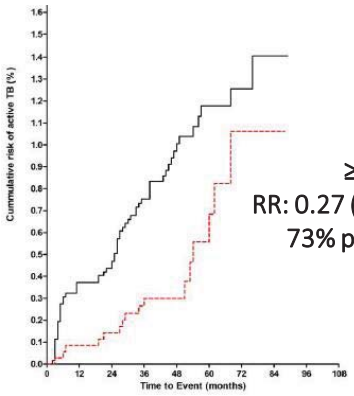
MOHW104-CDC-C-315-000203

接觸者：2008/4 ~ 2013/9
追蹤期限：2015/8/31

預防治療	<13Y			13-29Y			≥30Y		
	No.	TB	Incidence	No.	TB	Incidence	No.	TB	Incidence
是	9338	21	**63**	4773	17	**123**	3471	26	**113**
否	3059	43	**420**	3093	60	**1130**	5922	107	**404**

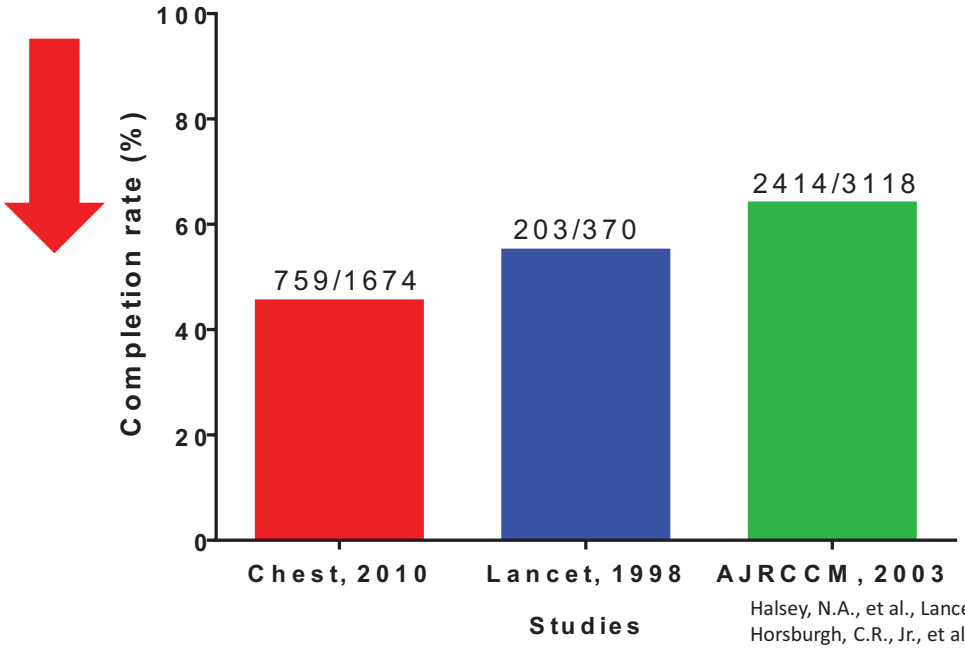


13-29Y
RR: 0.10 (0.03 ~ 0.22)
90% protection



≥30Y
RR: 0.27 (0.08 ~ 0.64)
73% protection

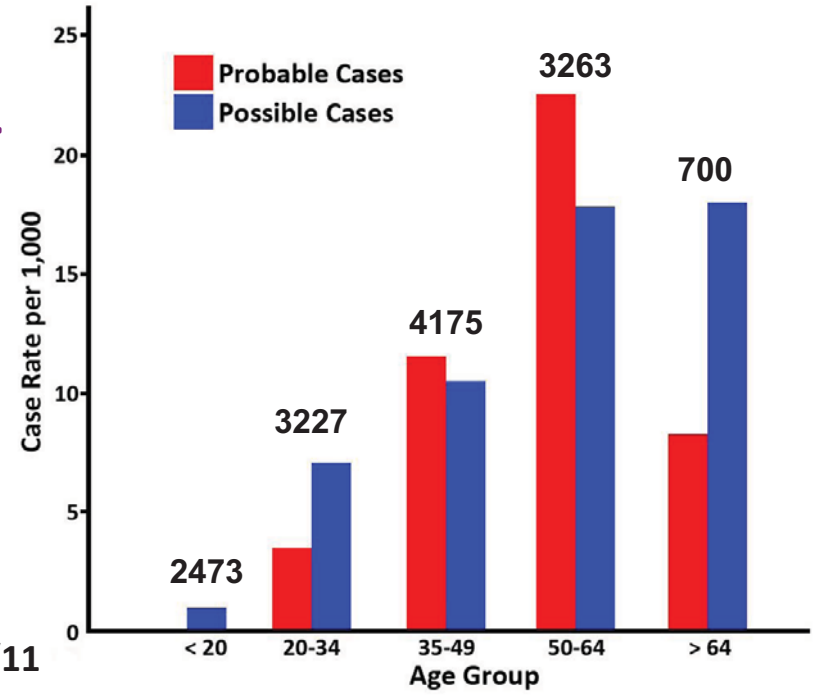
潛伏結核治療完成率



Halsey, N.A., et al., Lancet, 1998. **351**(9105): p. 786-92.
Horsburgh, C.R., Jr., et al.,Chest, 2010. **137**(2): p. 401-9.
LoBue, P.A. , et al., Am J Respir Crit Care Med, 2003. **168**(4): p. 443-7.

Risk of INH-induced hepatitis

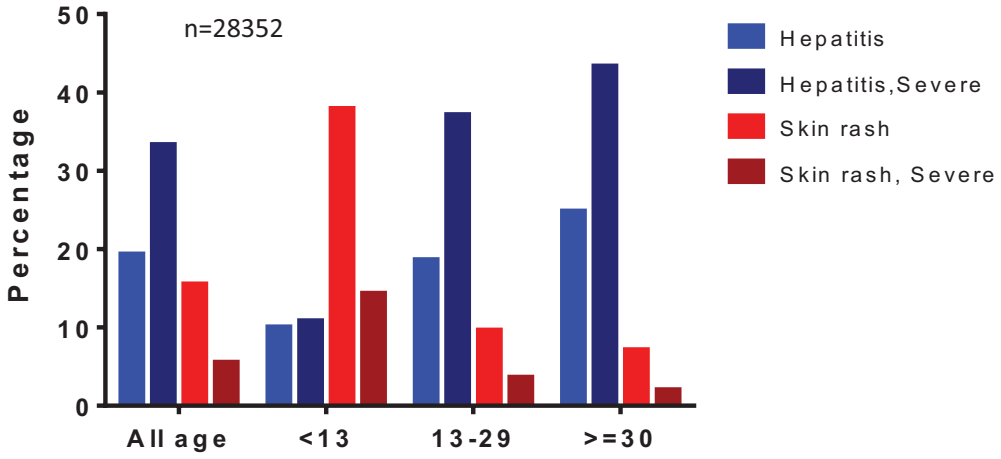
- USPHS
- 13838 cases
- 1971/07 ~ 1972/11



Kopanoff DE, et al. Am Rev Respir Dis 1978;117:991-1001.

潛伏結核感染治療期間因不良反應而永久停藥比率

依年齡分層, 9H

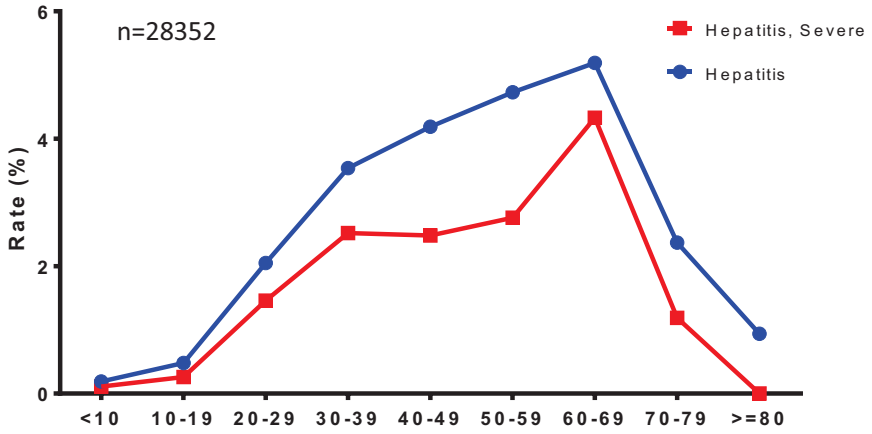


courtesy of Chan PC. MOHW103-CDC-C-315-000302

肝炎及嚴重肝炎 (ATS) 在13歲以上分別為56%, 68%
<13歲則以皮膚相關癢疹為最多(53%)
因肝炎導致住院:0.56‰(16/28,353)，沒有因不良反應導致死亡

潛伏結核感染治療期間因肝炎而永久停藥發生率

依年齡分層, 9H



courtesy of Chan PC. MOHW103-CDC-C-315-000302

肝炎(n=295)在30歲以上會有3-5%的發生率, trend test: p<0.001
若為嚴重肝炎 (n=187,即符合美國胸腔暨重症醫學會建議的肝炎標準)，
則<10歲的發生率為1‰，20歲達1%，30歲達2-4%, trend test: p<0.001。

推動潛伏結核感染診斷與治療

未診斷
潛伏結核感染者

2019 中傳染力個案之共同居住/患有慢性病接觸者納入LTBI診斷及治療
公衛及醫事人員潛伏結核感染宣導及篩檢治療活動

2018 推動長照機構老人族群TB暨LTBI整合計畫

2017 回溯高傳染性個案接觸者納入診斷/治療、高風險族群LTBI治療試辦計畫、新增4R處方

2016 於全國推動「潛伏結核全都治計畫」，導入「速克伏」短程治療處方

2015 於6縣市推動IGRA及「潛伏結核全都治試辦計畫」

2012 擴大LTBI治療服務對象至1986年以後出生接觸者

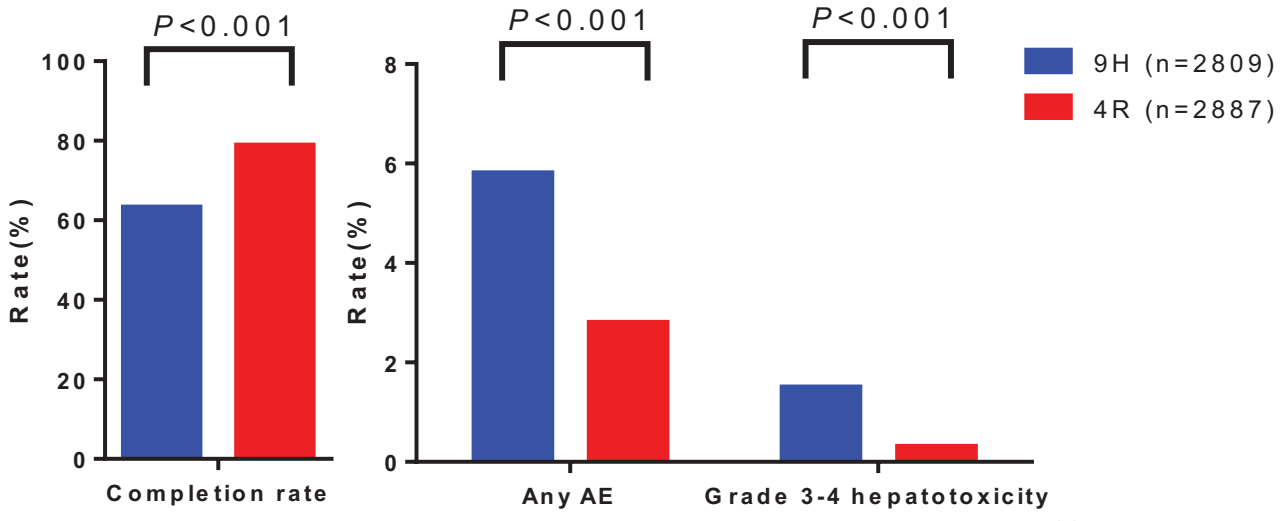
2008 推動<13歲接觸者LTBI治療

潛伏結核感染治療處方一覽

處方	9H	速克伏(3HP)	4R
處方藥品	Isoniazid (INH)	Isoniazid (INH) + Rifapentine (RPT)	Rifampin (RMP)
適用對象	・藥敏全敏感指標個案之接觸者適用 ・RMP抗藥指標個案之接觸者適用	藥敏全敏感指標個案之接觸者適用	僅限INH抗藥且RMP敏感指標之接觸者使用
服藥頻次	每日	每週	每日
療程	270天(9個月)	12個劑量(3個月)	120天(4個月)
使用限制	INH抗藥指標之接觸者不適用	未滿2歲接觸者、INH或RMP抗藥指標個案之接觸者、孕婦或準備懷孕的婦女不適用	RMP抗藥指標之接觸者不適用
加入都治計畫(DOPT)	建議	必須	必須

4R versus 9H

- 2009-2014, multicenter, open-label RCT
- Multination: Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea
- age ≥18 yr
- TST+ or IGRA+, increased risk of reactivation



Menzies D, et al. N Engl J Med. 2018 Aug 2;379(5):440-453.

4R versus 9H

Advantages	Disadvantages
• Similar effectiveness • Shorter course • Higher completion rate (78.8% > 63.2%) • Lower adverse events (2.8% < 5.8%)	• Drug-drug interaction (↑ P450 CYP3A) • Active TB → leading to RIF-R (more complicated than INH-R)

Menzies D, et al. N Engl J Med. 2018 Aug 2;379(5):440-453.

4R versus 9H

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Menzies D, et al. N Engl J Med. 2018 Aug 2;379(5):440-453.

潛伏結核全都治計畫
2016年全面推行

增加短程治療處方之選擇
短程處方須以傳統都治方式執行

短程處方(3HP速克伏)

once weekly x 3 months =

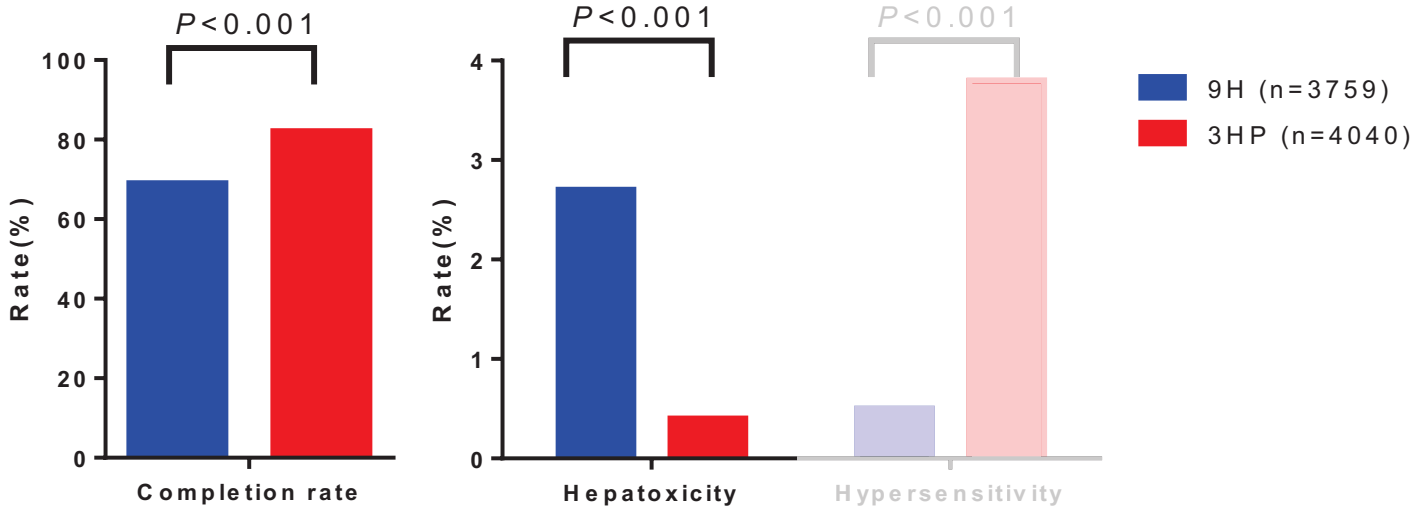
only 12 doses

900mg Isoniazid (INH) +
900mg Rifapentine (RPT)

中華民國疾管局

3HP versus 9H

- 2001-2008, multicenter, open-label RCT
- Multination: Brazil, Canada, Spain, and the United States
- Age ≥2 yr
- Spectrum of "high-risk" predicates



Timothy R. Sterling, et al. N Engl J Med 2011;365:2155-66.

3HP versus 9H

Advantages	Disadvantages
• Similar effectiveness • Shorter course (only 12 doses!) • Higher completion rate (82.1% > 69%) • Lower hepatotoxicity (0.4% < 2.7%)	• Drug-drug interaction (↑ P450 CYP3A4, 2C8/9) • INH-R or RPT-R TB → partial treatment ! •Higher adverse events

Timothy R. Sterling, et al. N Engl J Med 2011;365:2155-66.

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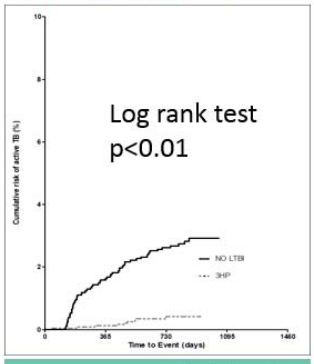
Timothy R. Sterling, et al. N Engl J Med 2011;365:2155-66.

接受LTBI治療之保護效果

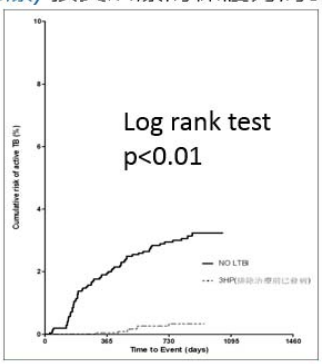
	發生率 (人年)	RR	95%CI		發生率 (人年)	RR	95%CI
3HP	**0.18**	0.13	(0.07-0.27)	3HP	**0.18**	0.64	(0.27-1.52)
未曾接受治療	**1.35**			9H	**0.28**		

LTBI 接觸者接受治療的保護力約87%



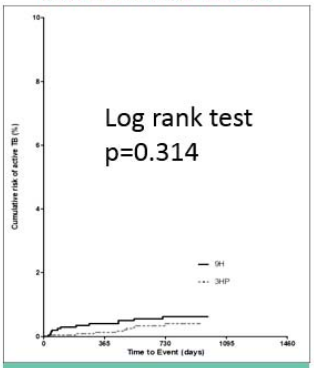
3HP vs. 未治療

LTBI 接觸者 (治療前已發病視為無治療) 接受治療的保護力約94%



3HP vs. 未治療

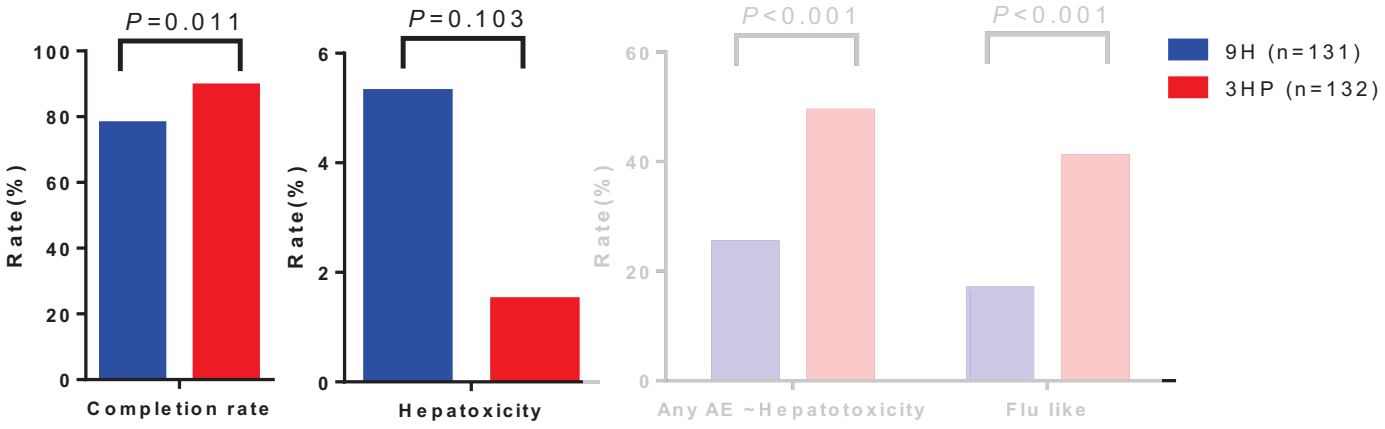
3HP與9H處方的保護力無顯著差異



3HP vs. 9H

3HP vs. 9H Taiwan experience

- 2014-20168, multicenter, open-label RCT
- Age ≥ 12 yr
- TST+ and AFB+ pulmonary TB contact



Sun HY et al.Tuberculosis (Edinb). 2018 Jul;111:121-126.

Possible Drug Hypersensitivity
臨床試驗定義

- 在PREVENT trial 中，預期會有RMP 類的過敏反應，其定義如下
- A broad definition of was used (以下任一)

  a) hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis that occurred in relation to study drug; or

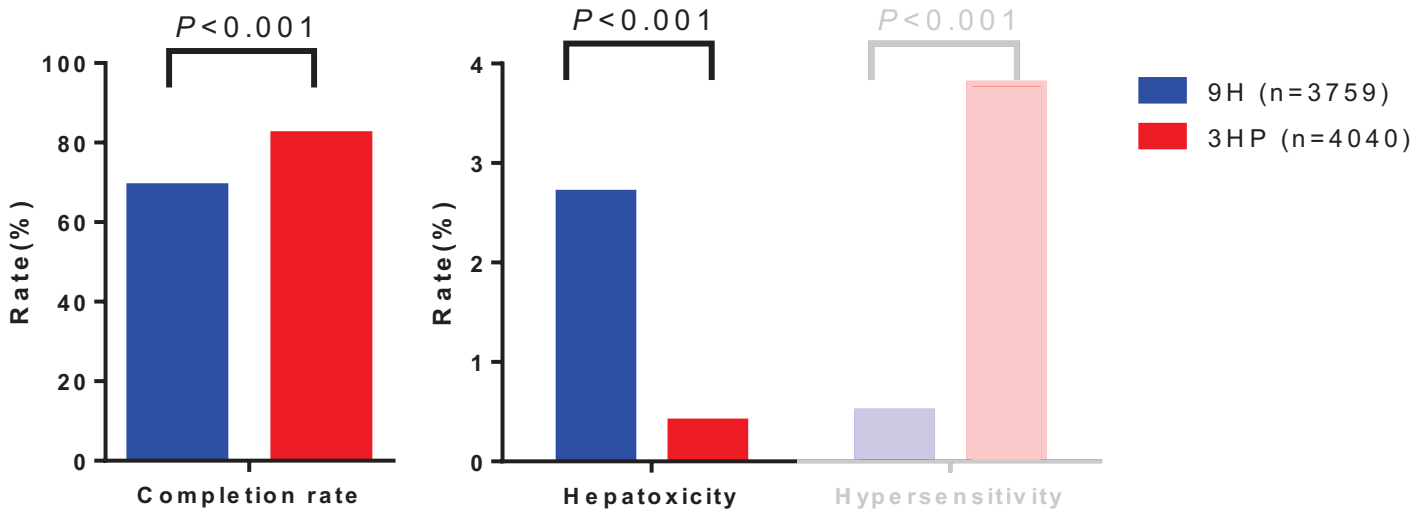
  b) > 4 of the following (one of which had to be > grade 2) that occurred in relation to study drug:

  - weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills.

Sterling, T.R., et al., N Engl J Med, 2011. **365**(23): p. 2155-66.

3HP versus 9H

- 2001-2008, multicenter, open-label RCT
- Multination: Brazil, Canada, Spain, and the United States
- Age ≥2 yr
- Spectrum of “high-risk” predicates



Timothy R. Sterling, et al. N Engl J Med 2011;365:2155-66.

Reported Adverse Events

Among persons receiving ≥ 1 dose
During treatment or within 60 days of the last dose
Accounting for attribution to study drug

HS: hypersensitivity reaction

Toxicity	9H N=3,759	**3HP** N=4,040 注意	P-value
Related to drug	206 (5.5)	**332 (8.2)**	<0.001
Rash only	21 (0.6)	31 (0.8)	0.26
Possible HS	17 (0.5)	**152 (3.8)**	<0.001
Other	65 (1.7)	**131 (3.2)**	<0.001
Not related	410 (10.9)	226 (5.6)	<0.001

使用短程處方較傳統9H多的是**過敏反應和其他副作用**

MAJOR ARTICLE

Flu-like and Other Systemic Drug Reactions Among Persons Receiving Weekly Rifapentine Plus Isoniazid or Daily Isoniazid for Treatment of Latent Tuberculosis Infection in the PREVENT Tuberculosis Study

Timothy R. Sterling,[1,a] Ruth N. Moro,[2,3,a] Andrey S. Borisov,[2] Elizabeth Phillips,[1,a] Gillian Shepherd,[5] Newton Franklin Adkinson,[6] Stephen Weis,[7] Christine Ho,[2] and Margarita Elsa Villarino[2]; for the Tuberculosis Trials Consortium

[1]Vanderbilt University School of Medicine, Nashville, Tennessee; [2]Centers for Disease Control and Prevention, and [3]CDC Foundation, Research Collaboration, Atlanta, Georgia; [4]Institute for Immunology and Infectious Diseases, Murdoch University, Perth, Australia; [5]New York-Presbyterian Hospital/Weill Cornell Medical Center, New York; [6]Johns Hopkins University School of Medicine, Baltimore, Maryland; and [7]University of North Texas Health Science Center at Ft. Worth

Background. Weekly rifapentine plus isoniazid for 3 months (3HP) is as effective as daily isoniazid for 9 months (9H) for latent tuberculosis infection in high-risk persons, but there have been reports of possible flu-like syndrome.

Methods. We identified clinically significant systemic drug reactions (SDR) and evaluated risk factors in patients who did not complete treatment in the PREVENT Tuberculosis study.

Results. Among 7552 persons who received ≥1 dose of study drug, 153 had a SDR: 138/3893 (3.5%) with 3HP vs 15/3659 (0.4%) with 9H ($P < .001$). In the 3HP arm, 87 (63%) had flu-like syndrome and 23 (17%) had cutaneous reactions; 13/3893 (0.3%) had severe reactions (6 were hypotensive) and 6 reported syncope. Symptoms occurred after a median of 3 doses, and 4 hours after the dose; median time to resolution was 24 hours. There were no deaths. In multivariate logistic regression analysis, factors independently associated with SDR included receipt of 3HP (adjusted odds ratio [aOR] 9.4; 95% confidence interval [CI], 5.5, 16.2), white non-Hispanic race/ethnicity (aOR 3.3; 95% CI, 2.3, 4.7), female sex (aOR 2.0; 95% CI, 1.4, 2.9), age ≥35 years (aOR 2.0; 95% CI, 1.4, 2.9), and lower body mass index (body mass index [BMI]; $P = .009$). In a separate multivariate analysis among persons who received 3HP, severe SDR were associated with white non-Hispanic race/ethnicity (aOR 5.4; 95% CI, 1.8, 16.3), and receipt of concomitant non-study medications (aOR 5.9; 95% CI, 1.3, 27.1).

Conclusions. SDR were more common with 3HP, and mostly flu-like. Persons of white race, female sex, older age, and lower BMI were at increased risk. Severe reactions were rare and associated with 3HP, concomitant medication, and white race. The underlying mechanism is unclear.

Clinical Trials Registration. NCT00023452.

Sterling, T.R., et al., Clin Infect Dis, 2015. **61**(4): p. 527-35.

因為hypersensitivity 是RPT在PREVENT Trial 中較重要的副作用，接下來我們看看在PREVENT Trial 與 NYC 的衛生局經驗，了解發生的狀況和嚴重度。

全身性藥物反應
Systemic Drug Reaction

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA hivma

Treatment for Tuberculosis Infection With 3 Months of Isoniazid and Rifapentine in New York City Health Department Clinics

Natalie L. Stennis, Joseph N. Burzynski, Cheryl Herbert, Diana Nilsen, and Michelle Macaraig

New York City Department of Health and Mental Hygiene, Bureau of Tuberculosis Control, Long Island City, New York

Background. Completion of treatment for tuberculosis infection (TBI) with 9 months of self-administered daily isoniazid (9H) has historically been low (<50%) among New York City (NYC) Health Department tuberculosis clinic patients. Treatment of TBI with 3 months of once-weekly isoniazid and rifapentine (3HP) administered under directly observed therapy (DOT) might increase treatment acceptance and completion.

Methods. The study population included patients diagnosed with TBI at 2 NYC Health Department tuberculosis clinics from January 2013 through November 2013. Treatment acceptance and completion with 3HP were compared with historical estimates. Treatment outcomes, side effects, and reasons for refusing 3HP were described.

Results. Among 631 patients eligible for TBI treatment, 503 (80%) were offered 3HP; 302 (60%) accepted, 92 (18%) chose other treatment, and 109 (22%) refused treatment. The most common reason for refusing 3HP was the clinic-based DOT requirement. Forty (13%) patients treated with 3HP experienced side effects—9 were restarted on 3HP, 18 switched treatment regimens, and 13 discontinued. Although treatment acceptance did not differ from historical estimates (78% vs 79%, $P = .75$), treatment completion increased significantly (65% vs 34%, $P < .01$).

Conclusions. Implementation of 3HP in 2 NYC Health Department tuberculosis clinics increased TBI treatment completion by 31 percentage points compared with historical estimates. More flexible DOT options may improve acceptance of 3HP. Wider use of 3HP may substantially improve TBI treatment completion in NYC and advance progress toward tuberculosis elimination.

Keywords. latent tuberculosis infection; 3-month treatment; directly observed therapy; public health.

Stennis, N.L., et al., Clin Infect Dis, 2016. **62**(1): p. 53-9.

Systemic Drug Reaction in the PREVENT Tuberculosis Study

- 138 (3.5%)的3HP (n=3893) 接受者有systemic drug reaction (SDR)
- Symptoms occurred after a median of 3 doses, and 4 hours after the dose; median time to resolution was 24 hours.
  - 4/3893 (0.1 %) admission
  - 13/3893 (0.3%)有severe reactions
    - 8: Grade 4 toxicity (including 1 syncope)
    - 6: hypotensive
    - 6: syncope (no admission, 有一個有loss consciousness)
  - No death reported

Sterling, T.R., et al., Clin Infect Dis, 2015. **61**(4): p. 527-35.

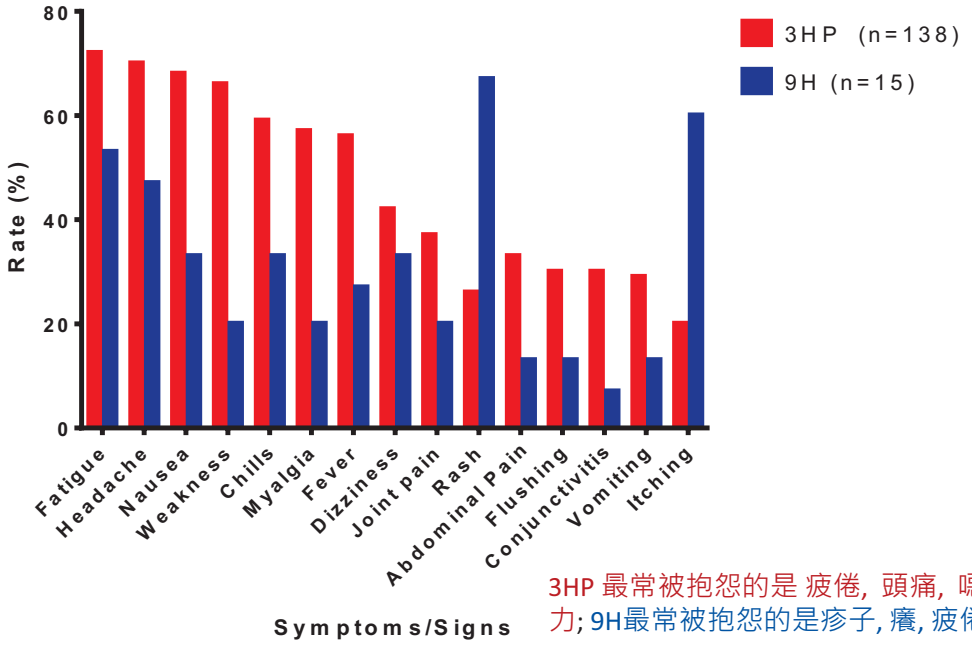
SDR

	3HP (n=138)	9H (n=15)
Cutaneous	23 (17%)	9 (60%)
Severe	3	1
nonsevere	20	8
Flu-like	**87 (63%)**	2 (13%)
Severe	**6**	0
nonsevere	**81**	2
Gastrointestinal	7 (5%)	1 (7%)
Severe	2	0
nonsevere	5	1
Respiratory	5 (4%)	0 (0%)
Severe	1	0
nonsevere	4	0
Not defined	16 (12%)	3 (20%)
Severe	1	0
nonsevere	15	3

注意

3HP的系統性藥物反應最常見的還是Flu-like syndrome (2.2%), 嚴重的類流感反應, 佔服藥總人數的0.15%

Frequency of signs and symptoms in 153 cases of systemic drug reactions (SDR), stratified by arm

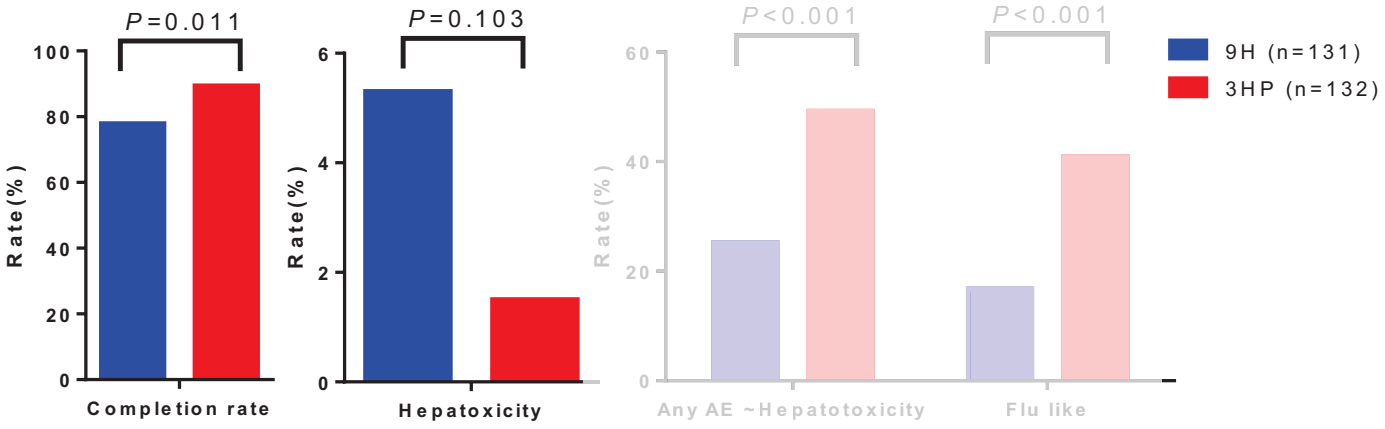


3HP 最常被抱怨的是 疲倦, 頭痛, 噁心, 無力; 9H最常被抱怨的是疹子, 癢, 疲倦

Sterling, T.R., et al., Clin Infect Dis, 2015. **61**(4): p. 527-35.

3HP vs. 9H Taiwan experience

- 2014-20168, multicenter, open-label RCT
- Age ≥ 12 yr
- TST+ and AFB+ pulmonary TB contact



Sun HY et al.Tuberculosis (Edinb). 2018 Jul;111:121-126.

ADRs Other than Hepatotoxicity

Taiwan (2014/1 – 2016/5)	3HP (N=132)	9H (N=131)
Any	49.2%	25.2%
Flu-like symptoms	40.9%	16.8%
Fever	12.9%	0.8%
Headache	7.6%	0.8%
Vomiting	7.6%	0.8%
Hot flushes	6.1%	0.8%
Leading to termination (Non-significant)	9.1%	5.3%

Sun HY et al.Tuberculosis (Edinb). 2018 Jul;111:121-126.

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結核病接觸者檢查規範

為強化並督導接觸者追蹤工作，自2007年7月1日起由公務預算支付接觸者檢查之部分負擔費用。

檢查對象

- 與確診之結核病個案共同居住者
- 與結核病個案於可傳染期間一天內接觸8小時以上或累積達40(含)小時以上之接觸者
- 其它專案

接觸者發病為一般民眾發病的8 - 240倍

接觸者檢查時間及方式

※於指標個案確診後，完成結核病接觸者之基本資料調查及檢查。

指標個案傳染性分類		C(MTB)之肺結核（<5歲之確診個案除外）				C(-)之肺結核（<5歲之確診個案除外）	單純肺外或<5歲之確診個案
		S(+)	S(-)				
接觸者檢查時間/項目		全年齡層	<13歲	≥13歲			1. 檢查目的為尋找感染源。 2. 單純肺外個案以≥5歲同住之接觸者為對象。 3. <5歲確診個案以≥5歲之接觸者為主。
				共同居住或慢性病患者	其他		
第1個月內	胸部X光	○	○	○	○	○	○
第3個月(終止有效暴露8週後)	**LTBI檢驗**	○	○	○	×	×	×
第12個月	胸部X光(LTBI陰性/持續或完成LTBI治療)	×	×	×	×	×	×
	胸部X光(未加入或中斷LTBI治療)	○	○	○			

- 自登記為RR/MDRTB起1個月內，應再次確認其RR/MDRTB可傳染期及符合接檢之對象。日後每半年追蹤1次，持續至指標個案痰培養陰轉後2年(或停止接觸後2年)。如LTBI檢驗陰性者，則無需再進行追蹤。
- **<5歲接觸者以TST為主要LTBI檢驗工具，應於指標個案確診日起1個月內執行，檢查陰性者須於第3個月執行第2次TST；≥5歲接觸者以IGRA為主要LTBI檢驗工具。**
- **系統勾稽顯示為慢性病風險族群，或接觸者自述患有慢性病(如：糖尿病、腎臟病、使用免疫抑制劑、器官移植、愛滋感染者等)，皆符合LTBI檢驗對象。**
- **LTBI檢驗陽性者應轉介合作醫師進行治療評估，並應有最近1個月內胸部X光檢查結果，以排除活動性結核病。**

LTBI診斷及治療服務對象

當年度高傳染性結核病個案之接觸者
當年度中傳染性結核病個案之未滿13歲、13歲(含)以上且共同居住、13歲(含)以上患有慢性病(如：糖尿病、腎臟病、使用免疫抑制劑、器官移植、愛滋感染者等)之接觸者

曾為高傳染性結核病個案之接觸者
- 未曾LTBI檢驗者，提供檢驗及治療服務
- 曾檢驗陽性，但未接受或未完成治療者，提供治療服務(可評估使用3HP)

縣市自辦高風險族群，如：**HIV、IDU、山地鄉、洗腎、器官移植、TNF-α-blocker使用者、血糖控制不佳之糖尿病患者、長照機構等族群**

潛伏結核全都治計畫

適用對象
- 高傳染性個案之全年齡層接觸者
- 中傳染性個案之未滿13歲接觸者、同住接觸者、患有慢性病之接觸者

檢驗方法
未滿5歲TST
5歲以上：IGRA

治療處方
- 傳統9H處方
- 短程處方速克伏(3HP)
- INH抗藥RMP敏感個案接觸者適用之4R處方

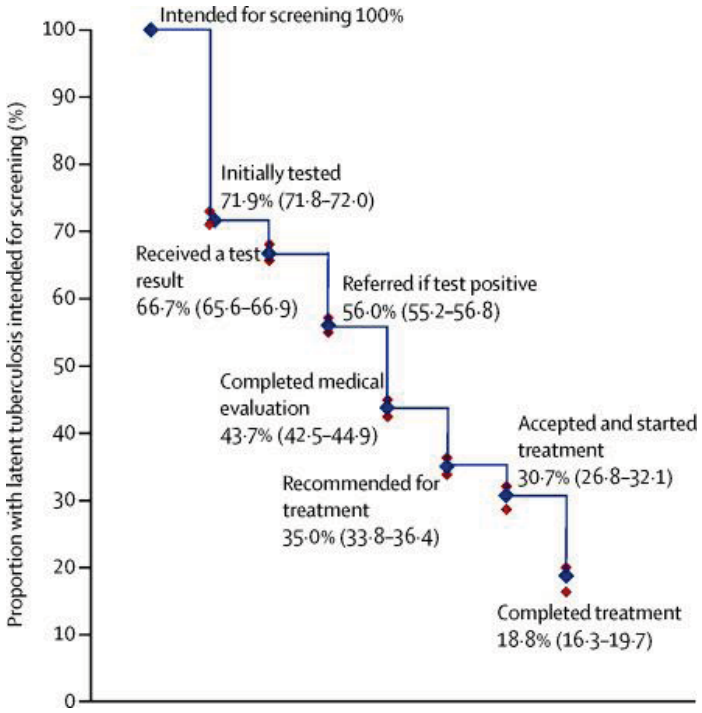
不適用3HP處方者

Ineligible Patients

孕婦 (或準備懷孕的婦女 Pregnant and those expecting to become pregnant during treatment	指標個案為INH或RMP抗藥 Source case is INH or RMP resistant	未滿2歲之兒童 < 2 years of age

正在使用coumadin, methadone, phenytoin等藥物者，須考慮藥物交互作用可能產生之影響。

Cascade of LTBI Care



Alsdurf, H. Lancet Infect Dis **2016**;16:1269-78.

LTBI診斷及治療Cascade

A.完成X光檢查
(99%)

B. 完成LTBI檢驗
(92%)

- LTBI檢驗政策對象
- 完成LTBI檢驗
- LTBI檢驗陽性
  (應接受LTBI治療評估)
- 完成LTBI治療評估

- 應接受LTBI治療
- 加入LTBI治療
- 完成LTBI治療

C. 檢驗陽性者加入LTBI治療
(67%)

D.完成LTBI治療
(49%)

說明：2016/1/1~2017/3/31結核確診個案之接觸者，追蹤至2017/9/30。

Targets by 2025

Treatment coverage
Number of people that developed TB, and were notified and treated, out of the total estimated number of incident cases in the same year (%).

≥ 90%

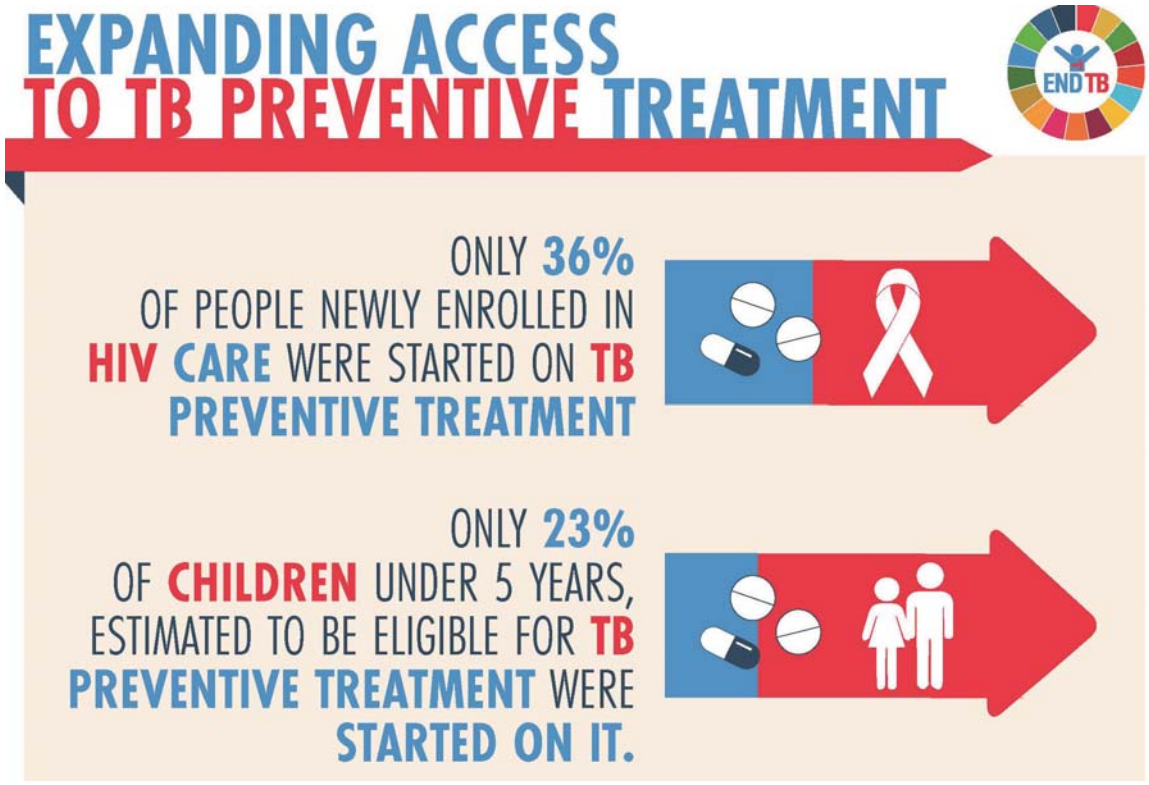
TB treatment success rate
Number of TB patients who were successfully treated out of all notified TB cases (%).

≥ 90%

Preventive treatment coverage
Number of people living with HIV and children who are contacts of cases who were started on preventive treatment for latent TB infection, out of all those eligible (%).

≥ 90%

WHO: The End TB Strategy 2015



被結核菌感染了，怎麼辦？

- 潛伏結核感染的診斷及治療是終結結核病的重要手段
- IGRA和TST可以幫忙潛伏結核感染的診斷,但仍不理想
- 3HP較9H,有較高的完治率,較低的肝功能異常,但副作用仍要注意

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