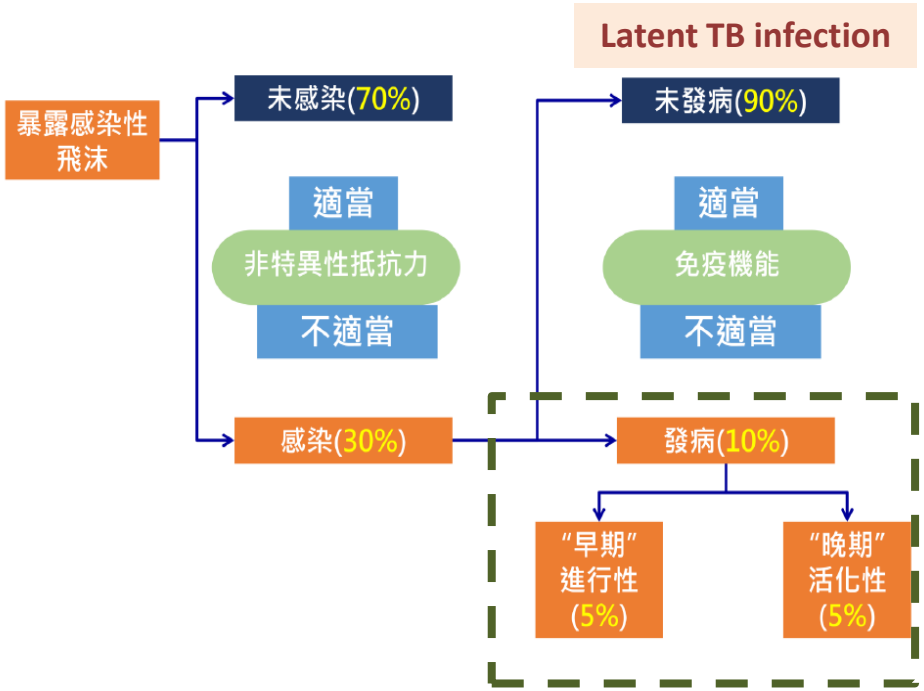
潛伏結核治療處方綜論
Overview of treatment of Latent TB infection (LTBI)

黃虹綾 醫師
高雄市立大同醫院(委託高醫經營) 胸腔內科
高雄醫學大學附設醫院 胸腔內科
高雄醫學大學醫學系助理教授

Nature course of TB disease

- Latent TB infection (LTBI) is a state of persistent immune response to stimulation by MTB antigens without evidence of clinically manifested active, including radiography
- One-quarter of global population had LTBI



Conditions That Increase The Risk of Developing Active TB

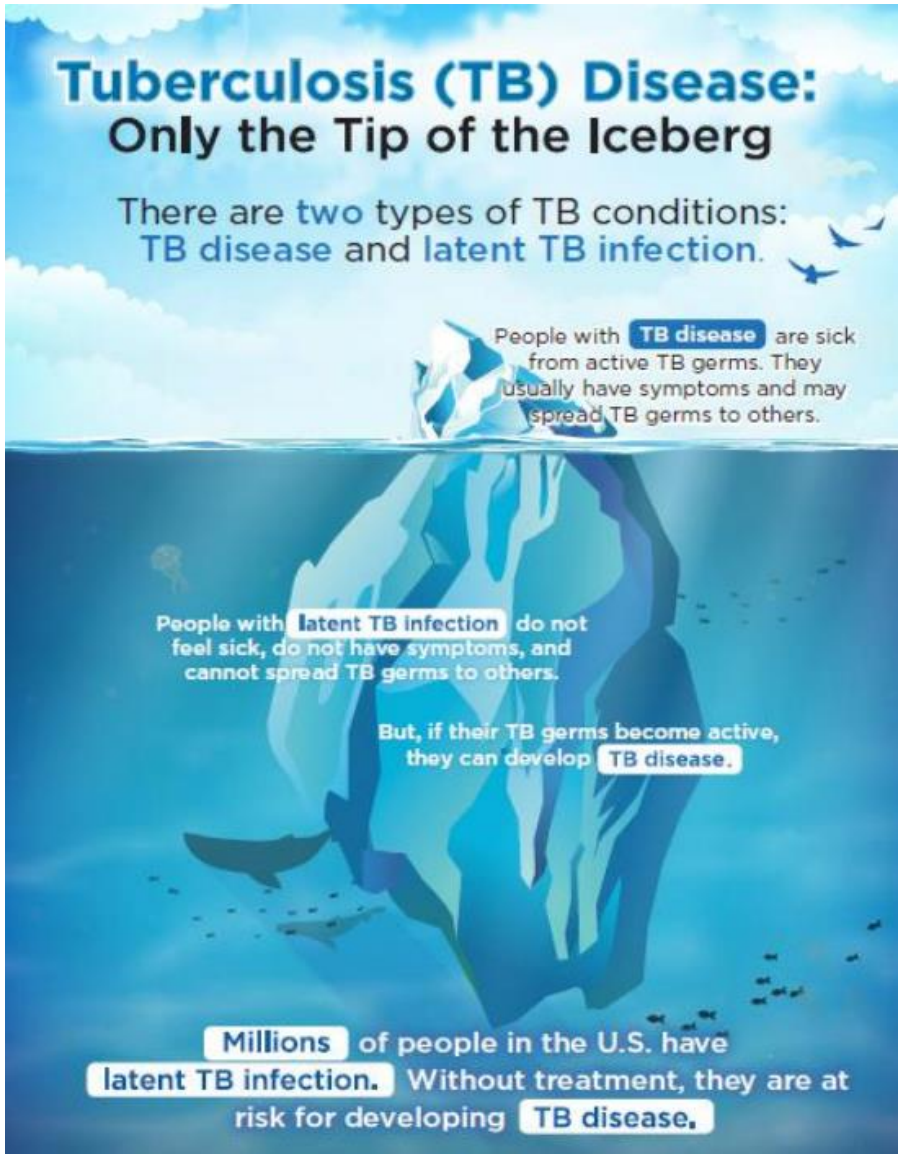
Condition	Relative Risk	Annual Risk of Developing Active TB (%)	Cumulative Lifetime Risk (%)†
AIDS	90-170	8-17	100
HIV infection	40-113	4-11.3	100
Transplantation	20-74	2-7.4	100
Pulmonary silicosis	30	3	100
Chronic renal failure/hemodialysis	10-25	1-2.5	50-100
Recent infection within 2 years	15	1.5	75
Carcinoma of head and neck	16	1.6	80
Fibronodular disease on chest radiograph	6-19	0.6-1.9	30-95
Diabetes mellitus	2-3.6	0.2-0.36	10-18
Granuloma on chest radiograph	2	0.2	10
No known risk factor	1	0.1	5

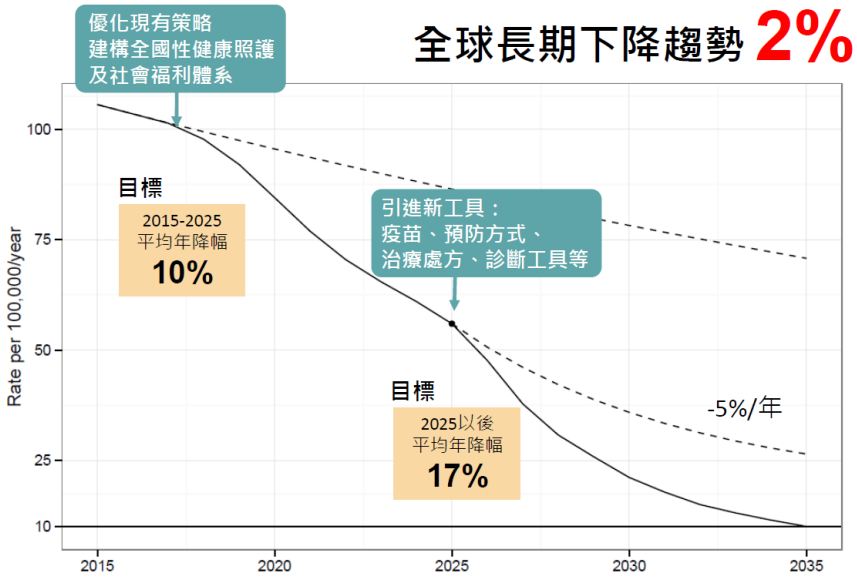
†Estimates for young adults

To identify the risk for LTBI reactivation is important

The Canadian Journal of CME / May 2001

Key for TB Elimination:
Treat active TB and LTBI simultaneously

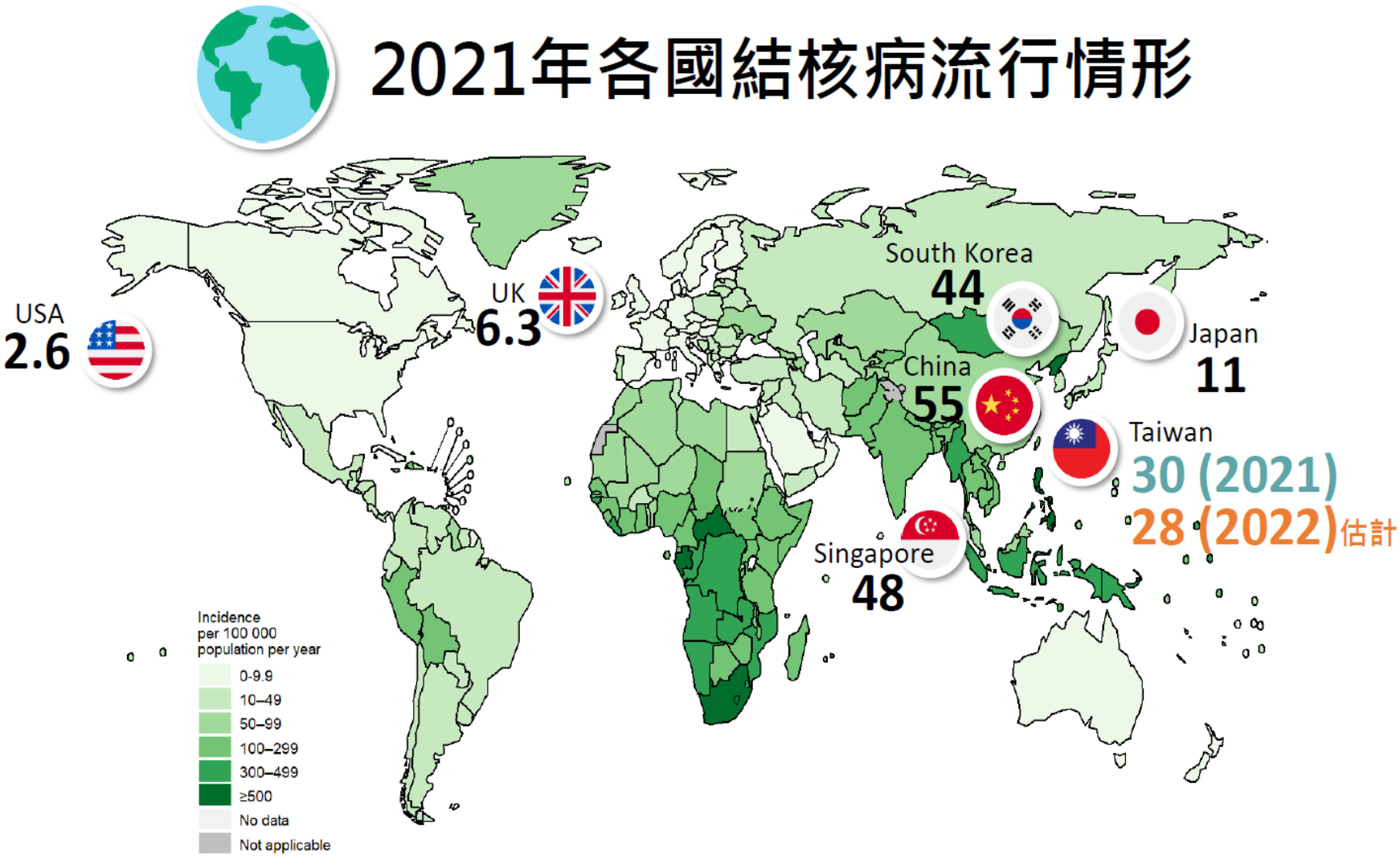




A Koul *et al. Nature* **469**, 483-490 (2011) doi:10.1038/nature09657

Global prevalence of TB disease

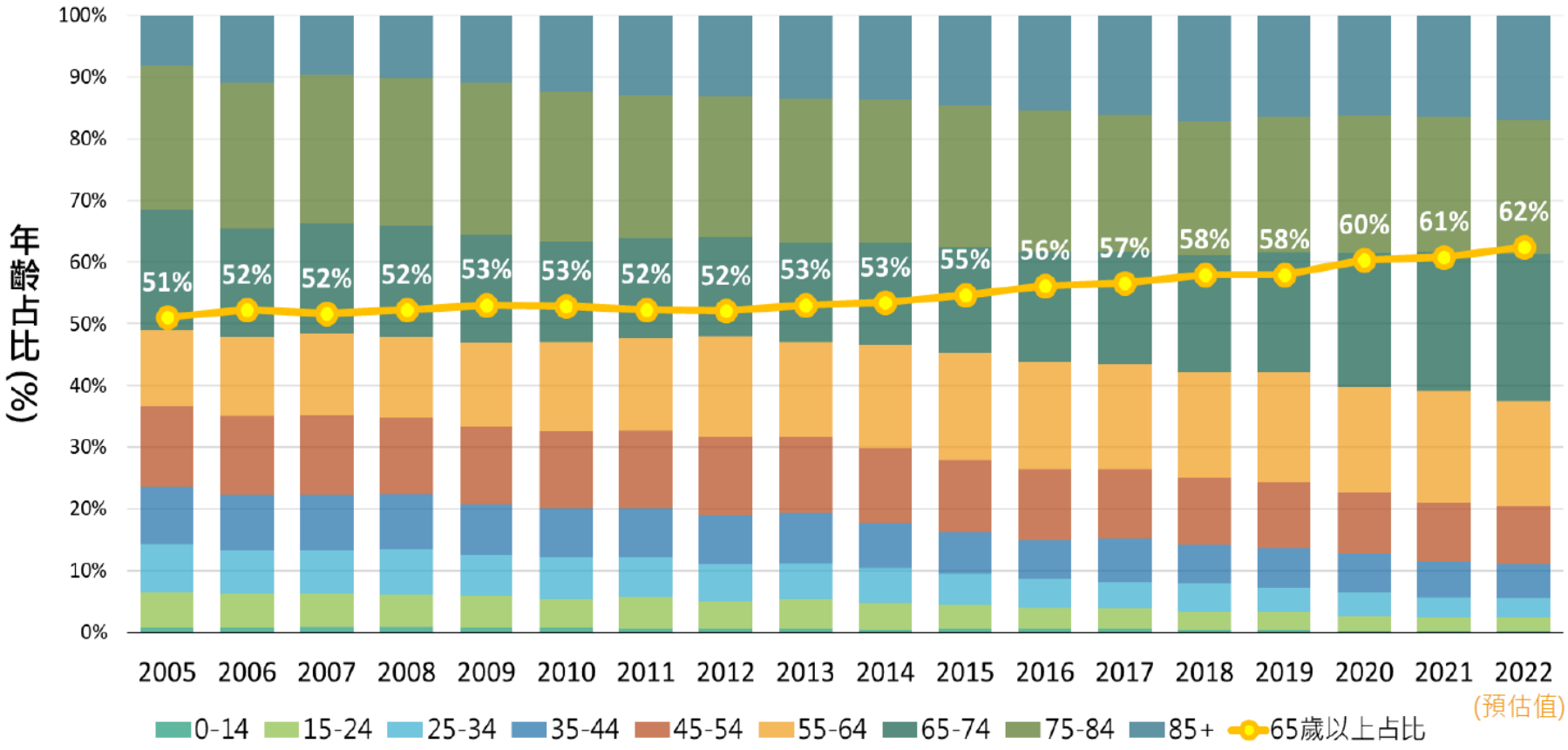
2021年各國結核病流行情形



資料來源： WHO Global tuberculosis report 2022

TB prevalence rate declined annually

Age distribution of TB new cases in Taiwan (2005-2022)

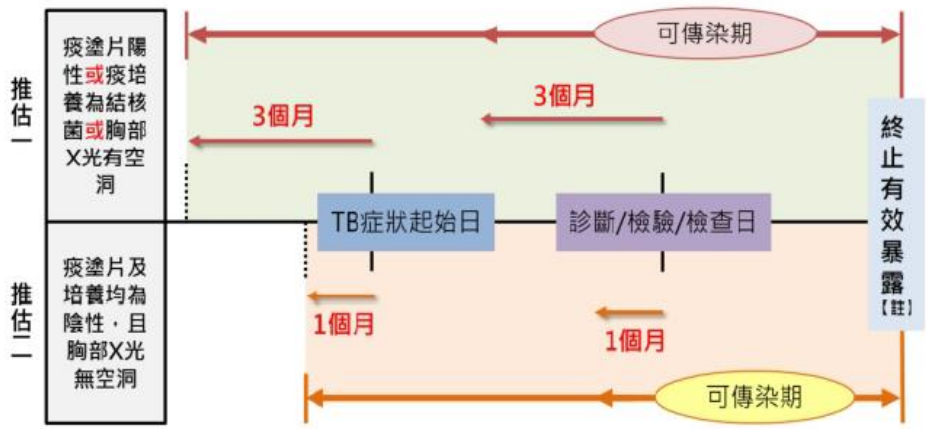


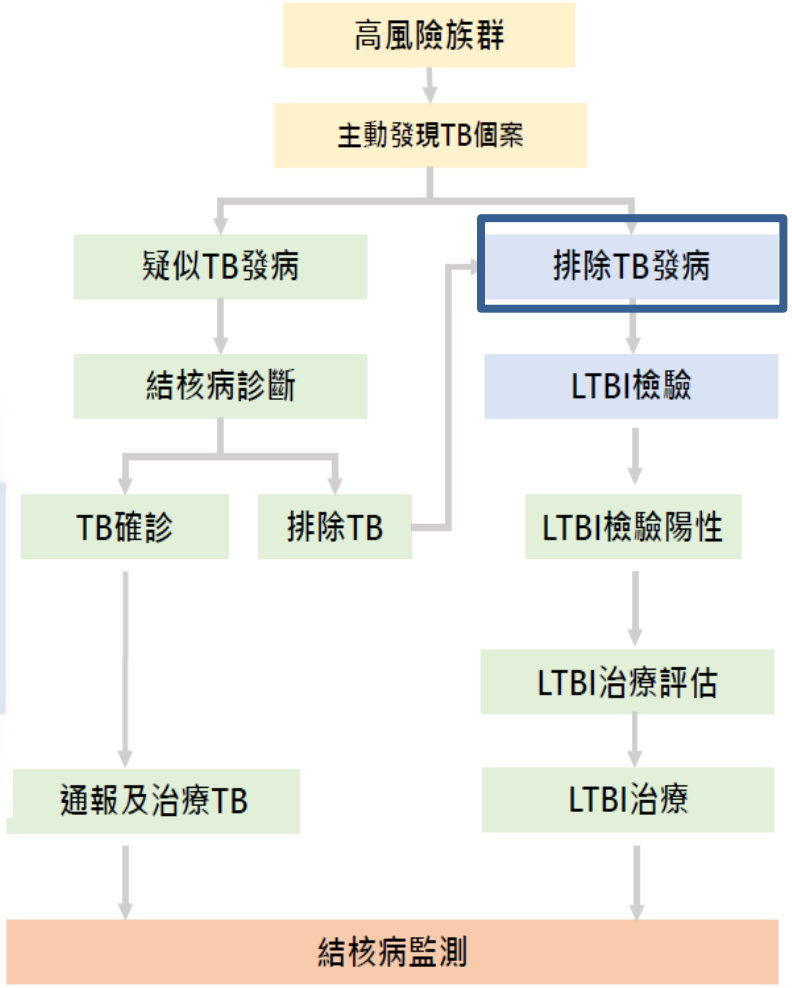
65歲以上個案占所有個案大於60%,

TB Reactivation rather Reinfection, LTBI is a big reservoir of TB disease

LTBI screening and diagnosis algorism

Definition of Infectious period





指標確診後儘速執行CXR及終止暴露滿8週進行IGRA檢驗

Target population for LTBI management in Taiwan

Definition of TB close contact
密切接觸者定義

- 與指標個案共同居住者
- 與指標個案於可傳染期間1天內接觸8小時(含)以上或累計達40小時(含)以上
- 其他(如：聚集事件等)有必要進行接觸者檢查之對象另行以專案處理
- 公衛可依指標個案傳染力，或暴露環境換氣不佳等實際情形，調整上述時數規定之標準(1天內接觸未達8小時或累計未達40小時亦可)

TB close contact

- 高傳染力指標(sputum smear positive and culture confirmed MTBC)
  - -全年齡層接觸者
- 中傳染力指標(sputum smear negative but culture confirmed MTBC)
  - -未滿13歲接觸者
  - -13歲(含)以上之
    - 共同居住接觸者
    - 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）的接觸者

High risk population

- 長照機構住民與工作人員
- 山地原鄉住民
- 矯正機關收容人與工作人員
- 愛滋感染者或注射藥癮個案
- 接受抗腫瘤壞死因子(TNF-alpha blocker)
- 慢性腹膜或血液透析
- 將接受器官移植患者
- 糖尿病血糖控制不佳(糖化血色素>9.0%)
- 來自結核病高負擔國家之新住民
- 縣市自提高風險族群並經疾管署核備同意對象(如遊民等)

接觸者發病為一般民眾發病的8 - 240倍

Diagnostic Tools for LTBI – IGRA
Interferon Gamma Release Assay

- In vitro whole blood stimulated by specific TB Antigen ESAT-6、CFP -10和TB7.7
- **Advantage**
  - Less false positive in NTM patients
  - Easy test, only one blood test
  - Quantitative

- Use in > 2 year-old population

- QFT-Plus measures the cell-mediated immune response to TB infection from both CD4+ and CD8+ T cells.
  - TB1 tube: detects CD4+ responses
  - TB2 is for both CD4+ and CD8+ responses.
  - CD8 cell secrete IFN-r to
    - Suppress MTB growth
    - Kill infected cells
    - Directly lyse intracellular MTB

Nil (IU/mL)	TB1抗原-Nil (IU/mL)	TB2抗原-Nil (IU/mL)	Mitogen-Nil (IU/mL)	QFT結果	結果判讀
≦8.0	≥0.35和 ≥25% Nil值	≥0.35和 ≥25% Nil值	任何	陽性	很可能感染結核菌
	<0.35	<0.35	≥0.5	陰性	不太可能感染結核菌
	≥0.35和 <25% Nil值	≥0.35和 <25% Nil值	≥0.5	陰性	不太可能感染結核菌
	<0.35	<0.35	<0.5	不確定性 (Mitogen<0.5)	對TB抗原的反應結果不確定
	≥0.35和 <25% Nil值	≥0.35和 <25% Nil值	<0.5	不確定性 (Mitogen<0.5)	對TB抗原的反應結果不確定
>8.0	任何	任何	任何	不確定性	對TB抗原的反應結果不確定

Screening test for LTBI: IGRA vs. TST

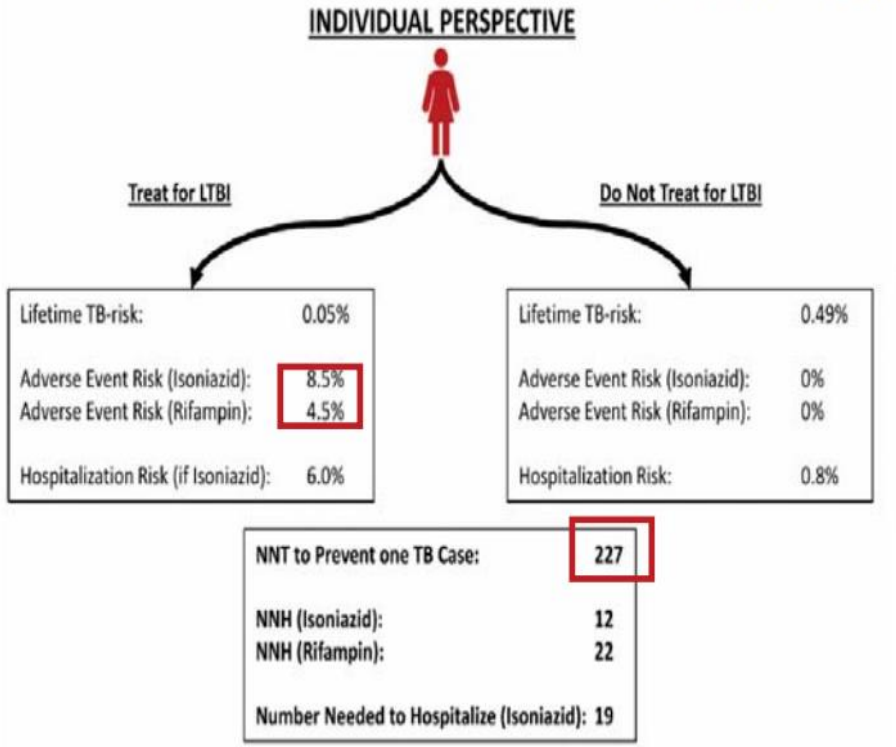
檢驗方法	丙型干擾素釋放試驗 (Interferon-gamma release assay，IGRA)	結核菌素測驗 (Tuberculin Skin Test，TST)
原理	利用結核分枝桿菌特異抗原在體外刺激淋巴球產生丙型干擾素(M. tuberculosis specific Interferon-γ)，加以定量來判定是否感染	結核菌素(PPD)注入人體之皮內，觀察有無特異過敏反應現象(delayed-type hypersensitivity)
方式	抽血4CC	皮內施打0.1CC
年齡	**2歲(含)以上**	**未滿2歲**
	2歲(含)至未滿5歲，倘無法執行IGRA檢驗，得使用TST	
LTBI治療標準	結果為陽性或不確定性(mitogen-nil<0.5)者	➢ 曾接種BCG者，TST硬結≥10 mm ➢ 未曾接種BCG者、免疫功能低下、惡性腫瘤或器官移植者TST硬結≥5 mm
特性	➢ 較不受BCG及環境中之非典型分枝桿菌(NTM)造成之偽陽性影響結果 ➢ 檢驗成本較高	➢ 48-72小時內須回診判讀，易受增強效應(booster effect)影響；施打及判讀人員須接受過訓練 ➢ 檢驗成本較低
共同特性	➢ 人體受到結核菌感染後因**免疫反應的延遲，約8至12週會陽轉反應**，故應於**與指標個案終止有效暴露滿8週後再進行檢驗**，未達8週檢驗可能會有偽陰性情形 ➢ 2者皆有使用上的限制，目前沒有標準檢驗可診斷TB infection，檢查結果**陰性者不能排除TB infection甚至發病**，有可能false-negative(免疫差或剛被感染…)，需藉由臨床評估、胸部X光、痰液檢查及個案症狀來加以判別	

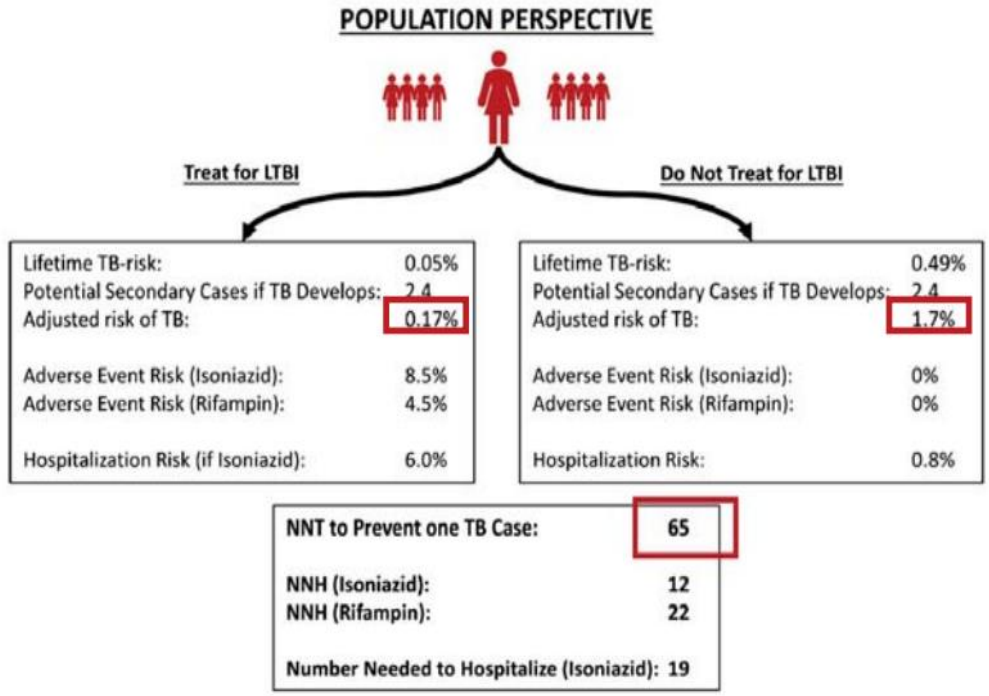
The benefit of LTBI treatment

結核防治-Individual

結核防治-Population

75歲女性預期有五年的存活期

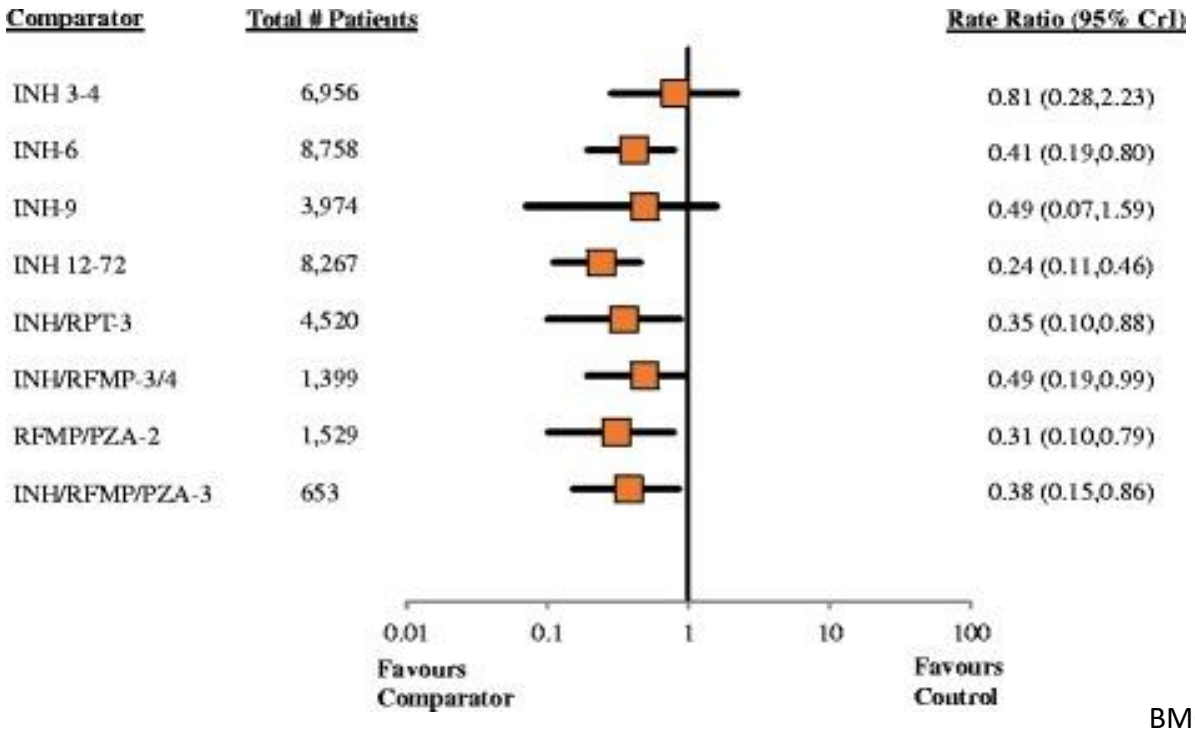




Campbell JR et al. Plos Med 2019

TB preventive efficacy after LTBI intervention

- Systemic review and network meta-analysis
  - 16 RCTs (*n* = 44,149) and 14 RCTs (*n* = 44,128)
  - Between 1968 and 2015
  - All regimens showed significant benefits in preventing active TB compared to placebo.
  - Shorter rifamycin-based regimens may offer comparable benefits to longer INH
  - Regimens of 3–4 months are more likely to be completed than longer regimens.

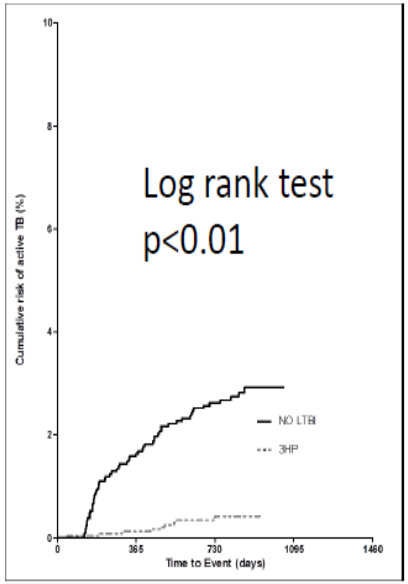


BMC Infect Dis. 2017; 17: 265

接受LTBI治療之保護效果 (科技計畫成果2016/1-2017/6 五歲及以上,N=11923)

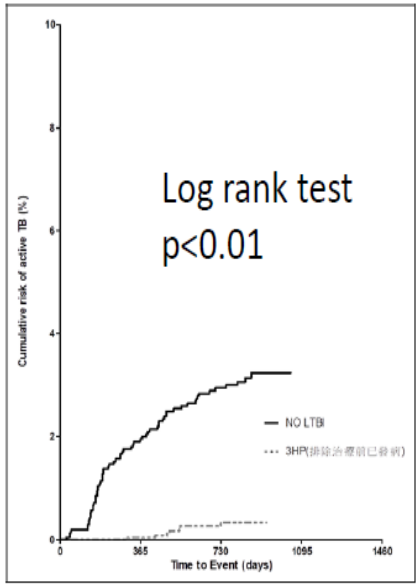
	發生率 (人年)	RR	95%CI		發生率 (人年)	RR	95%CI
3HP	**0.18**	0.13	(0.07-0.27)	3HP	**0.18**	0.64	(0.27-1.52)
未曾接受治療	**1.35**			9H	**0.28**		

LTBI 接觸者接受治療的保護力約87%



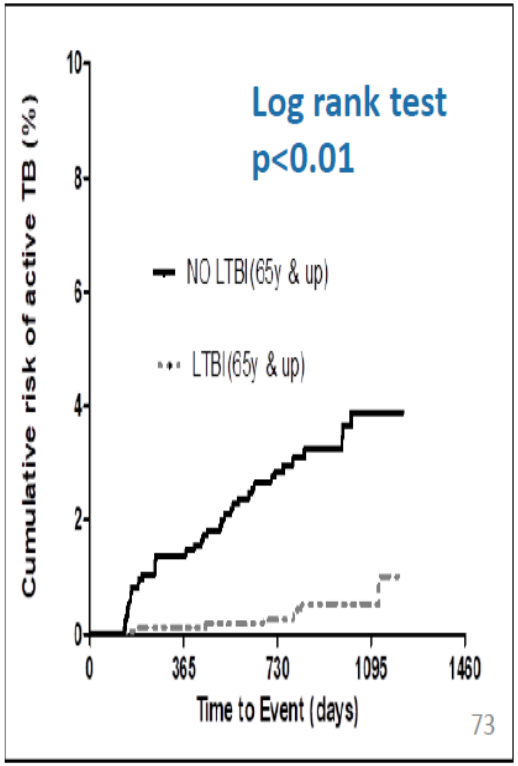
3HP vs. 未治療

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
(經病歷及影像調閱判斷)

即使在65歲及以上的優先族群的保護力也達85%



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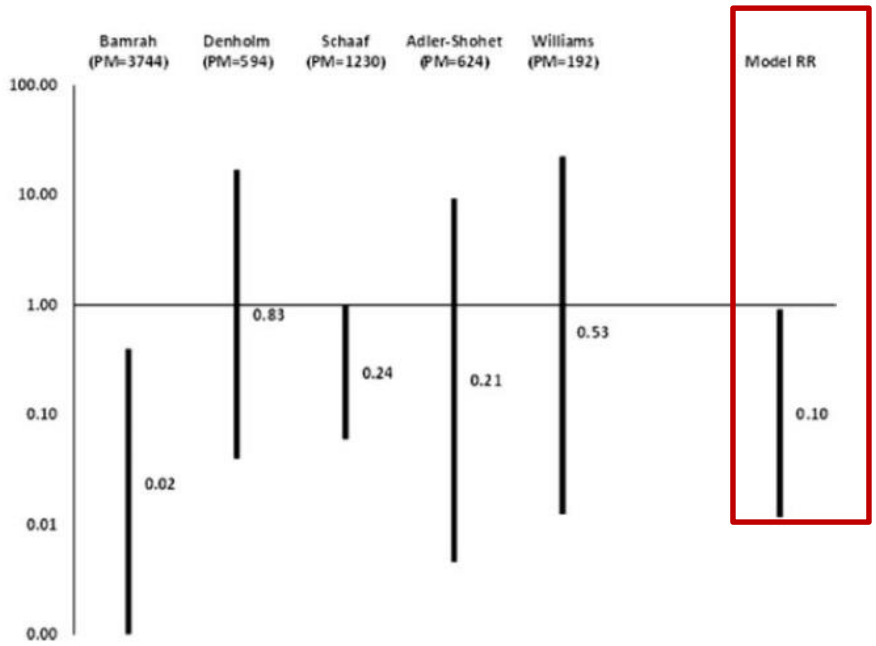
MDRTB preventive efficacy after LTBI intervention

- Systematic Review, Meta-analysis
- 1 January 1994–31 December 2014
- 22 studies
  - 6 studies LTBI treatment vs. none , others are single arm
  - Overall TB incidence was 3% in Micronesia (Bamrah et al), 4% in Australia (Denholm et al), and 14% in South Africa (Schaaf et al).
  - A **90%** risk reduction in MDR TB

Study	TB	No TB	Total
Adler-Shohet et al [22]			
LTBI Tx	0	26	26
No LTBI Tx	0	5	5
Total	0	31	31
Bamrah et al [19]			
LTBI Tx	0	104	104
No LTBI Tx	3	12	15
Total	3	116	119
Demholm et al [20]			
LTBI Tx	0	11	11
No LTBI Tx	2	36	38
Total	2	47	49
Schaaf et al [21]			
LTBI Tx	2	39	41
No LTBI Tx	13	51	64
Total	15	90	105
Williams et al [23]			
LTBI Tx	0	8	8
No LTBI Tx	0	4	4
Total	0	12	12



Clin Infect Dis. 2017 June 15; 64(12): 1670–1677

- High treatment discontinuation rates due to adverse effects in persons taking pyrazinamide-containing regimens.
- Cost-effectiveness was greatest using a fluoroquinolone/ethambutol combination regimen.

Treatment	Estimated Regimen Efficacy, %	Estimated Stop Due to AE, %	Estimated Completion, %	Estimated US MDR-TB Cases Over 40 Remaining Years of Life, No.	TB Cases Prevented, No.	Discounted Cases Prevented, No.	Remaining Lifetime QALYs, No.	Estimated Regimen Cost, 2014 $	Discounted Net Cost (Program Cost – Cost of TB Cases Prevented), 2014 $	Incremental Cost (Saving) per Case Prevented, 2014 $
No Tx				704	0	…	23.6858		$ 16 469 760	
PZA/FQ	90	57	40	451	253	146	23.6380	$1993	$ (13 716 976)	Saving
FQ alone	62	2	87	324	380	219	23.6935	$1461	$ (28 104 187)	Saving
PZA/EMB	62	11	89	316	388	224	23.6852	$1350	$ (30 579 993)	Saving
FQ/EMB	76	0	80	276	428	247	23.6966	$1893	$ (29 498 490)	Saving
FQ/ETA	69	0	100	218	486	281	23.6981	$4213	$ 4 133 156	Not cost effective

For the FQ/ETA regimen, AE and treatment completion data were based on a small number of patients (n = 12).

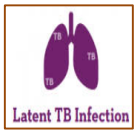
Abbreviations: AE, adverse effect; EMB, ethambutol; ETA, ethionamide; FQ, fluoroquinolone; MDR, multidrug-resistant; PZA, pyrazinamide; QALY, quality-adjusted life-year; TB, tuberculosis; Tx, treatment; US, United States.

Clinical Infectious Diseases 2017 June 15, 64 (12): 1670-1677

LTBI policy launched since 2008 in Taiwan

Comprehensive assessment before LTBI treatment can increase completion rate

- Comprehensive assessment
  - Drug resistance of index case : INH-R, RIF-R, MDR-TB-R …etc
  - Cormobidities for high risk factors for TB reactivation
    - DM, immunosuppressant, ESRD…etc
  - General assessment for health condition, medication use
- Before initiation of LTBI treatment, CXR within 1 month before initiation of LTBI treatment is necessary.
  - Sputum acid fast smear and culture: if CXR abnormality with suspicious of TB
  - Exclude TB disease before initiation of LTBI treatment to prevent DR-TB
- Symptom relieve medication for stomachache, headache, fever, pyridoxine (vit B_6) before LTBI treatment



治療處方原則及選擇

- **基本原則:**
  - 副作用的監測
  - 促進藥物治療的順從性與完成率
  - 在國家計畫的管理、監測及評估下推展新處方

- **指標個案(Index case)抗藥性:**
  - INH-Resistance: 4R
  - RIF-Resistance: 9H
  - MDR-TB:轉介至抗藥性結核病醫療照護體系(TMTC)加入專案計畫選擇使用fluoroquinolone類藥物作為LTBI治療

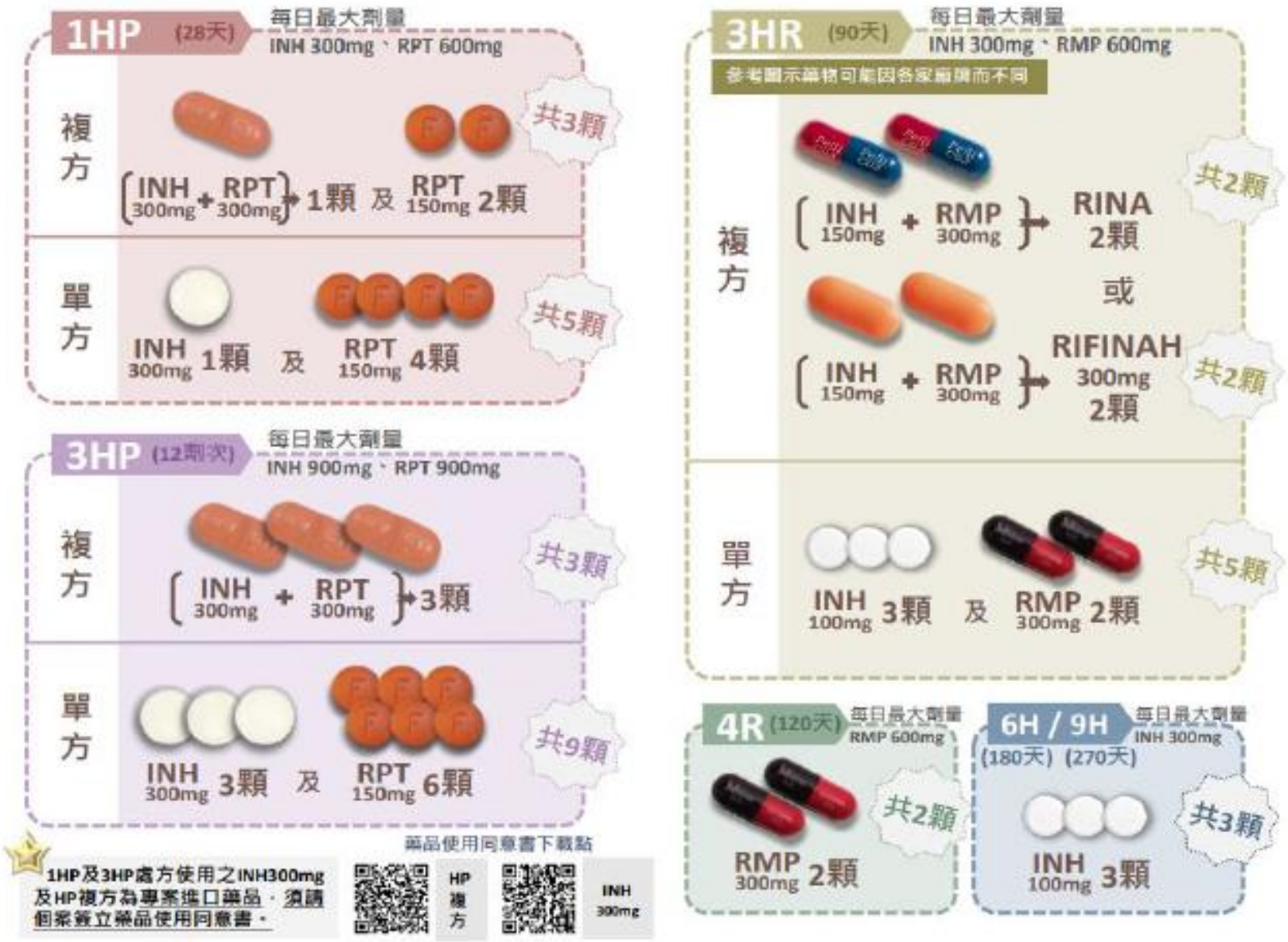
潛伏結核感染治療處方一覽表

處方	處方藥品		總劑數與療程頻率	劑量 每日最大劑量	劑量 兒童	劑量 成人	常見副作用	使用限制	都治 (DOPT)	推薦順序 (接觸者除指標抗藥或使用限制外)
1HP[a]	複方	Isoniazid(INH) 300mg+ Rifapentine (RPT) 300mg	28天 (1個月) 每日服用	300mg	固定1顆		皮疹(蕁麻疹)為主、(少數)肝毒性	◆ 指標個案INH或RMP抗藥之接觸者 ◆ <13歲兒童	必須	推薦處方
		Rifapentine (RPT) 150mg		300mg	◆ 35-45 kg 1顆 ◆ >45 kg 2顆					
		Isoniazid (INH) 300mg		300mg	300 mg					
3HP[a]	複方	Isoniazid(INH) 300mg+ Rifapentine (RPT) 300mg	12個劑量 (3個月) 每週服用	900 mg	體重50kg以上 固定劑量3顆		皮疹、類流感症狀、過敏反應、(少數)肝毒性	◆ 指標個案INH或RMP抗藥之接觸者 ◆ 孕婦[c]	必須	推薦處方
	單方	Isoniazid (INH) 300mg	12個劑量 (3個月) 每週服用	900 mg	◆ 2-11 歲 25mg/kg ◆ 12 歲(含)以上15mg/kg		皮疹、類流感症狀、過敏反應、(少數)肝毒性	◆ 指標個案INH或RMP抗藥之接觸者 ◆ <2歲兒童 ◆ 孕婦[c]	必須	推薦處方
		Rifapentine (RPT) 150mg		900 mg	◆ 10.0–14.0 kg 300 mg ◆ 14.1–25.0 kg 450 mg ◆ 25.1–32.0 kg 600 mg ◆ 32.1–49.9 kg 750 mg ◆ ≥50.0 kg 900 mg					
4R	Rifampin (RMP) 300mg		120天 (4個月) 每日服用	600 mg	15 (10-20)mg/kg	10 mg/kg	皮疹、腸胃不適/腸胃障礙、(少數)肝毒性	指標個案RMP抗藥之接觸者	必須	推薦處方
3HR[b]	Isoniazid (INH) 100mg		90天 (3個月) 每日服用	300 mg	10 (7-15)mg/kg	5 mg/kg	過敏反應、(少數)肝毒性	指標個案INH或RMP抗藥之接觸者	必須	推薦處方
	Rifampin (RMP) 300mg			600 mg	15 (10-20)mg/kg	10 mg/kg				
6H /9H	Isoniazid(INH) 100mg		180天(6個月) /270天(9個月) 每日服用	300 mg	10 (7-15)mg/kg	5 mg/kg	皮疹、周邊神經病變、肝毒性	指標個案INH抗藥之接觸者	建議	替代處方

The safety evidence of 1HP in non-HIV population is still lacking

a：3HP及1HP處方使用之INH300mg及HP複方為專案進口藥品，須請個案簽立藥品使用同意書 b：3HR可依體重使用INH+RMP之二合一劑型
c：目前尚未有足夠之孕婦臨床安全性相關試驗數據
參考資料：WHO operational handbook on tuberculosis (Module 1 – Prevention): Tuberculosis preventive treatment . World Health Organization. 2020及本署結核病診治診引

潛伏結核感染治療處方一覽表(藥品圖示)



匡列接觸者

- 依接觸者定義進行匡列
- 接觸者依與指標個案終止有效暴露達8週後進行LTBI檢驗
- 提升追蹤接觸者品質
- 執行接觸者追蹤檢查

DOPT執行

由關懷員每日關懷服藥，即時監測副作用發生，以提高完治率、或可參加雲端都治(e-DOPT)

採檢檢驗方式/流程

- 代檢網提供IGRA檢驗服務或縣市自行建立檢驗合作體系
- IGRA檢驗單位通過CAP或TAF認證
- 以IGRA/TST檢驗結果為陽性者轉介治療評估

2歲(含)以上建議處方

3HP、3HR、4R、6H、9H

1HP(13歲以上)

LTBI治療

- 推廣短程及複方治療處方
- 縣市建立合作醫師體系並確認品質
- 合作醫師評估符合治療條件者

未滿2歲建議處方

不建議3HP、1HP

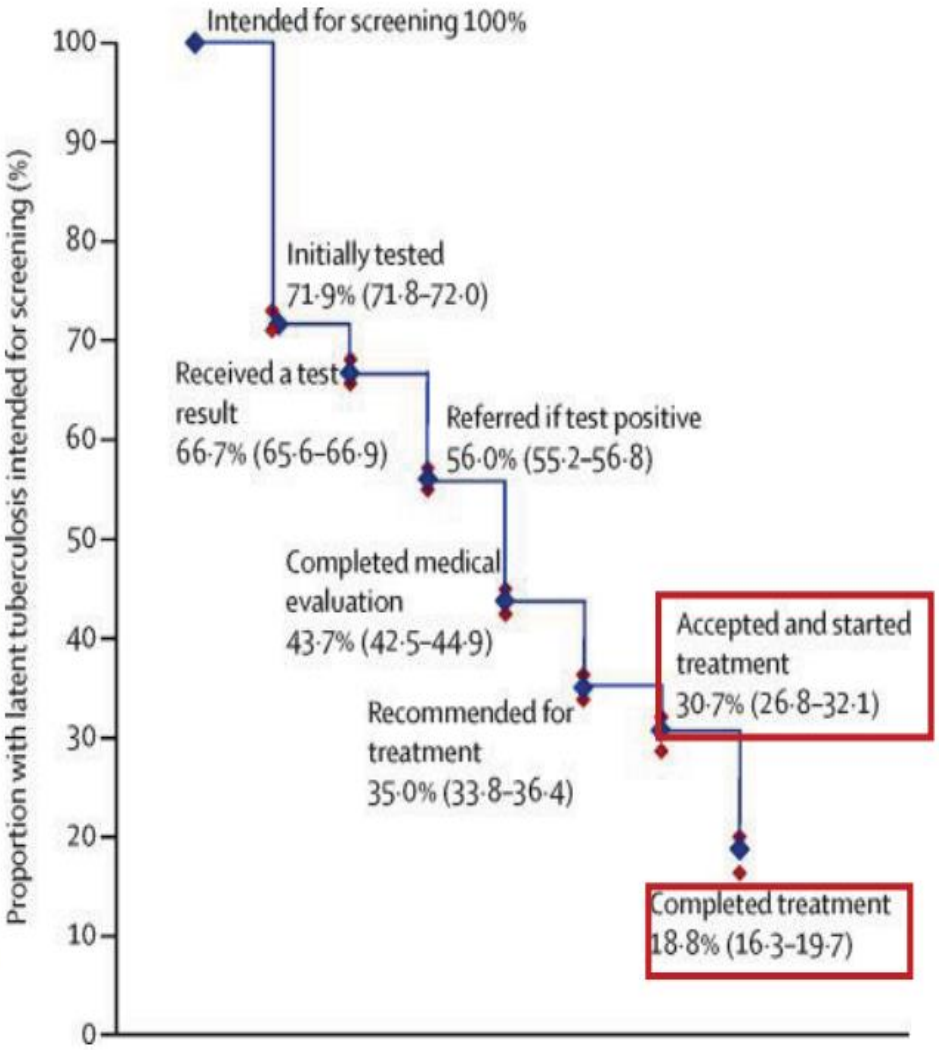
建議3HR、4R、6H、9H

Cascade care of diagnosis and treatment LTBI: systemic review and meta-analysis

- Meat-analysis
  - 58 studies,
  - 70 distinct cohorts
  - 748,572 people

- Participants lost in each step
  - Only 30% initiate LTBI tx
  - Only 18% complete LTBI tx

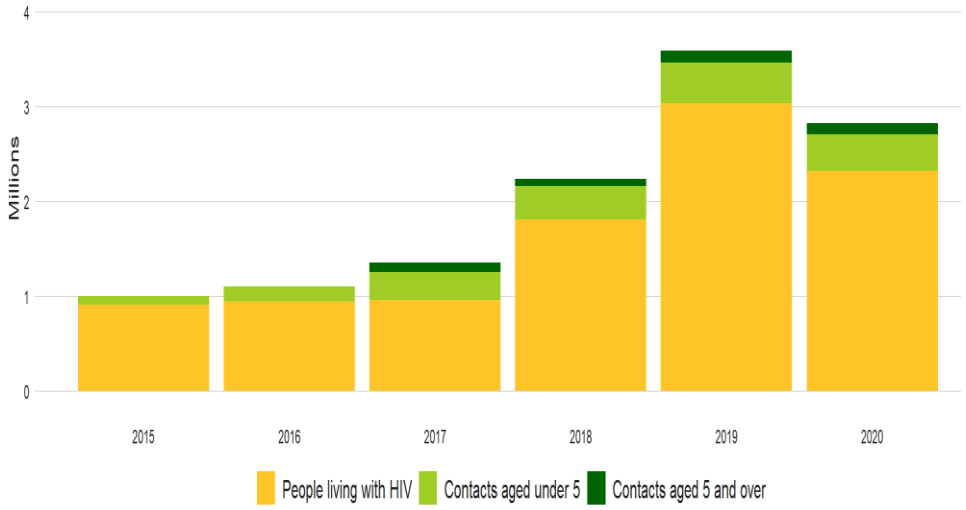
	Number of cohorts	Screened/eligible (n/N)*	Pooled event rate (95% CI)†	I^2
Treatment for latent tuberculosis				
Isoniazid	42	301 609/399 086	71·5% (60–83)	100·0%
Rifamycin containing (with or without isoniazid)	12	138 805/212 759	80·3% (64–97)	99·9%
Moxifloxacin and ethambutol	1	139/232	59·9% (0–100)	..
Not specified	10	76 993/122 660	71·5% (48–95)	100·0%
Years of data collection				
Up to 2000	25	362 480/461 814	79·0% (67–91)	98·0%
After 2000	40	155 066/272 923	69·0% (56–81)	99·0%

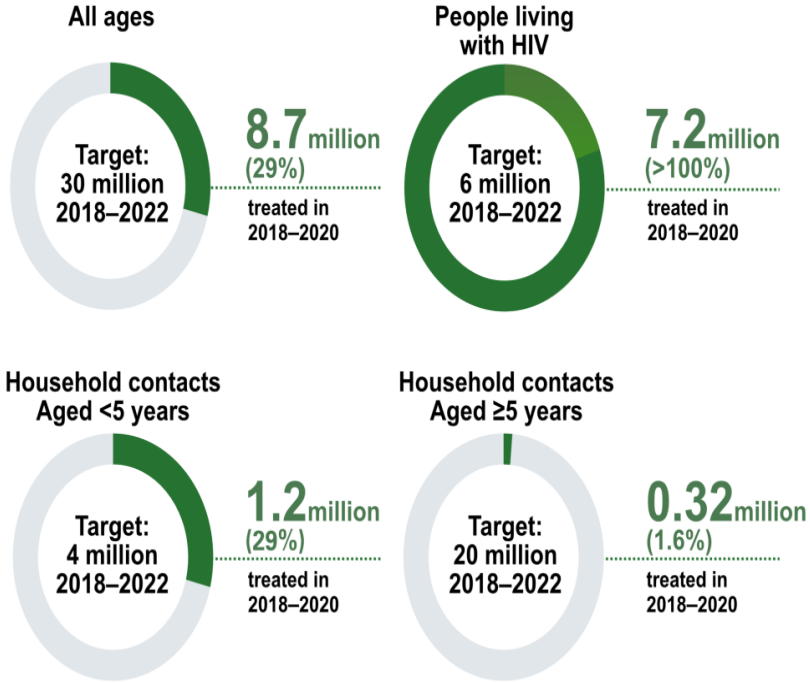


Alsdurf, H. Lancet Infect Dis 2016;16:1269-78.

To improve the screening rate and completion rate is important

The global number of people provided with TB preventive treatment 2015–2020





Reaching the target of End TB:

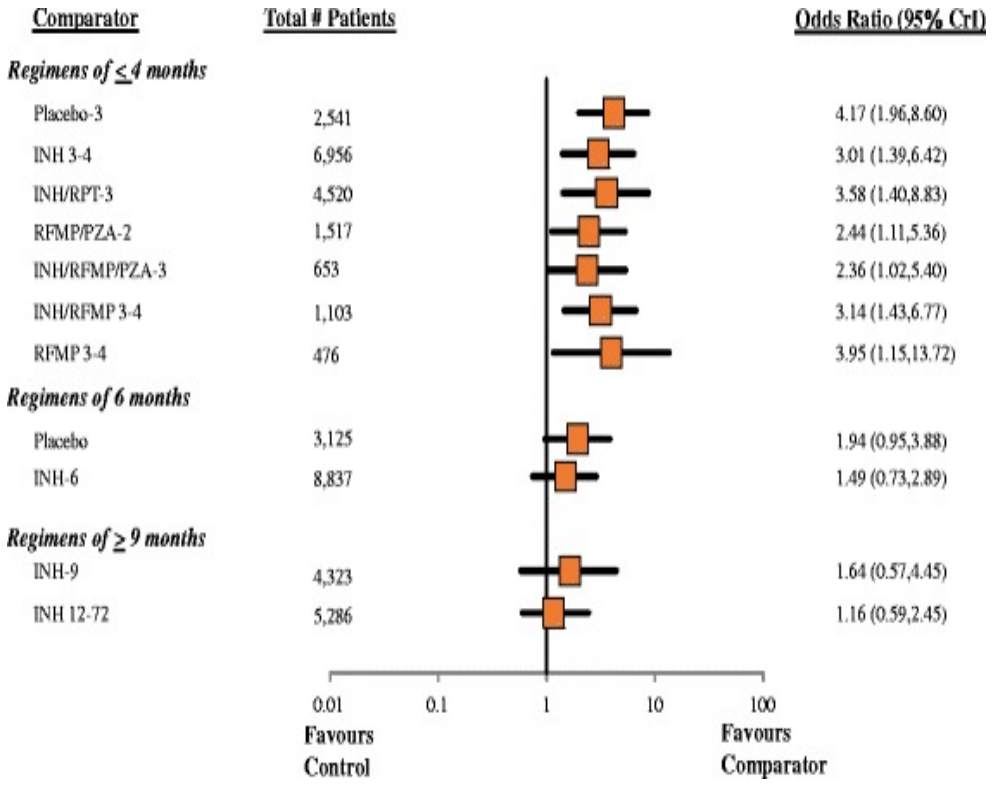
1. require more TB screening at household level
2. Strengthening the follow-up TB screening at household level and HIV people
3. Increase access to shorter rifamycin-based regimen

Shorter regimen can improve completion rate - Network meta-analysis

Table 1 Overview of characteristics of included randomized trials

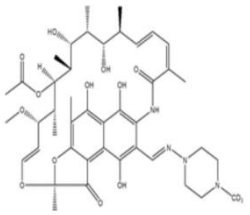
Characteristic	Summary measure
Study sample size	
Median (range)	352 (37–27,830)
Year of publication (median, range)	Median 2005 (range 1968–2016)
Before 1980	3 (10%)
1981–1990	1 (3.3%)
1991–2000	6 (20%)
2001–2010	10 (33.3%)
2011–2016	10 (33.3%)
% Female participants	
Median (range)	45.5% (0%–83.3%)
Average patient age (years)	
# studies reporting mean/median	23
# with average age between <20	3 (13.0%)
# with average age between 20 and 40	13 (56.5%)
# with average age > 40	7 (30.5%)
Other population characteristics of note	
# enrolling HIV patients	5 (17.2%)
# in prison populations	2 (6.9%)
# in population at risk of silicosis	3 (10.3%)
# in transplant patients	1 (3.5%)
Funding source	
Industry	3 (10%)
Academic/government	15 (50%)
Mixed funding	1 (3.3%)
Not reported	11 (36.7%)

Young age



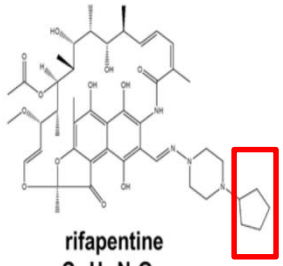
BMC Infectious Diseases (2017) 17:265

WHO guidelines on TB preventive treatment : Rifapentine-containing regimens will help LTBI treatment



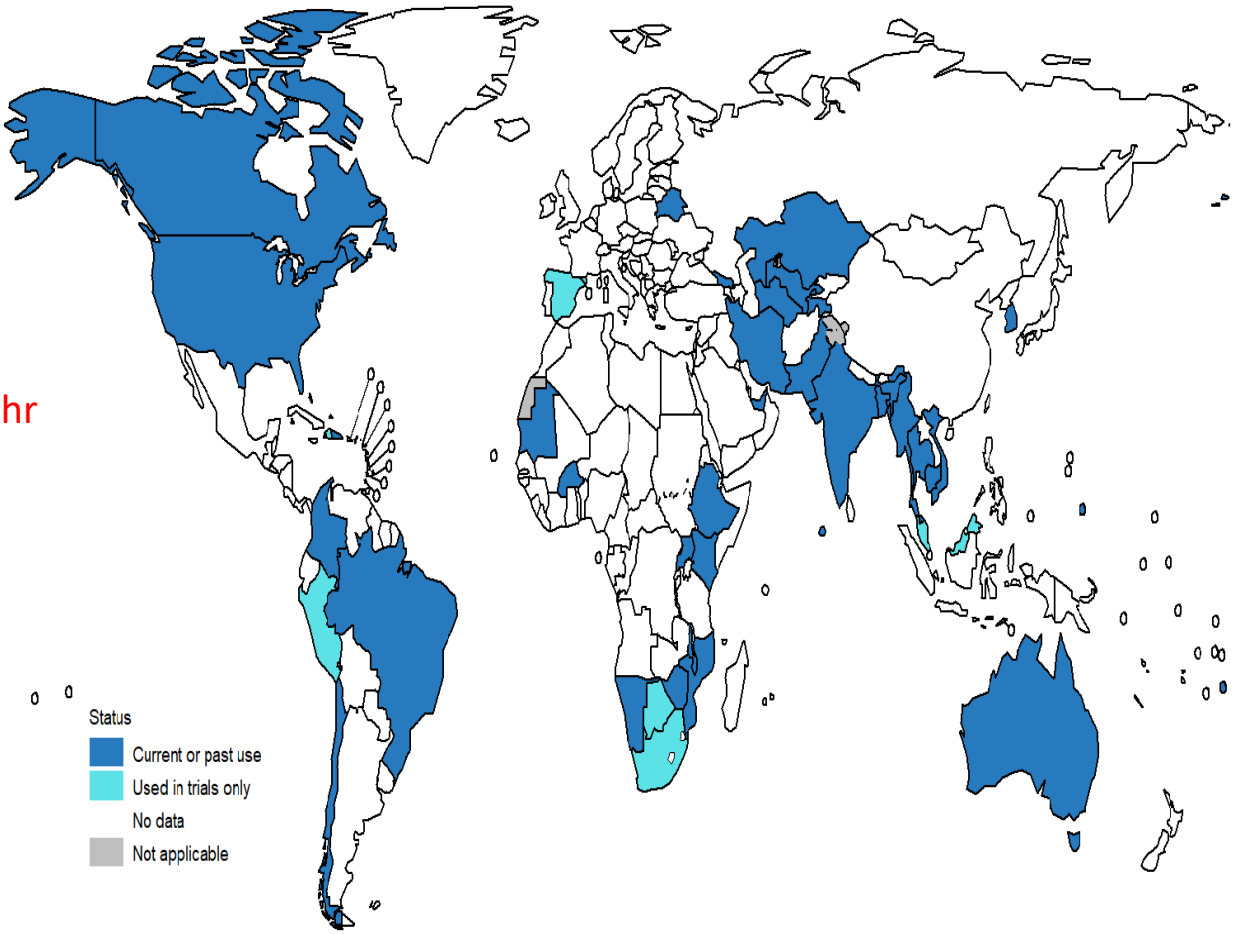
rifampin-d_3
$C_{43}H_{55}D_3N_4O_{12}$
826 *m/z*

Half life : 3 – 5 hr



rifapentine
$C_{47}H_{64}N_4O_{12}$
877 *m/z*

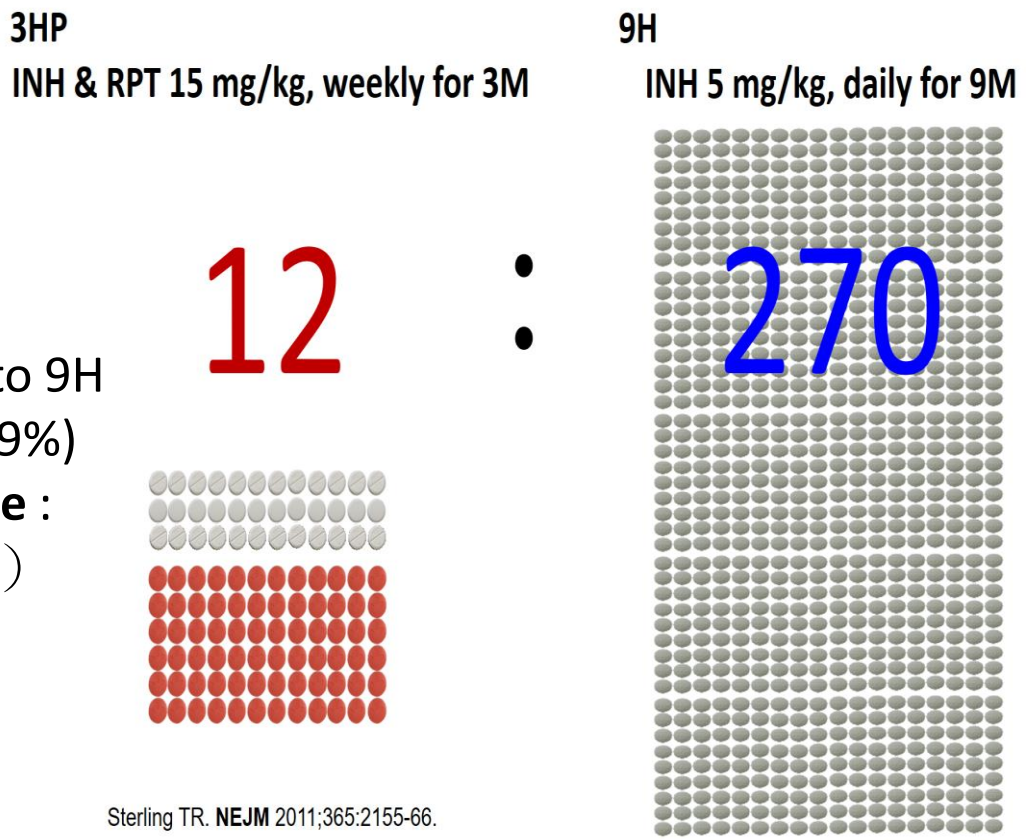
Half life : 13hr



Rifapentine is currently registered for use in China, Hong Kong Special Administrative Region, the Democratic Republic of the Congo, Ethiopia, Ghana, India, Indonesia, Mongolia, Myanmar, the Philippines, Singapore, South Africa, Thailand, Turkmenistan, Uganda and the United States of America (source: Sanofi, June 2021).

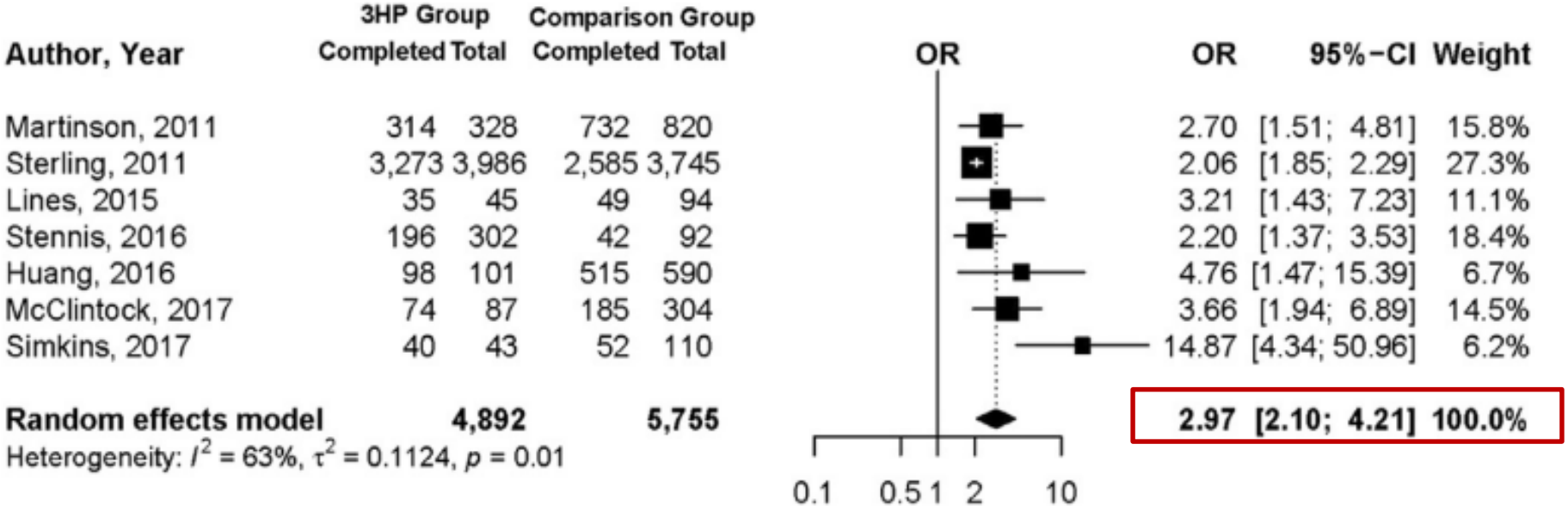
Short-course Rifapentine-containing regimen: 3HP

- **First in Prevent Tuberculosis Trial**
- TB preventive efficacy is non-inferior to 9H
- **Completion rate**: 3HP > 9H (82% vs. 69%)
- **Discontinue due to adverse effect rate** :
  3HP > 9H （7.9% vs. 3.7%，p = 0.009）
  - 3HP ADR : SDR, flu-like syndrome
  - 9H ADR : hepatitis



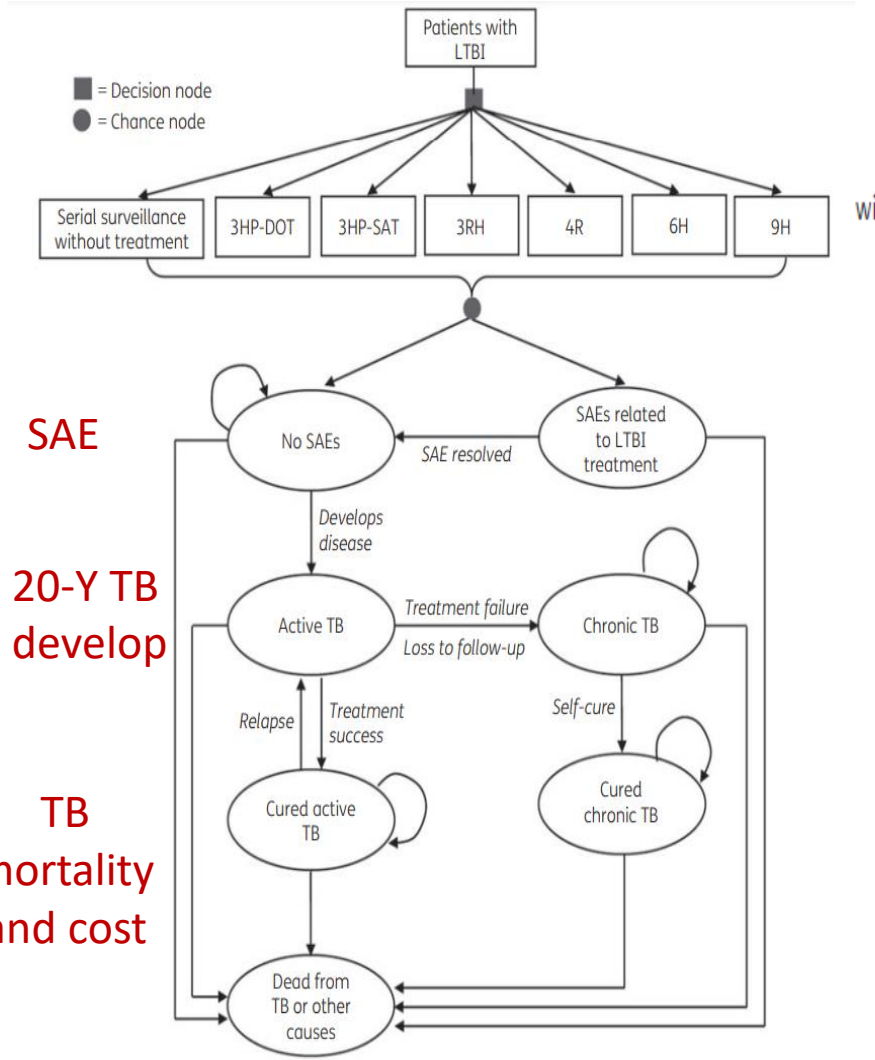
Higher completion rate of 3HP than other preventive regimens

- Systematic Review and Meta-analysis
- 15 studies selected from 292 studies during 2006-2017
- Comparable regimens: 6H, 9H, 4HR, 4R, 2-3RZ
- Equal preventive effectiveness of 3HP and other regimen (OR:0.89, 95% CI: 0.46, 1.70)
- Higher completion rate (OR: 2.97, 95% CI: 2.10, 4.21)



Am J Prev Med . 2018 Aug;55(2):244-252

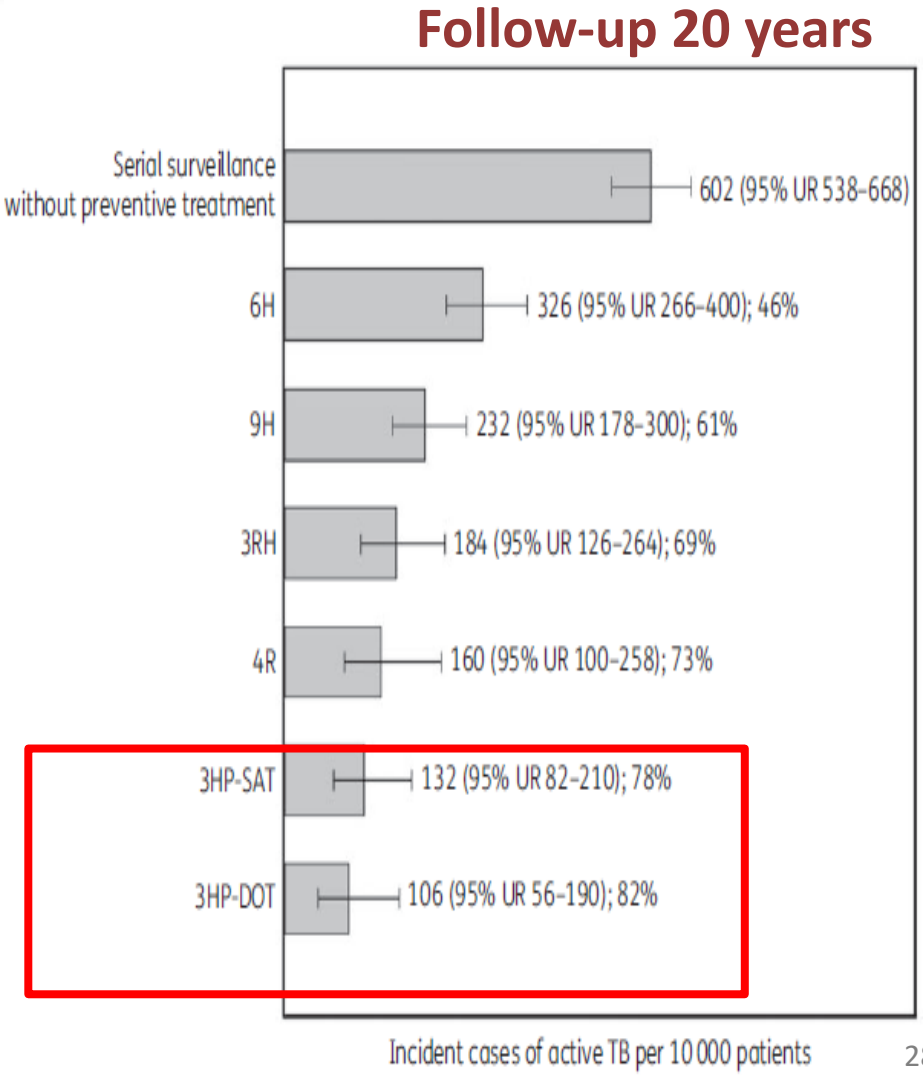
Cost-effectiveness of 3HP compared with other standard treatment regimens : A decision analysis study



SAE

20-Y TB develop

TB mortality and cost



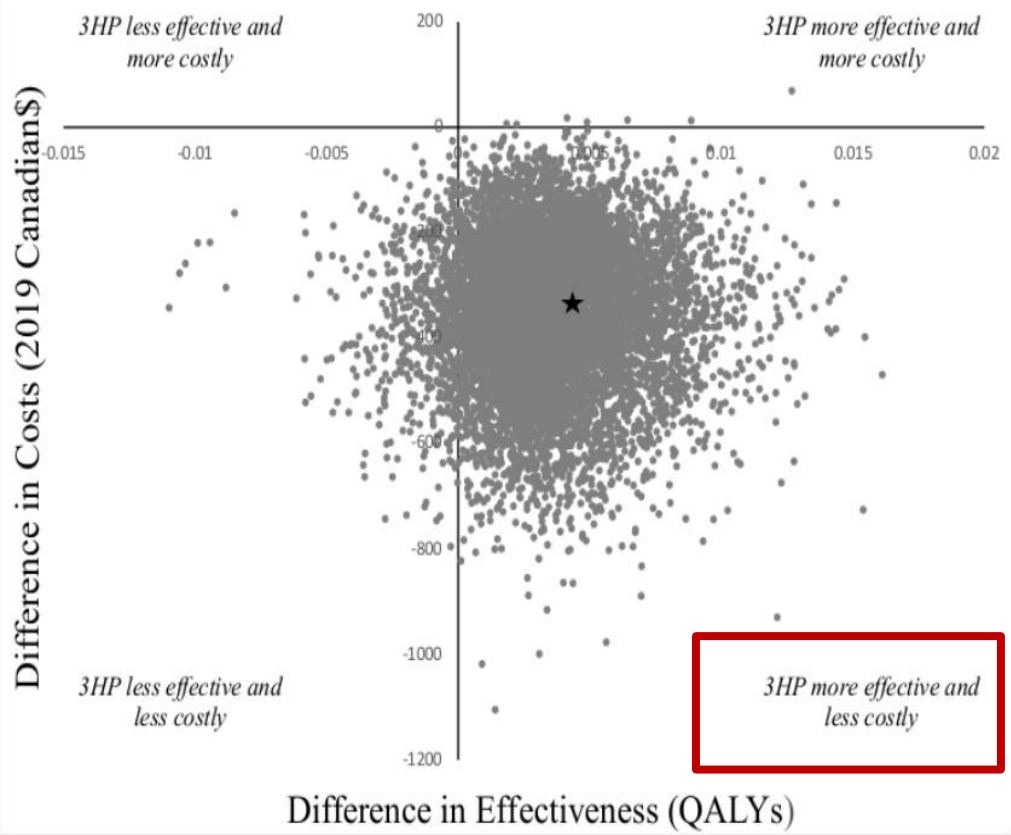
J Antimicrob Chemother 2019; 74: 218–227

Cost-effectiveness analysis of 3HP vs. 9H in a Canadian arctic setting

Table 3 Base case cost-effectiveness model outcomes

	9H	3HP
Clinical outcomes		
Overall effectiveness (QALYs)	20.13	20.14
TB cases per 1000 LTBI cases	30.16	27.89
TB deaths per 1000 LTBI cases	2.48	2.29
Cost outcomes (2019 US$)		
Total cost	$924	$628
Costs of LTBI treatment	$535	$260
Costs of AEs	$116	$108
Costs of TB disease treatment	$182	$168
Surveillance costs	$92	$92

Costs are in 2019 US dollars.
AEs, adverse events; 9H, 9 months of twice weekly isoniazid; 3HP, once weekly rifapentine and isoniazid for 12 weeks; LTBI, latent tuberculosis infection; QALY, quality-adjusted life years; TB, tuberculosis.



Pease C, et al. BMJ Open 2021;11:e047514.

High completion rate on 3HP in different Taiwan cohorts

	LTBI contacts (n=101)	LTBI contacts (n=132)	≥50y contacts (n=2348)	RA (n=21)	Hemolysis (n=26)	All age LTBI (n=579)	pDM (n=200)	Hemolysis (n=50)
Study design	Cohort study	RCT	Registry data	Cohort study	Cohort study	Cohort study	Cohort study	Cohort study
Publication	Hung YW *Medicine (2016)*	Sun HY *Tuberculosis (2018)*	Chan PC ERJ (2019)	Chen YM ARD (2018)	Lin SY *JMII (2019)*	Huang HL *CID (2021)*	Huang HL *CID (2021)*	Shu CC *AAC (2021)*
Male	43.6	61.4%	48.1%	29%	69%	46.8%	53.3%	72.0%
Age	34.9	31.7 ± 15.0	87.5% < 75Y	62.1 ± 14.9	63.8 ± 12.2	23.1% > 65y	64.2 ± 9.6	58.0 ± 12.7
Tx complete	97.0%	89.4%	83.9%	90%	65%	83.1%	82.5%	82.0%
Permanent stop								
Any AE	3.0%	9.1%	12.0%	10%	35%	14.8%	14.0%	14.0%
Hepatitis	0	1.5%	0.8%	0	0	3.1%	2.0%	0

- High completion rate: 65% - 90%
- Permanent discontinuation due to any AE: 3% - 35%

SDRs is related to high discontinuation rate

- Phenotypes of SDRs
  - Flu-like syndrome
    - Presence of fever, chills, weakness, fatigue or muscle pain, aches, syncope, heart rate >100, palpitations, flushing, dizziness, or sweats
  - Shock, Urticarial, Conjunctivitis, Bronchospasm…etc
- SDR occurred in 2%-10% of 3HP group
- Median dose prior to event dose: 3rd
- Median time from drug intake to event: 4 hrs (1.0-8.0)
- Median time to resolution: 24 hrs (12-48)

Prevent TB trial

Table 5. Multivariate Logistic Regression of Risk Factors for Systemic Drug Reactions

	Adjusted OR	95% CI	*P* Value
3HP vs 9H	9.4	5.5, 16.2	<.001
White-non-Hispanic race	3.3	2.3, 4.7	<.001
Female sex	2.0	1.4, 2.9	<.001
Age ≥35 y (median[a])	2.0	1.4, 2.9	<.001
Body mass index (BMI)			.009
18.5–24.9 (normal)	reference		
<18.5 (underweight)	0.9	.4, 2.2	.88
25–29.9 (overweight)	0.5	.3, .7	.001
≥30 (obese)	0.7	.4, 1.0	.05
Any concomitant non-study drug	1.2	.8, 1.7	.33

Clin Infect Dis. 2015 Aug 15; 61(4): 527–535.

Severe ADRs of 3HP in all-aged population

- A multicenter prospective observational study
- Completion rate: overall 81.8% (age ≥60 :78.4%, <60 y/o: 84.1%)
- SARs: ADRs ≥ Grade 2, not including hepatotoxicity
  - No difference of risk of SARs between age ≥60 years and <60 years.
  - Age ≥60 years had higher discontinuation , but insignificance
  - Independent risk factors for SARs

	Overall patients, *N* = 406		≥60 years old, *n* = 167		<60 years old, *n* = 239	
	aOR (95% CI)	*p*-Value	aOR (95% CI)	*p*-Value	aOR (95% CI)	*p*-Value
LTBI regimens						
9H	1.00	-	1.00	-	1.00	-
3HP	2.90 (1.14–7.40)	0.026	4.00 (0.73–22.04)	0.111	2.63 (0.79–8.80)	0.116
4R	0.94 (0.10–9.15)	0.957	-	-	1.35 (0.11–16.69)	0.818
Age (years)						
<35	1.00	-	-	-	1.00	-
35–59	3.46 (1.13–10.55)	0.029	-	-	3.58 (1.16–11.08)	0.027
60–79	3.05 (0.95–9.74)	0.060	1.00	-	-	-
≥80	3.75 (0.98–14.40)	0.054	1.18 (0.44–3.12)	0.747	-	-
Female	1.64 (0.92–2.93)	0.095	1.61 (0.68–3.79)	0.281	1.69 (0.74–3.87)	0.217
BMI < 23 kg/m^2	2.23 (1.26–3.96)	0.006	1.83 (0.77–4.32)	0.169	2.52 (1.13–5.62)	0.024
ESRD	3.96 (1.83–8.53)	<0.001	2.94 (1.06–8.16)	0.038	5.09 (1.54–16.90)	0.008
Immunosuppressant	0.76 (0.27–2.15)	0.603	0.74 (0.13–4.16)	0.729	0.72 (0.19–2.73)	0.626

J.-Y. Feng et al. / International Journal of Infectious Diseases 96 (2020) 550–557

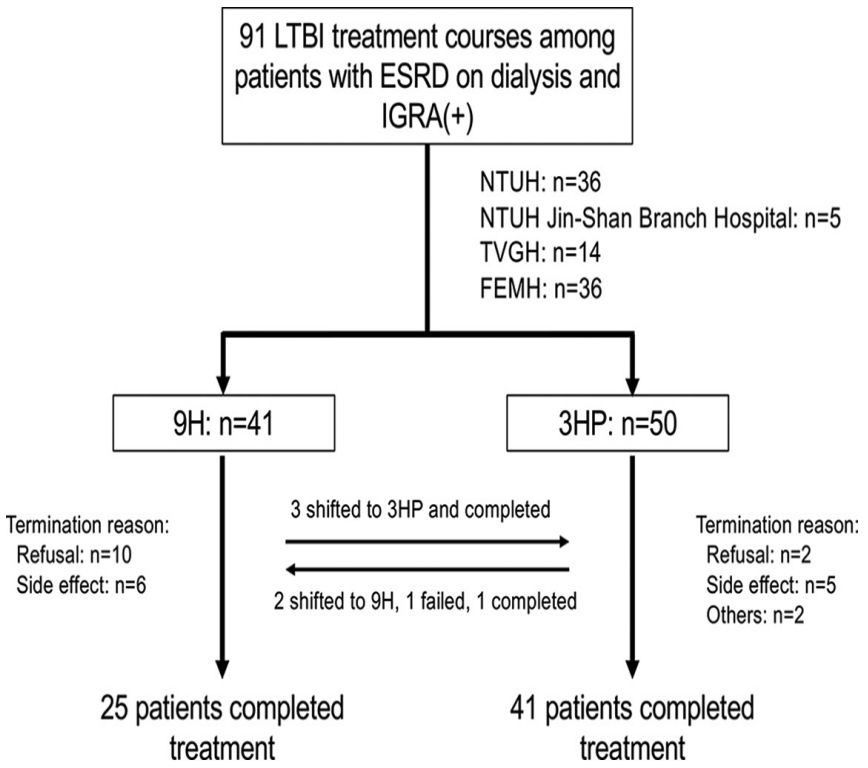
Different 3HP related SARs in various age group

- A prospective, multicenter study in Taiwan
- Overall completion rate in groups: 83.1%
  - Young (<35y/o): 94.5%, Middle-Age (35~65): 80.7%, Elder (≧65): 73.9%
- Middle-age group had higher SDR rate,
  - particularly flu-like symptoms than other two age groups
- Elders had higher uncontrolled hypertension rate
  - 86.3% can complete 3HP after temporarily modification of anti-HTN drugs

	Age < 35 (n=165)	Age 35 ~ 65 (n=280)	Age ≥ 65 (n=134)
SDR	8 (4.8%)	48 (17.1%)*	9 (6.7%)
Flu-like syndrome	6 (3.6%)	34 (12.1%)*	7 (5.2%)
Hypotension	2 (1.2%)	7 (2.5%)	1 (0.7%)
Urticaria	0 (0%)	6 (2.1%)*	0 (0%)
Conjunctivitis	0 (0%)	3 (1.1%)	1 (0.7%)
Hepatotoxicity	6 (3.6%)	19 (6.8%)	7 (5.2%)
ADR except SDR and hepatotoxicity	92 (55.8%)*	120 (42.9%)	54 (40.3%)
Grade ≥3	2 (1.2%)	5 (1.8%)	8 (6.0%)
Uncontrolled hypertension	0 (0%)	1 (0.4%)	4 (3.0%)*
Grade 2	20 (12.1%)	56 (20.0%)	27 (20.1%)
Individual symptom			
Any Flu-like symptoms	60 (36.4%)	135 (48.2%)*	66 (49.3%)
Gastrointestinal disorders	42 (25.5%)	101 (36.1%)	56 (41.8%)
Cutaneous reactions	21 (12.7%)	60 (21.4%)	20 (14.9%)
Hypertension	0 (0%)	7 (2.5%)	15 (11.2%)

Clin Infect Dis. 2021 Sep 7;73(5):e1064-e1071.

Higher completion rate but more ADRs of 3HP than 9H in HD group



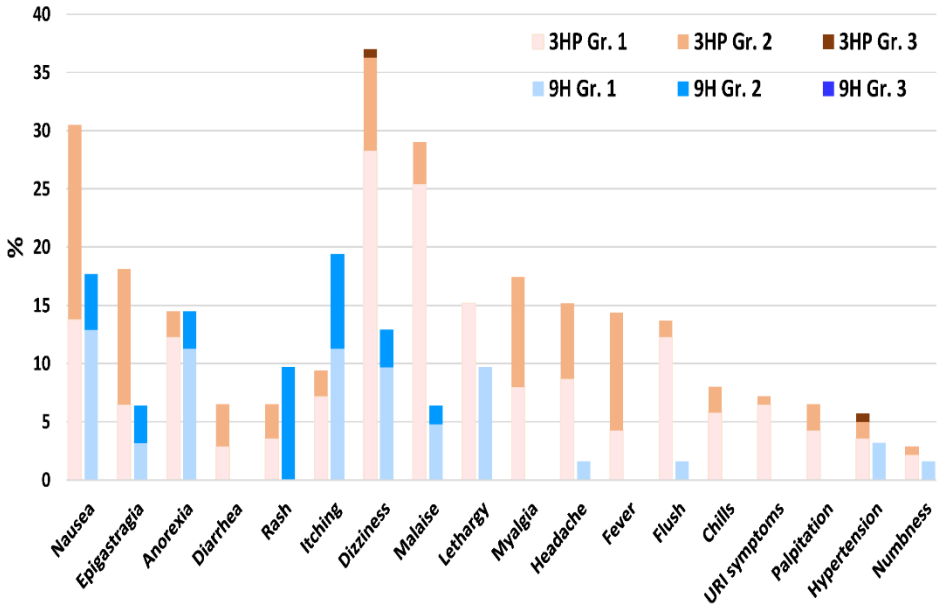
Variable	Value for group[a] 9H (*n* = 41)	3HP (*n* = 50)	*P* value[b]
Treatment completed, no. (%)	25 (61.0)	41 (82.0)	0.046
Treatment not completed reasons, no. (%)			0.176
Participant refusal	10 (24.4)	2 (4.0)	
Termination due to ADE or other reasons[c]	6 (14.6)	7 (14.0)	
ADE, no. (%)[d]	9H (*n* = 37)	3HP (*n* = 48)	
Hypersensitivity	4 (10.8)	14 (29.2)	0.040
Flu-like syndrome	3 (8.1)	7 (14.6)	0.502
Gastrointestinal symptoms	6 (16.2)	14 (29.2)	0.163
Hepatotoxicity	0 (0)	0 (0)	1.000
Hospitalization, attributed to LTBI treatment	0 (0)	3 (6.3)	0.249
Reported maximal grade of ADE[d]	9H (*n* = 37)	3HP (*n* = 48)	0.001
Grade 1	12 (32.4)	17 (35.4)	
Grade 2	2 (5.4)	16 (33.3)	
Grade 3	3 (8.1)	5 (10.4)	
Grade 4	0	1 (2.1)	
Grade 2 or more	5 (13.5)	22 (45.8)	0.002
Grade 3 or more	3 (8.1)	6 (12.5)	0.725

- The independent factors associated to ≥grade 2 ADE:
  3HP (aOR, 9.77 [2.55 to 37.49]; *P* = 0.001),
  DM (aOR, 7.73 [2.06 to 29.06]; *P* = 0.002), and PD (aOR, 7.21 [1.45 to 35.98]; *P* = 0.016)

Antimicrob Agents Chemother. 2021 Mar; 65(3): e02184-20

3HP is accessible in poorly DM patients under Endocrinist-Pulmonologist-Public multidiscipline corporation

- Prospective, multicenter study. April 2018 to June 2020
- **200 cases**
  - Age ≥ 45 years
  - ≥1 time HbA1c ≥9.0% within recent 1 year
- **LTBI screening performed by endocrinologist**
  - Pay-for-Performance project
  - QFT screening
  - Refer to Chest OPD if QFT-positivity
- **LTBI treatment evaluated by pulmonologist**
  - Evaluation
  - LTBI regimen 3HP or 9H: decision sharing strategy
    - Benefit
    - ADR inform and educate
  - DOTs
- Completion rate: 3HP v.s 9H (84.1% vs. 79.0%, p=0.494)
- SDRs: 3HP v.s 9H (4.3% vs. 0%, p=0.223)



- 3HP group had higher proportion of flu-like symptoms and GI symptoms
- 9H group had higher proportion of skin rash

Clin Infect Dis. 2021 Sep 15;73(6):e1252-e1260.

Health Insurance Database Research in Taiwan

- 3HP治療的上市後於2016-2019年期間，蒐集13,427位接受3HP治療的LTBI接觸者的資料顯示
  - 多變項分析: 年齡越大、女性、指標來自非高風險地區，因3HP不良反應導致永久停藥的機會越大。
  - 女性比同齡男性更容易發生因為不良反應而永久停藥的情況，在18-64歲年齡層有統計顯著
  - 糖尿病、需定血液透析慢性腎衰竭、慢性肝病、使用類固醇等共病接觸者皆較非共病接觸者有更高的風險發生不良反應而永久停藥
  - 藥物間交互作用可能是中高年齡病人完治率較沒有共病者低的主要可能原因。
  - 因嚴重不良反應造成永久停藥的過敏反應，發生機率為0.4%

Unpublished Data

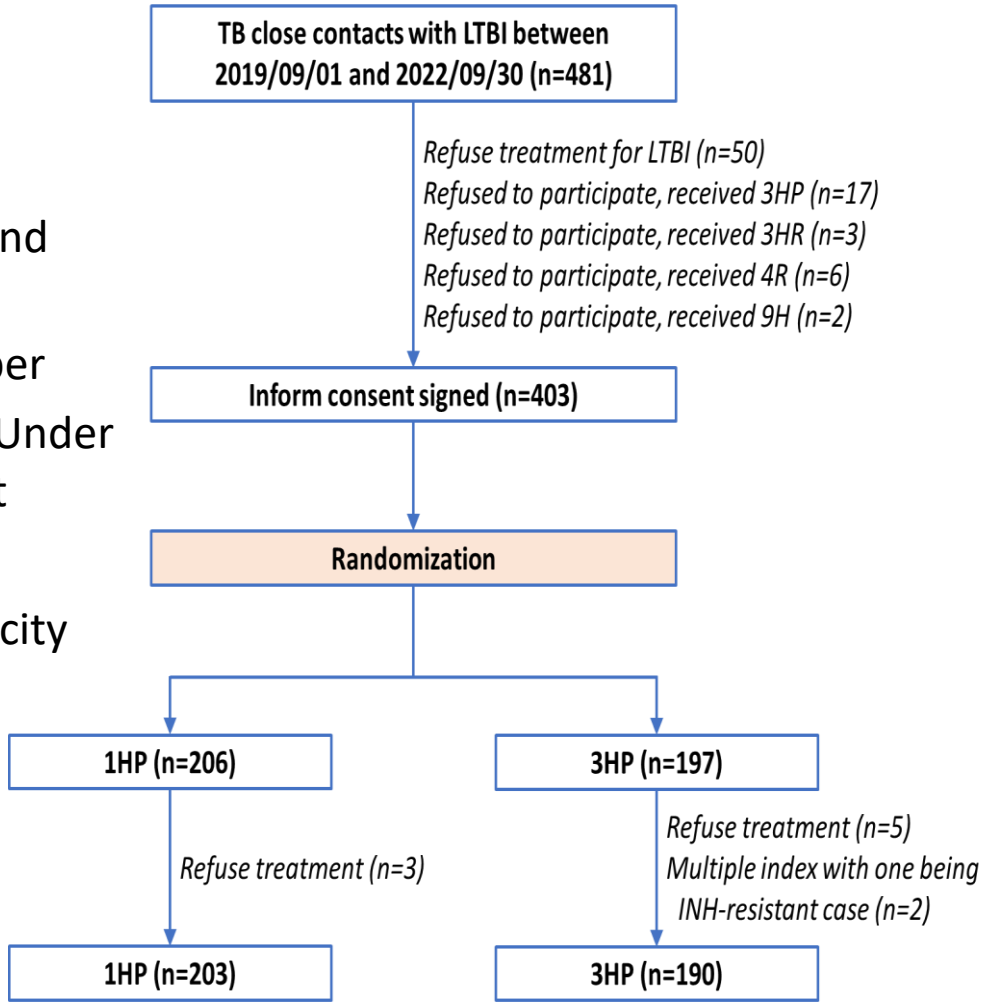
1HP in population with HIV

- A randomized, open-label, phase 3, noninferiority trial comparing 1HP and 9H in HIV patients
- **Primary end point:** the first diagnosis of tuberculosis or death from tuberculosis or an unknown cause
- **RESULTS**
  - 3000 patients were enrolled and followed for a median of 3.3 years.
  - 54% were women; the median CD4+ count was 470/mm^3, half received antiretroviral therapy.
  - Primary endpoint: 2% TB occurred in 1HP and 9H group, respectively
  - SAE: 6% of in 1HP group and in 7% of in 9H (P = 0.07).
  - Treatment completion was significantly higher in the 1HP than in 9H group (97% vs. 90%, P<0.001)
- The safety and efficacy report of 1HP in non-HIV group is still lacking

N Engl J Med. 2019 March 14; 380(11): 1001–1011

1HP in population with non-HIV

- A programmatic randomized controlled multicenter RCT in Taiwan
  - *ClinicalTrials.gov*: NCT04094012
- Conduction site: NTUH, KMUH, RMWH and their affiliated hospitals
- Duration : 2019 January to 2022 December
- **Aims:** Comparing Incidence Rate of SDR Under 3HP and 1HP Regimen for LTBI treatment
- **Secondary endpoints:**
  - ADRs: flu-like symptoms, Hepatotoxicity
  - Treatment completion
  - Plasma drug levels
  - Risk factors of SDR



Unpublished data

Baseline characteristics of enrolled population

- The baseline characteristics between groups are the same

	1HP (n=206)	3HP (n=197)	P-value
Age (yr)	54.8 ± 19.1	54.7 ± 16.8	0.935
>65	69 (33.5%)	60 (30.5%)	0.513
Male sex	102 (49.5%)	94 (47.7%)	0.718
BMI	24.5 ± 4.1	24.1 ± 4.2	0.405
<18.5	10 (5.0%)	12 (6.2%)	0.591
Smoking			
Current smoker	25 (12.4%)	36 (18.8%)	0.084
Ex-Smoker	28 (13.9%)	15 (7.8%)	0.052
Never smoker	153 (74.3%)	146 (74.1%)	0.971
Abnormal CxR	37 (18.0%)	37 (18.8%)	0.832

	1HP (n=206)	3HP (n=197)	P-value
Hypertension	54 (26.2%)	52 (26.4%)	0.967
DM	33 (16.0%)	42 (21.3%)	0.172
CKD III~V	24 (11.7%)	21 (10.7%)	0.752
Hyperlipidemia	21 (10.2%)	17 (8.6%)	0.591
Cerebral vascular attack	12 (5.8%)	7 (3.6%)	0.282
Dementia	9 (4.4%)	8 (4.1%)	0.878
Coronary artery disease	8 (3.9%)	6 (3.0%)	0.646
Cancer	6 (2.9%)	6 (3.0%)	0.937
GERD	6 (2.9%)	3 (1.5%)	0.504
COPD	4 (1.9%)	4 (2.0%)	>0.999
Arrhythmia	5 (2.4%)	1 (0.5%)	0.216
Hyperuricemia	4 (1.9%)	1 (0.5%)	0.373
Autoimmune	2 (1.0%)	4 (2.0%)	0.440
Hyperthyroidism	4 (1.9%)	0	0.124
History of seizure	3 (1.5%)	0	0.249
Liver cirrhosis	2 (1.0%)	0	0.499
HBV infection	15 (7.3%)	21 (10.7%)	0.235
HCV infection	5 (2.4%)	7 (3.6%)	0.506
HIV infection	0	1 (0.5%)	0.489

Unpublished data

Clinical Outcome

- Each group had more than 80% completion rate
- Adverse drug reactions is the major cause of incomplete treatment, no difference between groups

	1HP (n=188)	3HP (n=180)	P-value
Complete treatment	155 (82.4%)	153 (85.0%)	0.507
Incomplete treatment	33 (17.6%)	27 (15.0%)	
Adverse drug reaction	32 (17.0%)	20 (11.1%)	0.104
Mortality	0	1 (0.6%)	0.489
Active TB	0	1 (0.6%)	0.489
Others	1 (0.5%)	5 (2.8%)	0.115

Unpublished data

Different phenotypes of SDRs in 3HP & 1HP group

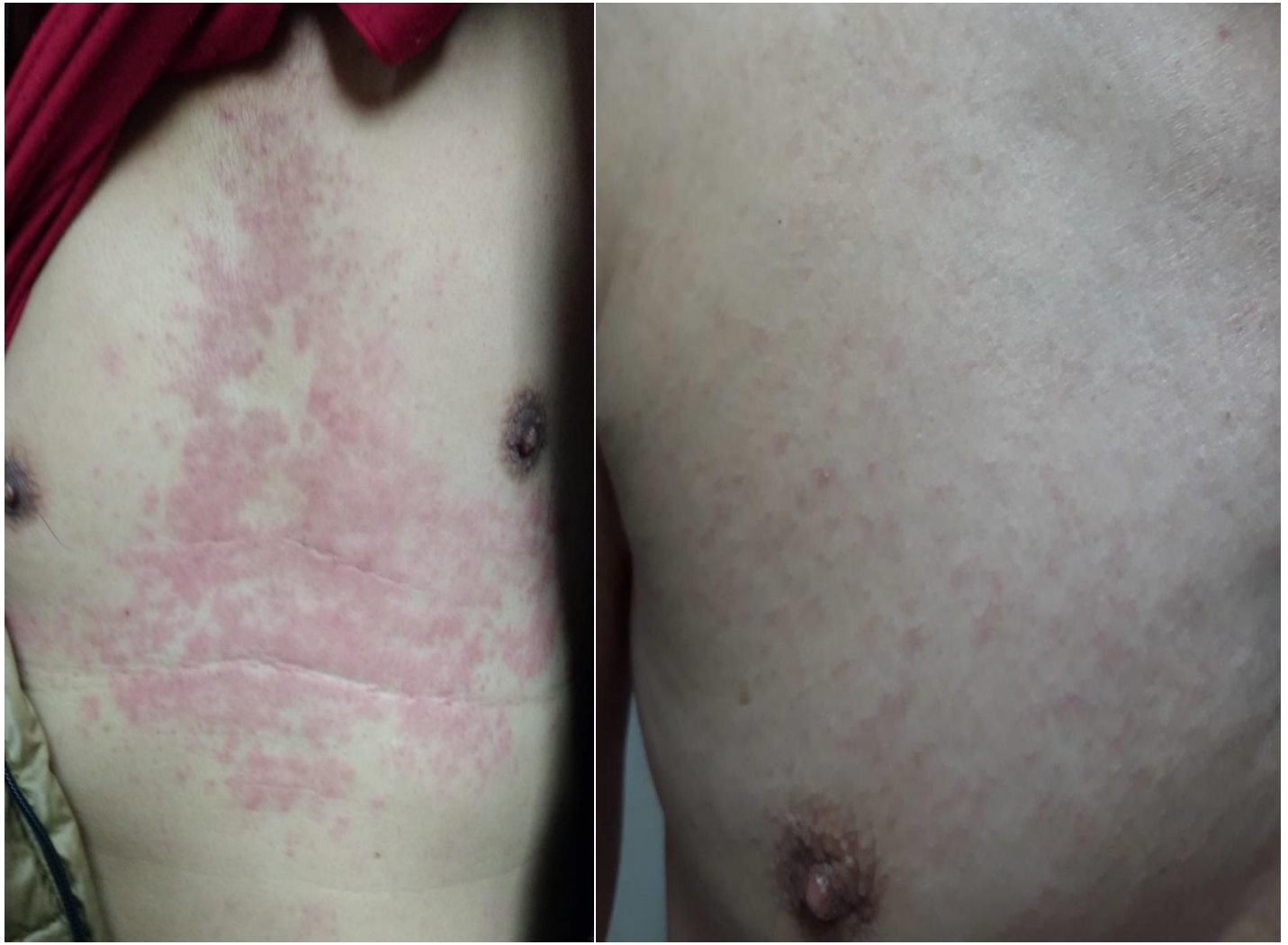
- The SDR risk is similar between 1HP and 3HP groups
- More cutaneous reactions was noted in 1HP group
- 3HP group had more flu-like related symptoms

	1HP (n=203)	3HP (n=190)	P-value
Systemic drug reaction	19 (9.2%)	18 (9.1%)	0.976
Flu-like syndrome	7 (3.4%)*	**15 (7.6%)**	0.075
Urticaria	**13 (6.3%)**	3 (1.5%)	0.014
Complete treatment	14 (74% of 19)	10 (56% of 18)	0.248

- The different phenotype of SDRs in 1HP and 3HP maybe associated with
  - Offending drug frequency、dosage and drug/metabolites concentration
  - Offending Host immunity response

Unpublished data

52 year-old male, post 14th dose1HP



Maculopapular eruption, not very itching

Unpublished data

不同處方劑量換算表

https://www.cdc.gov.tw/Category/MPage/Wo_UwSs9W0_T2bqqRN942A

1HP轉換其它處方

1HP (總療程28天)	1HP已服藥天數
	8
轉換後處方	還需服藥天數或次數
3HP	9 次
3HR	65 天
4R	86 天
6H	129 天
9H	193 天

3HP轉換其它處方

3HP (總療程12週)	3HP已服藥次數
	8
轉換後處方	還需服藥天數
1HP	10 天
3HR	30 天
4R	40 天
6H	60 天
9H	90 天

4R轉換其他處方

4R (總療程120天)	4R已服藥天數
	8
轉換後處方	還需服藥天數或次數
1HP	27 天
3HP	12 次
3HR	84 天
6H	168 天
9H	252 天

3HR轉換其它處方

3HR (總療程90天)	3HR已服藥天數
	8
轉換後處方	還需服藥天數或次數
1HP	26 天
3HP	11 次
4R	110 天
6H	164 天
9H	246 天

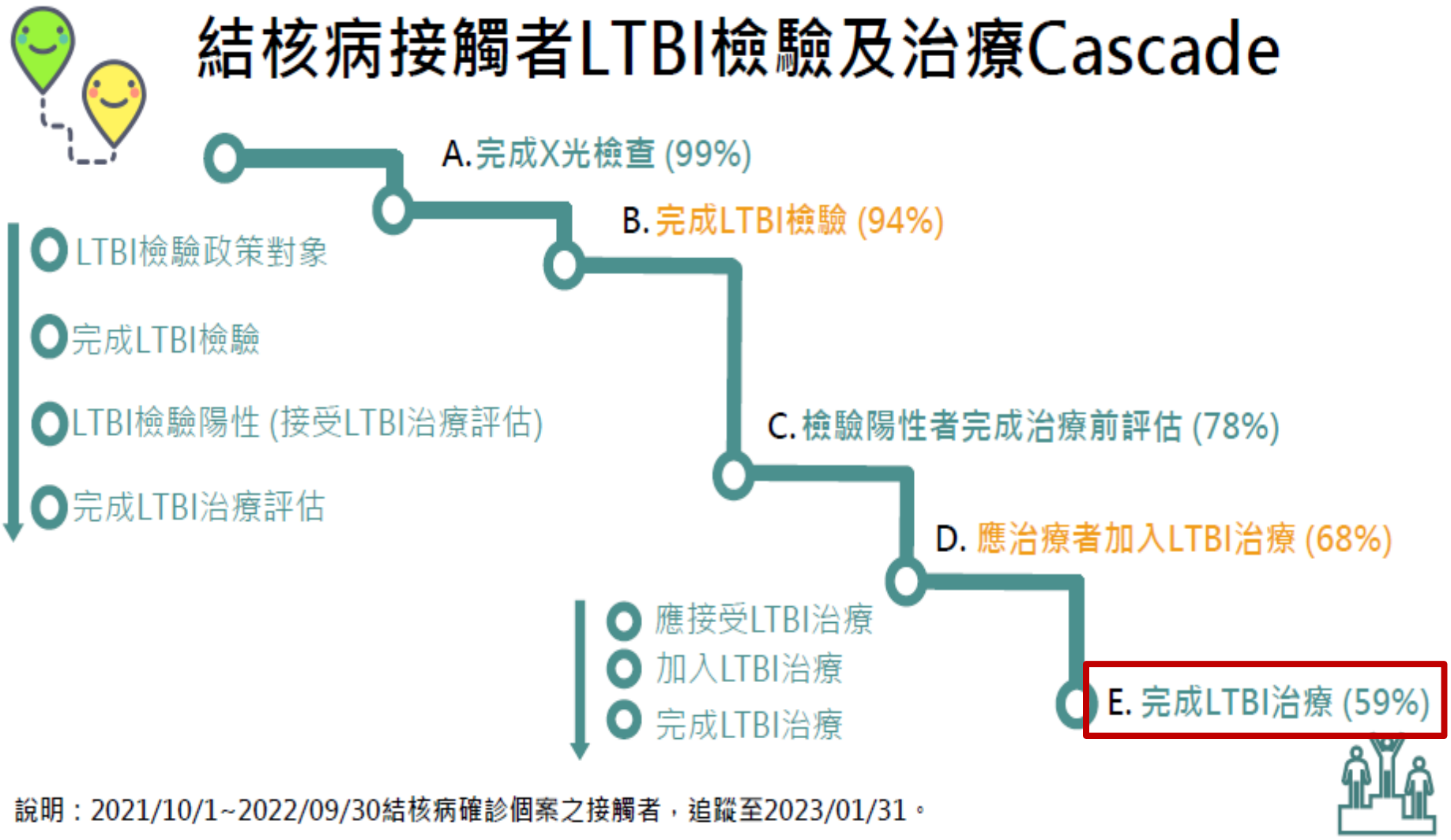
6H轉換其它處方

6H (總療程180天)	6H已服藥天數
	8
轉換後處方	還需服藥天數或次數
1HP	27 天
3HP	12 次
3HR	86 天
4R	115 天
9H	262 天

9H轉換其它處方

9H (總療程270天)	9H已服藥天數
	8
轉換後處方	還需服藥天數或次數
1HP	28 天
3HP	12 次
3HR	88 天
4R	117 天
6H	172 天

結核病接觸者LTBI檢驗及治療Cascade



說明：2021/10/1~2022/09/30結核病確診個案之接觸者，追蹤至2023/01/31。

END TB

World Health Organization

TARGETS

MILESTONES		SDG*	END TB
2020	2025	2030	2035