3HP藥物副作用的簡介、可能機制、危險因子、預測模式

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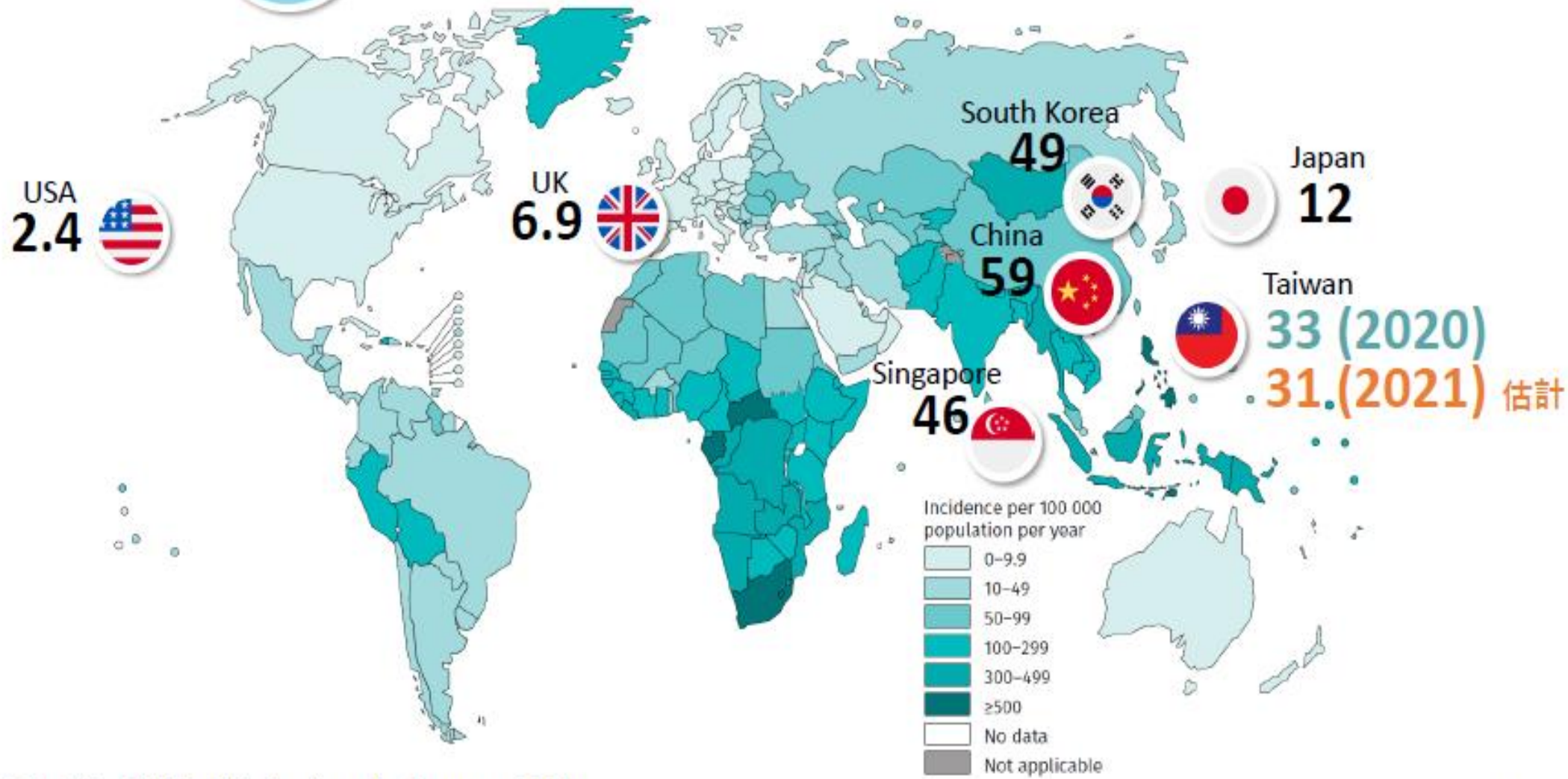
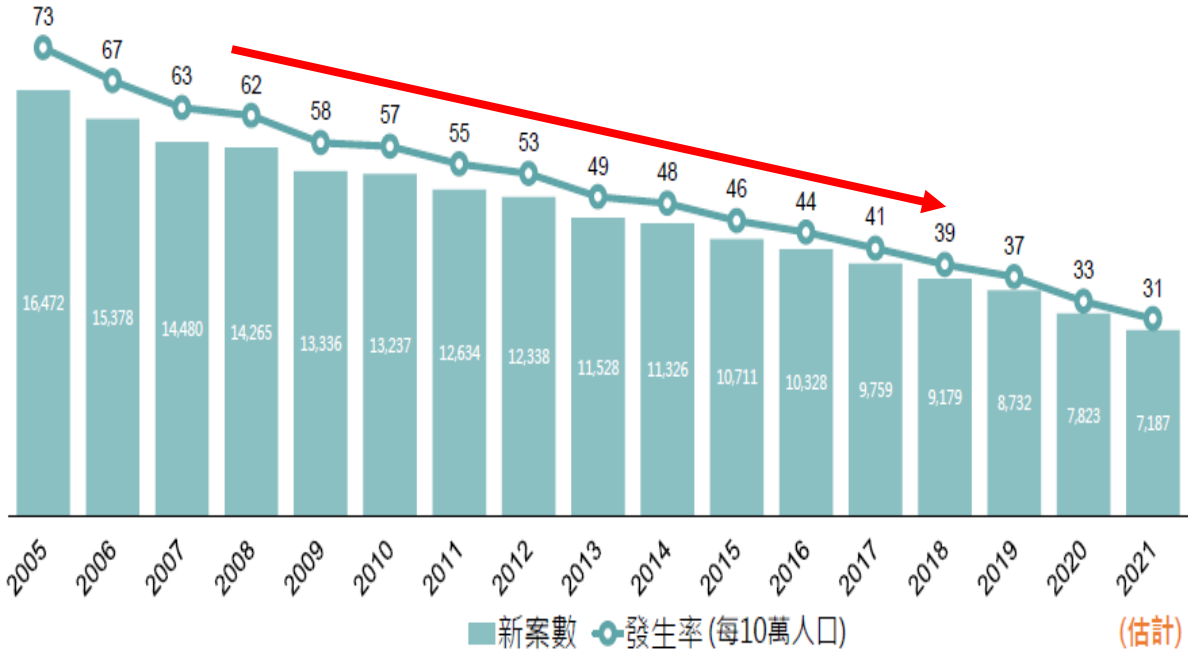
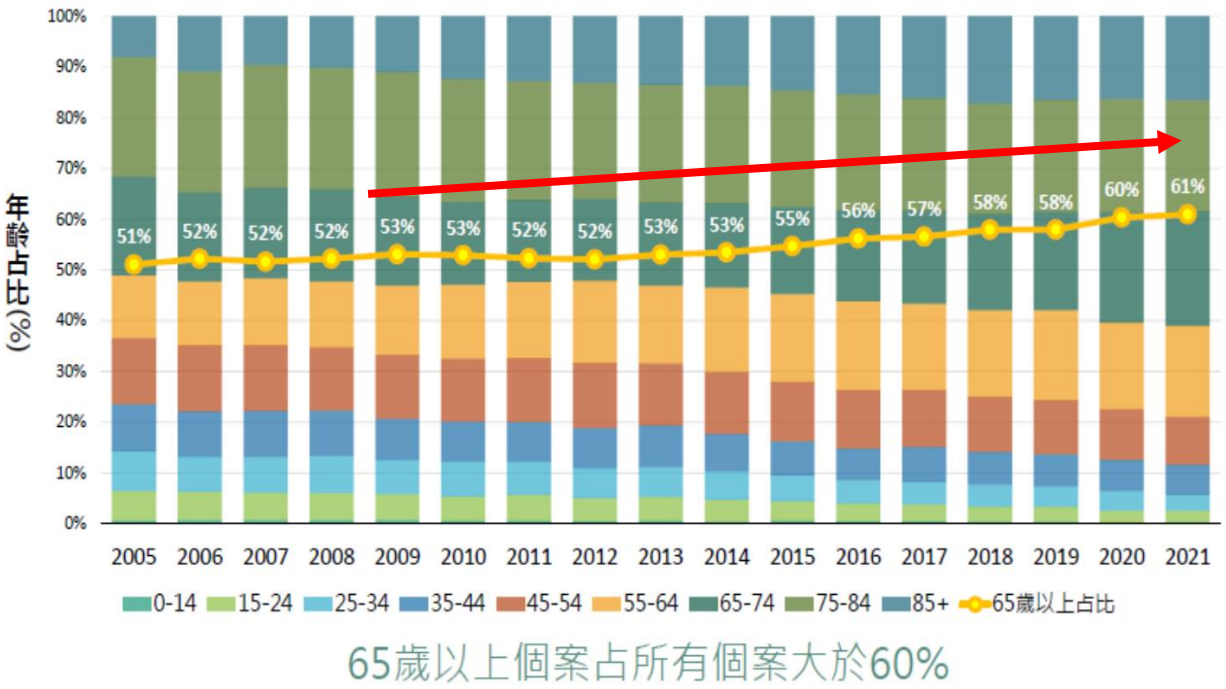
2020年各國結核病流行情形



資料來源： WHO Global tuberculosis report 2021

全國結核病發生率

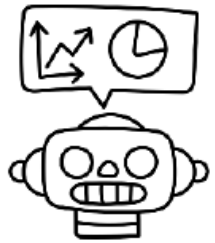




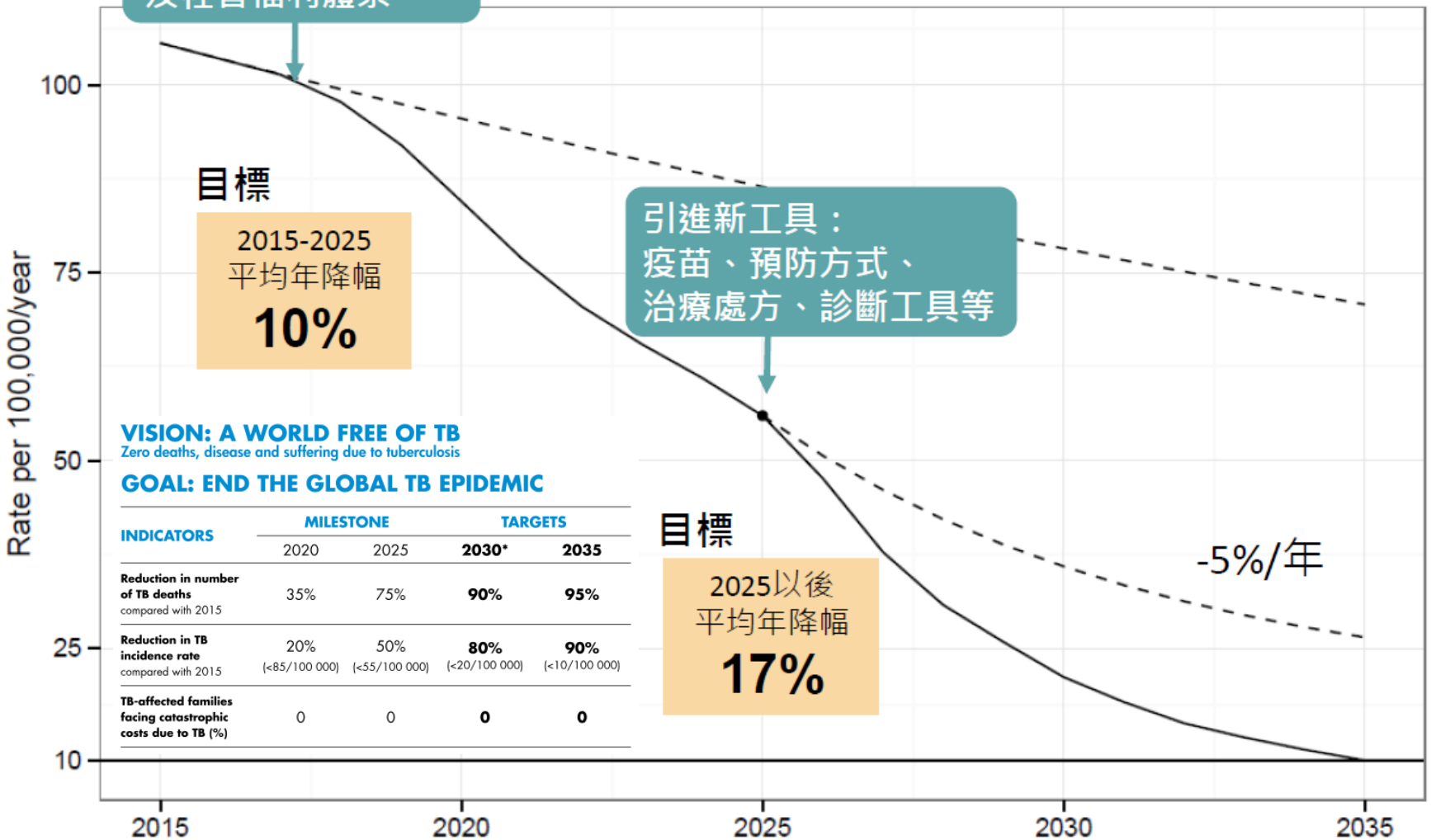
65歲以上個案占所有個案大於60%

CDC首頁>傳染病與防疫專題>傳染病介紹>第三類法定傳染病>結核病>重要指引及教材>結核病年度流病政策簡報

全球消除結核目標與趨勢



全球長期下降趨勢 **2%**



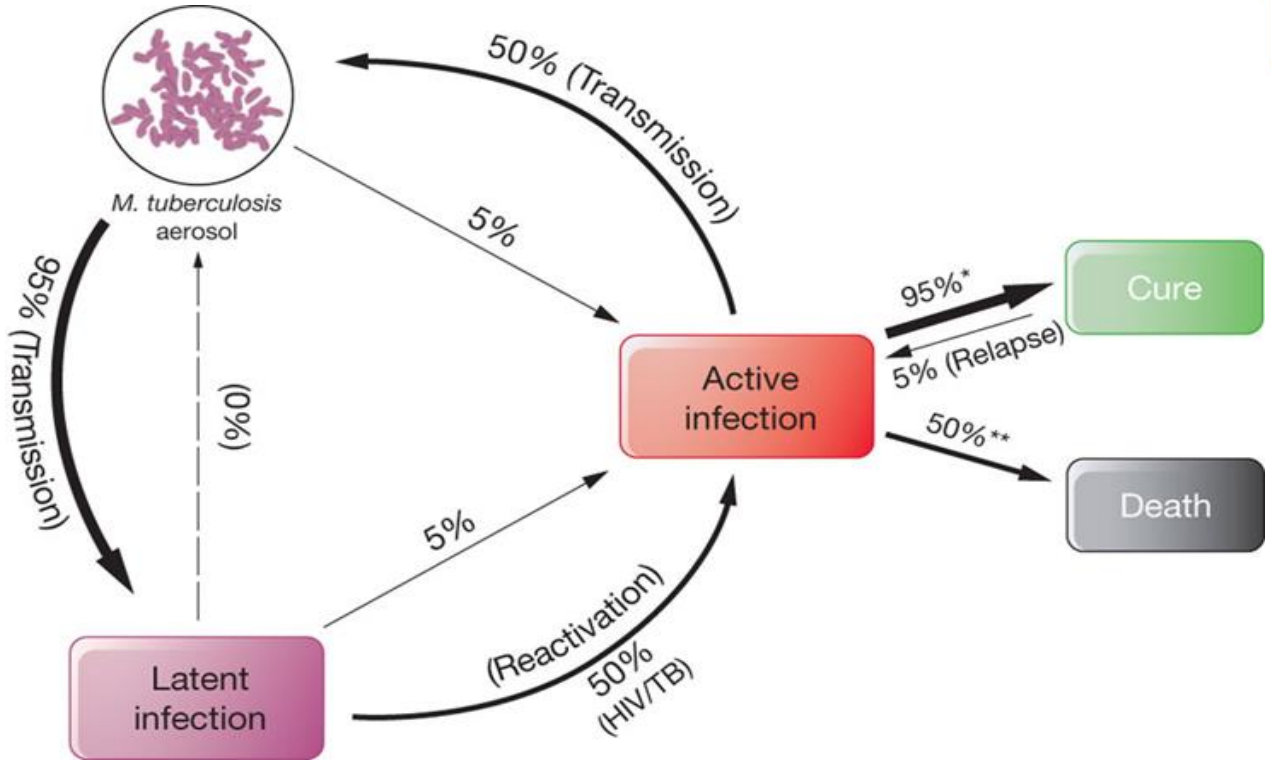
VISION: A WORLD FREE OF TB
Zero deaths, disease and suffering due to tuberculosis

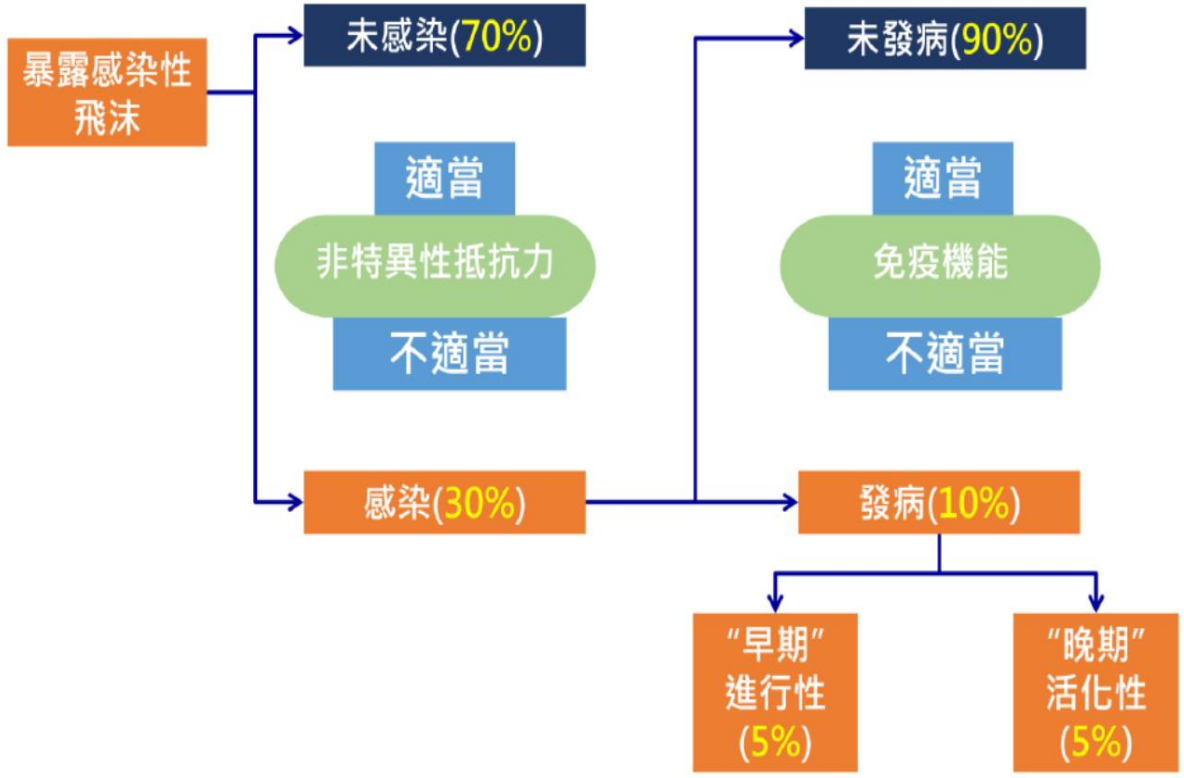
GOAL: END THE GLOBAL TB EPIDEMIC

INDICATORS	MILESTONE		TARGETS	
	2020	2025	**2030***	**2035**
Reduction in number of TB deaths compared with 2015	35%	75%	**90%**	**95%**
Reduction in TB incidence rate compared with 2015	20% (<85/100 000)	50% (<55/100 000)	**80%** (<20/100 000)	**90%** (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	0	0	**0**	**0**

Latent TB Infection (LTBI)

LTBI is a state of persistent immune response to stimulation by MTB antigens without evidence of clinically manifested active, including radiography





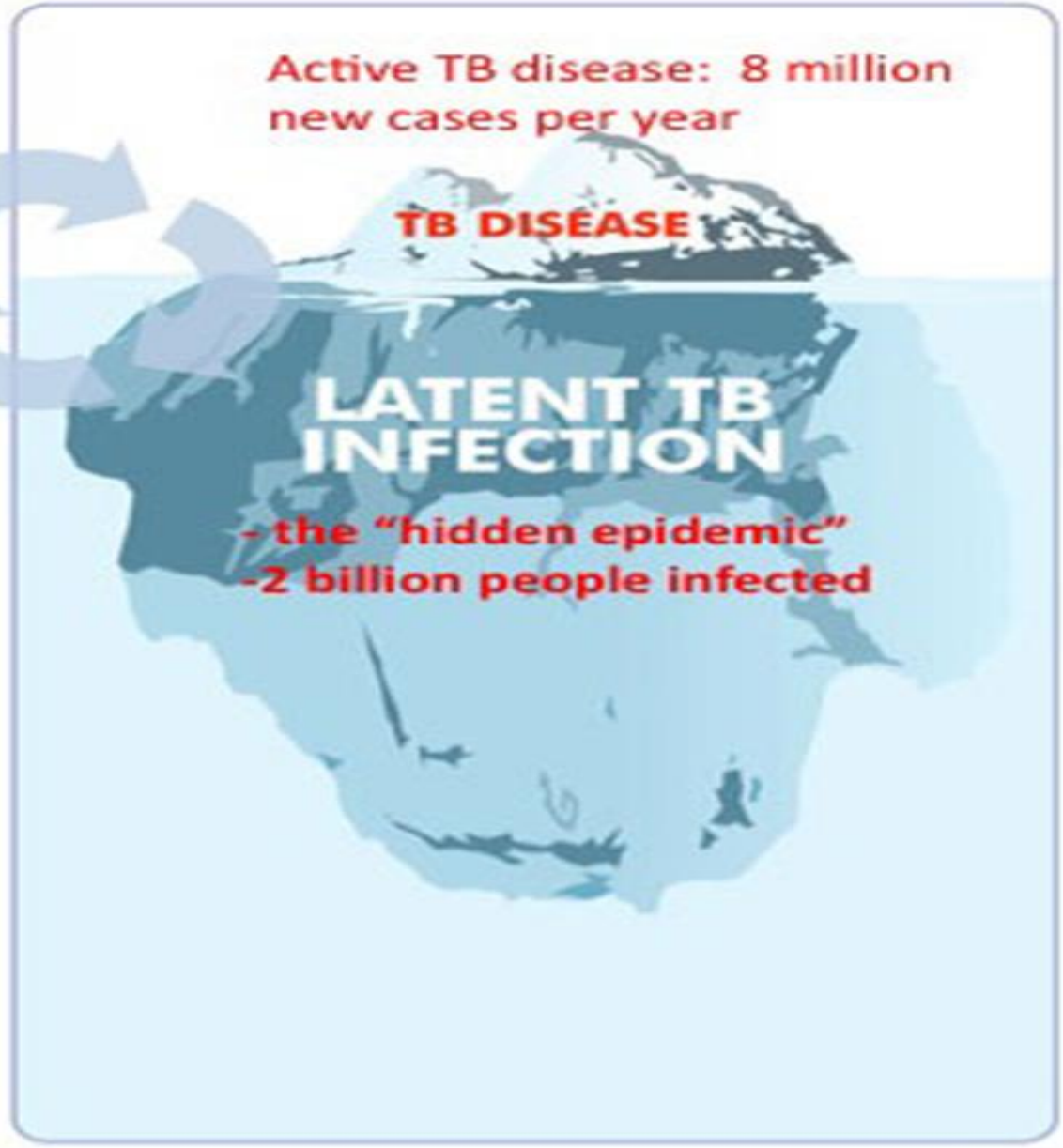
A Koul *et al. Nature* **469**, 483-490 (2011) doi:10.1038/nature09657

Priority group receiving LTBI diagnosis/treatment by WHO

- **First priority:**
  - HIV patients,
  - All-aged close contact group
  - Receiving TNF-a treatment patients,
  - Hemodialysis patients
  - Prepare organ/Hematological transplantation patients,
  - Silicolsis patients

- **Second priority:** less evidence, but benefit > harms
  - Nursing home/ Hospital workers,
  - Immigrants from high TB endemic area,
  - Nomad,
  - Prism,
  - Drug abuser …etc

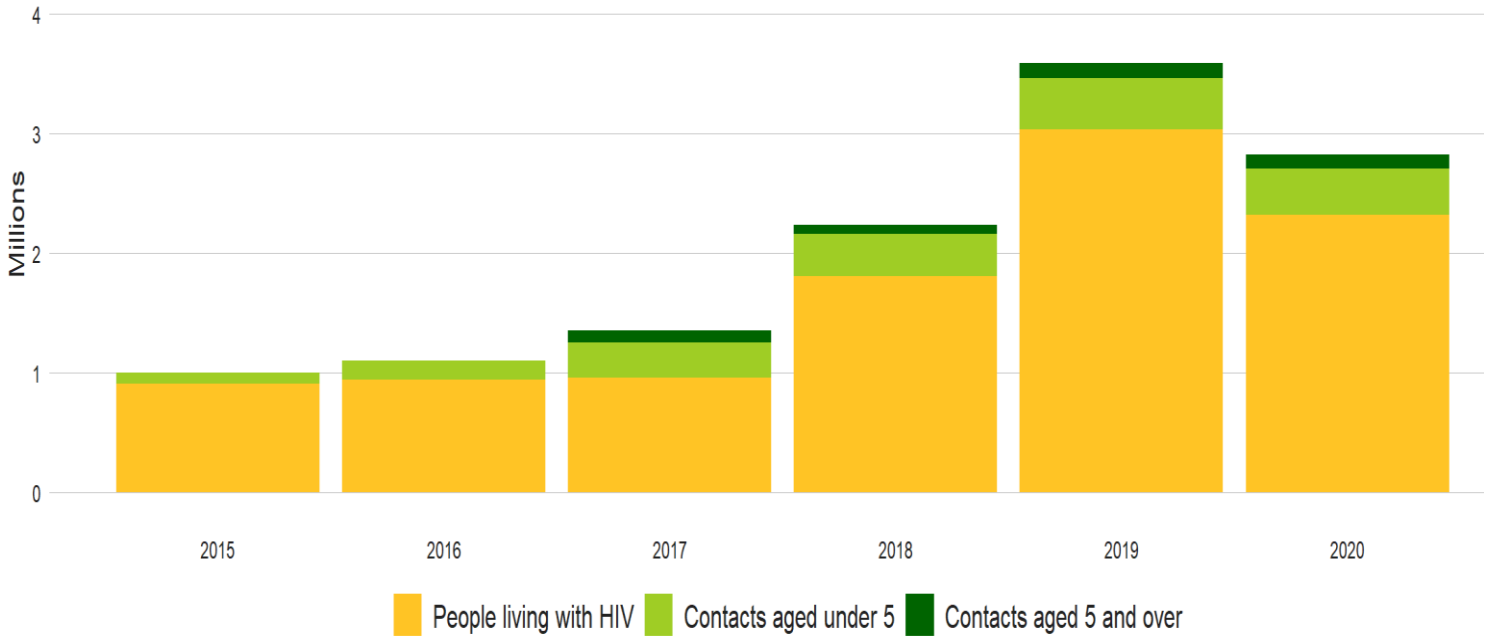
- **Third priority:** lack of evidences, depends on country resourses
  - DM
  - Alcoholism group
  - Underweight population

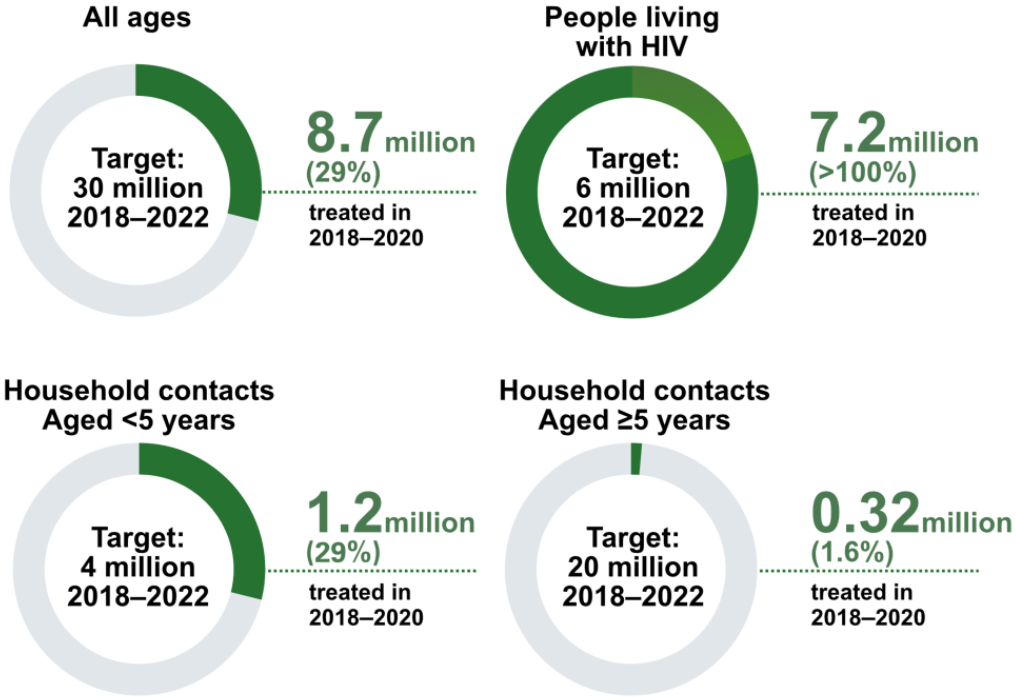


A Koul *et al. Nature* **469**, 483-490 (2011) doi:10.1038/nature09657

Taiwan Experience

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

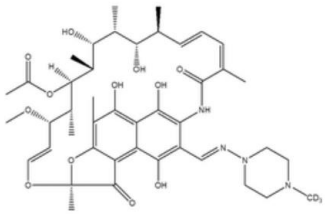




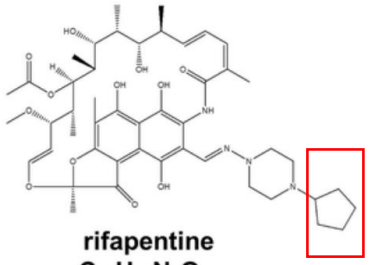
Reaching the target of End TB:

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

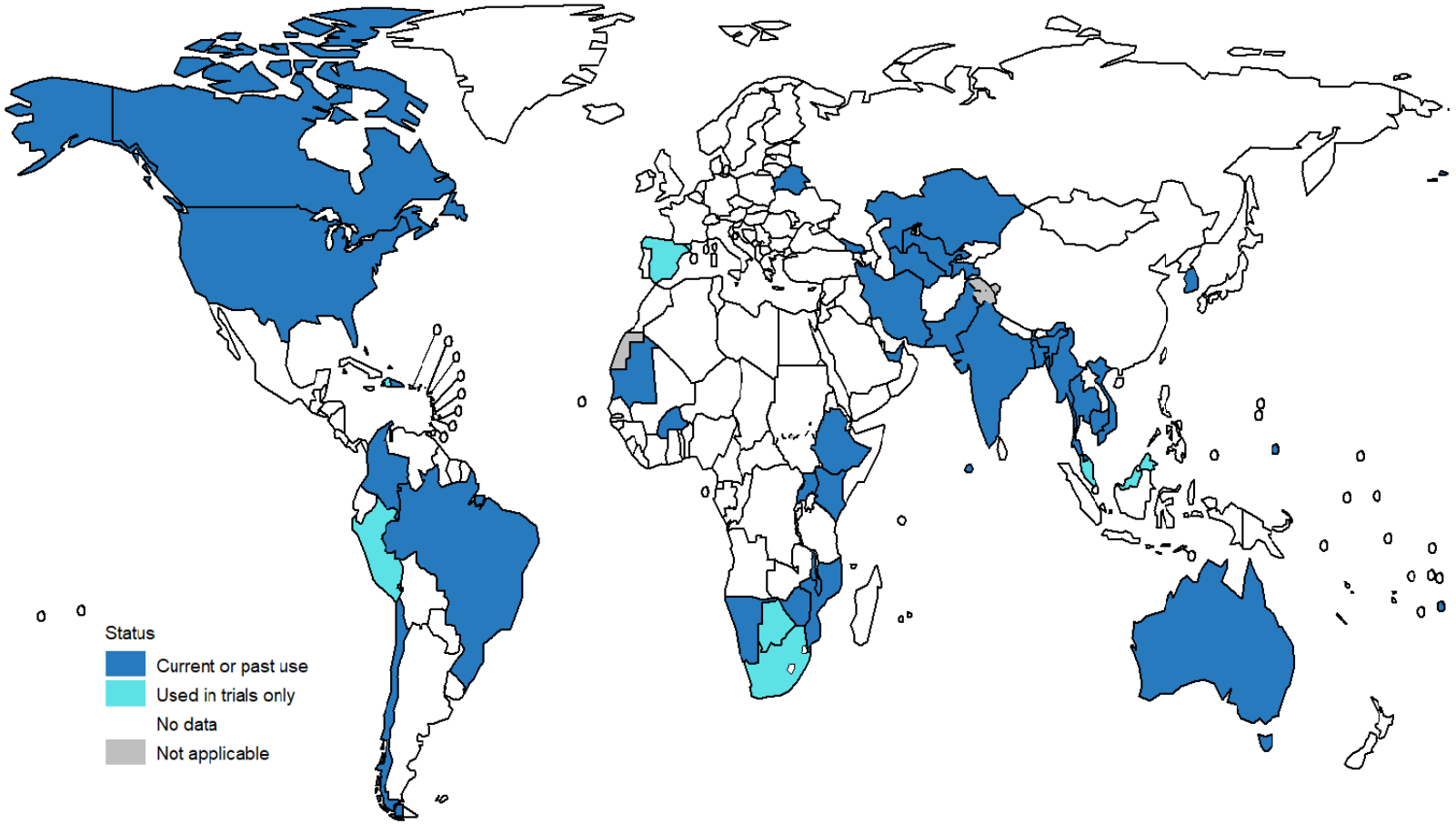
WHO guidelines on TB preventive treatment : Rifapentine-containing regimens will help LTBI treatment



rifampin-d_3 Half life : 3 – 5 hr
$C_{43}H_{55}D_3N_4O_{12}$
826 *m/z*



rifapentine
$C_{47}H_{64}N_4O_{12}$ Half life : 13hr
877 *m/z*



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).

WHO Recommendation vs. Taiwan use

	WHO建議	我國處方政策		
一般族群	6H (180 doses)或9H(270 doses)	**9H** (自2008年使用於未滿13歲接觸者)		
	4R (120 doses)	**4R**	自2017年限指標INH抗藥接觸者	
			2020年4月擴大到全面使用	
	3HR (90 doses)	**3HR(**自2020年國內LTBI治療處方)		
	3HP (12 doses) 單方和複方(每劑次服用3顆) FDC使用於**14歲以上≥30KG**	**3HP**	**單方**	自2016年4月
			複方 FDC	自2021年9月 **不限年紀體重≥50KG以上接觸者，** 每劑次服用3顆
	1HP (28 doses) 13歲以上固定劑量(INH300 RPT600mg/day)	**1HP** 13歲以上 1. INH固定300mg/day RPT 依體重 2. 疾管署專案計畫使用(2020年HIV感染者及矯正機關)		
MDR接觸者	levofloxacin for **six** months along with other TB agents such as ethambutol or ethionamide if tolerated	**9**個月fluoroquinolone ➢ 2019-2021年先驅計畫 ➢ 2022年為政策對象		

Shorter is better

HP 藥品使用同意書

衛生福利部疾病管制署潛伏結核感染治療藥品使用同意書

isoniazid 300mg/Tab

治療藥品：isoniazid 300 mg/Tab

個案姓名：

病歷號碼：　　身分證字號：

一、 治療疾病名稱：潛伏結核感染(感染尚未發病不會傳染他人，請接受完整潛伏結核感染治療，可有效降低後續結核病發病機會)

二、 給藥方法（含給藥途徑、給藥間隔、劑量、療程...等）：
isoniazid 300 mg/Tab 大多與rifapentine合併使用，並依據使用之潛伏結核感染處方組合給藥。

三、 可能產生的副作用、處理方式：
與國內isoniazid 100 mg/Tab副作用類似，可能出現肝炎、周邊神經炎等不良反應。但isoniazid 300 mg/Tab用於速克伏處方時肝炎機率較低：國內資料顯示常規監測肝炎的情況下，與藥物相關造成永遠停藥的肝炎發生比例，速克伏處方使用者(1.5%)較9個月isoniazid處方使用者(5.3%)來得低。

四、 治療進行中之注意事項：
(一) 使用此處方須依醫師醫囑服用。
(二) 潛伏結核感染應加入都治計畫，由都治關懷員以到府/到點親眼目睹或視訊方式關懷服藥及追蹤副作用。
(三) 領藥後請儘快與公衛人員聯繫，討論初次服藥時間，以利預先規劃個人行程。

- isoniazid 300 mg/Tab劑型，因國內缺藥，因此以專案進口方式向世界衛生組織委託之全球藥物購置機構Global Drug Facility(GDF)購買國際認可藥品。
※本藥品無衛生福利部藥品許可證，不適用藥害救濟法。
- 本藥品由衛生福利部疾病管制署公費提供使用，故必須接受衛生單位「都治」送藥服務。
- 本人已詳閱以上各項資料，有關本藥品之疑問業經使用醫師詳細予以解釋，本人同意使用本藥。

治療醫師簽署：　　日期：　年　月　日

服藥人簽署：　　日期：　年　月　日

法定代理人簽署：(未成年應由法定代理人同意)

衛生福利部疾病管制署潛伏結核感染治療藥品使用同意書

Isoniazid/Rifapentine 300 mg / 300 mg

治療藥品：Isoniazid/Rifapentine Coated Tablets 300 mg / 300 mg 複方錠

個案姓名：

病歷號碼：　　身分證字號：

一、治療疾病名稱及說明：本藥品為潛伏結核感染治療3HP處方之複方錠，潛伏結核感染係人體遭受結核菌感染，但尚未發病也不會傳染他人，請接受完整潛伏結核感染治療，可有效降低後續結核病發病機會。

二、給藥方法：限體重50公斤(含)以上使用(固定劑量，不依年齡及體重調整劑量)，口服給藥，每週服藥1次，每次3顆，共需服用12個劑量，治療期間預計12週（約3個月）。

三、可能產生的副作用：因含有Isoniazid和Rifapentine成分，可能出現肝炎、周邊神經炎、姿勢性低血壓、昏厥和類流感(flu-like syndrome)相關症狀等不良反應；服藥後體液(小便、眼淚和汗水)可能出現紅色，毋須恐慌，停藥後會恢復正常，建議可和油脂類食物一起服用提高藥物吸收。如同一般口服藥，極少數人因體質關係可能發生藥物急性過敏反應，倘發生請停止用藥，儘速回診。

四、治療進行中之注意事項：
(一)使用此處方須依醫師醫囑服用。
(二)治療者應加入「都治計畫」，由都治關懷員關懷服藥及觀察副作用。
(三)領藥後請儘快與公衛人員聯繫，討論初次服藥時間，以利預先規劃個人行程。

- 本藥品以專案進口方式向世界衛生組織委託之全球藥物購置機構(Global Drug Facility, GDF)購買，為世界衛生組織推薦之新劑型複方藥品。
※本藥品無衛生福利部藥品許可證，不適用藥害救濟法。
- 本藥品由衛生福利部疾病管制署公費提供使用，故必須接受衛生單位「都治」送藥服務。
- 本人已詳閱以上各項資料，有關本藥品之疑問業經開立醫師詳細予以解釋，本人同意使用本藥。

治療醫師簽署：　　日期：　年　月　日

服藥人簽署：　　日期：　年　月　日

法定代理人簽署：(未成年應由法定代理人同意)

LTBI 治療處方原則及選擇

- **基本原則:**
  - Safety: 副作用的監測
  - High Completion rate and good compliance: 促進藥物的順從性與完成率
  - New regimen: 在國家計畫的管理、監測及評估下推展新處方

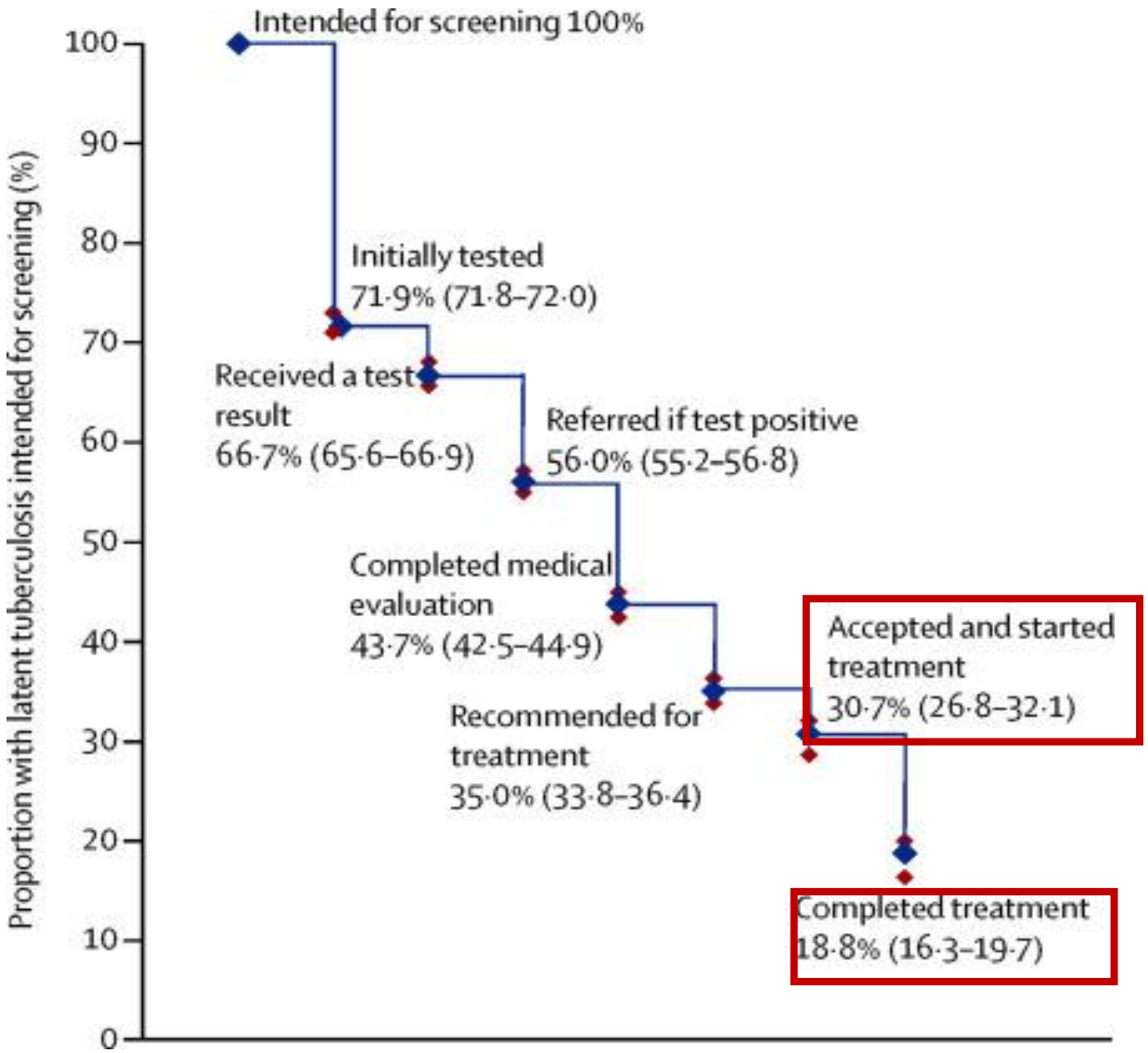
- **指標個案(Index case)抗藥性:**
  - INH-Resistance: 4R
  - RIF-Resistance: 9H
  - MDR-TB:轉介至抗藥性結核病醫療照護體系(TMTC)加入專案計畫選擇使用fluoroquinolone類藥物作為LTBI治療

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%



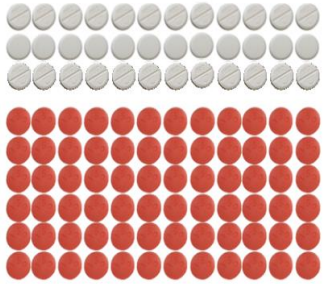
Alsdurf, H. Lancet Infect Dis 2016;16:1269-78.

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

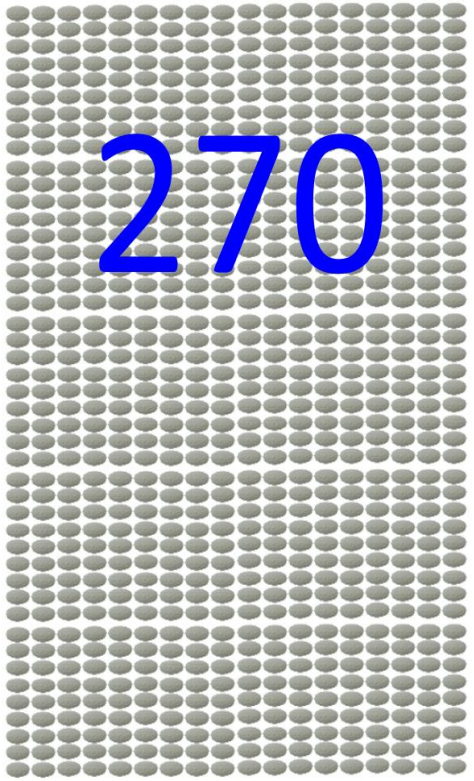
3HP
INH & RPT 15 mg/kg, weekly for 3M

12



9H
INH 5 mg/kg, daily for 9M

270

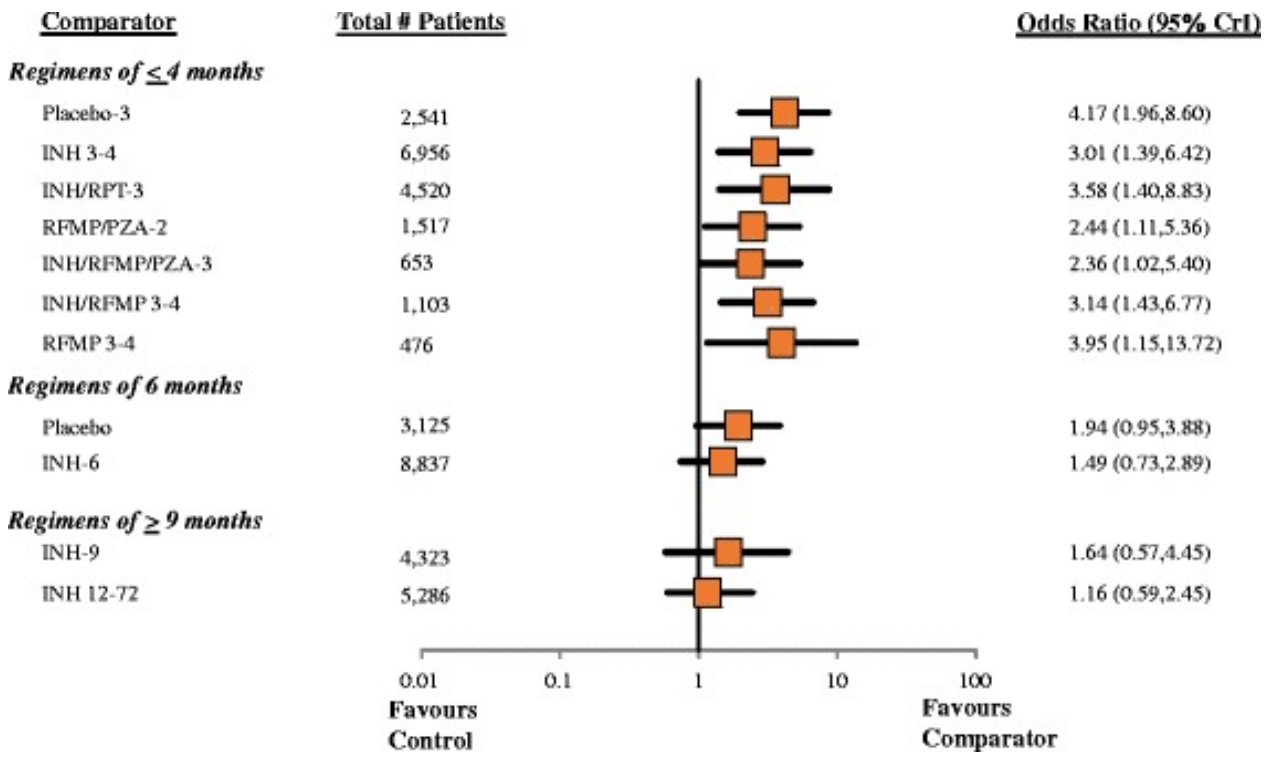


Sterling TR. **NEJM** 2011;365:2155-66.

Sterling TR. NEJM 2011;365:2155-66.

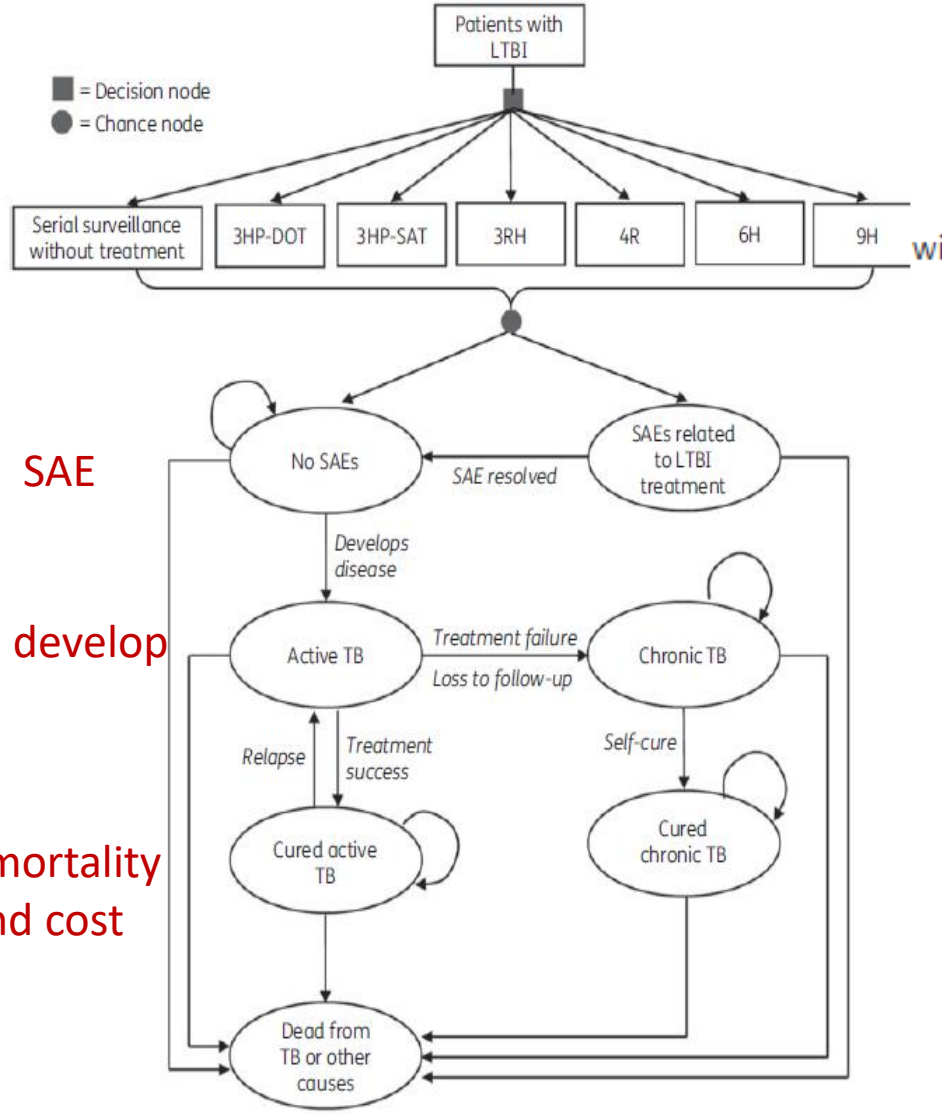
Similar efficacy of active TB prevention in various LTBI treatment regimens - Network meta-analysis

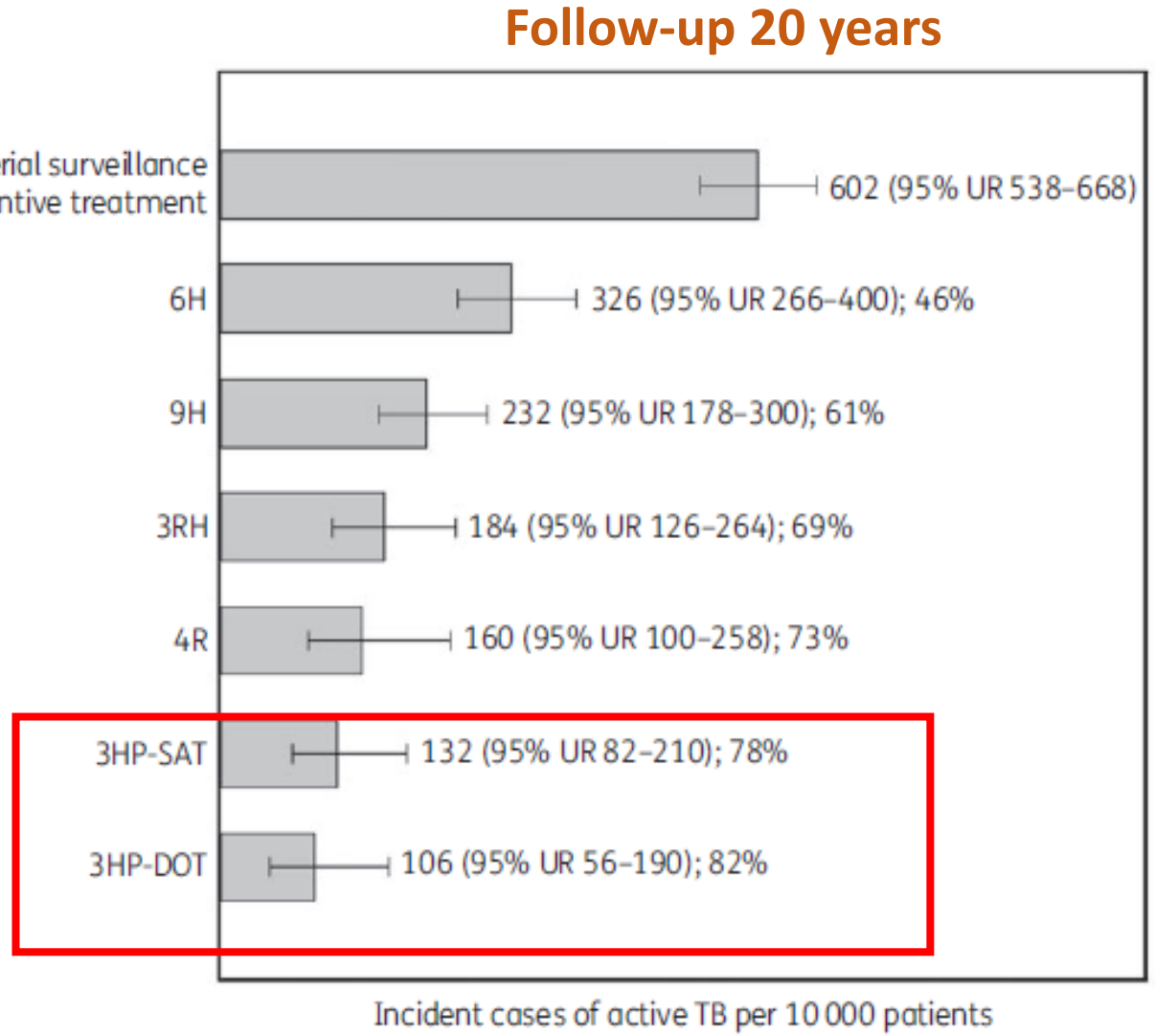
Characteristic	Summary measure
Study sample size	
Median (range)	352 (37–27,830)
Year of publication (median, range)	Median 2005 (range 1968–)
Before 1980	3 (10%)
1981–1990	1 (3.3%)
1991–2000	6 (20%)
2001–2010	10 (33.3%)
2011–2016	10 (33.3%)
% Female participants	
Median (range)	45.5% (0%–83.3%)
Average 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%)



BMC Infectious Diseases (2017) 17:265

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





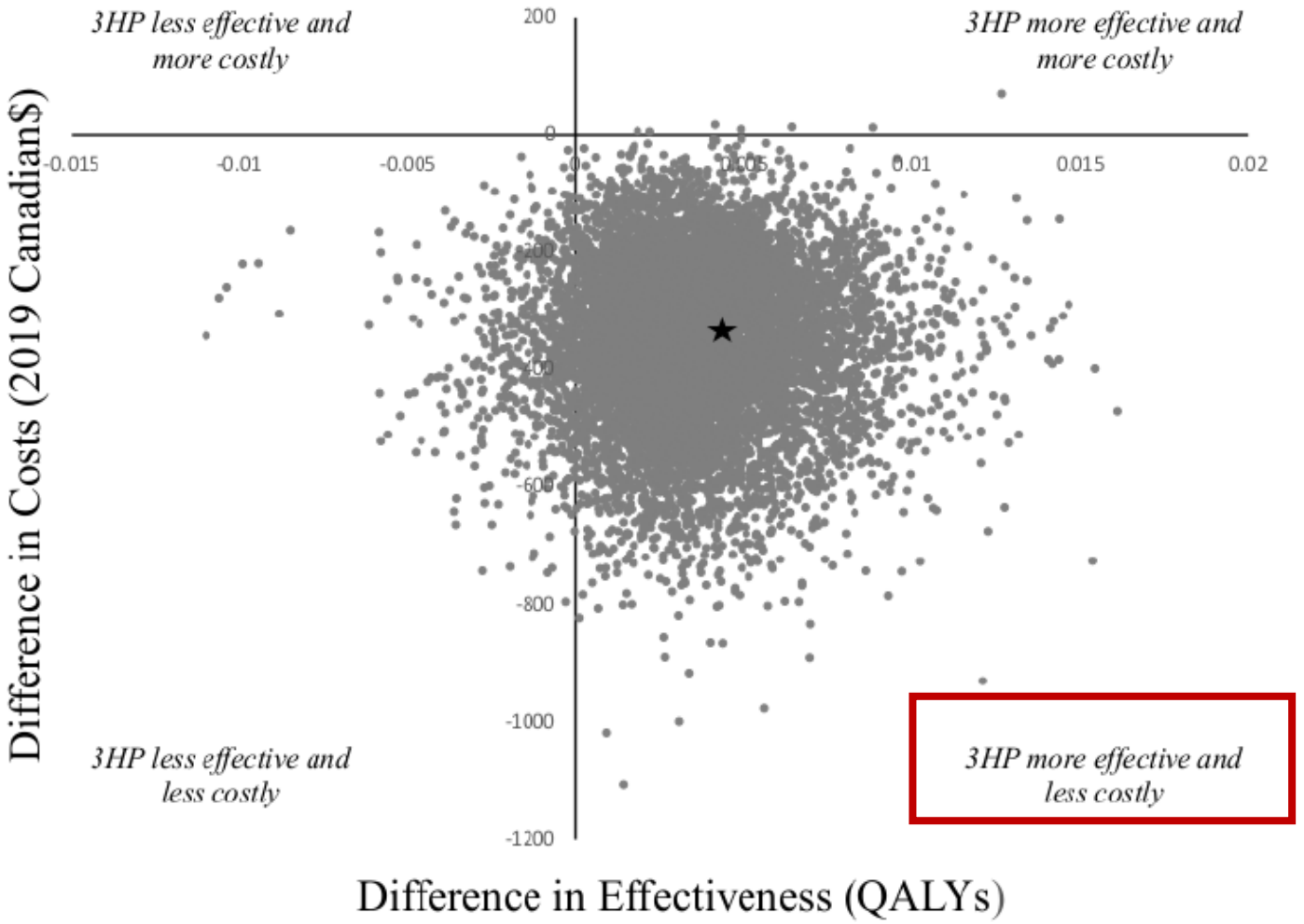
J Antimicrob Chemother 2019; 74: 218–227

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.



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%

However, SDRs results in high discontinuation rate

- **Prevent Tuberculosis Trial.**
- **Systemic drug reactions (SDR)**
  - 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% of total population
  - 3HP: 3.5% vs 9H: 0.4% (p<0.01)
- 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)

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.

3HP vs. 9H: A pilot study in Taiwan (2014-2018)

- Multicetere, randomize controlled study: 3HP vs. 9H
- 3HP had:
  - **Higher completion rate:** 89.4% vs. 77.9%
  - **Less hepatotoxicity:** 1.5% vs. 5.4%
  - **More Gr.2 non-hepatitis ADR:** 12.9% vs. 3.8%
  - **More flu-like symptoms:** 40.9% vs. 16.8%
  - **Systemic drug reaction:** 3.8%
  - 3HP related SDRs occurred more in age ≥ 35, female

Variables	3HP (n=132)	9H (n=131)
Age, mean ± SD, years	31.7 ± 15.0	32.0 ± 16.4
Men, n (%)	81 (61.4)	71 (54.2)
BMI, mean ± SD	23.3 ± 4.0	22.8 ± 4.1
Current smoking, n (%)	13 (9.8)	16 (12.2)
Household contact, n (%)	66 (50.0)	60 (45.8)

Variables, n (%)	Men (n=81)	Women (n=51)
Fatigue	3 (3.7)	2 (3.9)
Dizziness	4 (4.9)	1 (2.0)
Nausea	1 (1.2)	2 (3.9)
Vomiting	3 (3.7)	4 (7.8)
Fever*	1 (1.2)	7 (13.7)
Chills#	1 (1.2)	4 (7.8)
Hot flushes	0 (0)	0 (0)
Headache	2 (2.5)	2 (3.9)
Myalgia	1 (1.2)	2 (3.9)
Cutaneous reaction#	1 (1.2)	4 (7.8)
Diarrhea	0 (0)	1 (2.0)

***ClinicalTrials.gov*: NCT02208427**

Sun HY. Tuberculosis 2018;111:121-6.

Conclusions on 3HP vs. 9H in Asian Population

3HP had …..

1. Higher completion rate: 89.4% *vs.* 77.9%
2. Less hepatotoxicity: 1.5% *vs.* 5.4%
3. More Gr.2 non-hepatitis ADR: 12.9% *vs.* 3.8%
4. More flu-like symptoms: 40.9% *vs.* 16.8%
5. Sometimes systemic drug reaction: 3.8%
6. Usually transient and Gr. 1: 69.1%
7. 3HP related SDRs occured more in age ≥ 35, female

Variables, n (%)	Men (n=81)	Women (n=51)
Fatigue	3 (3.7)	2 (3.9)
Dizziness	4 (4.9)	1 (2.0)
Nausea	1 (1.2)	2 (3.9)
Vomiting	3 (3.7)	4 (7.8)
Fever*	1 (1.2)	7 (13.7)
Chills#	1 (1.2)	4 (7.8)
Hot flushes	0 (0)	0 (0)
Headache	2 (2.5)	2 (3.9)
Myalgia	1 (1.2)	2 (3.9)
Cutaneous reaction#	1 (1.2)	4 (7.8)
Diarrhea	0 (0)	1 (2.0)

Sun HY. Tuberculosis 2018;111:121-6.

Safety of 3HP in elders and high-risk population

- A multicenter prospective observational study : 167 cases age ≥60 years and 239 cases <60 year
- SARs: ADRs ≥ Grade 2, not including hepatotoxicity
- No difference of risk of SARs between age ≥60 years and <60 years (p=0.436)
- Age ≥60 years had higher discontinuation (21.6% vs. 15.9%)

	Overall patients, *N* = 406	
	aOR (95% CI)	*p*-Value
LTBI regimens		
9H	1.00	–
3HP	2.90 (1.14–7.40)	0.026
4R	0.94 (0.10–9.15)	0.957
Age (years)		
<35	1.00	–
35–59	3.46 (1.13–10.55)	0.029
60–79	3.05 (0.95–9.74)	0.060
≥80	3.75 (0.98–14.40)	0.054
Female	1.64 (0.92–2.93)	0.095
BMI < 23 kg/m^2	2.23 (1.26–3.96)	0.006
ESRD	3.96 (1.83–8.53)	<0.001
Immunosuppressant	0.76 (0.27–2.15)	0.603

	≥60 years old, *n* = 167		<60 years old, *n* = 239	
	aOR (95% CI)	*p*-Value	aOR (95% CI)	*p*-Value
LTBI regimens				
9H	1.00	–	1.00	–
3HP	4.00 (0.73–22.04)	0.111	2.63 (0.79–8.80)	0.116
4R	–	–	1.35 (0.11–16.69)	0.818
Age (years)				
<35	–	–	1.00	–
35–59	–	–	3.58 (1.16–11.08)	0.027
60–79	1.00	–	–	–
≥80	1.18 (0.44–3.12)	0.747	–	–
Female	1.61 (0.68–3.79)	0.281	1.69 (0.74–3.87)	0.217
BMI < 23 kg/m^2	1.83 (0.77–4.32)	0.169	2.52 (1.13–5.62)	0.024
ESRD	2.94 (1.06–8.16)	0.038	5.09 (1.54–16.90)	0.008
Immunosuppressant	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

3HP extent to elders and high-risk population: Will it increase SDR ??

- A Prospective, multicenter Study in Taiwan
- IGRA positive and receive ≥1 3HP dose under DOT
  - Close contact to pulmonary TB
  - High risk population
    - Long term care facility residents/workers
    - Poorly diabetic controlled patients

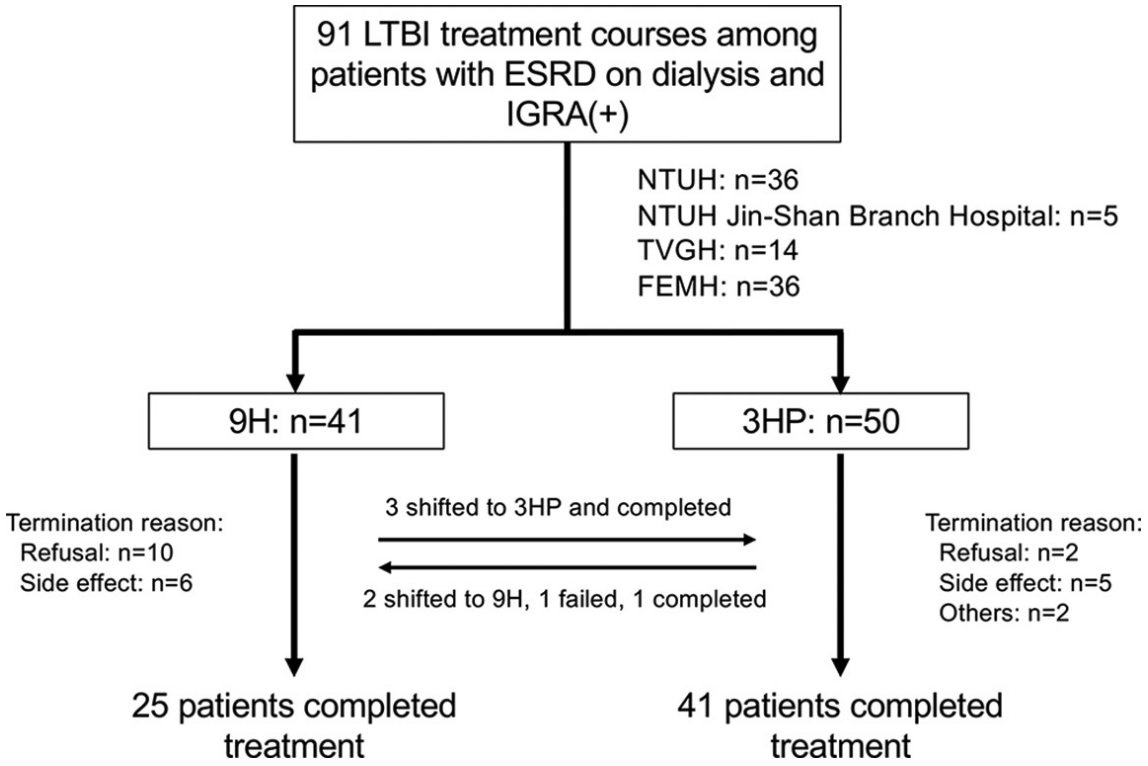
- Age stratified:
  - younger group (≤35 years),
  - middle-aged group (35-65 years)
  - elderly group (≥65 years, 23.1%)

- Outcome
  - Overall completion rate: 83.1%
  - The young-age group had highest completion rate, the elder-age group had the lowest
  - Middle-age group had higher SDR rate, particularly flu-like symptoms
  - SDR accounts for the highest permanent discontinuation
  - Uncontrolled hypertension accounts for >50% of discontinuation rate among elders

	Age ≤ 35 (n=165)	Age 35 ~ 65 (n=280)	Age ≥ 65 (n=134)
Complete treatment	156 (94.5%)*	226 (80.7%)	99 (73.9%)
No ADRs	58 (35.2%)	101 (36.1%)	58 (43.3%)
Presence of ADR without Tx interruption	86 (52.1%)*	106 (37.9%)	34 (25.4%)
Presence of ADR with Tx interruption	12 (7.3%)	19 (6.8%)	7 (5.2%)
Permanent discontinuation	9 (5.5%)	54 (19.3%)	35 (26.1%)*
No of doses before discontinuation	4.3 ± 2.3	4.4 ± 2.1	4.2 ± 2.4
Cause of discontinuation			
SDR	4 (2.4%)	27 (9.6%)*	6 (4.5%)
Hepatotoxicity	0 (0%)	12 (4.3%)	6 (4.5%)*
ADRs except SDR/hepatotoxicity	5 (3.0%)	10 (3.6%)	14 (10.4%)*
Withdraw consent	0 (0%)	5 (1.8%)	4 (3.0%)
Tuberculosis confirmed	0 (0%)	0 (0%)	2 (1.5%)*
Other reasons	0 (0%)	1 (0.4%)	2 (1.5%)

Clinical Infectious Diseases, 2021 Sep 7;73(5):e1064-e1071

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



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

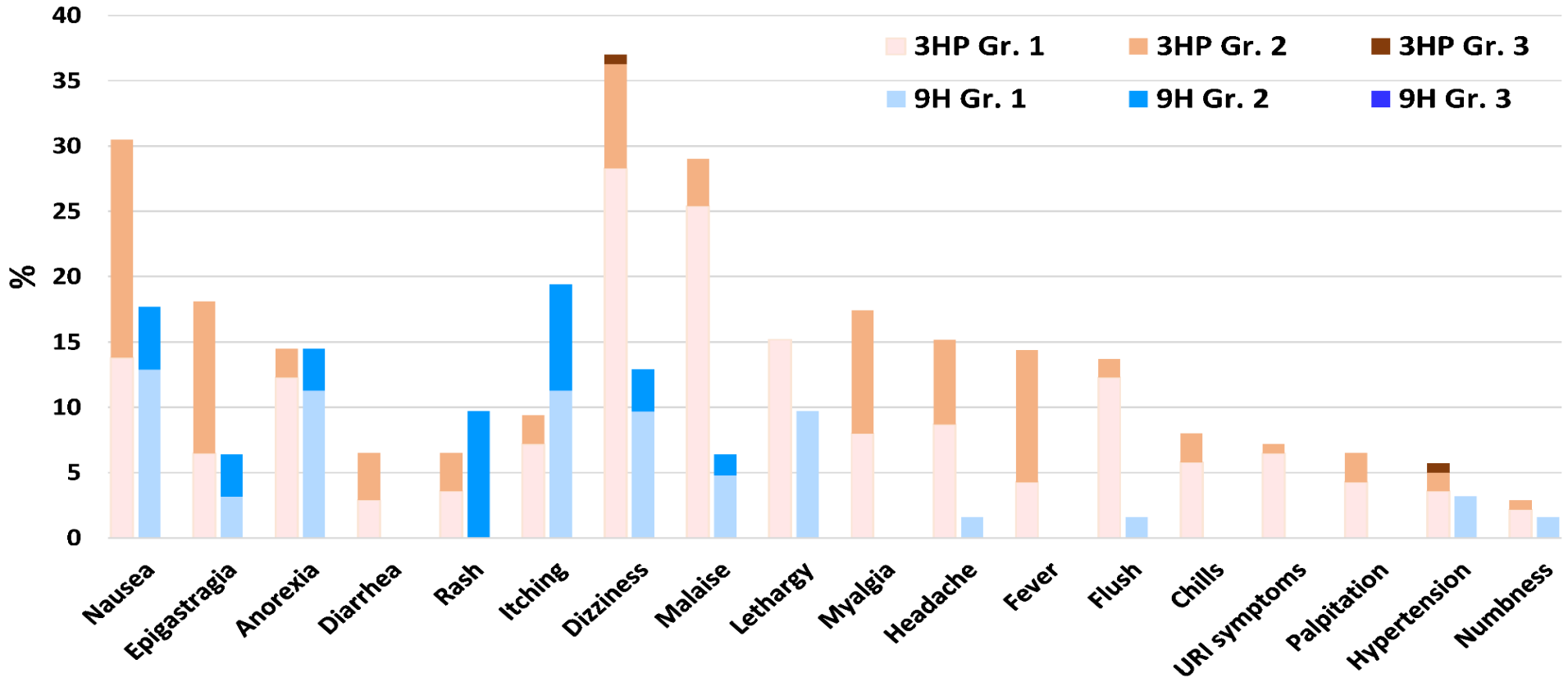
- Prospective, multicenter study. April 2018 to June 2020
  - Taichung Veterans General Hospital
  - Kaohsiung Maniple Ta-Tung Hospital
- **200 cases**
  - Age ≥ 45 years
  - ≥1 time HbA1c ≥9.0% within recent 1 year
- **LTBI screening performed by endocrinologist**
  - Pay-for-Performance project
  - 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

	Total (n=200)	3HP (n=138)	9H (n=62)	*p*-value
Complete treatment	165 (82.5%)	116 (84.1%)	49 (79.0%)	0.494
No adverse drug reactions	59 (29.5%)	30 (21.7%)	29 (46.8%)	<0.001
Permanent discontinuation	35 (17.5%)	22 (15.9%)	13 (21.0%)	0.494
Dose received		5.0 ± 2.7	56.7 ± 40.8	
Cause of discontinuation				
Adverse Drug Reaction	28 (14.0%)	20 (14.5%)	8 (12.9%)	0.764
Systemic drug reaction	6 (3.0%)	6 (4.3%)	0	0.223
Hypotension	1 (0.5%)	1 (0.7%)	0	0.680
Flu-like syndrome	5 (2.5%)	5 (3.6%)[a]	0	0.301
Urticaria	1 (0.5%)	1 (0.7%)	0	0.680
Hepatotoxicity	4 (2.0%)	2 (1.4%)	2 (3.2%)	0.776
Other adverse drug reactions	18 (9.0%)	12 (8.7%)	6 (9.7%)	0.822
Patient refusal	5 (2.5%)	2 (1.4%)	3 (4.8%)	0.352
Other reasons	2 (1.0%)	0	2 (3.2%)[b]	0.176

Clinical Infectious Diseases, ciab209, https://doi.org/10.1093/cid/ciab209

Safety Profile

- 3HP group had higher proportion of flu-like symptoms and GI symptoms
- 9H group had higher proportion of skin rash
- None of patients experienced uncontrolled hyper/hypoglycemia events



Clinical Infectious Diseases, ciab209, https://doi.org/10.1093/cid/ciab209

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

LTBI治療處方轉換建議表

已服用3HP劑次 每週服用(總療程12週)	轉換為3HR處方 每天服用(總療程90天)	轉換為4R處方 每天服用(總療程120天)	轉換為9H處方 每天服用(總療程270天)
已服用1劑次	餘83天	餘110天	餘248天
2	75	100	225
3	68	90	203
4	60	80	180
5	53	70	158
6	45	60	135
7	38	50	113
8	30	40	90
9	23	30	68
10	15	20	45
11	8	10	23

備註:

- 1個月以30天計算；4R需服用滿120天、9H需服用滿270天、3HR需服用滿90天
- 各處方間若因副作用或缺藥等因素，得相互轉換；除指標個案對原治療處方抗藥外，轉換後處方須按已服用比例，接續服用滿該處方的療程，並儘可能不要短少
- 接觸者於LTBI治療期間或已完成LTBI治療後，發現指標個案藥敏具抗藥性，建議依指標個案藥敏情形重新治療，以確保治療效果；倘無法重新 以有效處方治療，則建議仍完成該療程，惟目前無證據確認其保護效果

The possible mechanism related to 3HP related SDR – RPT

- **Immunologic basis:** Rifampicin-antibody complexes may be associate with "flu-like" reaction
- **Circulating anti-rifampin antibodies (IgM):**
  - Not detectable during daily administration, only when receiving intermittent dosing at high dose (> 900mg)
  - Flu-like reaction coincided with peak concentration of rifampin (2-4 hrs) and level of antibody fell during reaction
- Daily administration of rifapentine could produce immune tolerance
  - RCT of daily rifapentine followed by intermittent dosing, no reports of flu-like syndrome or hypersensitivity

Poole. et al. BMJ 1971
O'Mahony.et al. Clin Allergy. 1973
Jindani.et al. NEJM. 2014

INH Metabolic Enzyme Genetic Polymorphisms associated with ADRs

- A multicenter observational study
  - 377 close contacts aged >12 years receiving 3HP
  - February 2017 - October 2018.
  - Mean age was 45.7 years
  - 208 participants (55.2%) were women,
  - 144 participants (38.2%) had comorbidities
  - 184 (48.8%) developed ADRs
    - Grade 1: 77.68%
    - Grade 2: 20.63%
    - Grade 3: 1.42%, Flu accounts 80%
- CY2PE1 and NAT2 associated with ADRs

Variable	ALL (n = 754)	Non-ADR (n = 386)	ADR (n = 368)	OR (95% C.I.)	p Value
CYP5A6 (rs28399433)					
A allele	570 (75.6%)	286 (74.1%)	284 (77.2%)	1.000 (reference)	
C allele	184 (24.4%)	100 (25.9%)	84 (22.8%)	0.846 (0.606–1.181)	p = 0.325
CYP2B6 (rs8192709)					
T allele	722 (95.8%)	375 (97.2%)	347 (94.3%)	1.000 (reference)	
C allele	32 (4.2%)	11 (2.8%)	21 (5.7%)	2.063 (0.980–4.341)	p = 0.056
CYP2C19 (rs4986893)					
G allele	718 (95.2%)	372 (96.4%)	346 (94.0%)	1.000 (reference)	
A allele	36 (4.8%)	14 (3.6%)	22 (6.0%)	1.690 (0.851–3.355)	p = 0.134
CYP2C19 (rs12248560)					
C allele	752 (99.7%)	384 (99.5%)	368 (100.0%)	1.000 (reference)	
T allele	2 (0.3%)	2 (0.5%)	0 (0.0%)	-	-
CYP2E1 (rs2070676)					
C allele	610 (80.9%)	322 (83.4%)	288 (78.3%)	1.000 (reference)	
G allele	144 (19.1%)	64 (16.6%)	80 (21.7%)	1.398 (0.970–2.013)	p = 0.072
CYP2E1 (rs2515641)					
C allele	590 (78.3%)	319 (82.6%)	271 (73.6%)	1.000 (reference)	
T allele	164 (21.7%)	67 (17.4%)	97 (26.4%)	**1.704 (1.200–2.421)**	p = 0.003 *
NAT2 (rs1495741)					
G allele	398 (52.8%)	220 (57.0%)	178 (48.4%)	1.000 (reference)	
A allele	356 (47.2%)	166 (43.0%)	190 (51.6%)	**1.415 (1.062–1.885)**	p = 0.018 *
NAT2 (rs1799930)					
G allele	566 (75.1%)	286 (74.1%)	280 (76.1%)	1.000 (reference)	
A allele	188 (24.9%)	100 (25.9%)	88 (23.9%)	0.899 (0.646–1.251)	p = 0.528

Int J Environ Res Public Health. 2020 Jan; 17(1): 210.

INH maybe related to 3HP related SDR

- INH induced flu-like syndrome also reported
- A prospective multicenter study in Taiwan: Age ≥ 12 years, In close contact with TB patients

	Pharmacokinetics	Single nucleotide polymorphisms: NAT2, AADAC, CYP2E1
Case number	C6: 52 cases, C24: 144 cases	129 cases
Age	37.1±17.8	44.8±17.2
Completion rate	90%	83%
SDR incidence	8%	10.1%
SDR risk factors	• Older age • Inferior renal function • NAT2 rs1041983(T): Slow acetylater • CYP2E1 rs2070673 (A)	• C24 plasma INH level • No association with C6 plasma INH leve and RPT level

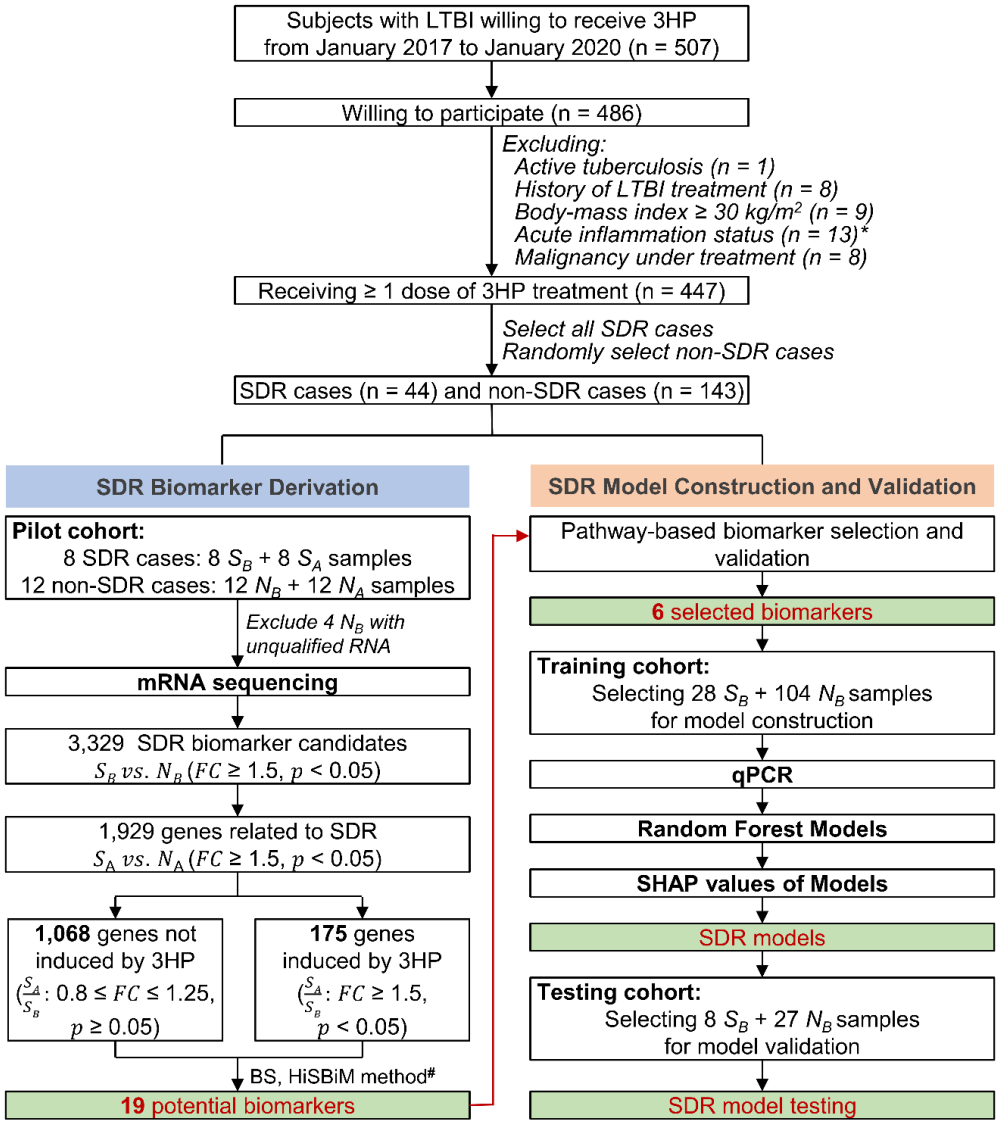
Limitations:

- No population PK/PD data for INH and RPT
- Small sample size
- Ethnic difference should be considered

J. Clin. Med. 2019, 8, 812

Whole blood transcriptome based signature as an aid for 3HP related SDR prediction

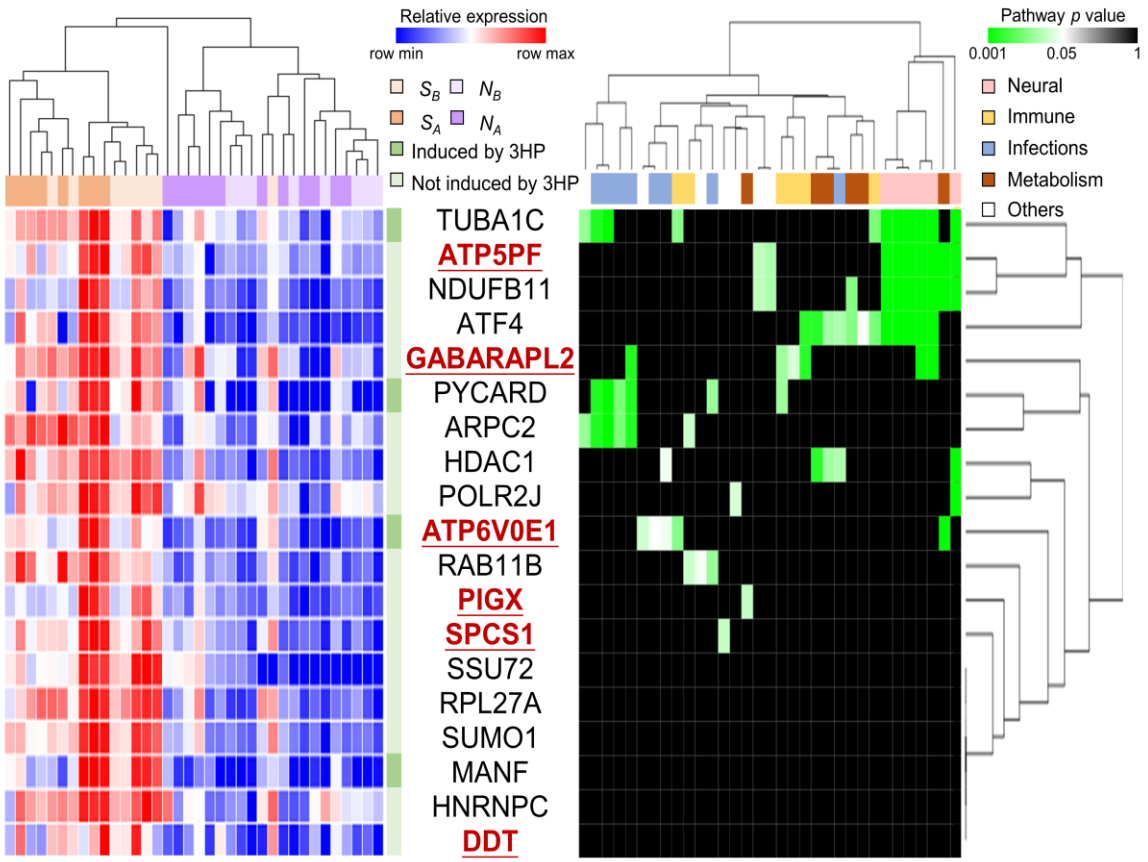
- Prospective, multicenter study
- A first phenotype anchoring genotyping study on 3HP related SDR prediction biomarkers
- The development of SDRs: multifactorial and controversial
- Population:
  - a. Pilot: 8 SDR + 12 non-SDR
    b. Training: 28 SDR + 104 non-SDR
    c. Testing: 8 SDR + 27 non-SDR
- Baseline characteristics between 3 groups are similar

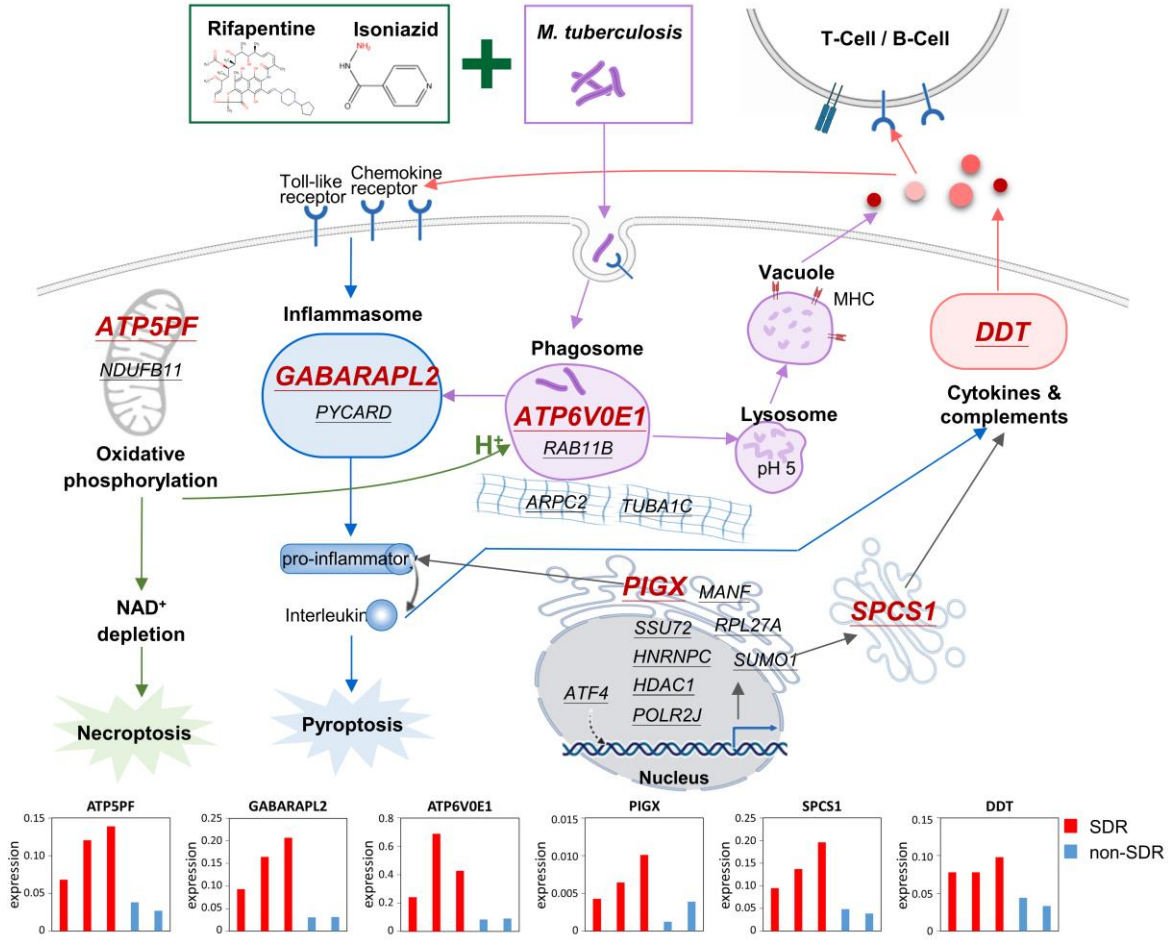


Clinical Infectious Diseases, 2022 Jan 5;ciac003

Gene expression signature and therapy–biomarker pathway for predicting SDR

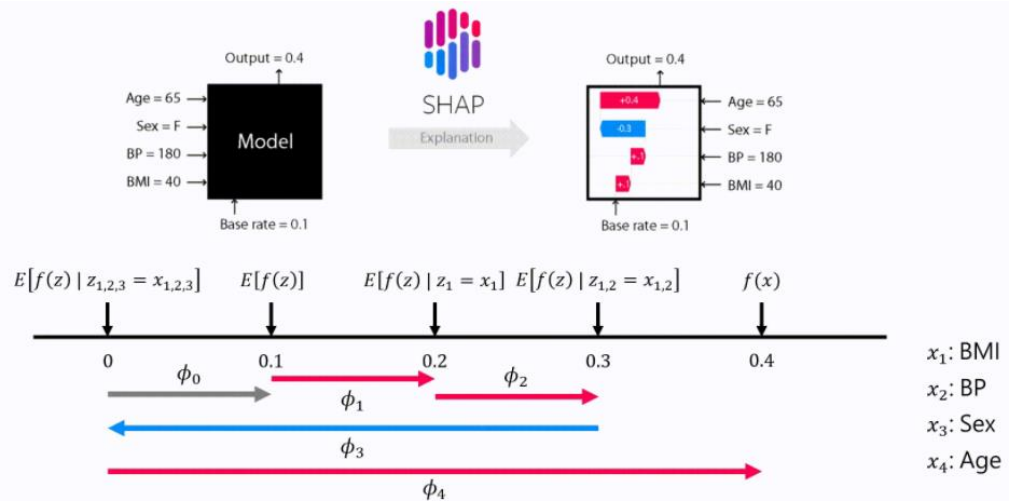
KEGG functional clustering

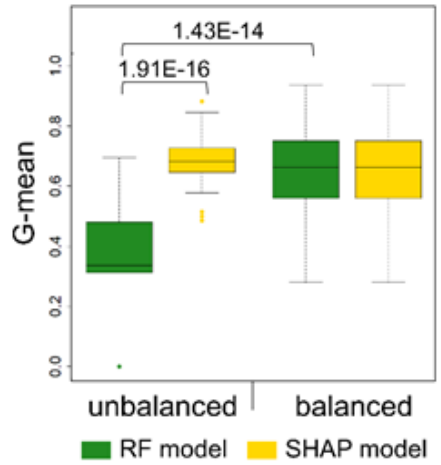


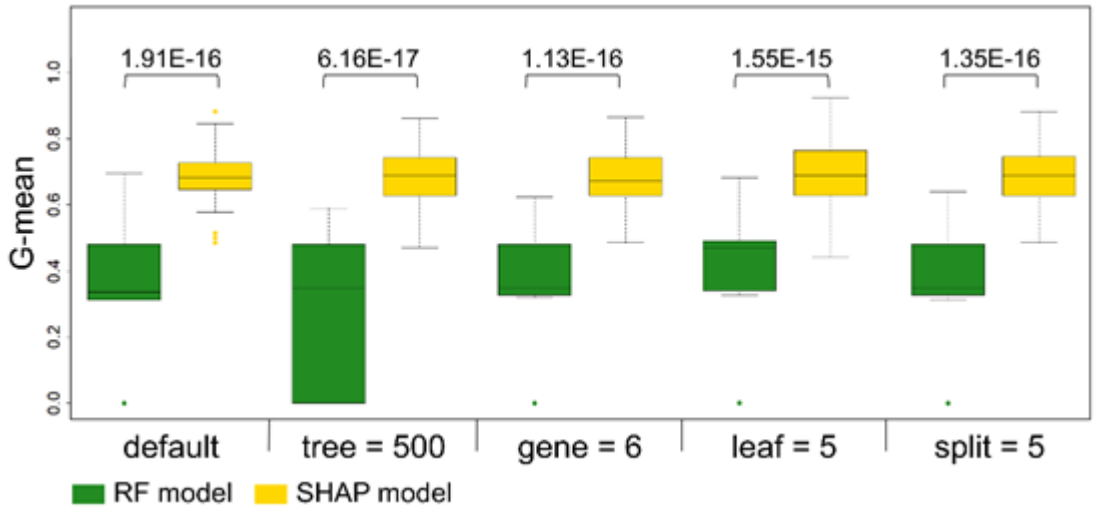


Clinical Infectious Diseases, 2022 Jan 5;ciac003

SHAPLY value model: Interpretable AI to quantify each feature





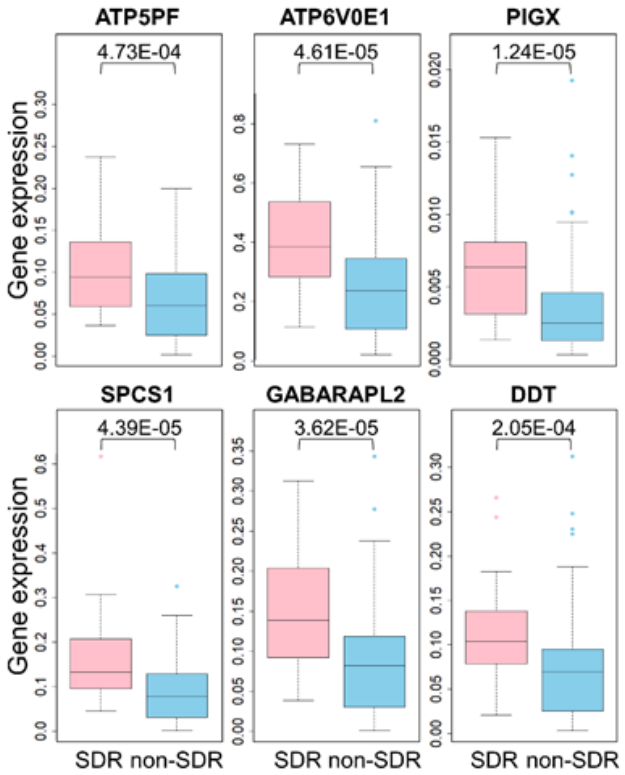


- Compare to Random Forest Model, SHAPLY vale provide a more stable predictive model in small number sized population

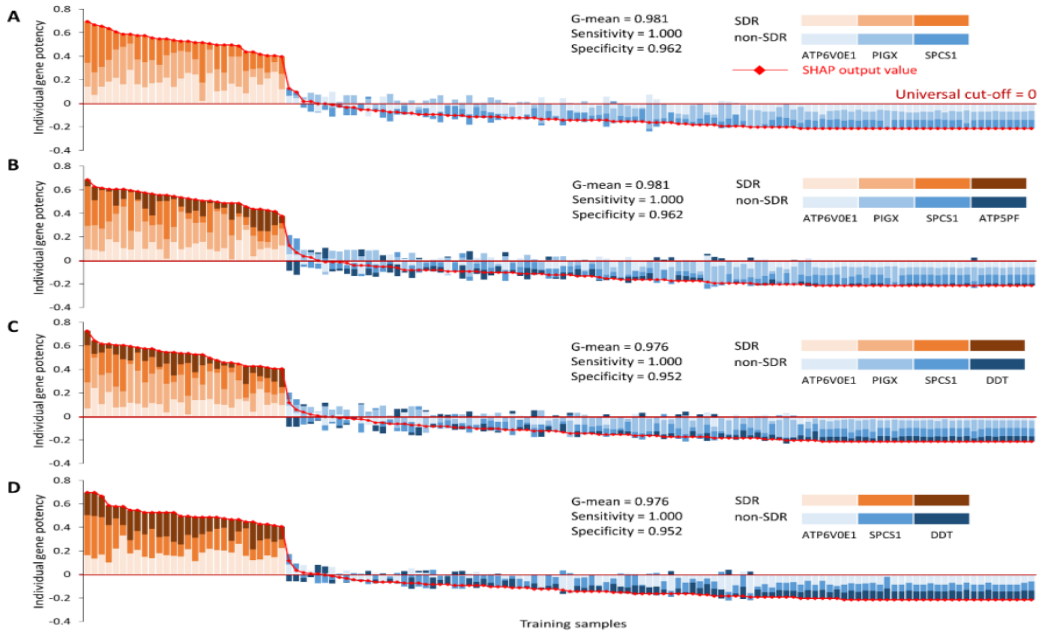
Clinical Infectious Diseases, 2022 Jan 5;ciac003

Construct SHAPLY predictive model from training cohort

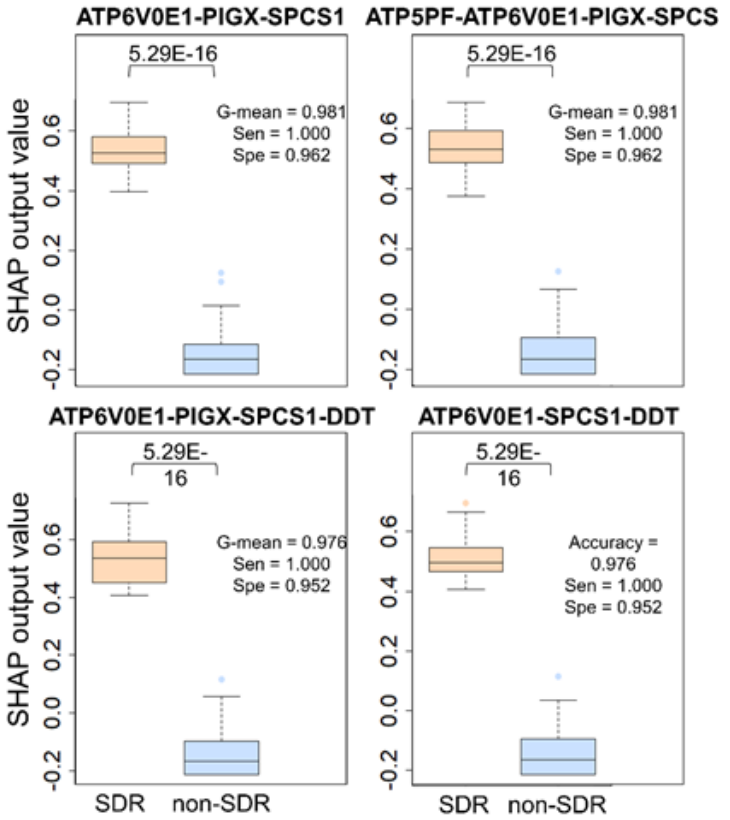
Gene expression



SHAPLY model for 3-Gene combination

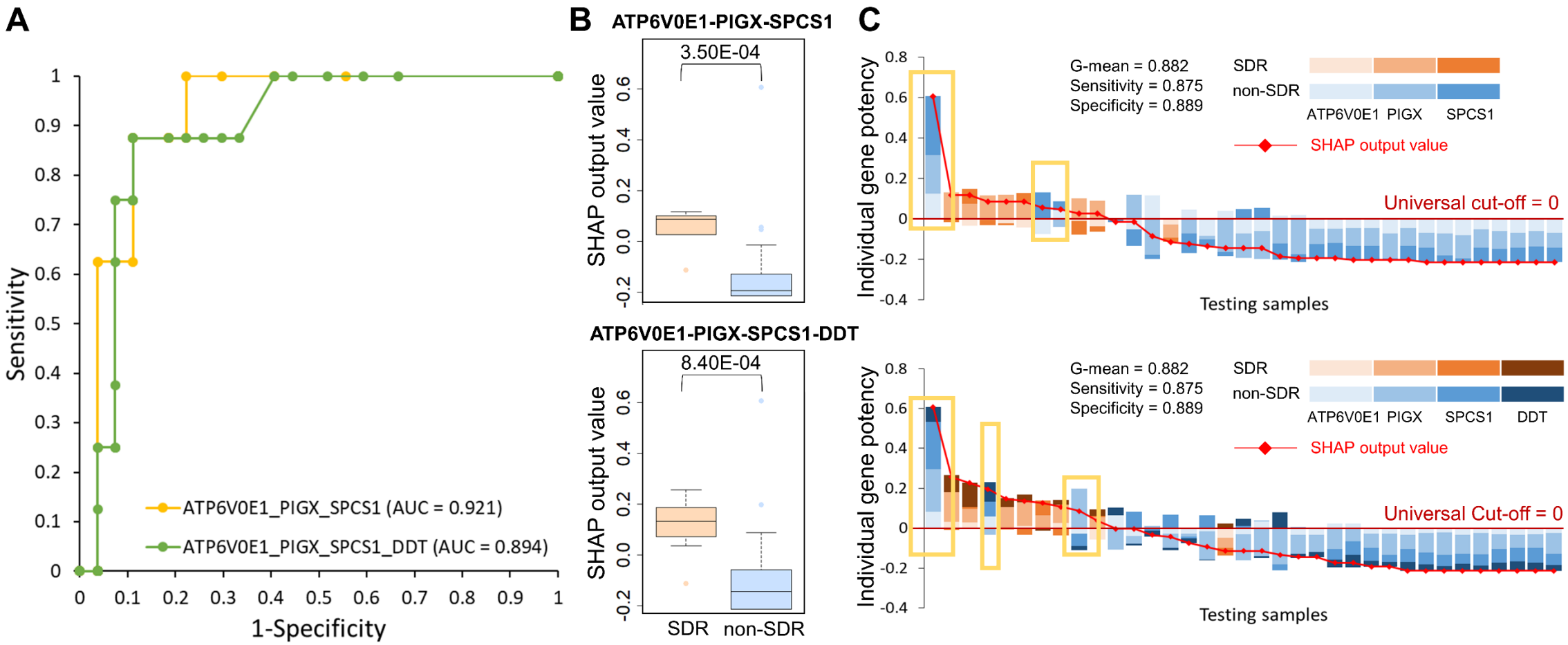


Performance of SHAPLY model



Clinical Infectious Diseases, 2022 Jan 5;ciac003

Performance of prediction model in testing cohort



- **Though the validation performance is good, individual difference still existed**

Conclusion

- To persuade a safe and effectiveness short-term therapy is essential for LTBI treatment
- The risk factors for development of 3HP related SDRs is multifactorial
  - Patient characters : female, age> 35, comorbidities
  - The serum level of INH or RPT
  - The genotypes
- The mechanism of 3HP related SDRs are still uncertain
- The perfect prediction model for 3HP related SDRs is still lacking
- Further studies should be conducted for strategy adjustments

台灣現行處方及建議劑量

處方	處方藥品		療程頻率	劑量			常見副作用	使用限制(不適用對象)	都治 DOPT	推薦順序 (接觸者除指標抗藥或使用限制外)
				每日最大劑量	兒童	成人				
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	推薦推薦
	單方	Isoniazid (INH)	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 • 孕婦 • <2歲兒童	必須	推薦處方
		Rifapentine (RPT)		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					
3HR[b]	Isoniazid (INH)		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)			600 mg	15 (10-20)mg/kg	10 mg/kg				
4R	Rifampin (RMP)		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
9H	Isoniazid (INH)		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
1HP[a]	Isoniazid (INH)		28天 (1個月) 每日服用	300mg	300 mg		皮疹 肝毒性	• 指標個案INH或RMP抗藥之接觸者 • <13歲兒童	必須	限疾管署專案計畫使用
	Rifapentine (RPT)			600mg	• <35 kg：300 mg • 35-45 kg：450mg • >45 kg：600 mg					

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

INH300mg藥品使用同意書

HP複方藥品使用同意書

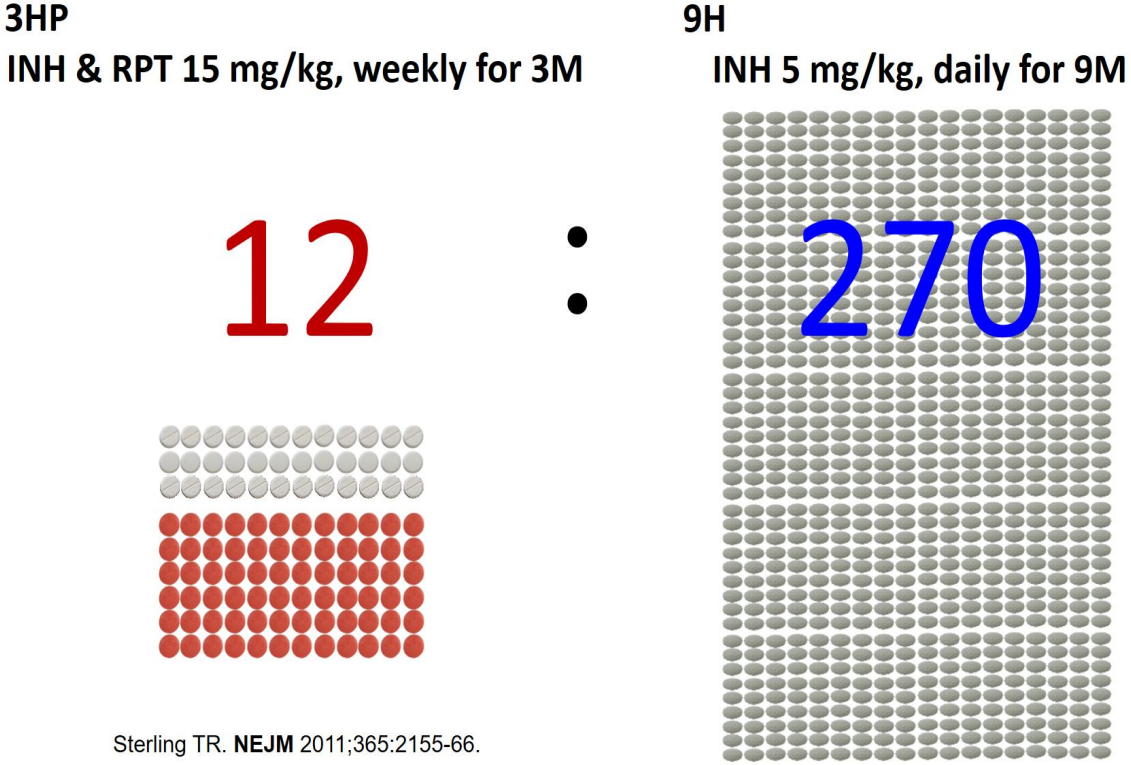
Thank you !

END TB

World Health Organization

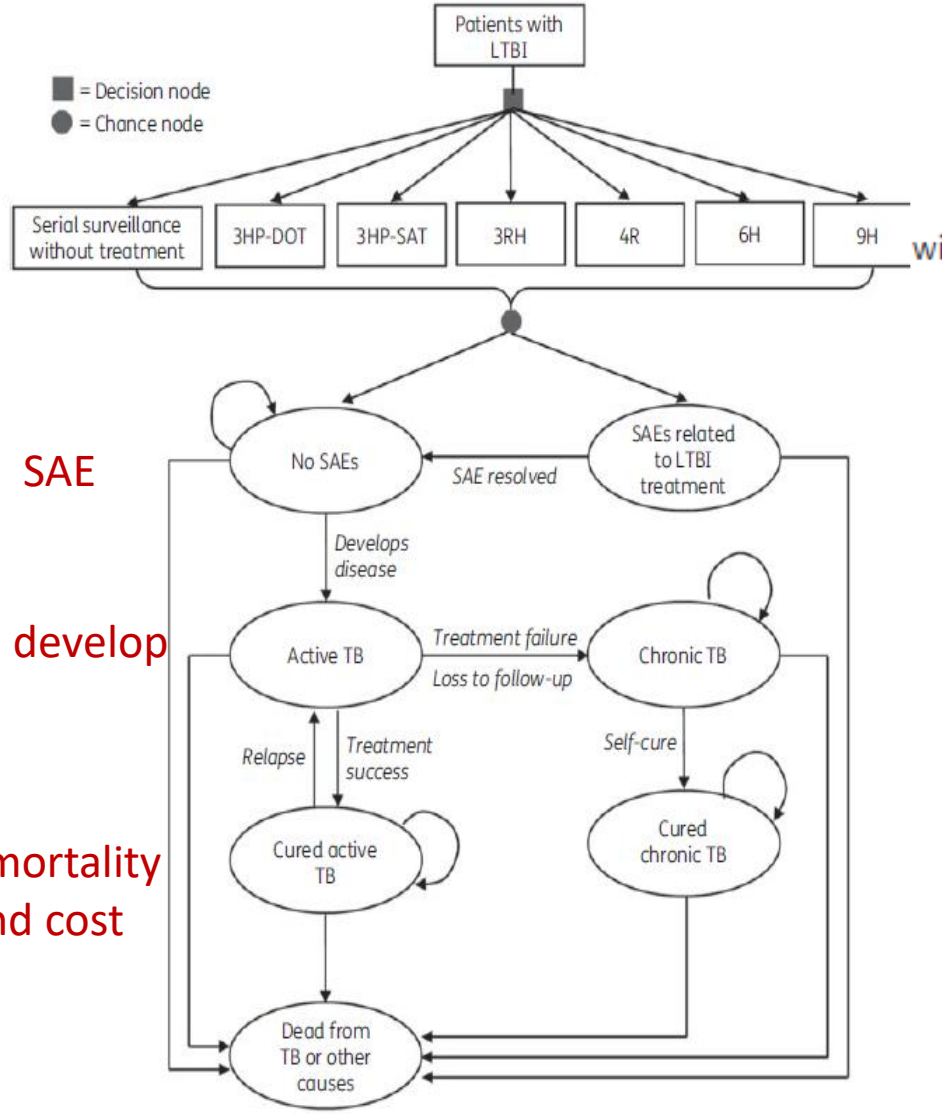
Advantages of Rifapentine-containing regimens

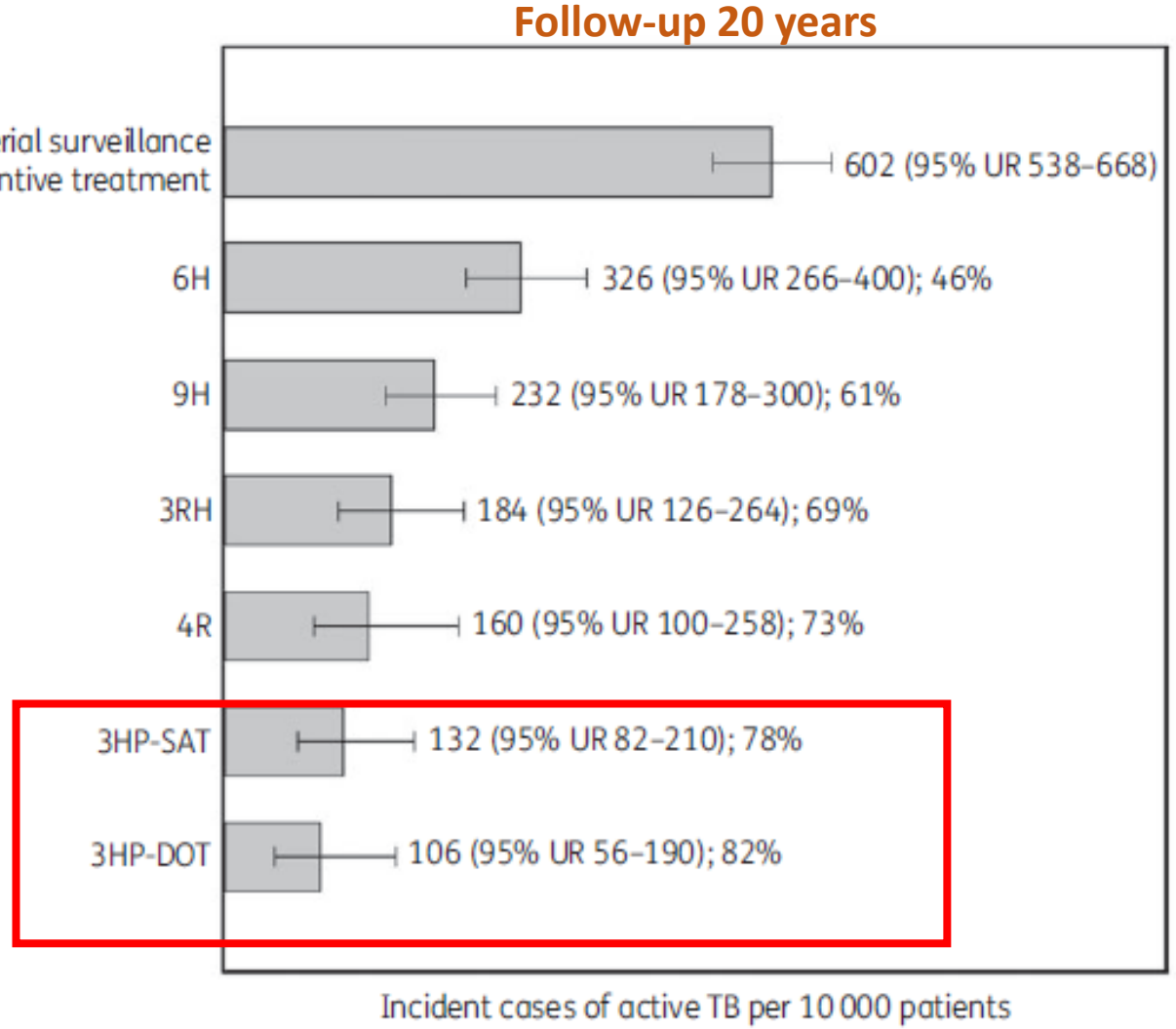
- **3HP**
  - **First in Prevent Tuberculosis Trial**
  - TB preventive efficacy is non-inferior to 9H
  - **Completion rate**: 3HP > 9H (82% vs. 69%)
  - **Discontinue due to adverse effect rate** :
    3HP > 9H （7.9% vs. 3.7%，p = 0.009）
    - 3HP ADR : SDR, flu-like syndrome
    - 9H ADR : hepatitis



Sterling TR. NEJM 2011;365:2155-66.

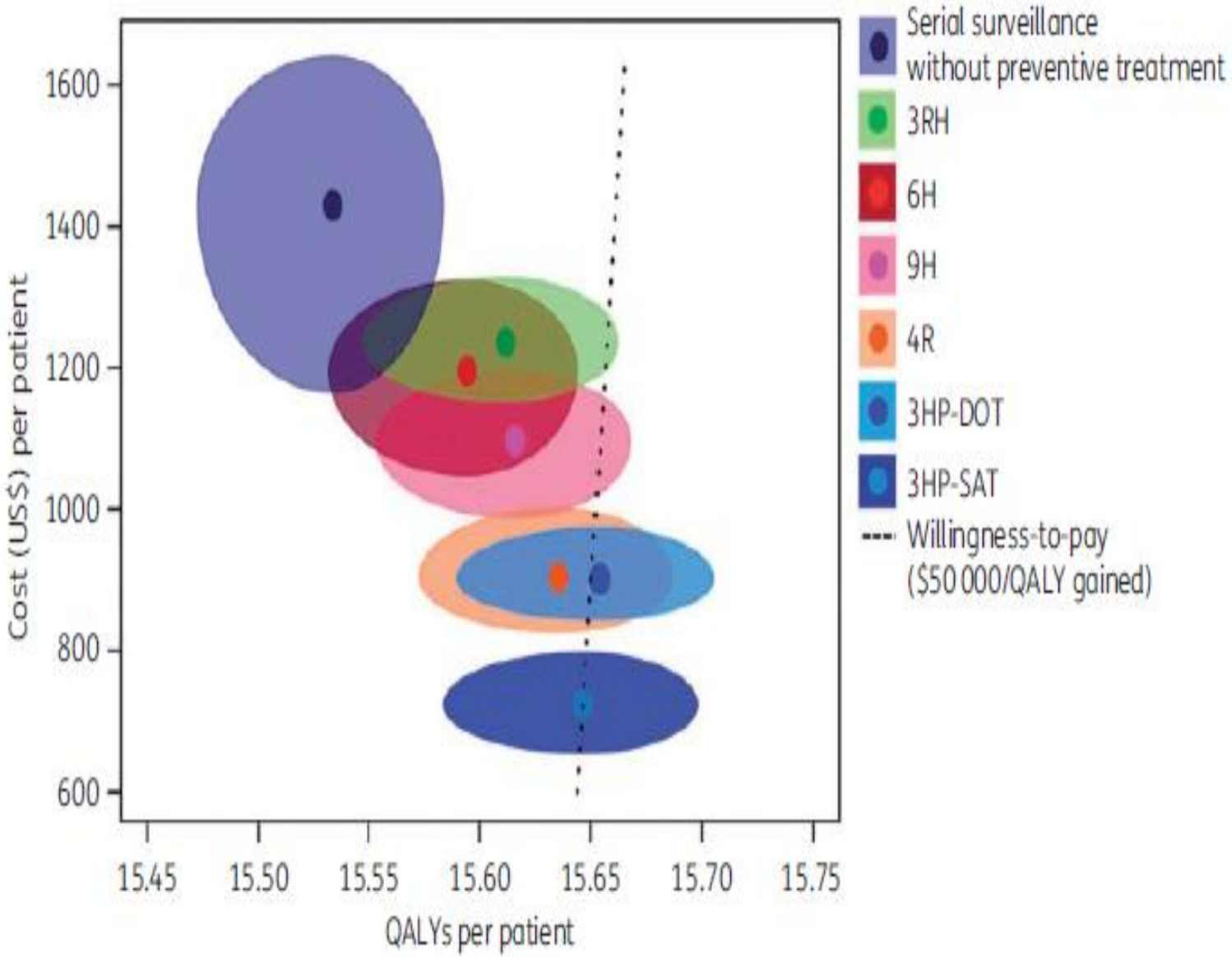
Cost-effectiveness of 3HP compared with other standard treatment regimens : A decision analysis study





J Antimicrob Chemother 2019; 74: 218–227

Cost-effectiveness plane for each of the seven simulated strategies



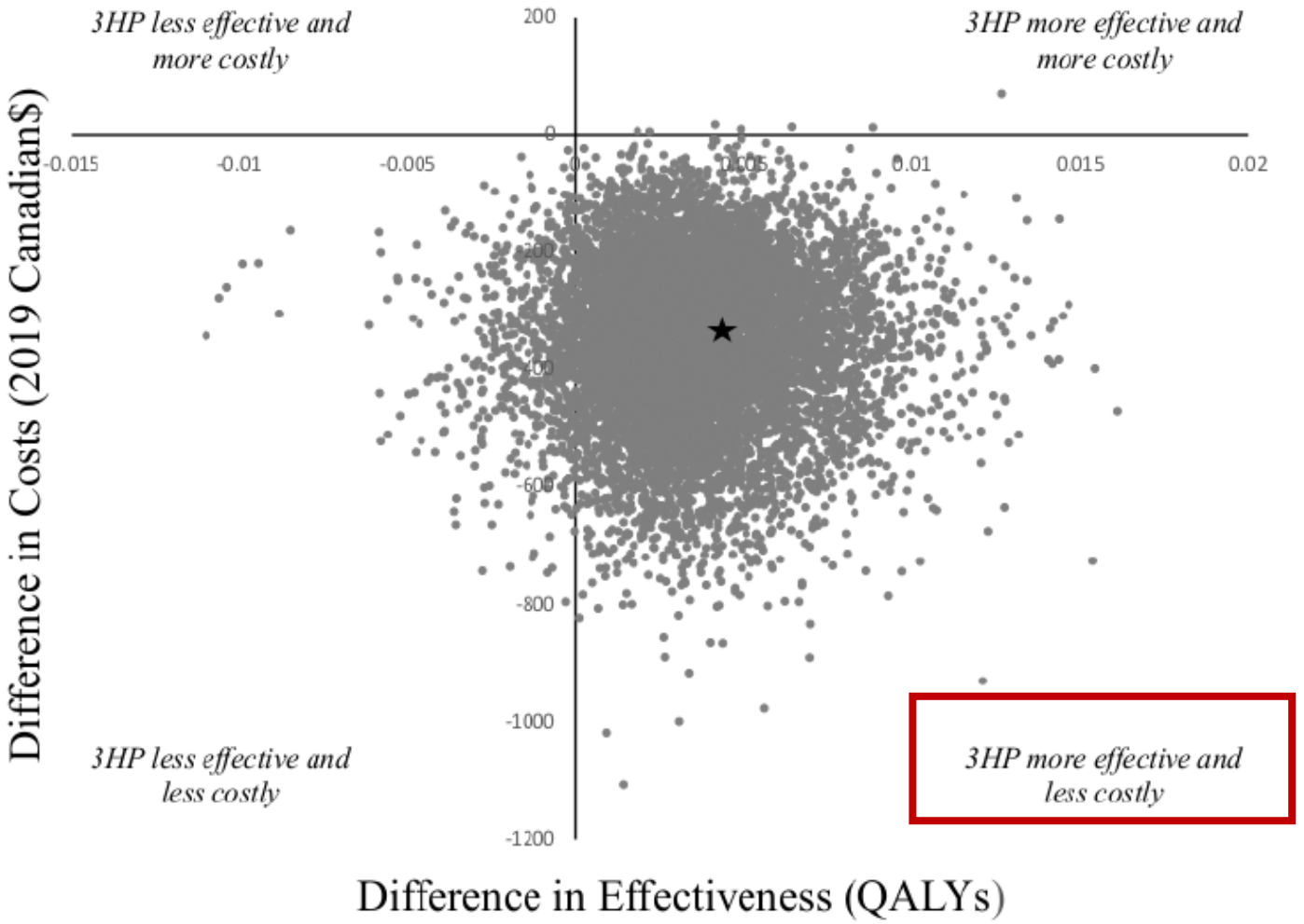
J Antimicrob Chemother 2019; 74: 218–227

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.



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

Treatment Regimens for Latent TB Infection

World Health Organization

Regimen	Dose by weight band
★ 9H — or 9 months of daily isoniazid monotherapy (6H, 9H)	Age 10 years & older: 5 mg/kg/day
★ 4R — our months of daily rifampicin (4R)	
★ 3HR — Three months of daily rifampicin us isoniazid (3HR)	Age <10 years: 15 mg/kg/day (range, 10–20 mg)

Drug dosage: 9H/4R/3HR是按照體重來計算，

- INH在兒童的劑量是成人的2倍為10mg/kg，成人則為5mg/kg，每日最大劑量INH 300mg
- RMP在兒童的劑量是成人的1.5倍為15mg/kg，成人為 10mg/kg，每日最大劑量RMP 600mg

★ 3HP — Three months of rifapentine us isoniazid eekly 2 doses) (3HP)						
	Age 2–14 years					
	Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg
	Isoniazid, 100 mg*	3	5	6	7	7
	Rifapentine, 150 mg	2	3	4	5	5
	Age >14 years					
	Medicine, formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
	Isoniazid, 300 mg	3	3	3	3	3
	Rifapentine, 150 mg	6	6	6	6	6
	* 300mg formulation can be used to reduce pill burden					

1HP — One month rifapentine us isoniazid aily (28 doses) (1HP)	Age ≥13 years (regardless of weight band) Isoniazid, 300 mg/day Rifapentine, 600 mg/day
Six months of levofloxacin daily (preventive treatment of MDR-TB)	Age >14 years, by body weight: < 46 kg, 750 mg/day; >45 kg, 1g/day Age <15 years (range, approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day; 10–15 kg: 200–300mg/day; 16–23 kg: 300–400mg/day; 24–34 kg: 500–750mg/day

Safety profile in non-HIV population is still lacking

台灣現行處方及建議劑量

處方	處方藥品	療程 頻率	劑量			使用限制	都治 DOPT
			每日最大劑量	兒童	成人		
3HP	Isoniazid (INH)	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		不適用對象: • 未滿2歲幼兒 • 指標個案INH或RMP抗藥之接觸者 • 孕婦或準備懷孕的婦女	必須
	Rifapentine (RPT)		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			
3HR	Isoniazid (INH)	90天 (3個月) 每日服用	300 mg	10 (7-15)mg/kg	5 mg/kg	指標個案INH或RMP抗藥之接觸者不適用	必須
	Rifampin (RMP)		600 mg	15 (10-20)mg/kg	10 mg/kg		
4R	Rifampin(RMP)	120天 (4個月) 每日服用	600 mg	15 (10-20) mg/kg	10 mg/kg	指標個案RMP抗藥之接觸者不適用	必須
9H	Isoniazid (INH)	270天(9個月) 每日服用	300 mg	10 (7-15) mg/kg	5 mg/kg	指標個案INH抗藥之接觸者不適用	建議

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

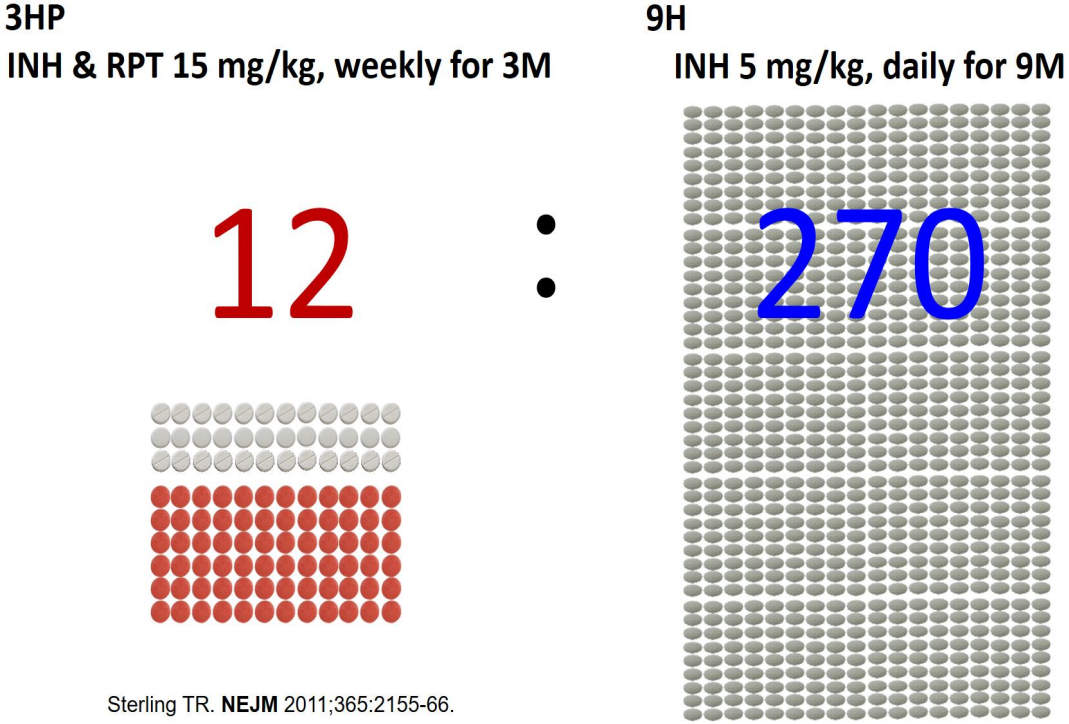
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Prevent Tuberculosis Trial : during 2001-2008, enrolled 8,053 latent TB cases, >12 y/o

- 9H : isoniazid 5 mg/kg x 270 days
- 3HP: rifapentine 15 mg/kg & isoniazid 15 mg/kg
- Modified intent-to-treat & per-protocol analysis : 3HP 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



Sterling TR. **NEJM** 2011;365:2155-66.

Sterling TR. NEJM 2011;365:2155-66.

SDRs in Prevent Tuberculosis Trial

- Systemic drug reaction accounts for the high termination rate of 3HP
  - 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% of total population
  - 3HP: 3.5% vs 9H: 0.4% (p<0.01)
- 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)

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

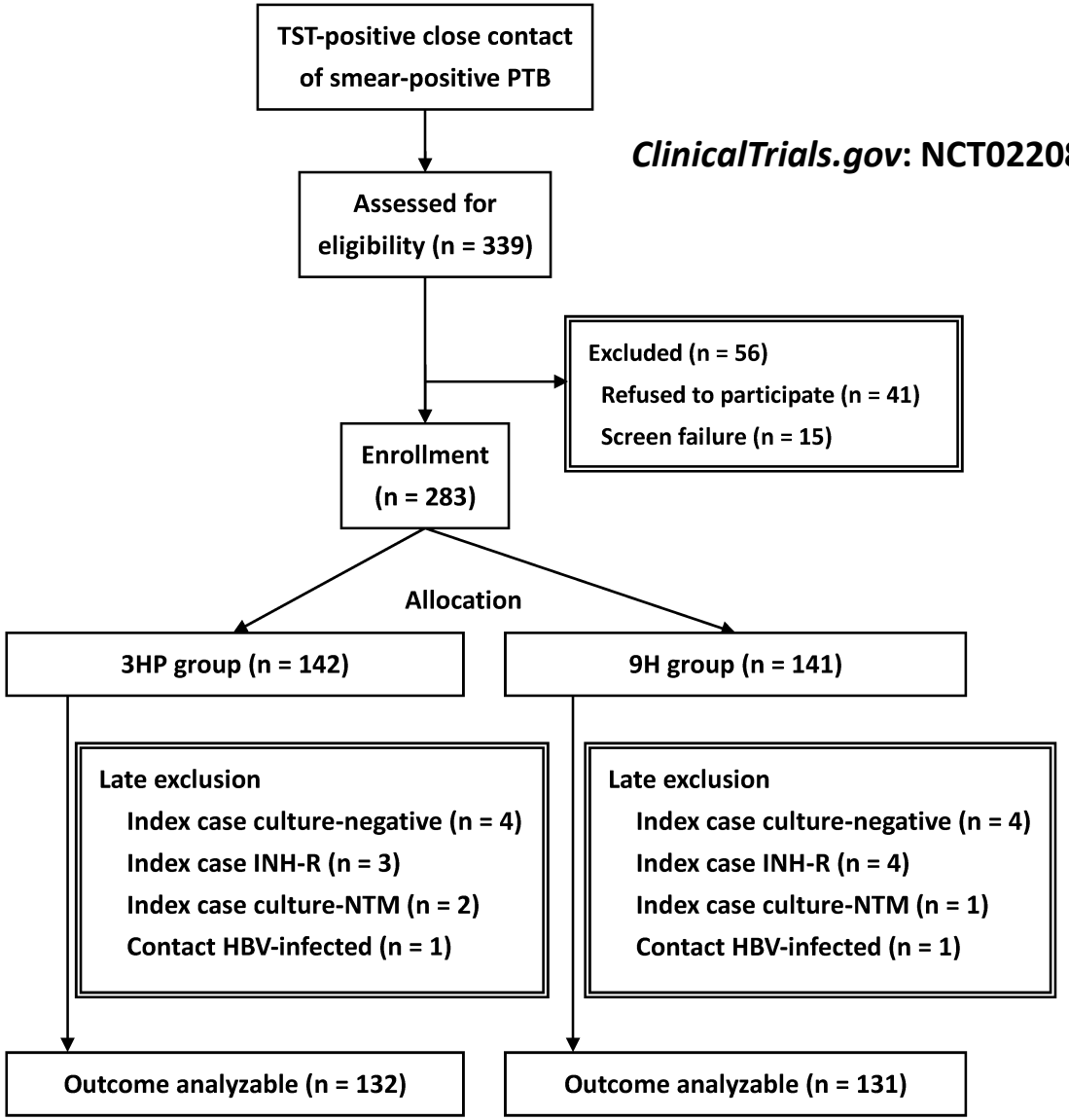
	Adjusted OR	95% CI	*P* Value
3HP vs 9H	9.4	5.5, 16.2	<.001
White-non-Hispanic race	3.3	2.3, 4.7	<.001
Female sex	2.0	1.4, 2.9	<.001
Age ≥35 y (median[a])	2.0	1.4, 2.9	<.001
Body mass index (BMI)			.009
18.5–24.9 (normal)	reference		
<18.5 (underweight)	0.9	.4, 2.2	.88
25–29.9 (overweight)	0.5	.3, .7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

3HP vs. 9H: A pilot study in Taiwan (2014)

- Multicetere, randomize controlled study
- 6 Hospitals
- Study Period: 2014 – 2018
- Primary endpoints: Completion rate
- Secondary endpoints:
  - Active TB within subsequent 2 years

Variables	3HP (n=132)	9H (n=131)
Age, mean ± SD, years	31.7 ± 15.0	32.0 ± 16.4
Men, n (%)	81 (61.4)	71 (54.2)
BMI, mean ± SD	23.3 ± 4.0	22.8 ± 4.1
Current smoking, n (%)	13 (9.8)	16 (12.2)
Household contact, n (%)	66 (50.0)	60 (45.8)



ClinicalTrials.gov: NCT02208427

Sun HY. Tuberculosis 2018;111:121-6.

Conclusions on 3HP vs. 9H in Asian Population

3HP had …..

1. Higher completion rate: 89.4% *vs.* 77.9%
2. Less hepatotoxicity: 1.5% *vs.* 5.4%
3. More Gr.2 non-hepatitis ADR: 12.9% *vs.* 3.8%
4. More flu-like symptoms: 40.9% *vs.* 16.8%
5. Sometimes systemic drug reaction: 3.8%
6. Usually transient and Gr. 1: 69.1%
7. 3HP related SDRs occured more in age ≥ 35, female

Variables, n (%)	Men (n=81)	Women (n=51)
Fatigue	3 (3.7)	2 (3.9)
Dizziness	4 (4.9)	1 (2.0)
Nausea	1 (1.2)	2 (3.9)
Vomiting	3 (3.7)	4 (7.8)
Fever*	1 (1.2)	7 (13.7)
Chills#	1 (1.2)	4 (7.8)
Hot flushes	0 (0)	0 (0)
Headache	2 (2.5)	2 (3.9)
Myalgia	1 (1.2)	2 (3.9)
Cutaneous reaction#	1 (1.2)	4 (7.8)
Diarrhea	0 (0)	1 (2.0)

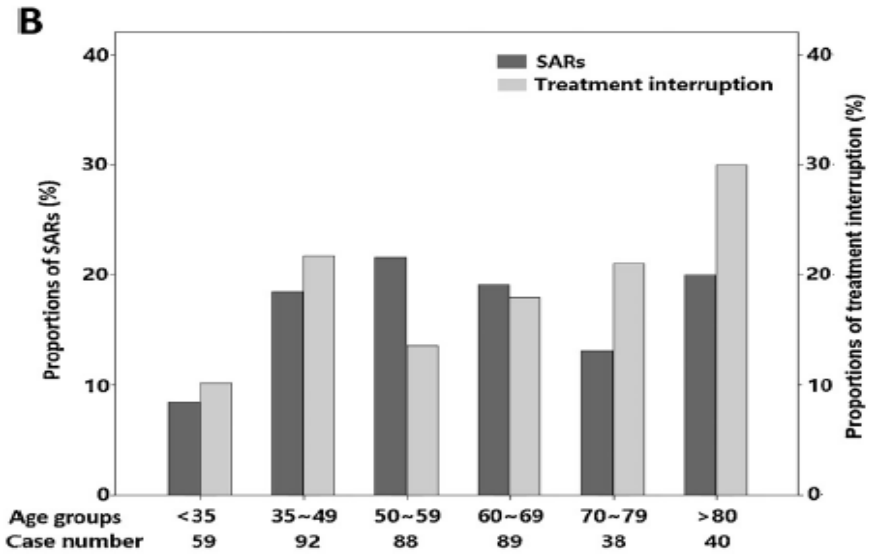
Sun HY. Tuberculosis 2018;111:121-6.

Extend 3HP use in all-aged and high-risk population: Taiwan-1

- A multicenter prospective observational study
- 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

	Overall	Age		*p*-Value
		≥60 years	<60 years	
Number of patients	406	167	239	
Occurrence of SARs	66 (16.3%)	30 (18%)	36 (15.1%)	0.436
SAR types				
Gastrointestinal reaction				
Abdominal pain	5 (1.2%)	1 (0.6%)	4 (1.7%)	0.653
Nausea/vomiting	17 (4.2%)	8 (4.8%)	9 (3.8%)	0.612
Anorexia	11 (2.7%)	5 (3%)	6 (2.5%)	0.768
Flu-like symptoms				
Fatigue	26 (6.4%)	12 (7.2%)	14 (5.9%)	0.591
Dizziness	21 (5.2%)	10 (6%)	11 (4.6%)	0.535
Headache	15 (3.7%)	6 (3.6%)	9 (3.8%)	0.928
Fever	14 (3.4%)	4 (2.4%)	10 (4.2%)	0.331
Myalgia/arthralgia	16 (3.9%)	5 (3%)	11 (4.6%)	0.412
Hypersensitivity reaction	8 (2.0%)	4 (2.4%)	4 (1.7%)	0.607
Other drug reactions	2 (0.5%)	0	2 (0.8%)	0.515
Elevated liver enzymes[b]				
Any	39 (9.6%)	11 (6.6%)	28 (11.7%)	0.084
1–3 × ULN	31 (7.6%)	11 (6.6%)	20 (8.4%)	
3–5 × ULN	6 (1.5%)	0	6 (2.5%)	
>5 × ULN	2 (0.5%)	0	2 (0.8%)	
Jaundice[c]				
Any	10 (2.5%)	5 (3%)	5 (2.1%)	0.564
1.5–3 mg/dl	8 (2%)	3 (1.8%)	5 (2.1%)	
>3 mg/dl	2 (0.5%)	2 (1.2%)	0	
Hepatotoxicity[d]	5 (1.2%)	1 (0.6%)	4 (1.7%)	0.334

	Overall	All patients	
		≥60 years	<60 years
Number of patients	406	167	239
Treatment status			
Completed	332 (81.8%)	131 (78.4%)	201 (84.1%)
Discontinuation	74 (18.2%)	36 (21.6%)	38 (15.9%)
SARs	27 (36.5%)	15 (41.7%)	12 (31.6%)
Mild adverse reactions	10 (13.5%)	4 (11.1%)	6 (15.8%)
Hepatotoxicity	5 (6.8%)	1 (2.8%)	4 (10.5%)
Patient refusal	16 (21.6%)	8 (22.2%)	8 (21.1%)
Others	16 (21.6%)	8 (22.2%)	8 (21.1%)



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

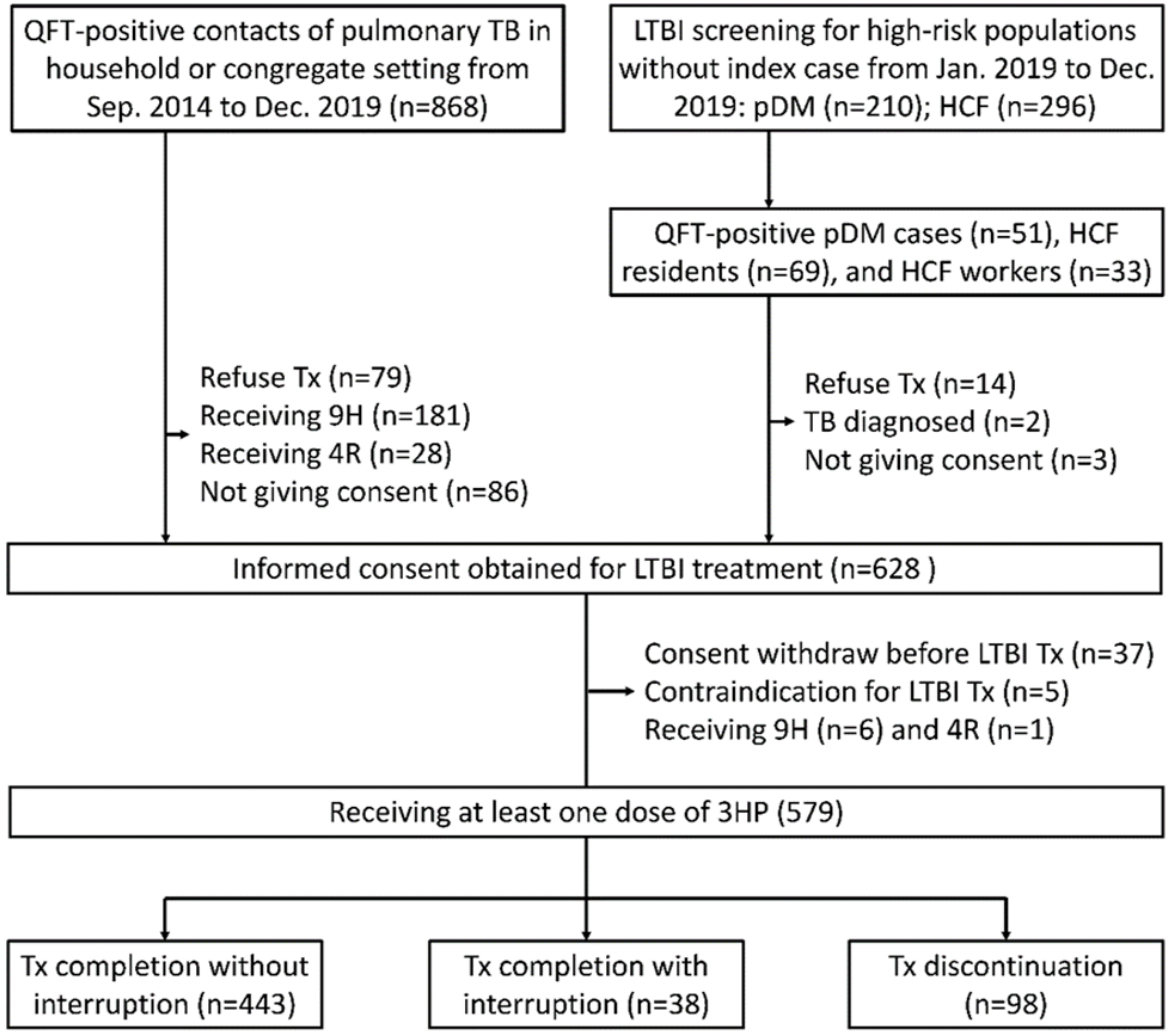
Independent clinical factors associated SARs

	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

Extend 3HP use in all-aged and high-risk population: Taiwan-2

- A Prospective, multicenter Study
- IGRA positive and receive ≥1 3HP dose under DOT
  - Close contact to pulmonary TB
  - High risk population
    - Long term care facility residents/workers
    - Poorly diabetic controlled patients
- Age stratified:
  - younger group (≤35 years),
  - middle-aged group (35-65 years)
  - elderly group (≥65 years, 23.1%)
- Programmatic ADR follow-up and management
- Endpoint: Treatment completion rate and risk of SDR in different age groups



Course and outcome on 3HP treatment in age groups

	Age ≤ 35 (n=165)	Age 35 ~ 65 (n=280)	Age ≥ 65 (n=134)
Complete treatment	156 (94.5%)*	226 (80.7%)	99 (73.9%)
No ADRs	58 (35.2%)	101 (36.1%)	58 (43.3%)
Presence of ADR without Tx interruption	86 (52.1%)*	106 (37.9%)	34 (25.4%)
Presence of ADR with Tx interruption	12 (7.3%)	19 (6.8%)	7 (5.2%)
Permanent discontinuation	9 (5.5%)	54 (19.3%)	35 (26.1%)*
No of doses before discontinuation	4.3 ± 2.3	4.4 ± 2.1	4.2 ± 2.4
Cause of discontinuation			
SDR	4 (2.4%)	27 (9.6%)*	6 (4.5%)
Hepatotoxicity	0 (0%)	12 (4.3%)	6 (4.5%)*
ADRs except SDR/hepatotoxicity	5 (3.0%)	10 (3.6%)	14 (10.4%)*
Withdraw consent	0 (0%)	5 (1.8%)	4 (3.0%)
Tuberculosis confirmed	0 (0%)	0 (0%)	2 (1.5%)*
Other reasons	0 (0%)	1 (0.4%)	2 (1.5%)

- Overall completion rate: 83.1%
- The young-age group had highest completion rate, the elder-age group had the lowest
- SDR accounts for the highest permanent discontinuation rate in middle-age group
- Uncontrolled hypertension accounts for >50% of discontinuation rate among elders

Clinical Infectious Diseases, ciaa1741

Details of 3HP related drug adverse reactions

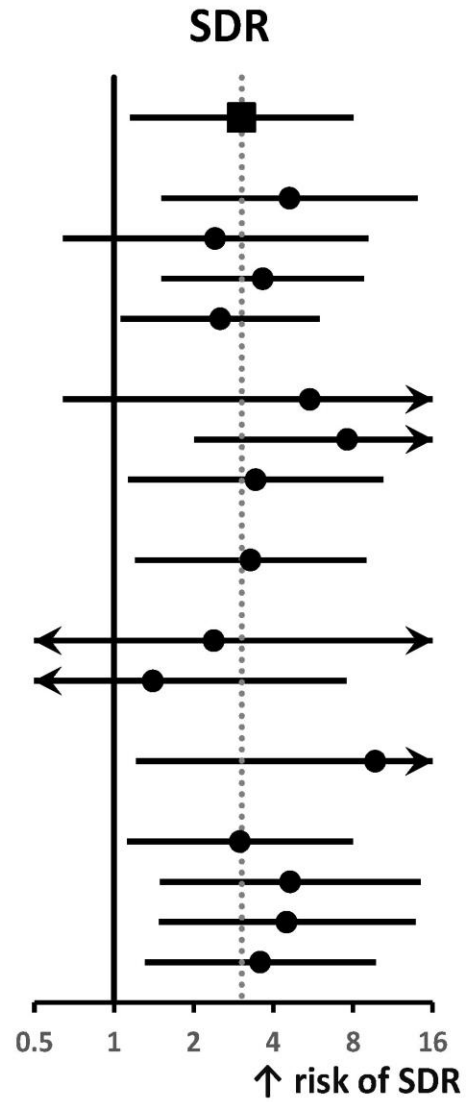
	Age < 35 (n=165)	Age 35 ~ 65 (n=280)	Age ≥ 65 (n=134)
SDR	8 (4.8%)	48 (17.1%)*	9 (6.7%)
Flu-like syndrome	6 (3.6%)	34 (12.1%)*	7 (5.2%)
Hypotension	2 (1.2%)	7 (2.5%)	1 (0.7%)
Urticaria	0 (0%)	6 (2.1%)*	0 (0%)
Conjunctivitis	0 (0%)	3 (1.1%)	1 (0.7%)
Hepatotoxicity	6 (3.6%)	19 (6.8%)	7 (5.2%)
ADR except 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%)

- 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

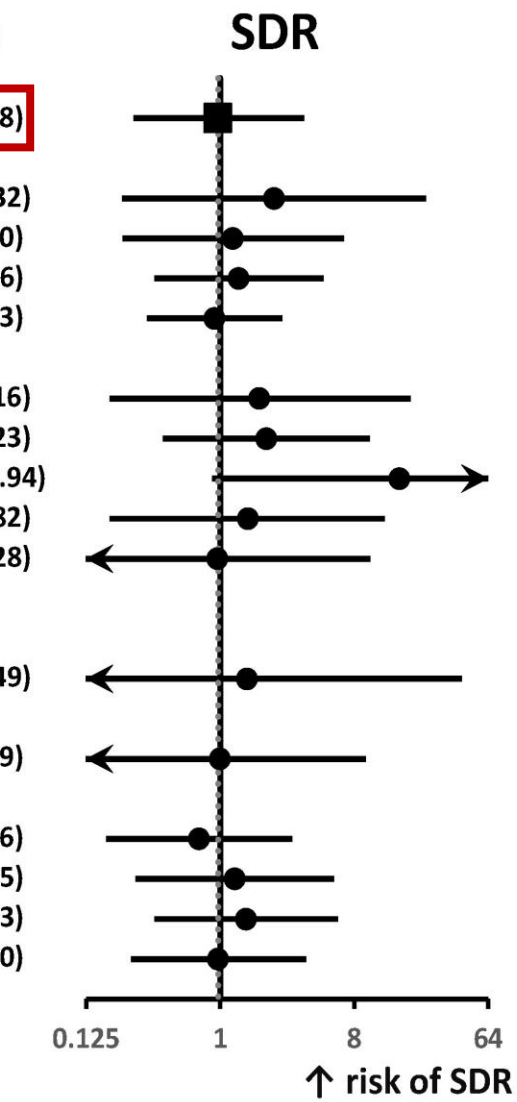
Clinical Infectious Diseases, ciaa1741

- Compare to elder group, middle-age was significantly associated with increased SDR risk during 3HP even in most clinical settings
- The risk of SDR was not different between the elderly and younger groups

Middle-age vs. Elder	aOR (95% CI)
Overall	3.04 (1.15 - 8.03)
Male	4.60 (1.51 - 14.01)*
Women	2.41 (0.64 - 9.14)
Normal BMI	3.64 (1.51 - 8.78)*
Never smoker	2.52 (1.06 - 5.98)
Comorbidity	
None	5.49 (0.64 - 46.84)
Without CKD	7.61 (2.01 - 28.75)*
Hypertension	3.43 (1.13 - 10.43)
DM	
At least one	3.28 (1.20 - 8.97)*
Exposure setting	
Household	2.38 (0.35 - 16.40)
High-risk (no index)	1.40 (0.26 - 7.57)
Exposure intensity	
Same house	9.70 (1.21 - 78.03)
Lab data	
QFT Response >1 IU/mL	2.99 (1.12 - 8.01)
Hb >12	4.63 (1.49 - 14.42)*
WBC 5000-9000	4.49 (1.48 - 13.77)*
Platelet >140K	3.57 (1.31 - 9.75)*



Younger vs. Elder	aOR (95% CI)
Overall	0.97 (0.26 - 3.68)
Male	2.31 (0.22 - 24.32)
Women	1.22 (0.22 - 6.80)
Normal BMI	1.34 (0.36 - 4.96)
Never smoker	0.92 (0.32 - 2.63)
Comorbidity	
None	1.84 (0.18 - 19.16)
Without CKD	2.05 (0.41 - 10.23)
Hypertension	16.20 (0.88 - 298.94)
DM	1.54 (0.18 - 12.82)
At least one	0.96 (0.09 - 10.28)
Exposure setting	
Household	
High-risk (no index)	1.52 (0.05 - 42.49)
Exposure intensity	
Same house	1.00 (0.10 - 9.59)
Lab data	
QFT Response >1 IU/mL	0.72 (0.17 - 3.06)
Hb >12	1.26 (0.27 - 5.85)
WBC 5000-9000	1.50 (0.36 - 6.23)
Platelet >140K	0.97 (0.25 - 3.80)



Clinical Infectious Diseases, ciaa1741

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

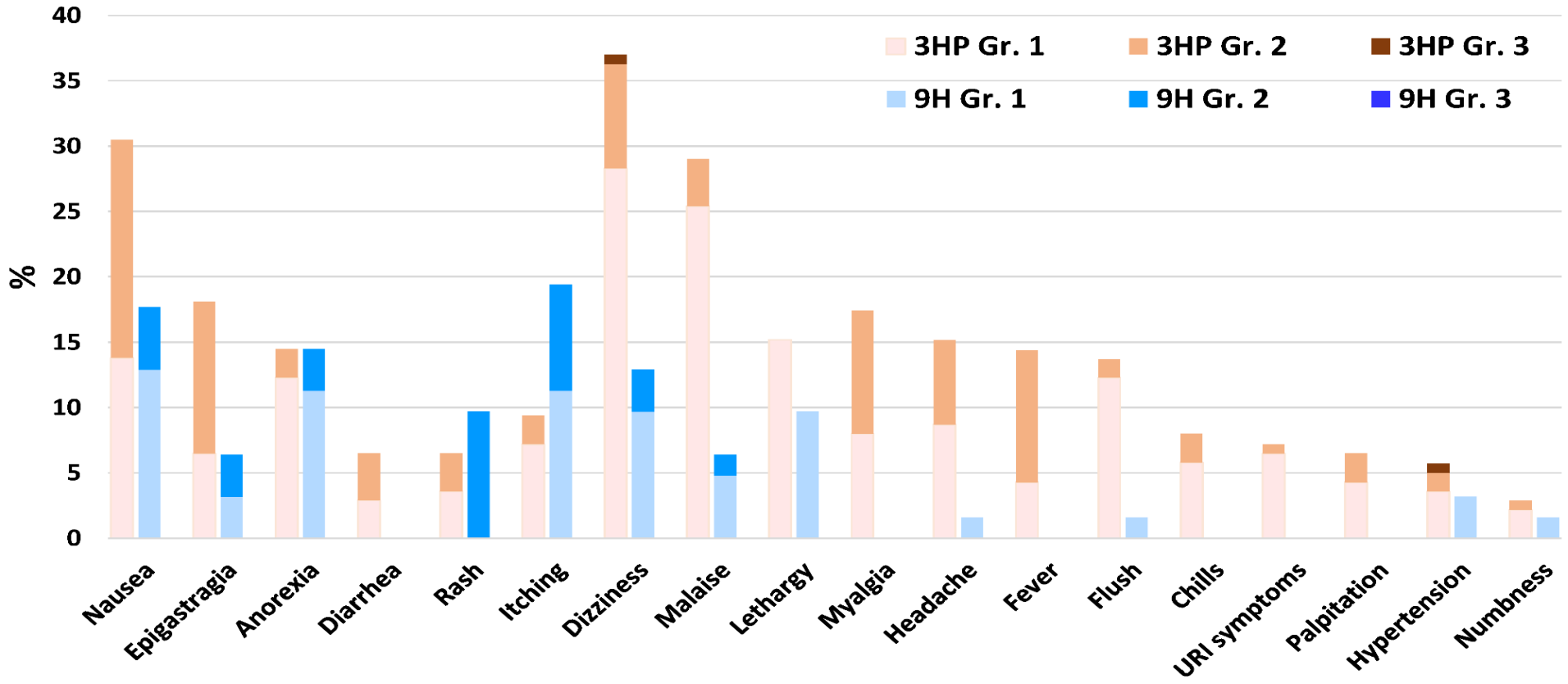
- Prospective, multicenter study. April 2018 to June 2020
  - Taichung Veterans General Hospital
  - Kaohsiung Maniple Ta-Tung Hospital
- **200 cases**
  - Age ≥ 45 years
  - ≥1 time HbA1c ≥9.0% within recent 1 year
- **LTBI screening performed by endocrinologist**
  - Pay-for-Performance project
  - 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

	Total (n=200)	3HP (n=138)	9H (n=62)	*p*-value
Complete treatment	165 (82.5%)	116 (84.1%)	49 (79.0%)	0.494
No adverse drug reactions	59 (29.5%)	30 (21.7%)	29 (46.8%)	<0.001
Permanent discontinuation	35 (17.5%)	22 (15.9%)	13 (21.0%)	0.494
Dose received		5.0 ± 2.7	56.7 ± 40.8	
Cause of discontinuation				
Adverse Drug Reaction	28 (14.0%)	20 (14.5%)	8 (12.9%)	0.764
Systemic drug reaction	6 (3.0%)	6 (4.3%)	0	0.223
Hypotension	1 (0.5%)	1 (0.7%)	0	0.680
Flu-like syndrome	5 (2.5%)	5 (3.6%)[a]	0	0.301
Urticaria	1 (0.5%)	1 (0.7%)	0	0.680
Hepatotoxicity	4 (2.0%)	2 (1.4%)	2 (3.2%)	0.776
Other adverse drug reactions	18 (9.0%)	12 (8.7%)	6 (9.7%)	0.822
Patient refusal	5 (2.5%)	2 (1.4%)	3 (4.8%)	0.352
Other reasons	2 (1.0%)	0	2 (3.2%)[b]	0.176

Clinical Infectious Diseases, ciab209, https://doi.org/10.1093/cid/ciab209

Safety Profile

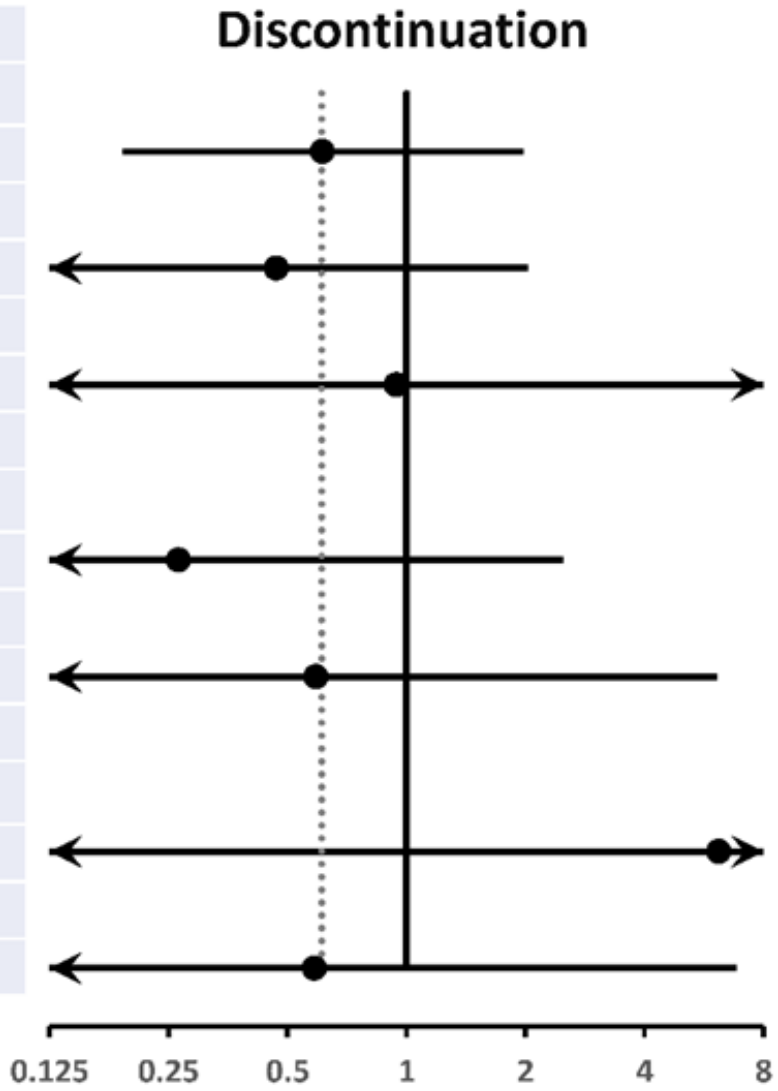
- 3HP group had higher proportion of flu-like symptoms and GI symptoms
- 9H group had higher proportion of skin rash



Clinical Infectious Diseases, ciab209, https://doi.org/10.1093/cid/ciab209

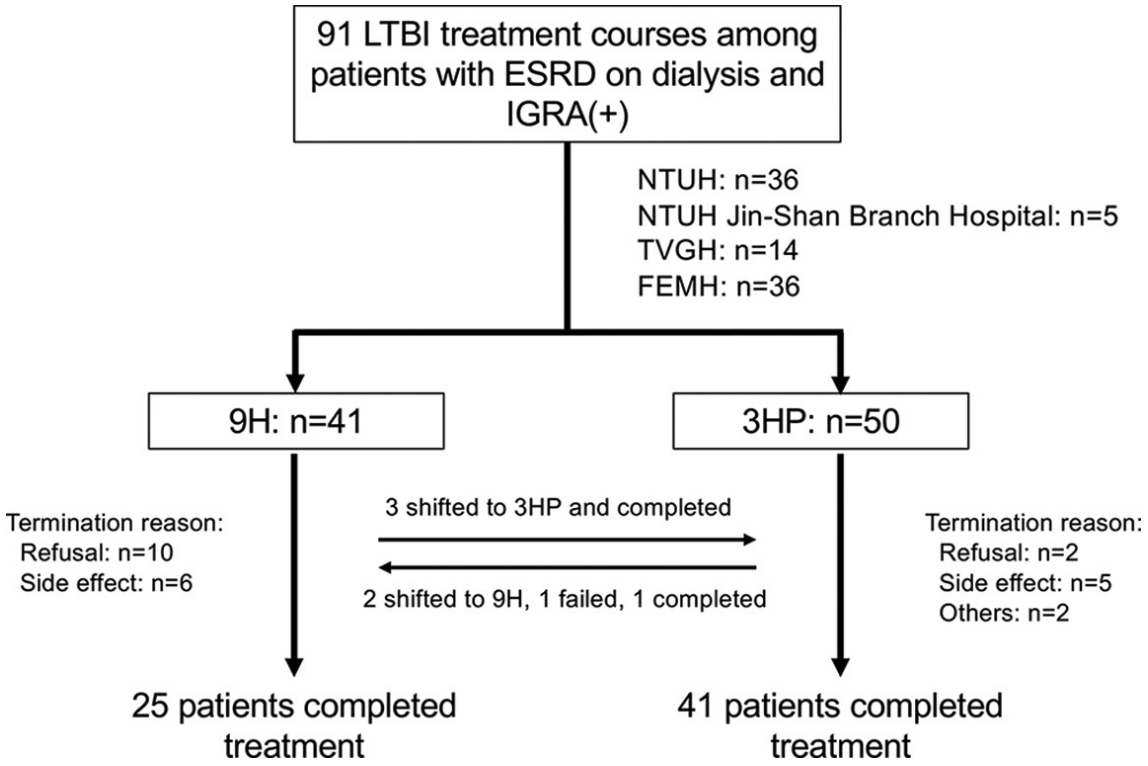
The completion rate is independent from regimen under decision sharing and multidiscipline setting

3HP vs. 9H	aOR (95% CI)	*p* value
Overall	0.61 (0.19 - 1.97)	0.411
Age ≥65	0.47 (0.11 - 2.03)	0.310
Age <65	0.94 (0.01 - 136)	0.981
Female	0.27 (0.03 - 2.50)	0.246
Male	0.59 (0.06 - 6.12)	0.659
Cases with Gr. ≥2 ADR	6.17 (0.01 - 4564)	0.590
Cases with Gr. 1 ADR	0.59 (0.05 - 6.85)	0.670



Clinical Infectious Diseases, ciab209, https://doi.org/10.1093/cid/ciab209

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



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

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

Outcome of 3HP Tx in different Taiwan cohorts

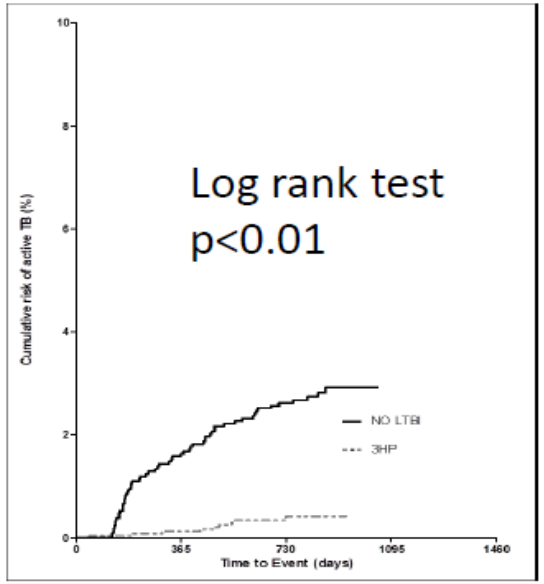
	LTBI contacts (n=101)	LTBI contacts (n=132)	LTBI contacts ≥50Y (n=2348)	RA with LTBI (n=21)	Hemodialysis with LTBI (n=26)
Study design	Cohort study	Randomized Cohort study	Registry database	Cohort study	Cohort study
Reference	Huang YW. ***Medicine*** 2016;95:34	Sun HY. ***Tuberculosis*** 2018;111:121	Chan PC. ***ERJ*** 2019;53:1802396	Chen YM. ***ARD*** 2018;77:1688	Lin SY. ***JMII*** 2019;52:158
Male	43.6%	61.4%	48.1%	6 (29%)	18 (69%)
Age	34.9	31.7 ± 15.0	87.5%(age <75)	62.1 ± 14.9	63.8 ± 12.2
Tx completed	97.0%	89.4%	83.9%	90%	65%
Permanent stop					
Any AE	3.0%	9.1%	12.0%	10%	35%
Hepatotoxicity	0%	1.5%	0.8%	0 (0%)	0 (0%)

從 2020 年起，鑒於 3HP 仍有一定比例民眾無法耐 受，以及各國及世界衛生組織推薦 3HR 及 4R 處方，故擴大 3HR 及 4R 予全年齡層接觸者使用，增加 LTBI 處方的選擇。

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)

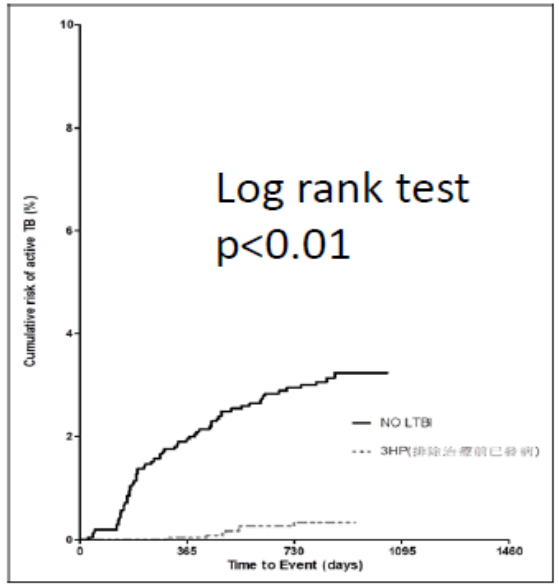
	發生率 (人年)	RR	95%CI		發生率 (人年)	RR	95%CI
3HP	**0.18**	0.13	(0.07-0.27)	3HP	**0.18**	0.64	(0.27-1.52)
未曾接受治療	**1.35**			9H	**0.28**		

LTBI 接觸者接受治療的保護力約87%



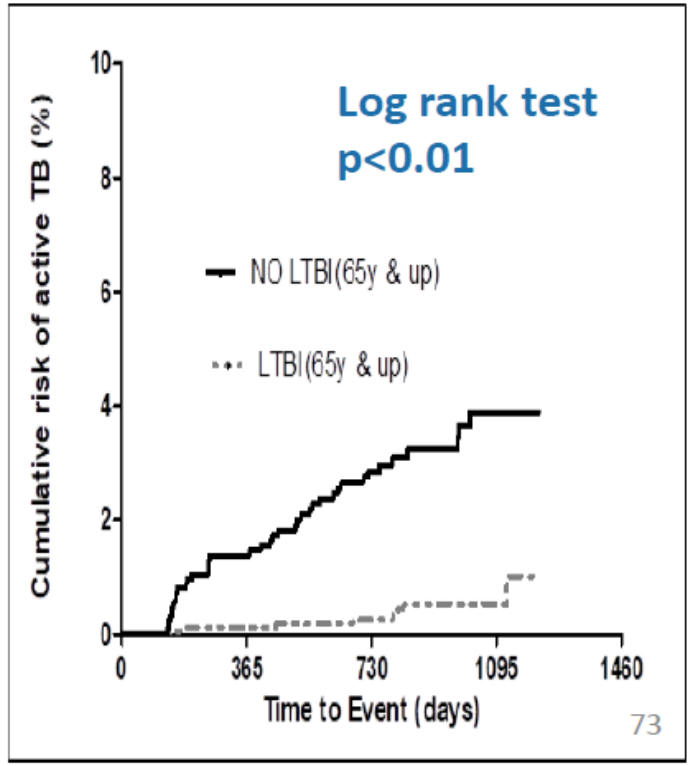
3HP vs. 未治療

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%



Higher completion rate and less ADRs of 4R than 9H

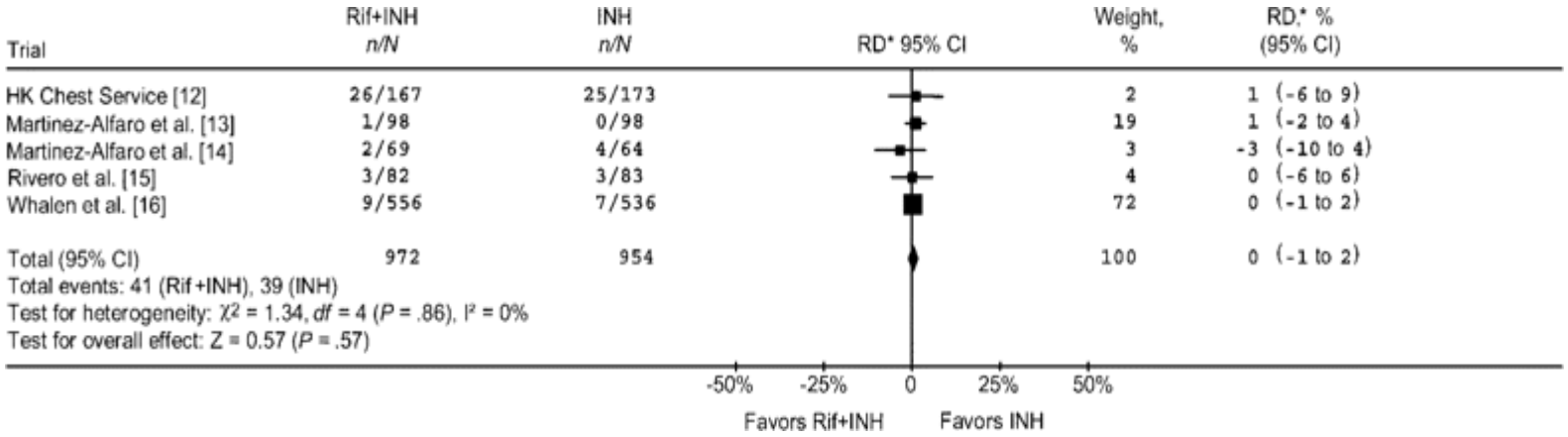
Table 2. Completion of Treatment in the Phase 3 Trial (Modified Intention-to-Treat Population).*

Variable	Isoniazid (N = 2989)	Rifampin (N = 3023)	Difference (95% CI)	P Value
			percentage points	
Treatment completed — no. (%)†	1890 (63.2)	2382 (78.8)	15.1 (12.7–17.4)	<0.001
Within allowed time	1727 (57.8)	2136 (70.7)	12.1 (9.6–14.6)	<0.001
Not within time allowed by protocol	163 (5.5)	246 (8.1)	2.8	
Treatment not completed for any reason — no. (%)‡	1099 (36.8)	641 (21.2)	−15.1	
Death during treatment period deemed to be not related to therapy	3 (0.1)	0	−0.1	
Diagnosis of active tuberculosis during treatment period	1 (<0.1)	1 (<0.1)	<0.1	
Never started therapy, by participant's decision	180 (6.0)	136 (4.5)	−2.6	
Therapy stopped permanently for event, and participant had not already completed treatment				
Grade 1–4 event	143 (4.8)	68 (2.2)	−2.6	
Grade 3 or 4 event	90 (3.0)	37 (1.2)	−1.8	
Therapy started, but participant decided to stop treatment§	772 (25.8)	436 (14.4)	−11.4	
Received 50–79% of doses	188 (6.3)	142 (4.7)	−1.7	
Received 1–49% of doses	585 (19.6)	295 (9.8)	−9.6	
Median no. of doses taken by participants who did not complete treatment but received ≥1 dose (interquartile range)	84 (33–122)	30 (22–60)	—	

N Engl J Med. 2018 Aug 2;379(5):440-453

Preventive efficacy and risk of ADRs of 3HR is non-inferior to INH monotherapy (6-12M)

- From meta-analysis of 5 RCTs, similar risk of active tuberculosis development



- Similar risk of severe side effects requiring drug discontinuation

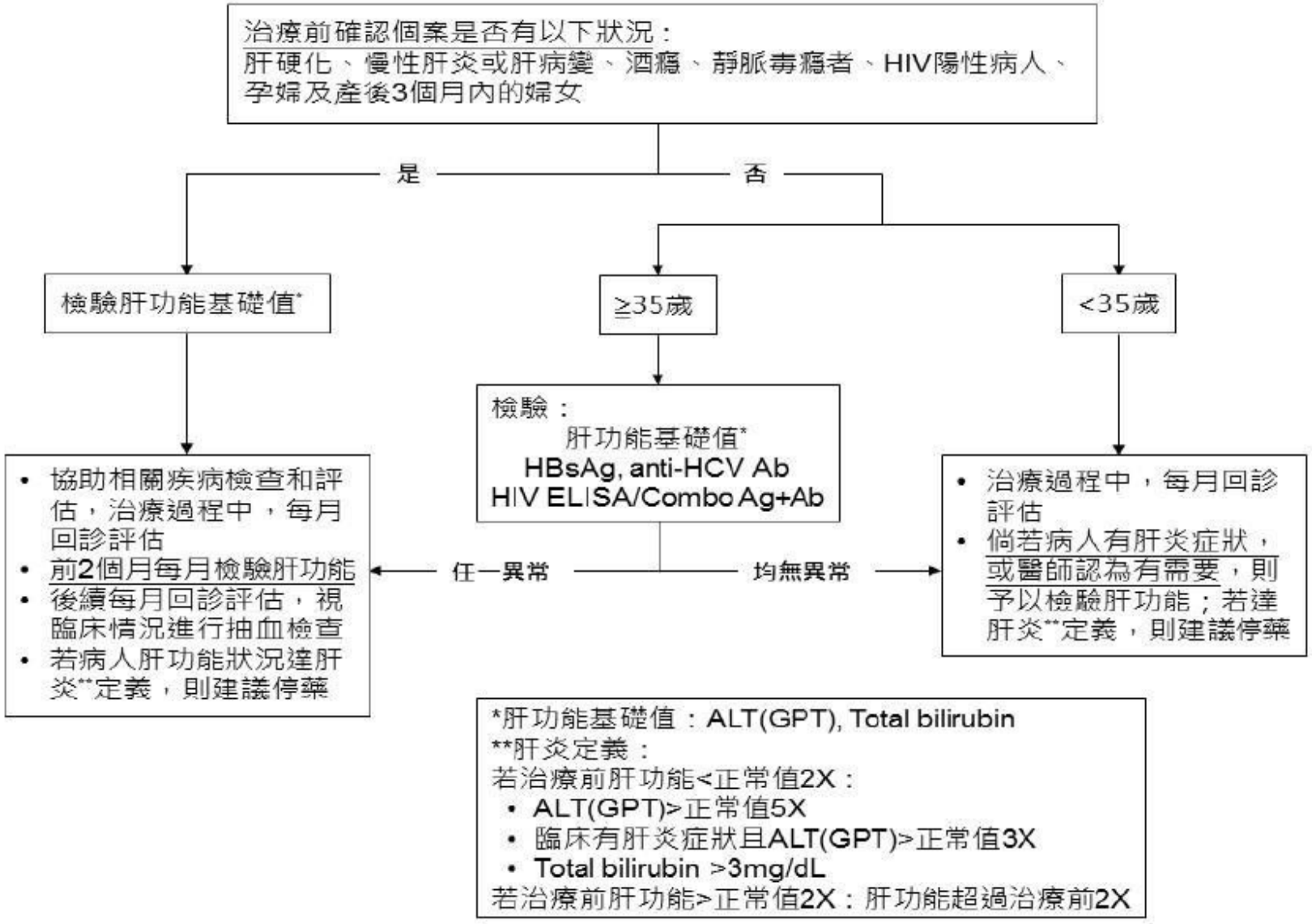
Trial [reference]	Hepatotoxicity		Rash		Gastrointestinal intolerance		Other		Not specified		Total	
	Rif + INH	INH	Rif + INH	INH	Rif + INH	INH	Rif + INH	INH	Rif + INH	INH	Rif + INH	INH
Hong Kong Chest Service [12]	…	…	…	…	…	…	…	…	8 (5)	13 (8)	8 (5)	13 (8)
Martinez-Alfaro et al. [13]	6 (6)	8 (8)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	7 (10)	9 (13)
Martinez-Alfaro et al. [14]	4 (6)	11 (18)	…	…	…	…	…	…	1 (1)	4 (6)	5 (7)	15 (24)
Rivero et al. [15]	1 (1)	4 (5)	7 (8)	1 (1)	5 (6)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)	15 (18)	6 (7)
Whalen et al. [16]	…	…	…	…	…	…	…	…	13 (2)	3 (1)	13 (2)	3 (1)

NOTE. Data are the no. (%) of patients who required drug discontinuation because of a severe side effect. INH, isoniazid; Rif, rifampin.

Clin Infect Dis. 2005 Mar 1;40(5):670-6

Monitor and Management of ADRs

- Hepatitis: Baseline and regular follow-up hepatic function (GOT/GPT/Bil), HBV, HCV

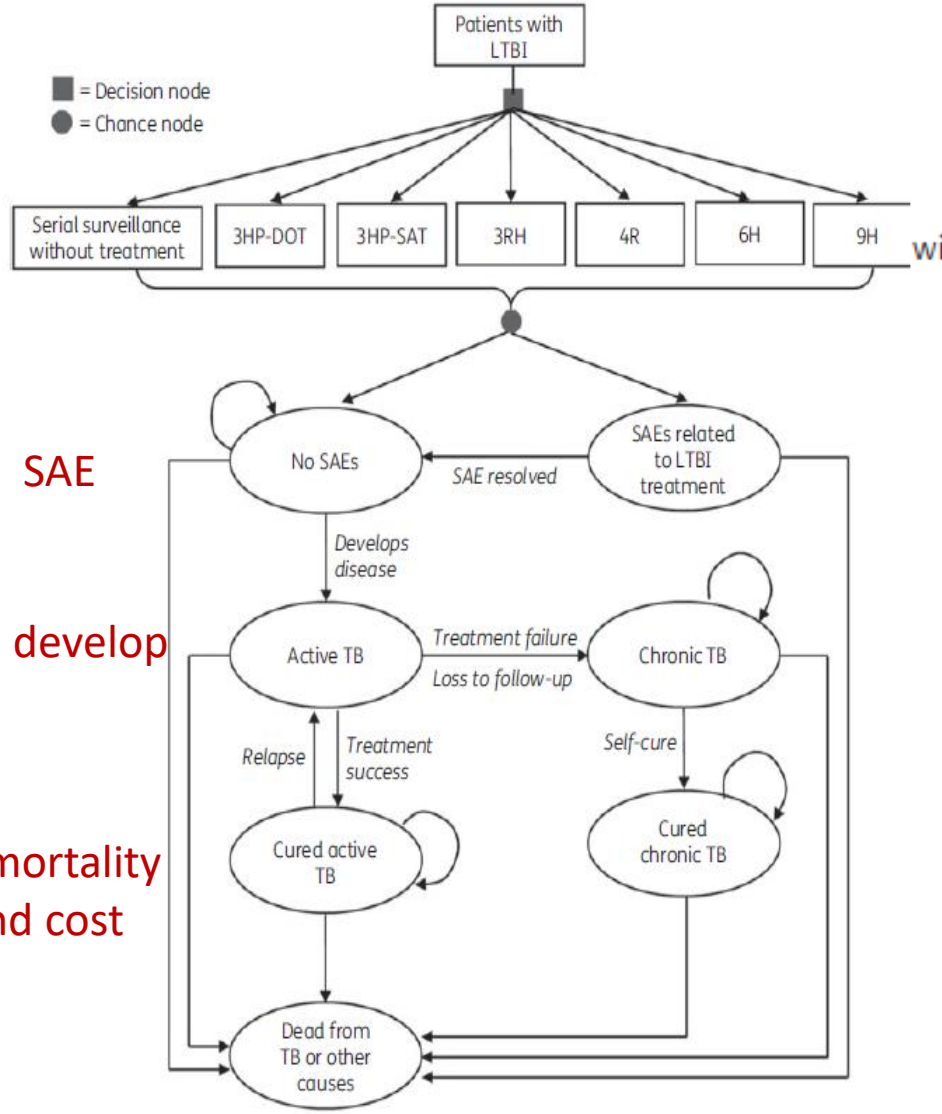


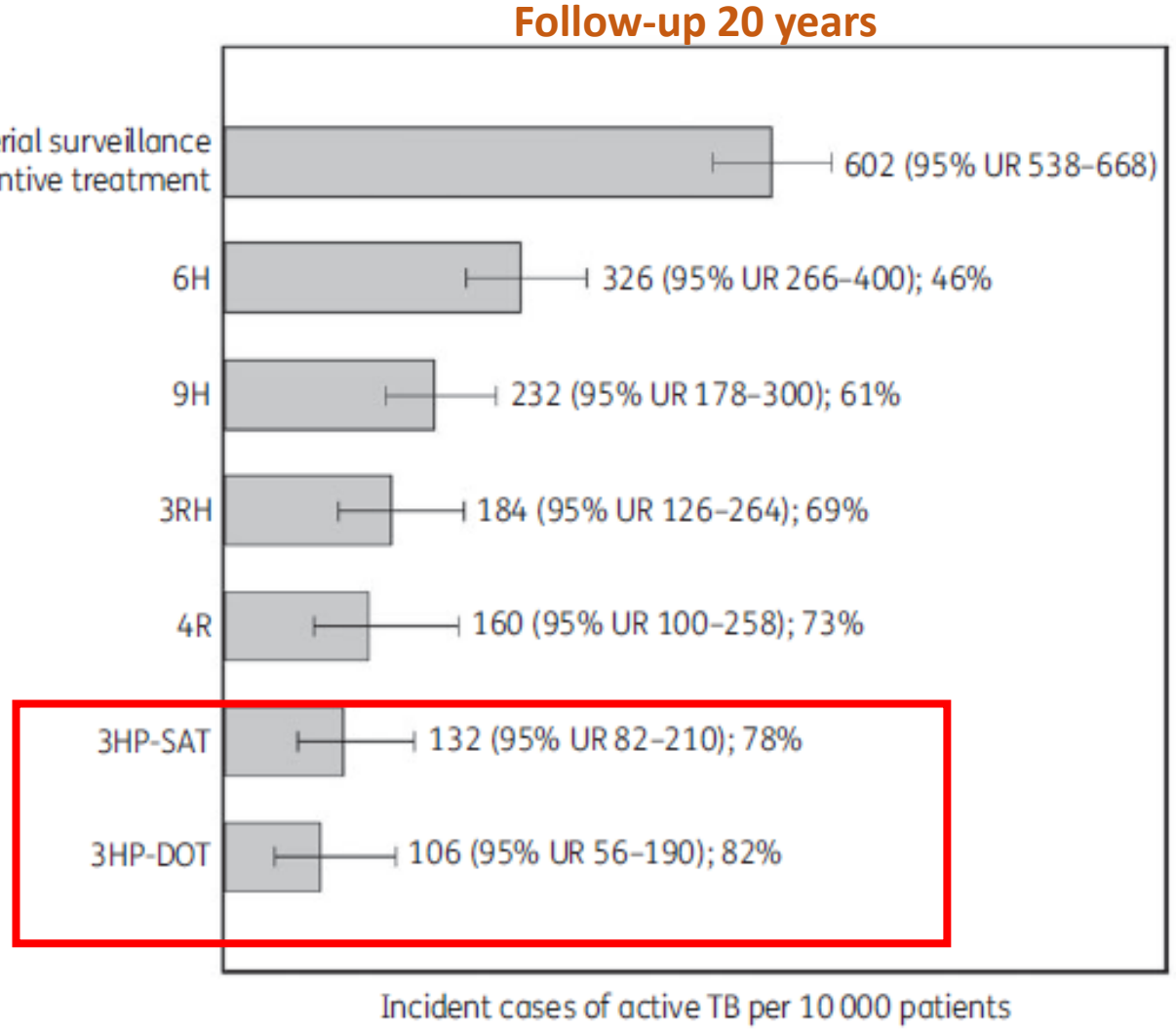
已服用3HP治療轉換處方表

已服用3HP劑次 每週服用(總療程12週)	轉換為3HR處方 每天服用(總療程90天)	轉換為4R處方 每天服用(總療程120天)	轉換為9H處方 每天服用(總療程270天)
已服用1劑次	餘83天	餘110天	餘248天
2	75	100	225
3	68	90	203
4	60	80	180
5	53	70	158
6	45	60	135
7	38	50	113
8	30	40	90
9	23	30	68
10	15	20	45
11	8	10	23

轉換處方後藥量原則上不要少於此建議表

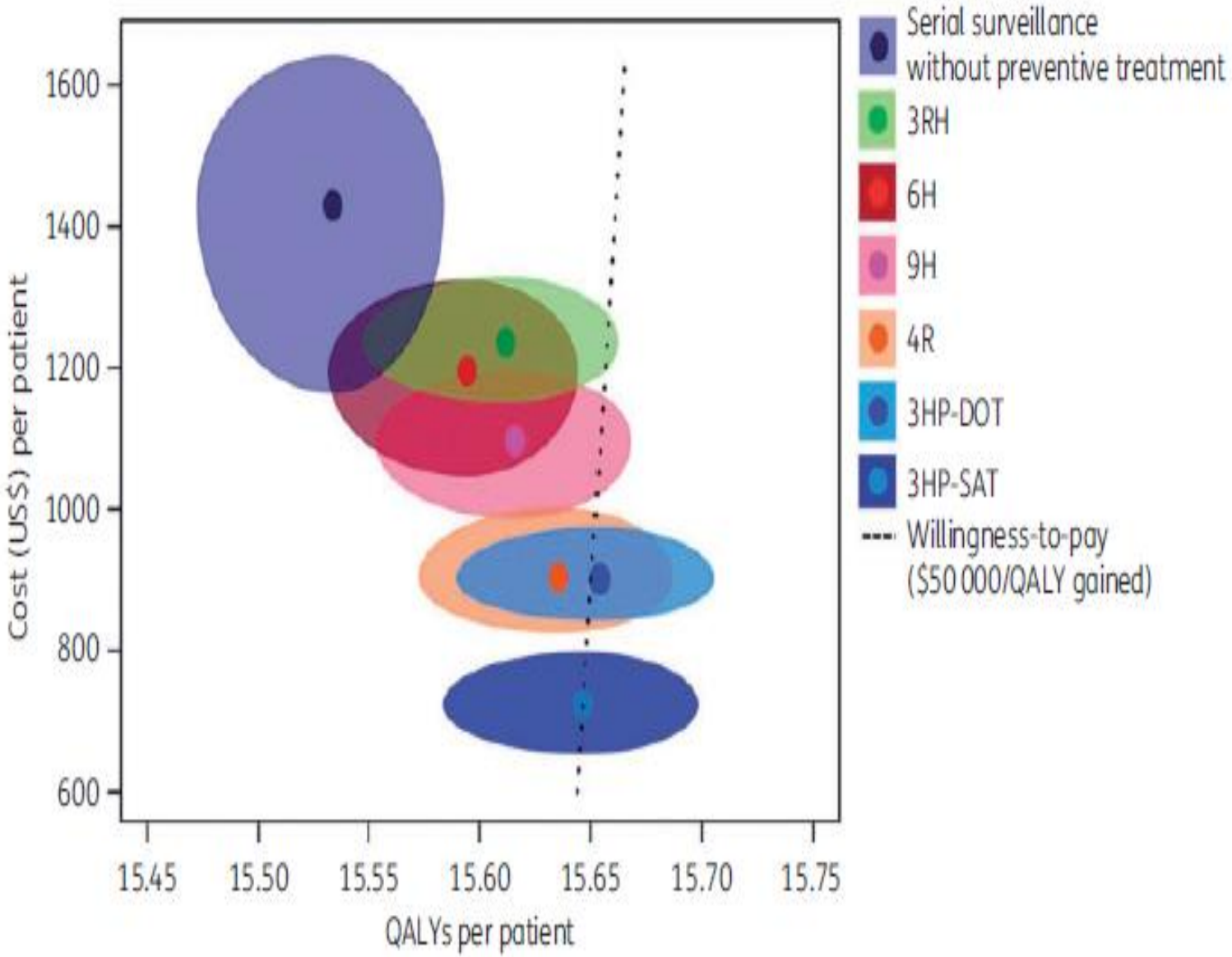
Cost-effectiveness of 3HP compared with other standard treatment regimens : A decision analysis study





J Antimicrob Chemother 2019; 74: 218–227

Cost-effectiveness plane for each of the seven simulated strategies



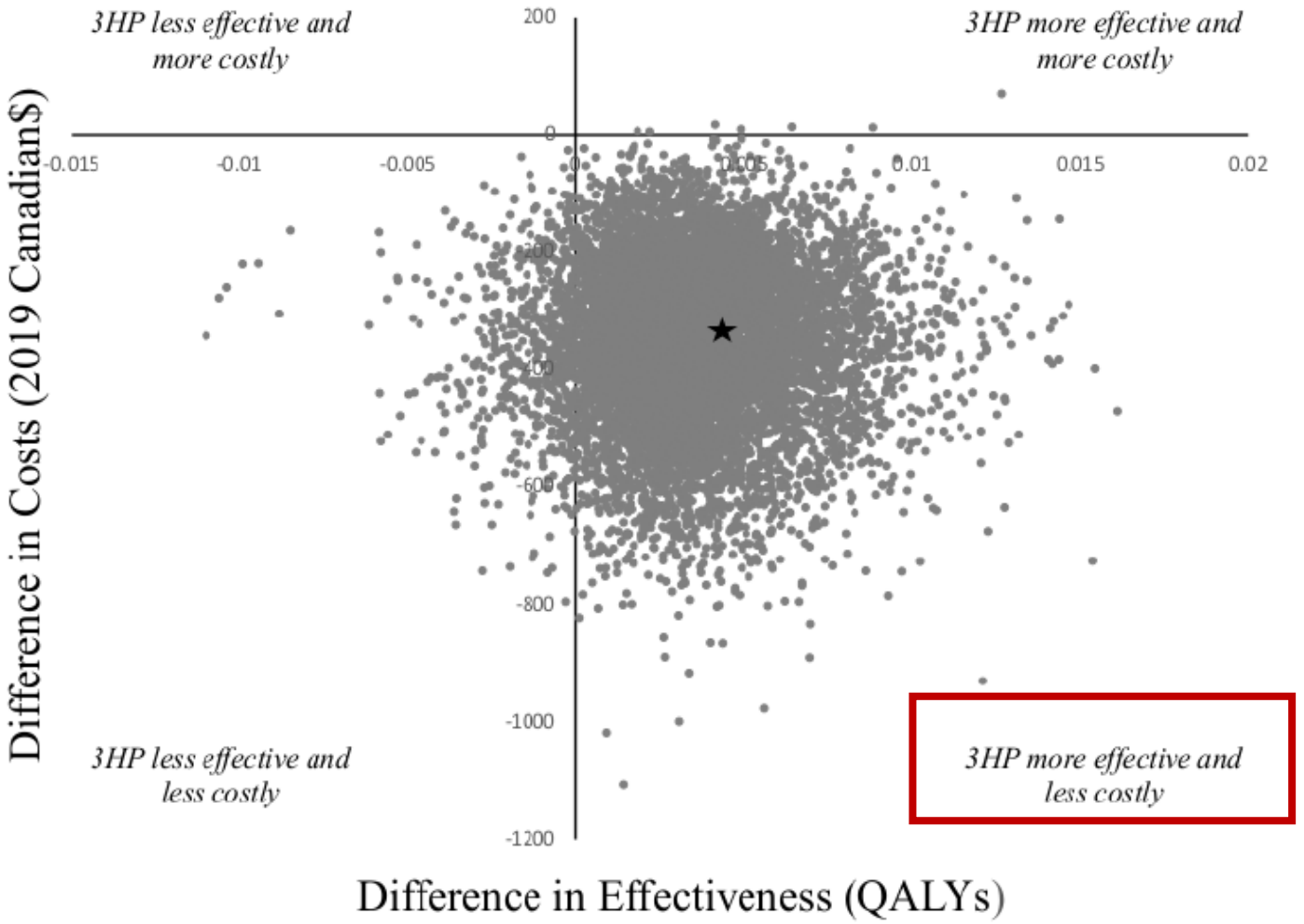
J Antimicrob Chemother 2019; 74: 218–227

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.



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

Precautions related to 3HP

- **Groups not suitable for use 3HP**
  - 孕婦（目前兩大臨床試驗已證實未對寶寶產生影響，但仍須更大量的經驗累積）
  - INH或RMP抗藥指標個案的接觸者、
  - 未滿2歲之兒童
- 潛伏結核感染者同時服用其他易與**RMP或**RPT產生藥物交互作用之藥物（如：coumadin，methadone，phenytoin…等)，亦須評估是否適用
- RMP及RPT皆因為透過活化CYP450酵素的活動，影響其他藥物的體內濃度(通常導致偏低)，若病人併用的藥物療效不足可能危及生命時，要格外謹慎。
  - 使用Proteases inhibitors的感染者會因與RPT交互作用而影響愛滋治療
  - 已有文獻發表使用Efavirenz、Raltegravir或Dolutegravir等抗病毒藥物治療時，雖然仍然與3HP中的RPT有藥物交互作用，但不影響潛伏結核感染治療期間對愛滋病毒抑制的效果

J. Clin. Med. 2019, 8, 812

The possible mechanism related to 3HP-SDR – RPT

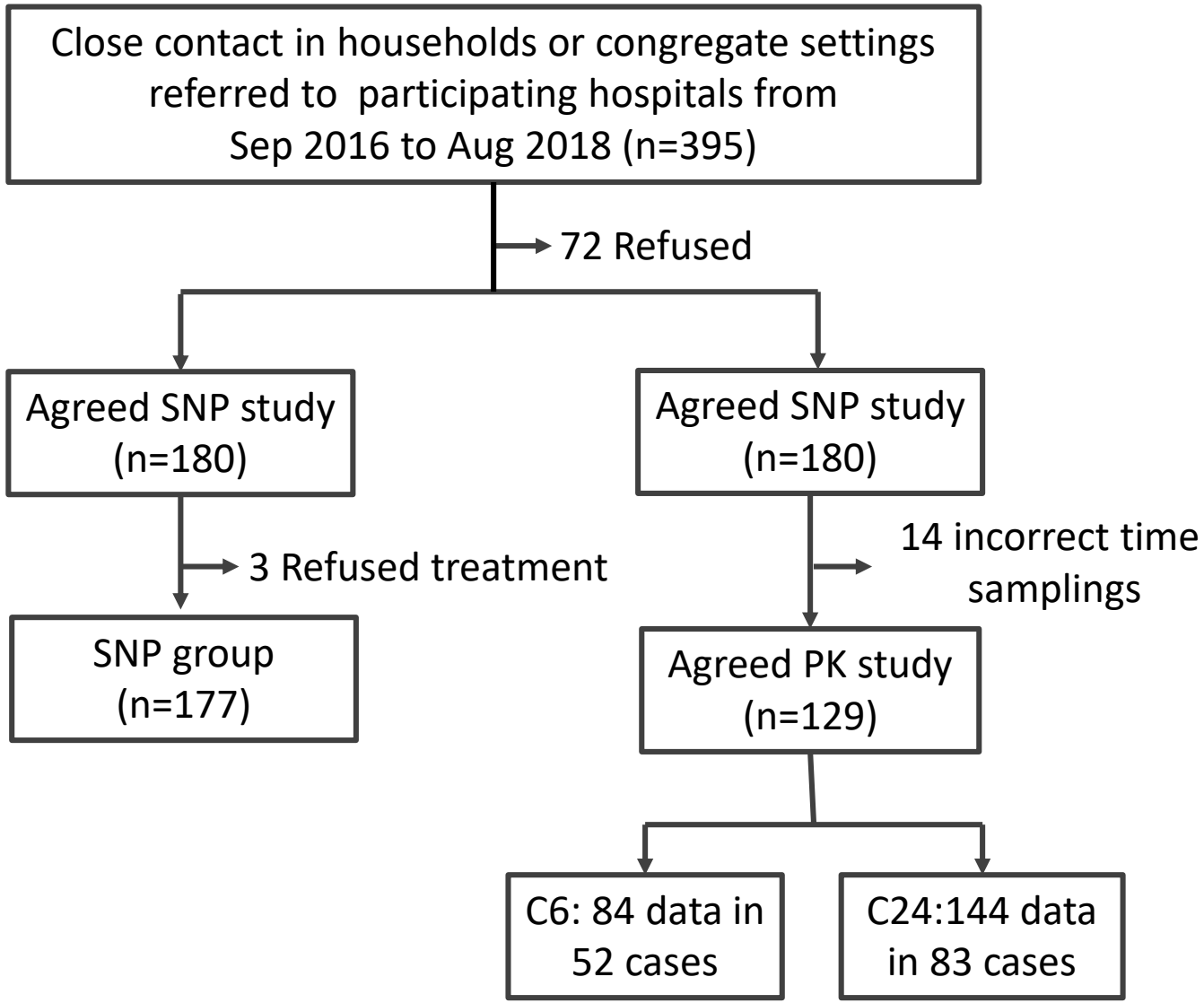
- **Immunologic basis:** Rifampicin-antibody complexes may be associate with “flu-like” reaction

- **Circulating anti-rifampin antibodies (IgM):** not detectable during daily administration, only when receiving intermittent dosing at high dose (> 900mg)
  - Flu-like reaction coincided with peak concentration of rifampin (2-4 hrs) and level of antibody fell during reaction
- Daily administration of rifampin could produce immune tolerance
  - RCT of daily rifapentine followed by intermittent dosing, no reports of flu-like syndrome or hypersensitivity

Poole. et al. BMJ 1971
O’Mahony.et al. Clin Allergy. 1973
Jindani.et al. NEJM. 2014

INH maybe related to 3HP-SDR

- INH induced flu-like syndrome also reported
- A prospective multicenter study in Taiwan
  - Pharmacokinetics: C6 and C24
  - Single nucleotide polymorphisms of INH/RPT metabolizing enzyme: NAT2, AADAC, CYP2E1
- Enrolled population:
  - Age ≥ 12 years
  - In close contact with TB patients
  - Diagnosed as LTBI under TST or QFT



J. Clin. Med. 2019, 8, 812

Single neucleotide polymorphism of *NAT2* and *CYP2E1* associated to SDRs

- **177 participants**
- Age: 37.1±17.8
- 6% had underlying comorbidity
- Completion rate: 90%
- SDR: 14 cases, 8%
- SDR occurred more in
  - older age (p=0.038)
  - inferior renal function (p=0.009)
- SDR associated with
  - *NAT2* rs1041983(T): Slow acetylater
  - *CYP2E1* rs2070673 (A)

		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Additive model			
NAT2 rs1041983	CC	Ref	Ref
	CT	0.85 (0.14 - 5.29)	0.87 (0.14-5.46)
	TT	7.67 (1.51 - 39.0) *	5.82 (1.08-35.1) *
CYP2E1 rs2070673	TT	Ref	Ref
	TA	0.84 (0.20-3.52)	2.01 (0.41-9.96)
	AA	3.21 (0.79-15.0)	3.28 (0.43-5.20)
Dominant model			
NAT2 rs1041983	CC	Ref	Ref
	CT+TT	2.41 (0.51-11.3)	2.01 (0.41-9.96)
CYP2E1 rs2070673	TT	Ref	Ref
	TA+AA	1.43 (0.42-4.84)	1.49 (0.43-5.20)
Recessive model			
NAT2 rs1041983	CC+CT	Ref	Ref
	TT	8.47 (2.55-28.1) *	7.00 (2.03-24.1) *
CYP2E1 rs2070673	TT+TA	Ref	Ref
	AA	3.51 (1.05-11.7) *	3.50 (1.02-12.0) *

Adjust with age, sex and estimated glomerular filtration rate * p<0.005

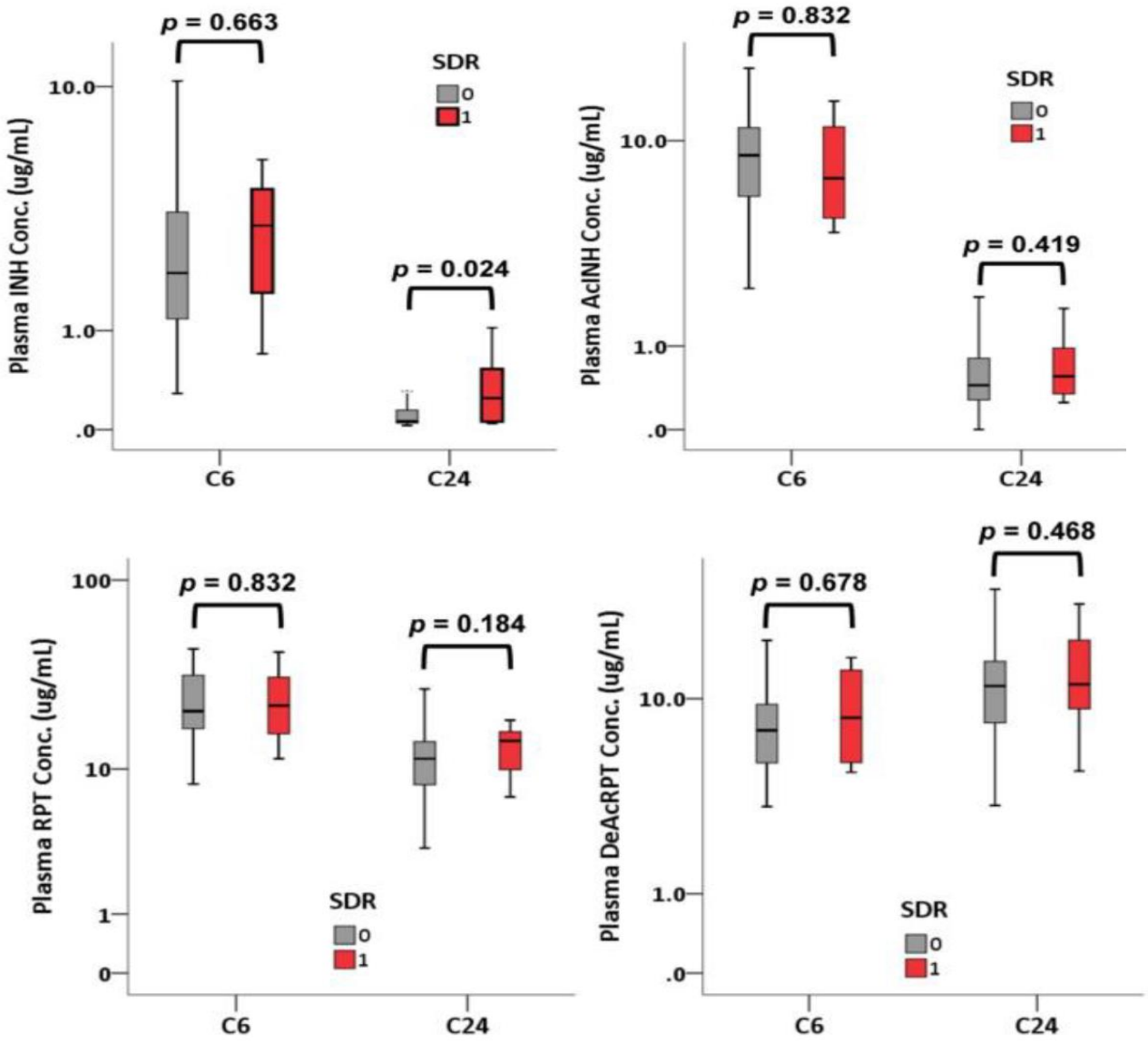
J. Clin. Med. 2019, 8, 812

INH serum concentration associated with SDRs

- 129 participants
- Age: 44.8±17.2
- Completion rate: 83%
- SDR: 13 cases, 10.1%
- C24 INH level was significantly higher in SDR (0.25 [0.06–0.53] vs. 0.06 [0.05–0.15] g/mL, p = 0.024)

Generalized estimating equation (GEE) model:

- C24 plasma INH level was associated with a higher risk of SDR development (OR [95% CI]: 1.61 [1.15–2.25], p = 0.006) but not RPT
- C6: no drug concentration correlated to SDR



INH Metabolic Enzyme Genetic Polymorphisms associated with ADRs

- A multicenter observational study
  - 377 close contacts aged >12 years receiving 3HP
  - February 2017 - October 2018.
  - Mean age was 45.7 years
  - 208 participants (55.2%) were women,
  - 144 participants (38.2%) had comorbidities
  - 184 (48.8%) developed ADRs
    - Grade 1: 77.68%
    - Grade 2: 20.63%
    - Grade 3: 1.42%, Flu accounts 80%
- CY2PE1 and NAT2 associated with ADRs

Variable	ALL (n = 754)	Non-ADR (n = 386)	ADR (n = 368)	OR (95% C.I.)	p Value
CYP5A6 (rs28399433)					
A allele	570 (75.6%)	286 (74.1%)	284 (77.2%)	1.000 (reference)	
C allele	184 (24.4%)	100 (25.9%)	84 (22.8%)	0.846 (0.606–1.181)	p = 0.325
CYP2B6 (rs8192709)					
T allele	722 (95.8%)	375 (97.2%)	347 (94.3%)	1.000 (reference)	
C allele	32 (4.2%)	11 (2.8%)	21 (5.7%)	2.063 (0.980–4.341)	p = 0.056
CYP2C19 (rs4986893)					
G allele	718 (95.2%)	372 (96.4%)	346 (94.0%)	1.000 (reference)	
A allele	36 (4.8%)	14 (3.6%)	22 (6.0%)	1.690 (0.851–3.355)	p = 0.134
CYP2C19 (rs12248560)					
C allele	752 (99.7%)	384 (99.5%)	368 (100.0%)	1.000 (reference)	
T allele	2 (0.3%)	2 (0.5%)	0 (0.0%)	-	-
CYP2E1 (rs2070676)					
C allele	610 (80.9%)	322 (83.4%)	288 (78.3%)	1.000 (reference)	
G allele	144 (19.1%)	64 (16.6%)	80 (21.7%)	1.398 (0.970–2.013)	p = 0.072
CYP2E1 (rs2515641)					
C allele	590 (78.3%)	319 (82.6%)	271 (73.6%)	1.000 (reference)	
T allele	164 (21.7%)	67 (17.4%)	97 (26.4%)	**1.704 (1.200–2.421)**	p = 0.003 *
NAT2 (rs1495741)					
G allele	398 (52.8%)	220 (57.0%)	178 (48.4%)	1.000 (reference)	
A allele	356 (47.2%)	166 (43.0%)	190 (51.6%)	**1.415 (1.062–1.885)**	p = 0.018 *
NAT2 (rs1799930)					
G allele	566 (75.1%)	286 (74.1%)	280 (76.1%)	1.000 (reference)	
A allele	188 (24.9%)	100 (25.9%)	88 (23.9%)	0.899 (0.646–1.251)	p = 0.528

Int J Environ Res Public Health. 2020 Jan; 17(1): 210.

- INH serum concentration rather than RPT plays a role in the development of 3HP-related SDRs
  - Population PK study is essential for further correlation

- NAT2/CYP2E1 SNP could be used for risk stratification among TB contacts receiving 3HP regimen
  - Ethnic difference should be considered
  - External validation should be conducted

A new, shorter-course regimen (1HP) is coming

- 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

Comparing Incidence Rate of SDR Under 3HP and 1HP Regimen for LTBI Tx: a Pragmatic Multicenter RCT

***ClinicalTrials.gov*: NCT04094012**

Primary endpoints:

- **Incidence rate of SDR**

Secondary endpoints:

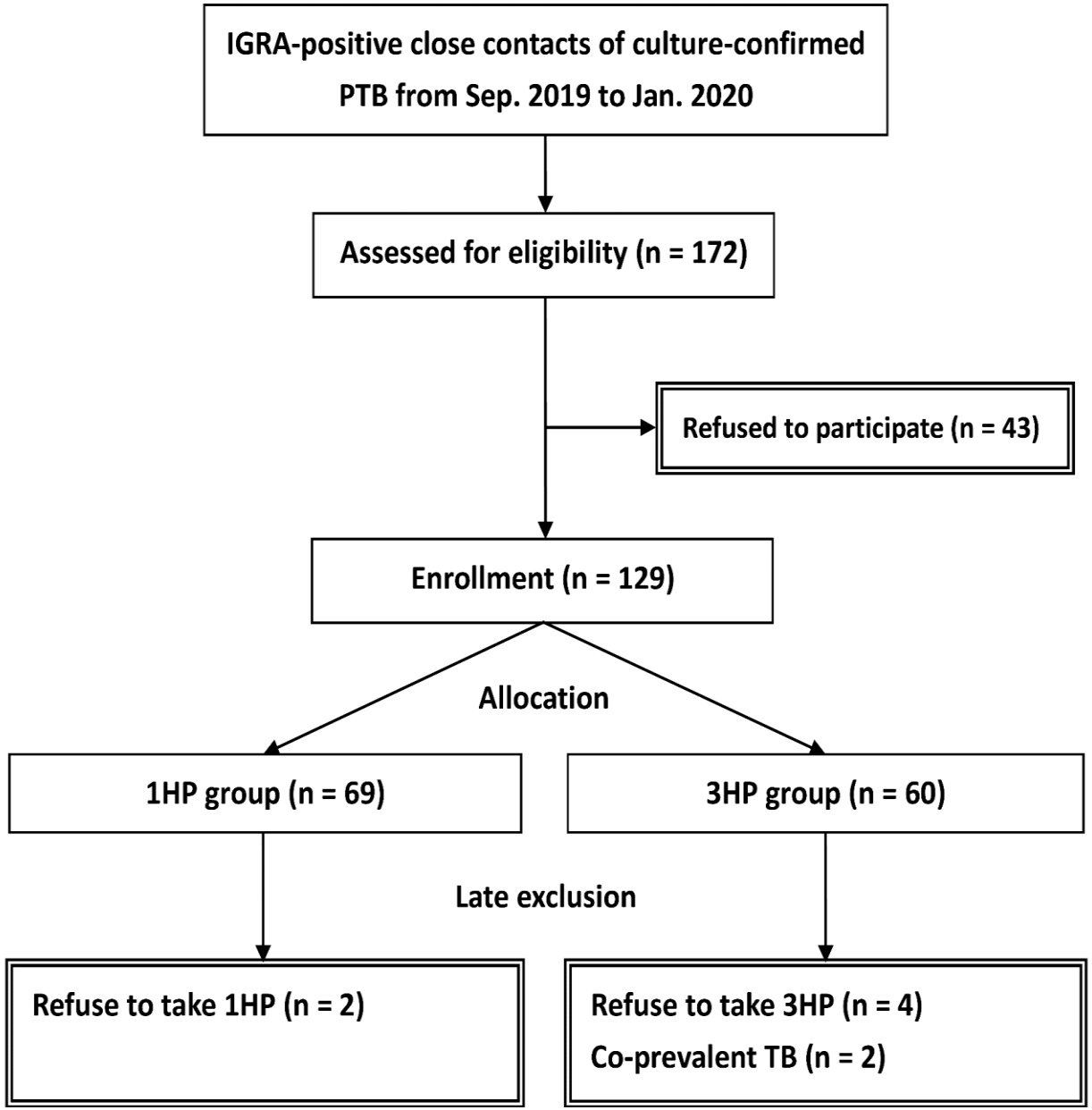
1. ADRs: flu-like symptoms, Hepatotoxicity
2. treatment completion
3. plasma drug levels
4. risk factors of SDR

Number needed: 245 * 2

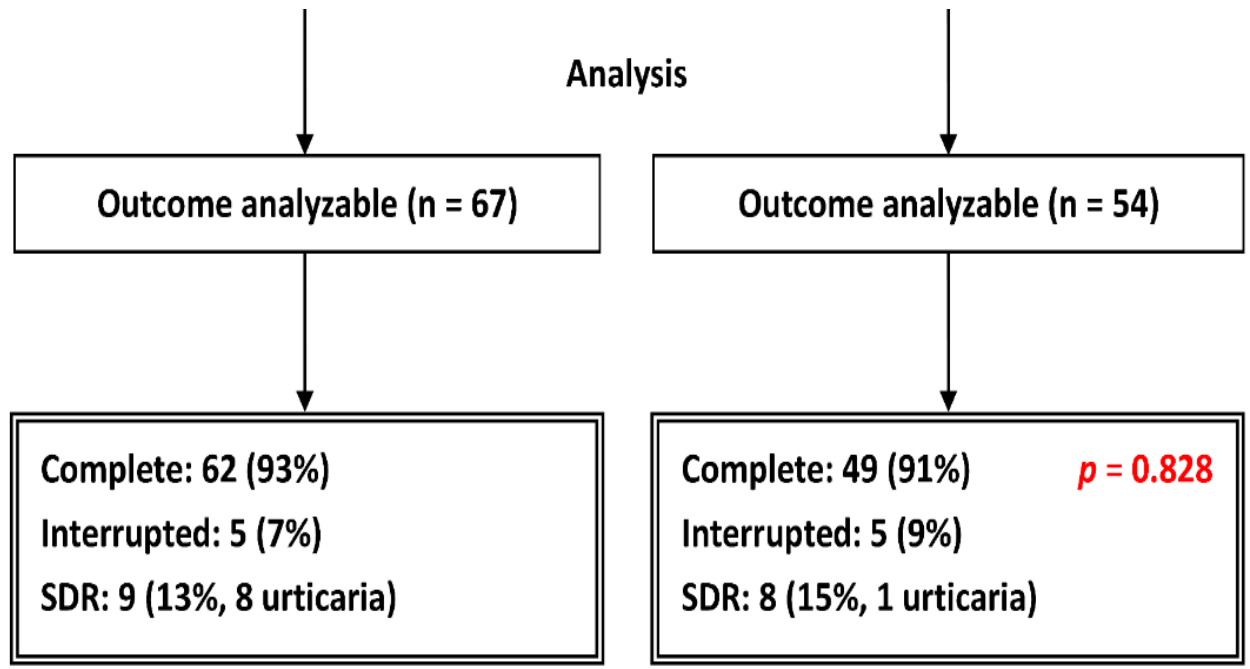
Study period: 2019 – 2022

First case in: 2019/9/24

Unpublish data



Characteristics	1HP (n=67)	3HP (n=54)	*p* value
Age: mean ± SD	51.9 ± 22.2	52.8 ± 18.1	0.819
Male sex: No. (%)	39 (58%)	21 (39%)	**0.035**
Body-mass index:	24.1 ± 4.9	23.6 ± 4.1	0.529
Smoking Status: No. (%)			**0.008**
Current smoker	3 (5%)	7 (13%)	
Ex-smoker	14 (21%)	2 (4%)	
Never smoker	50 (74%)	45 (83%)	
INH dose (mg/kg/dose)	4.8 ± 1.0	14.6 ± 2.4	
RPT dose (mg/kg/dose)	9.5 ± 1.9	14.7 ± 2.1	



The details of ADRS in 1HP group and 3HP group

ADR	1HP (n=67)				3HP (n=54)				*P* value
	Gr. 3	Gr. 2	Gr. 1	Total	Gr. 3	Gr. 2	Gr. 1	Total	
SDR	1	8	0	9 (13%)	2	6	0	8 (15%)	0.828
Cutaneous reactions	1	15	11	27 (40%)	0	5	5	10 (19%)	**0.010**
Itching	1	11	7	19 (28%)	0	3	4	7 (13%)	**0.040**
rash	0	10	5	15 (22%)	0	3	2	5 (9%)	0.053
urticaria	1	7	0	8 (12%)	0	1	0	1 (2%)	**0.042**
Fever	0	9	1	10 (15%)	1	12	3	16 (30%)	**0.050**
Flush	0	3	2	5 (7%)	0	1	6	7 (13%)	**0.314**
Chills	0	4	1	5 (7%)	0	3	3	6 (11%)	**0.537**
Vomiting	0	2	0	2 (3%)	0	3	9	**12 (22%)**	**0.001**
Nausea	0	2	1	3 (4%)	0	3	13	**16 (30%)**	**<0.001**

- 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
- The study is still ongoing …..

Unpublish data

Thank you


END TB
World Health Organization


TARGETS
MILESTONES
SDG*
END TB
2020
2025
2030
2035