潛伏結核感染之臨床進展
Clinical Progress of Latent Tuberculosis Infection

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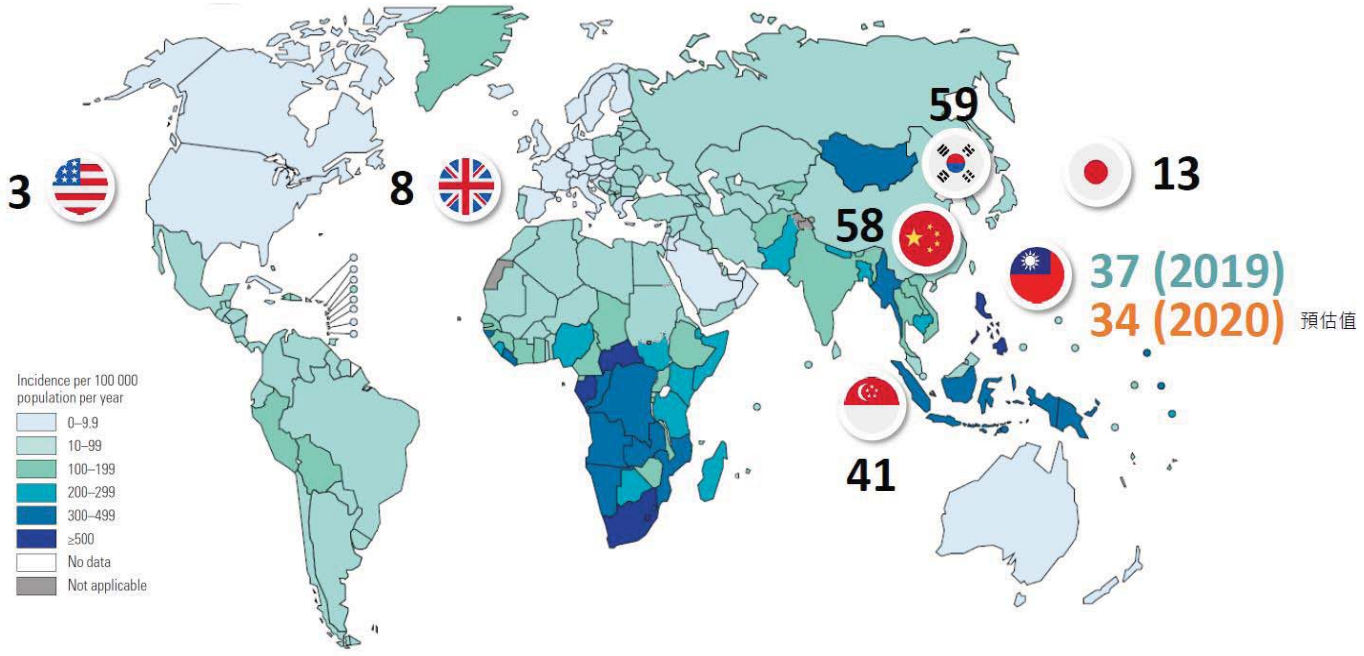
Outlines

- **Rationale for LTBI treatment**
- **Diagnosis of LTBI**
- **Regimen for Latent TB Infection Treatment**

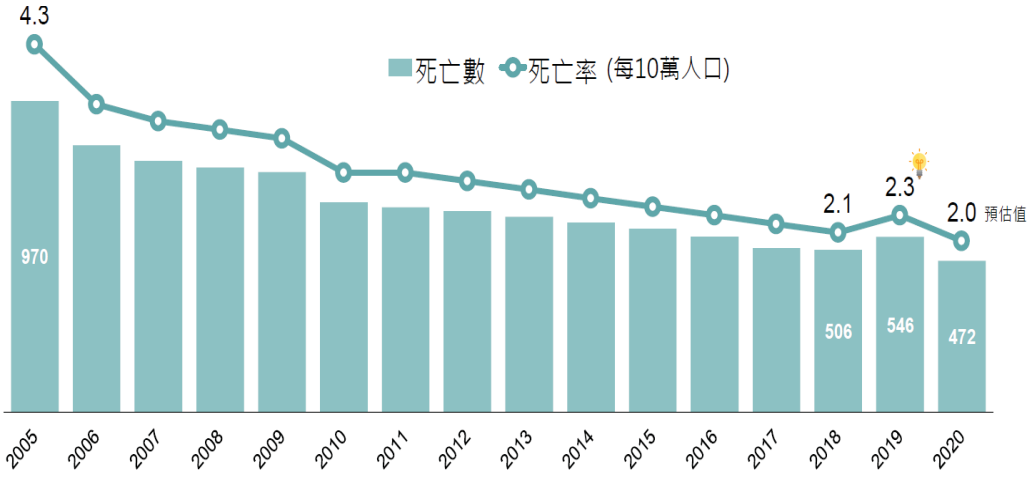
Global incidence of TB in 2019

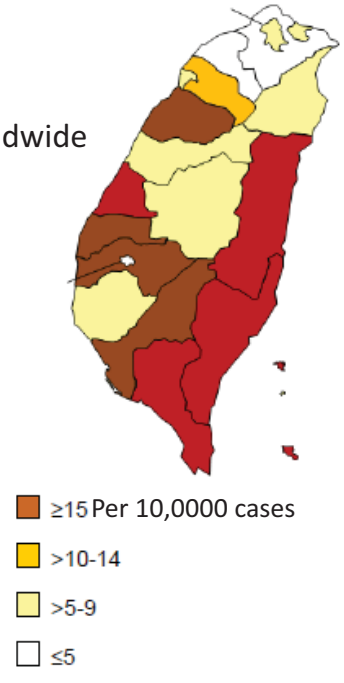


資料來源： WHO Global tuberculosis report 2020

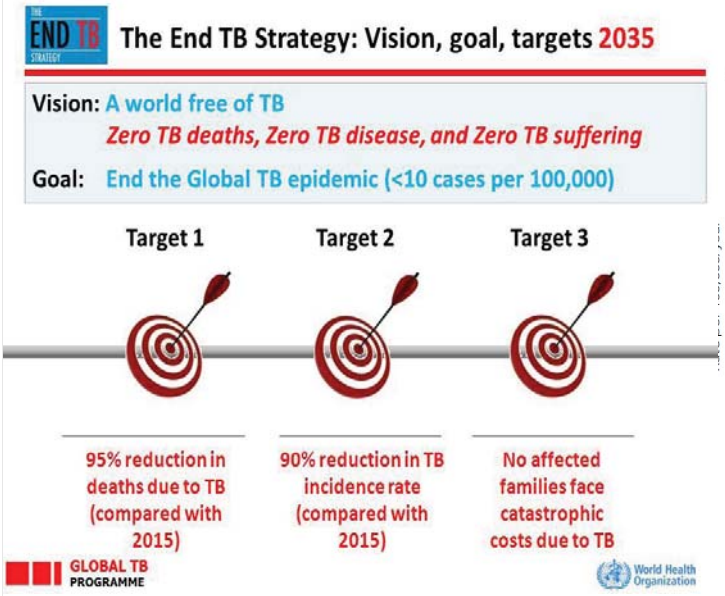
TB related mortality

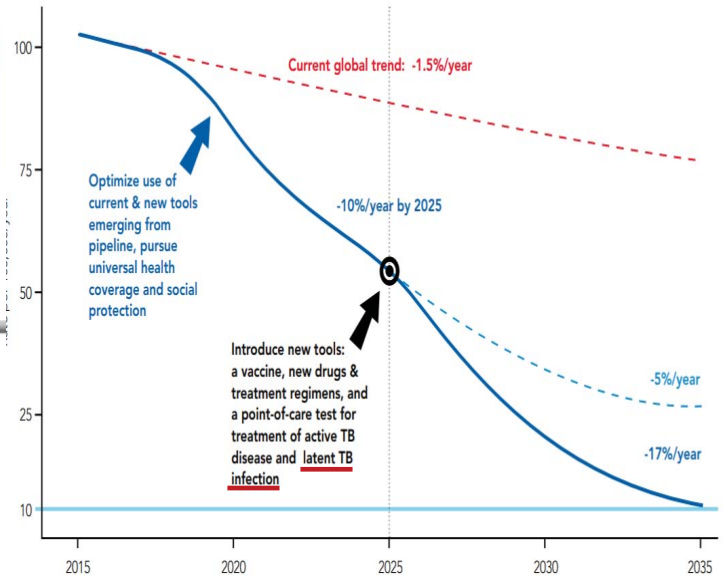
- In 2017, 1.7 million TB deaths were reported
  - Almost infected cases can be cured , but still high mortality rate
  - Innate reactivation rather than re-infection in developing countries
  - The most common opportunistic infection in individuals with HIV worldwide





Projected acceleration in the decline of global TB incidence rates to target levels is important





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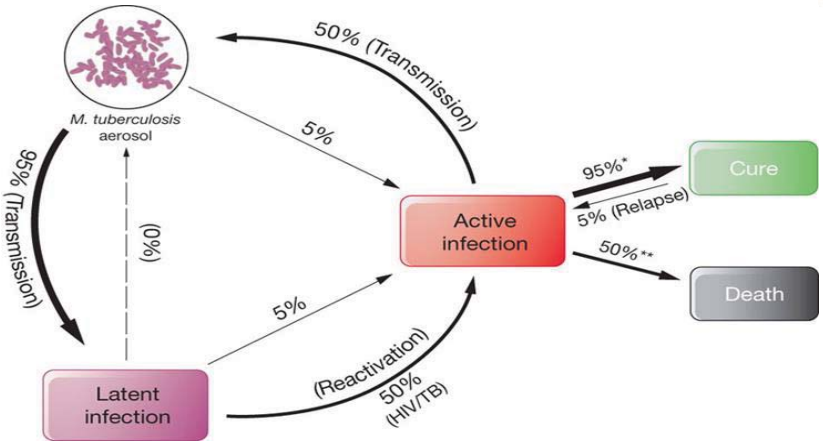
Latent TB Infection

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



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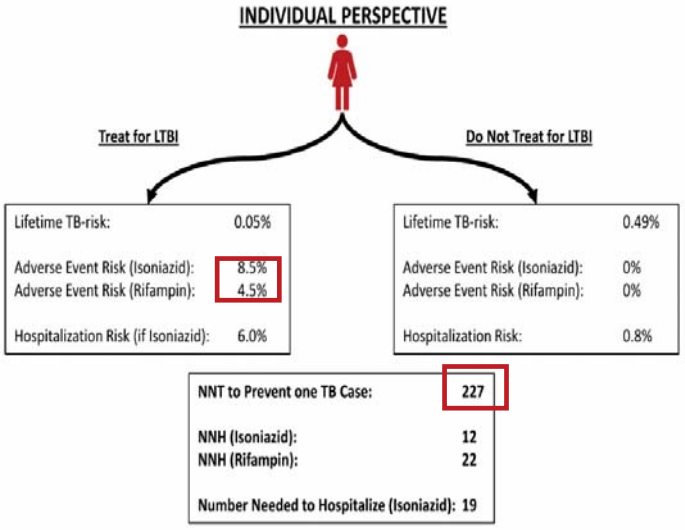
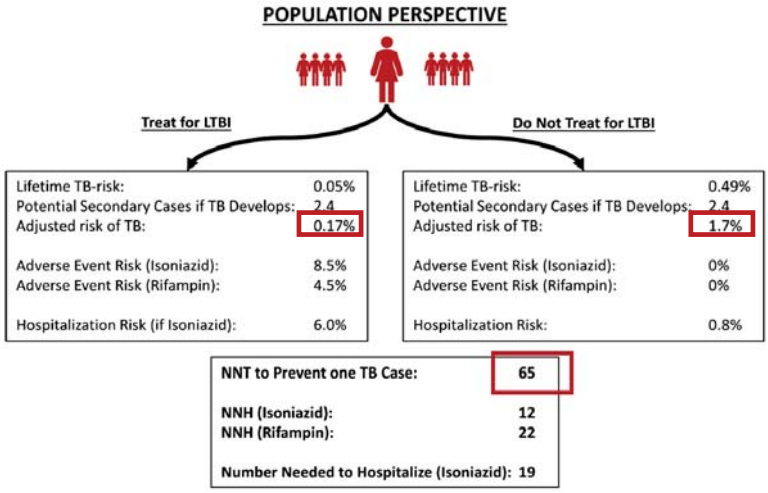
A Koul *et al. Nature* **469**, 483-490 (2011) doi:10.1038/nature09657

結核防治-Individual

結核防治-Population

75歲女性預期有五年的存活期

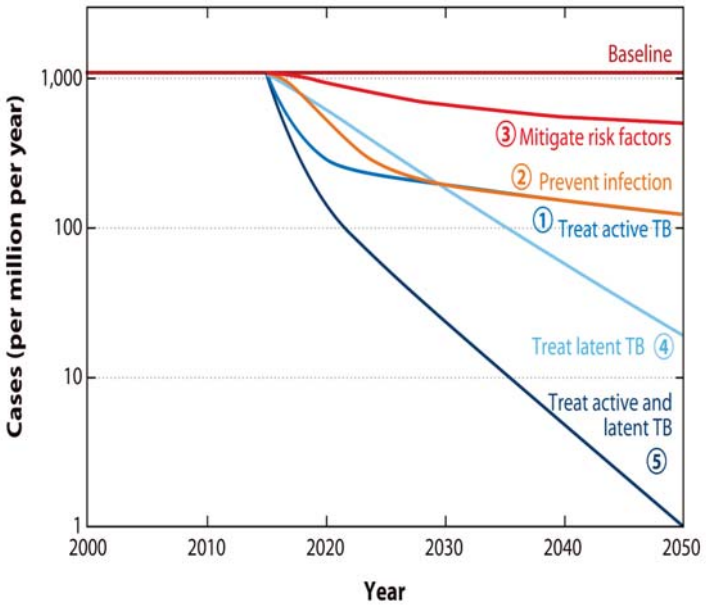




Campbell JR et al. Plos Med 2019

Key for TB Elimination: Treat active TB and LTBI simultaneously

Identify the risk population is essential !



Risk factor for active TB disease	Odds
Close contacts of TB	>20
HIV/AIDS	9.9
Receiving biological agents	7.9
Old TB	5.2
Diabetes mellitus	3.1
Smoker	2.69
End-Stage Renal Disease	2.4
Silicosis	1.7
Gastrectomy	1.4
Low body weight	1.6

Dye C. *Annu Rev Public Health* 2013;34:271-86.
US CDC. http://www.cdc.gov/tb/topic/basics/risk.htm

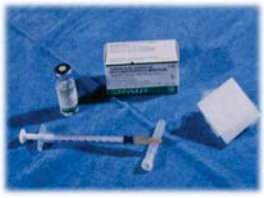
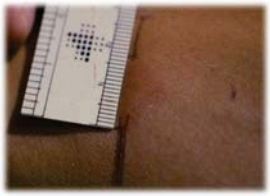
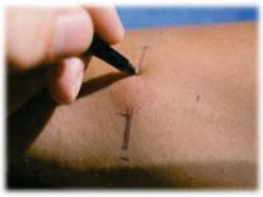
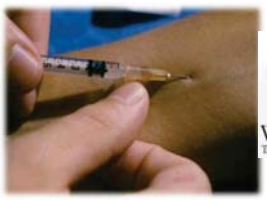
Priority group receiving LTBI diagnosis/treatment by WHO

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

THE END TB STRATEGY

World Health Organization

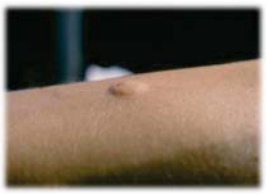
Diagnostic Tools for LTBI – Tuberculin Skin Test

WIKIPEDIA The Free Encyclopedia

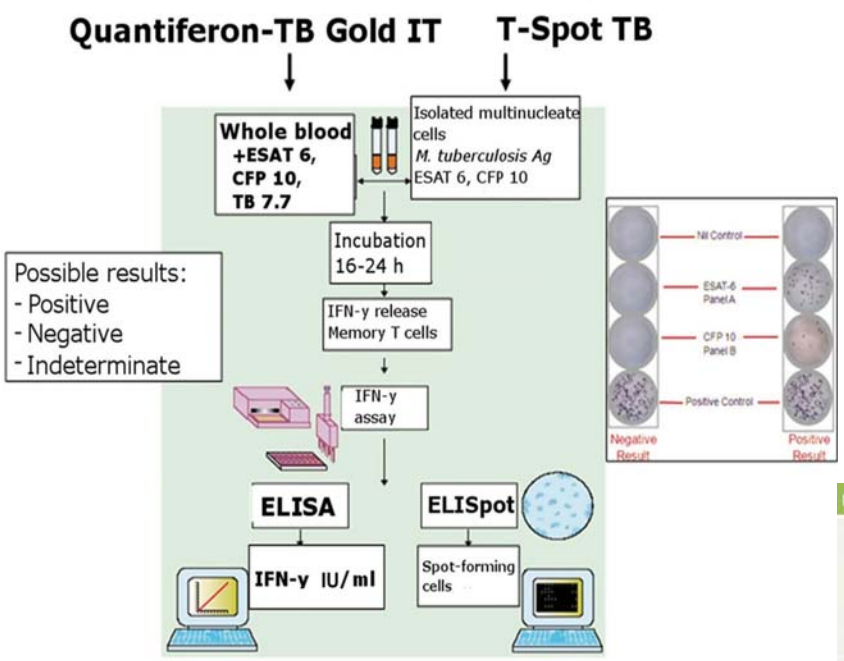
Purified protein derivative (**PPD**) is a poorly defined, complex mixture of antigens. Tests based upon PPD are Relatively unspecific since many of its proteins are found In different mycobacterial species



- Post injection 48 – 72 hrs
- **For HIV, malignancy, organ transplantation, under immunosuppresent**
  - Induration ≧5 mm: Positive
- **For health populations**
  - Induration ≧10 mm: Positive
- **Disadvantage:**
  - False negative in immunosuppressant patients
  - Individual skill depends
  - False positive in NTM infection

Diagnostic Tools for LTBI - IGRA-Interferon Gamma Release Assay



- **Advantage**
  - Less false positive in NTM patients
  - Easy test, only one blood test
  - Quantitative
- Use in > 2year-old population

Nil (IU/mL)	TB Ag - Nil (IU/mL)	Mitogen-Nil (IU/mL)	檢驗結果
	≥ 0.35 和≥25%Nil 值	任何	陽性
≤0.8	<0.35 或<25%Nil 值	≥0.5	陰性
	<0.35 或<25%Nil 值	<0.5	不確定 (mitogen<0.5)
>8.0	任何	任何	不確定

Evolution of IGRA test

1st generation QuantiFERON®-TB	2nd generation QuantiFERON®-TB Gold (liquid antigen)	3rd generation QuantiFERON®-TB Gold (QFT® in tube)	4th generation QuantiFERON®-TB Gold Plus (QFT®-Plus)
2001: FDA approval	2004: FDA approval	2007: FDA approval	Q4 2014: CE-IVD 2017: FDA approved
• Measured cell-mediated immunity to tuberculin purified protein derivative (PPD) • **Breakthrough:** TST becomes a blood test	• "Liquid antigen" version • Antigens specific for *M.tb with* 99% specificity • **Clinical benchmark:** No cross reactivity with BCG	• Logistical advantage – remote incubation • **Lab benchmark:** Scalable and easily automated • Explosion of peer reviewed publications >1500	• Addition of patented CD8 antigens – potential biomarker of intracellular TB burden • New flexible blood draw options • High-throughput automation options
			

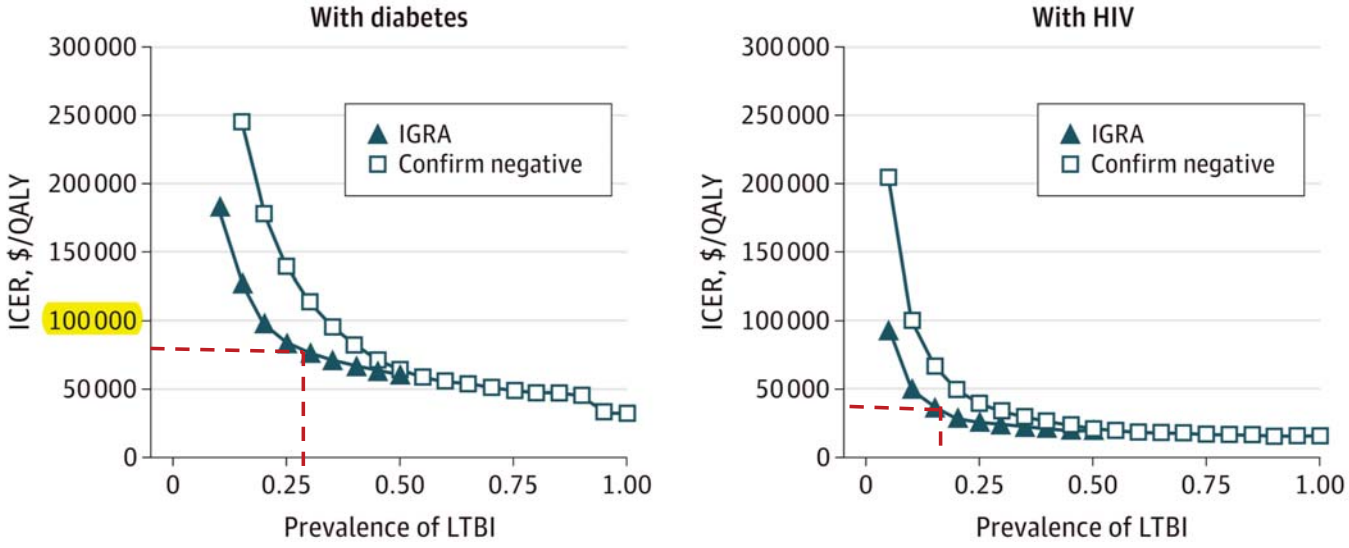
MTB-specific CD8 T cells secrete IFN-γ and other soluble factors to (1–3):

- Suppress MTB growth
- Kill infected cells
- Directly lyse intracellular MTB

- Advantage of 4th generation QFT-plus
  - Higher sensitivity, same specificity
  - Higher positive rates in HIV/AIDS, immunocompromise
  - Potential to minimize indeterminate rate
  - More flexible workflow

Latent Tuberculosis Infection – Taiwan Experience

LTBI盛行率對於治療成本效益的影響



遞增成本效果比值(Incremental cost-effectiveness ratio, ICER)

Tasillo A. JAMA Int Med 2017;177: 1755-64.

LTBI prevalence using IGRA and TST in dialysis patients

Table 5 Initial positivity rate of TST and IGRAs in patients on dialysis.

Reference	Country (TB burden)	TST (Cut-off >10 mm)	IGRAs	
			T-SPOT.TB	QuantiFERON
Passalent et al. 2007[39]	Canada (Low)	19/203 (9.40%)	72/203 (35.5%)	–
Winthrop et al. 2008[a,40]	USA (Low)	26/100 (26.0%)	27/100 (27.0%)	21/100 (21.0%)
Inoue et al. 2009[41]	Japan (Intermediate)	–	–	28/162 (17.3%)
Lee et al. 2009[6]	Taiwan (Intermediate)	20/32 (62.5%)	15/32 (46.9%)	12/32 (37.5%)
Triverio et al. 2009[42]	Switzerland (Low)	12/62 (19.4%) (CO > 5 mm)	18/62 (29.0%)	13/62 (21.0%)
Chung et al. 2010[43]	South Korea (Intermediate)	38/167 (22.75%)	96/167 (57.5%)	67/167 (40.1%)
Lee et al. 2010[10]	Taiwan (Intermediate)	27/91 (29.7%)	–	32/93 (34.4%)
Seyhan et al. 2010[44]	Turkey (Intermediate)	34/100 (34.0%)	–	43/100 (43.0%)
Sayarlioğlu et al. 2011[45]	Turkey (Intermediate)	28/89 (31.5%)	–	40/89 (44.9%)
Anibarro et al. 2012[a,46]	Spain (Low)	11/52 (21.2%)	–	18/52 (34.6%)
Grant et al. 2012[47]	Canada (Low)	2/77 (2.60%)	22/79 (27.8%)	22/79 (27.8%)
Shu et al. 2012[7]	Taiwan (Intermediate)	–	–	91/427 (21.3%)
Soysal et al. 2012[20]	Turkey (Intermediate)	158/408 (38.72%)	239/391 (61.1%)	–
Al-Jahdali et al. 2013[5]	Saudi Arabia (Intermediate)	26/200 (13.0%)	–	65/200 (32.5%)
Kim et al. 2013[19]	South Korea (Intermediate)	20/112 (17.9%)	–	47/112 (42.0%)
Shu et al. 2013[48]	Taiwan (Intermediate)	–	–	45/204 (22.1%)
Savaj et al. 2014[49]	Iran (Intermediate)	20/47 (43.5%)	–	11/47 (23.4%)
Agarwal et al. 2015[50]	India (High)	32/185 (17.3%)	–	66/185 (35.7%)
Lee et al. 2015[51]	South Korea (Intermediate)	–	–	39/93 (41.9%)
Shu et al. 2015[8]	Taiwan (Intermediate)	–	–	106/425 (24.9%)
Shu et al. 2016[52]	Taiwan (Intermediate)	–	–	210/981 (21.4%)
Shu et al. 2016[4]	Taiwan (Intermediate)	–	–	193/940 (20.5%)
Baek et al. 2019[25]	South Korea (Intermediate)	–	–	20/90 (22.2%)
Our Study	Taiwan (Intermediate)	–	–	123/636 (19.3%)
Overall	Low	70/494 (14.2%)	139/444 (31.3%)	74/293 (25.3%)
	Intermediate	371/1246 (29.8%)	350/590 (59.3%)	1172/4798 (24.4%)
	High	32/185 (17.3%)	–	66/185 (35.7%)

Journal of the Formosan Medical Association (2021) 120, 1350e1360

LTBI prevalence in DM patients

- The prevalence of LTBI in DM patients is more than twice than non-DM group
  - United states: 11.6% vs 4.6%
  - Taiwan: 21.1% vs. 9.7%
- Meta-analysis 13 observational studies, 38263 DM participants
  - Odds ratio for LTBI was 1.18 (95% CI: 1.06-1.30)
  - No correct HbA1c
- The prevalence of LTBI increased with DM severity
  - A cross-sectional study in Atlanta refugee hospital, the prevalence of LTBI
    25.9% in non-DM (median HbA1c: 5.4%)
    39.1% in pre-DM (median HbA1c: 5.8%)
    43.4% in DM (median HbA1c: 7.2%)

Clin Infect Dis. 2017 Mar 15; 64(6): 719–727
Int J Tuberc Lung Dis. 2016 Jan; 20(1): 71–78.

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

- For poorly DM controlled patients (HbA1c >9.0%)
  - Multicenter cohort study in Taiwan 26.7% IGRA (+) in 978 patients with HbA1c >9.0% in previous 1 year
  - Risk factors associated IGRA (+)

Variables	Adjusted OR	95% CI	*P* value
Age (per year increment)	1.02	1.00–1.04	.026
Duration of DM (per year increment)	1.04	1.02–1.07	<.001
Chronic kidney disease, stage ≥3	1.80	1.23–2.65	.003
Metformin use	0.56	.39–.80	.001
Use of dipeptidyl peptidase 4 inhibitor	1.51	1.08–2.13	.018

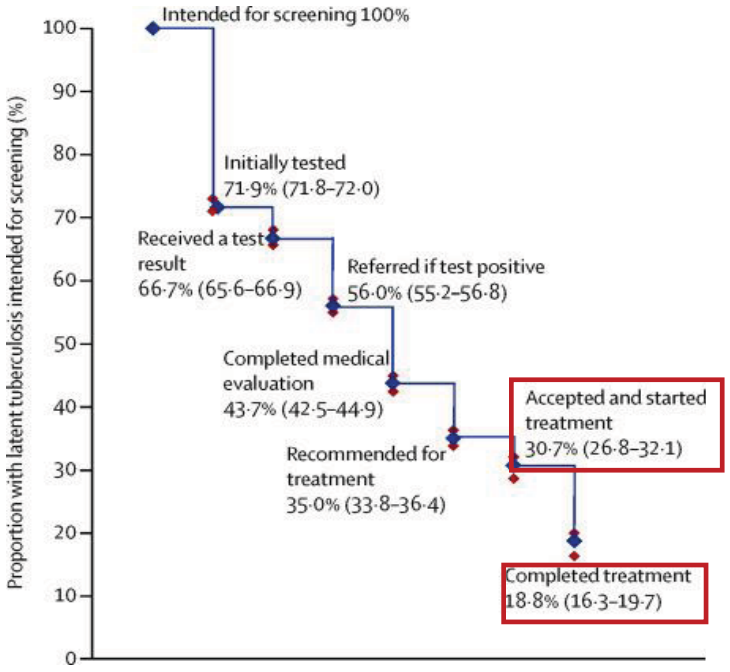
Clinical Infectious Diseases, ciab209, https://doi.org/10.1093/cid/ciab209

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.

Treatment Regimens for Latent TB Infection

World Health Organization

	Regimen	Dose by weight band
9H	6 or 9 months of daily isoniazid monotherapy (6H, 9H)	Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg)
4R	Four months of daily rifampicin (4R)	Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)
3HR	Three months of daily rifampicin plus isoniazid (3HR)	Isoniazid: Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg) Rifampicin: Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)
3HP	Three months of rifapentine plus isoniazid weekly (12 doses) (3HP)	Age 2–14 years

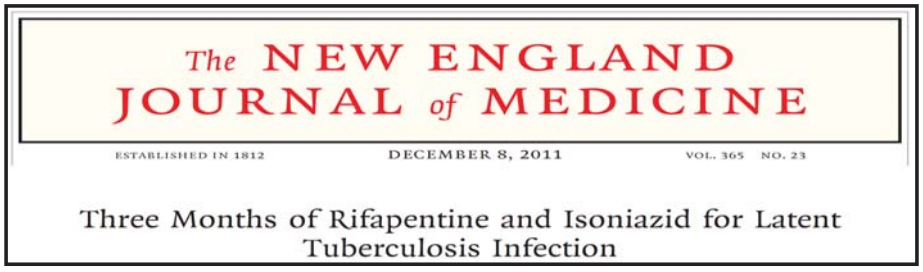
Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg
Isoniazid, 100 mg*	3	5	6	7	7
Rifapentine, 150 mg	2	3	4	5	5

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 of rifapentine plus isoniazid daily (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


The NEW ENGLAND JOURNAL of MEDICINE

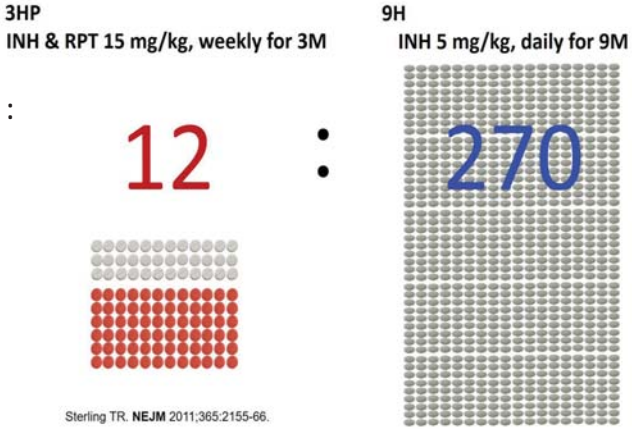
ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

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

- **3HP was used for > 2 year-old LTBI cases in Taiwan since 2019**



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

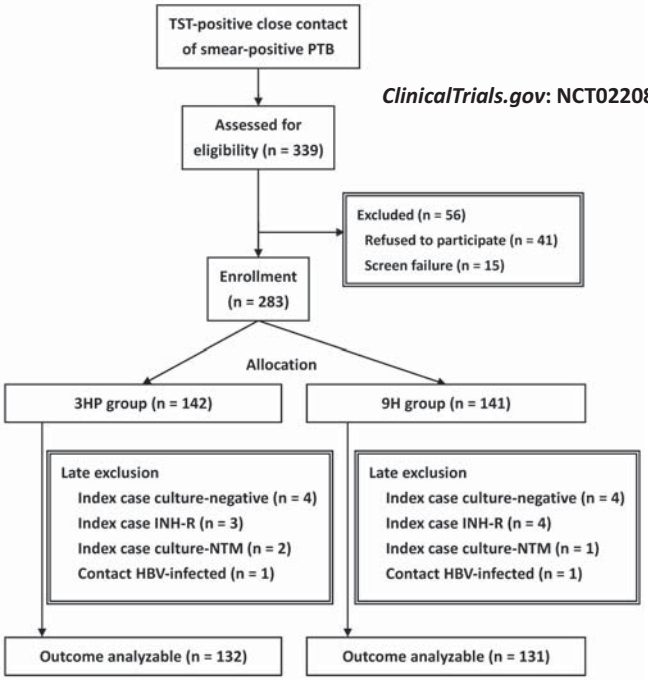
	Adjusted OR	95% CI	*P* Value
3HP vs 9H	9.4	5.5, 16.2	<.001
White-non-Hispanic race	3.3	2.3, 4.7	<.001
Female sex	2.0	1.4, 2.9	<.001
Age ≥35 y (median[a])	2.0	1.4, 2.9	<.001
Body mass index (BMI)			.009
18.5–24.9 (normal)	reference		
<18.5 (underweight)	0.9	.4, 2.2	.88
25–29.9 (overweight)	0.5	.3, .7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

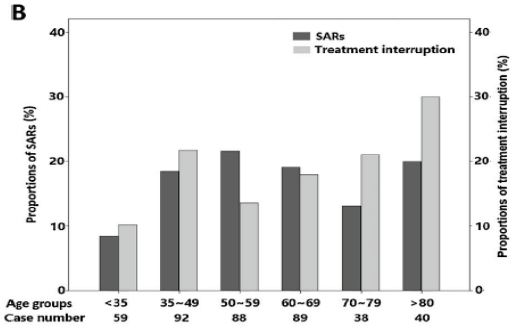
Sun HY. Tuberculosis 2018;111:121-6.

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

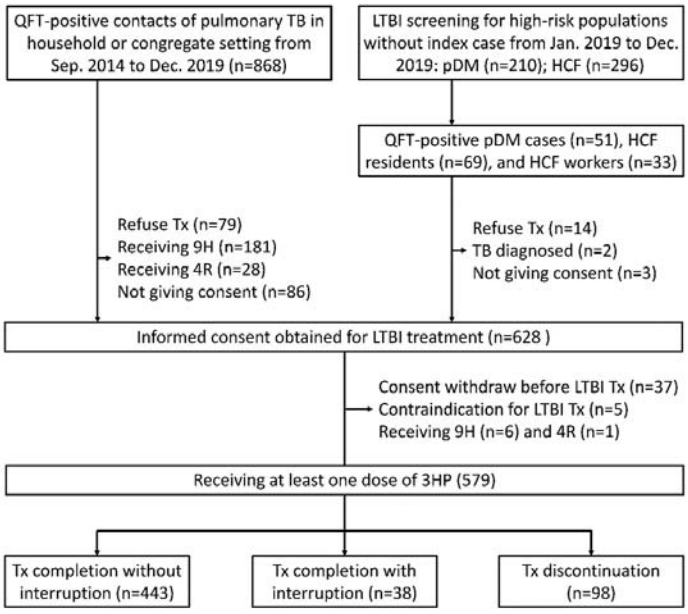
	Overall patients, N = 406	
	aOR (95% CI)	p-Value
LTBI regimens		
9H	1.00	–
3HP	2.90 (1.14–7.40)	0.026
4R	0.94 (0.10–9.15)	0.957
Age (years)		
<35	1.00	–
35–59	3.46 (1.13–10.55)	0.029
60–79	3.05 (0.95–9.74)	0.060
≥80	3.75 (0.98–14.40)	0.054
Female	1.64 (0.92–2.93)	0.095
BMI < 23 kg/m^2	2.23 (1.26–3.96)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

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



Clinical Infectious Diseases, ciaa1741

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

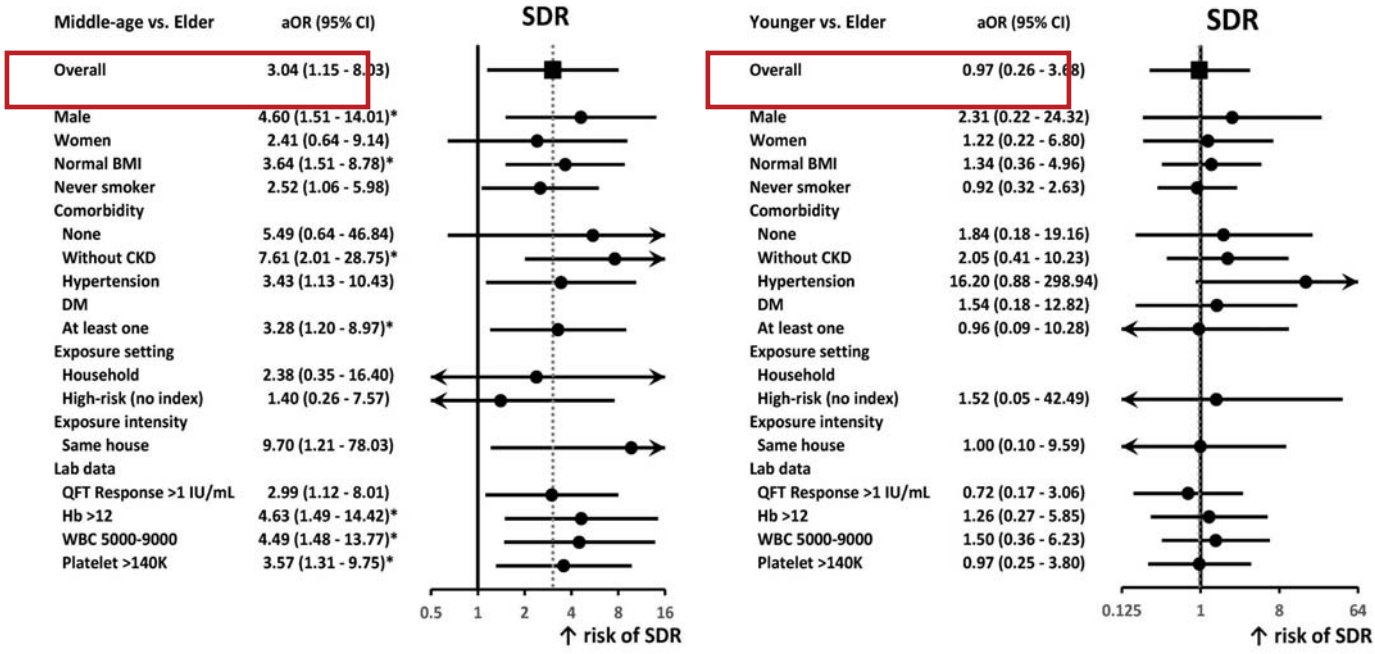
Details of 3HP related drug adverse reactions

	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



Clinical Infectious Diseases, ciaa1741

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

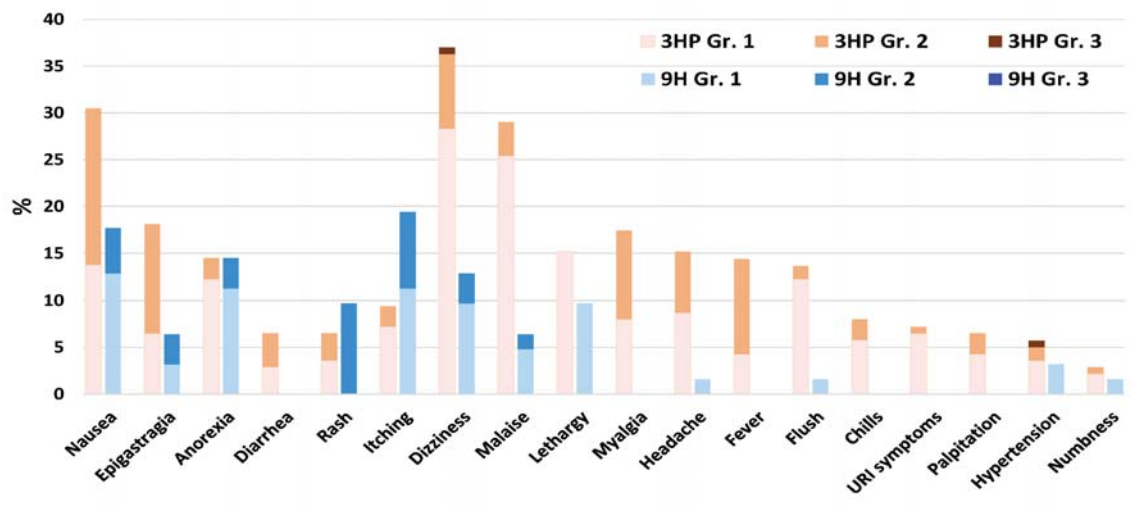
- Prospective, multicenter study. April 2018 to June 2020
  - Taichung Veterans General Hospital
  - Kaohsiung Maniple Ta-Tung Hospital
- **200 cases**
  - Age ≥ 45 years
  - ≥1 time HbA1c ≥9.0% within recent 1 year
- **LTBI screening performed by endocrinologist**
  - Pay-for-Performance project
  -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

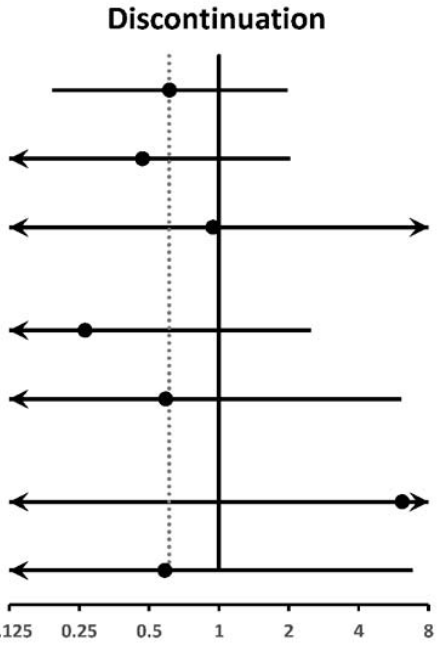
- 3HP group had higher proportion of flu-like symptoms and GI symptoms
- 9H group had higher proportion of skin rash



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

The completion rate is independent from regimen

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

Health Insurance Database Research in Taiwan

- 全國推動3HP治療的上市後蒐集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
  - 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。

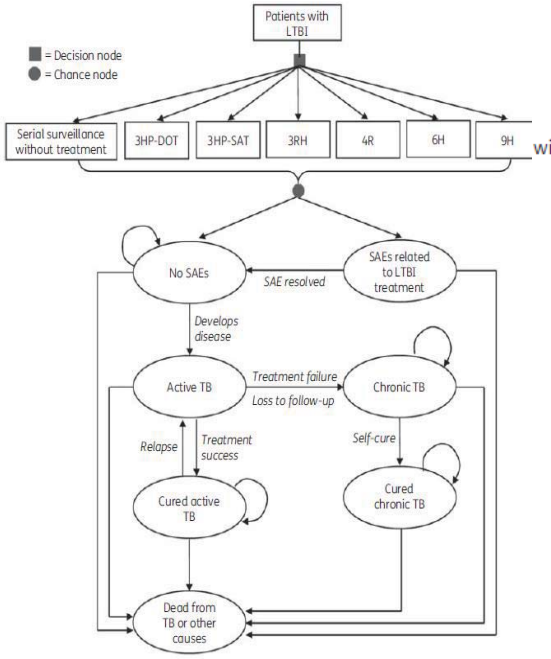
Unpublished Data

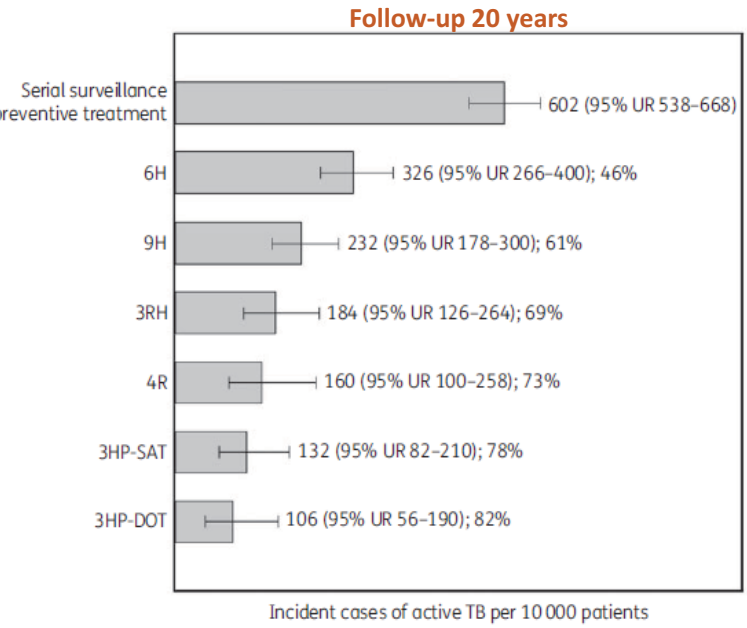
Outcome of 3HP Tx in different Taiwan cohorts

	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。

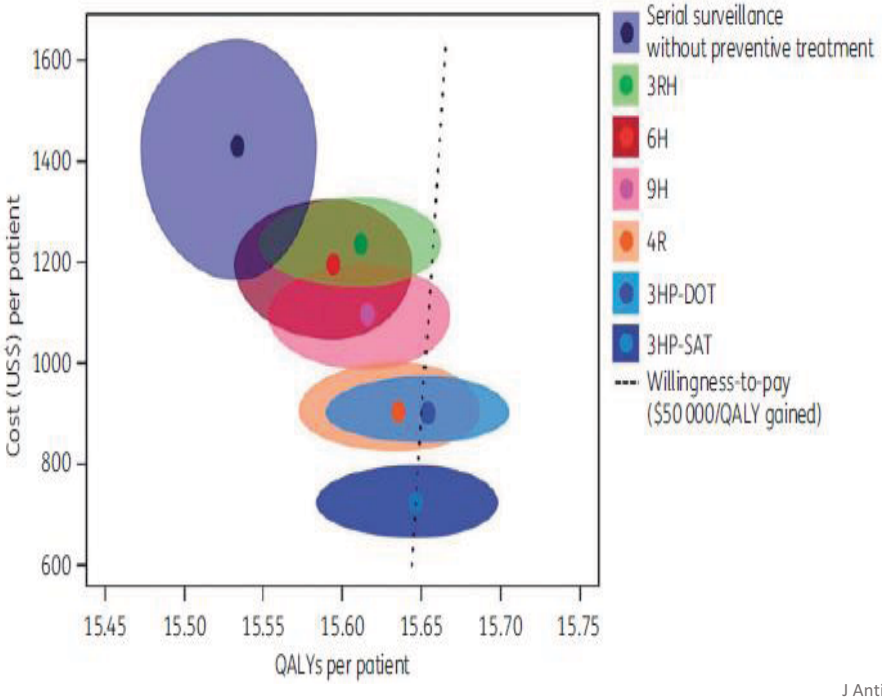
Cost-effectiveness of 3HP compared with other standard treatment regimens : A decision analysis study





J Antimicrob Chemother 2019; 74: 218–227

Cost-effectiveness plane for each of the seven simulated strategies

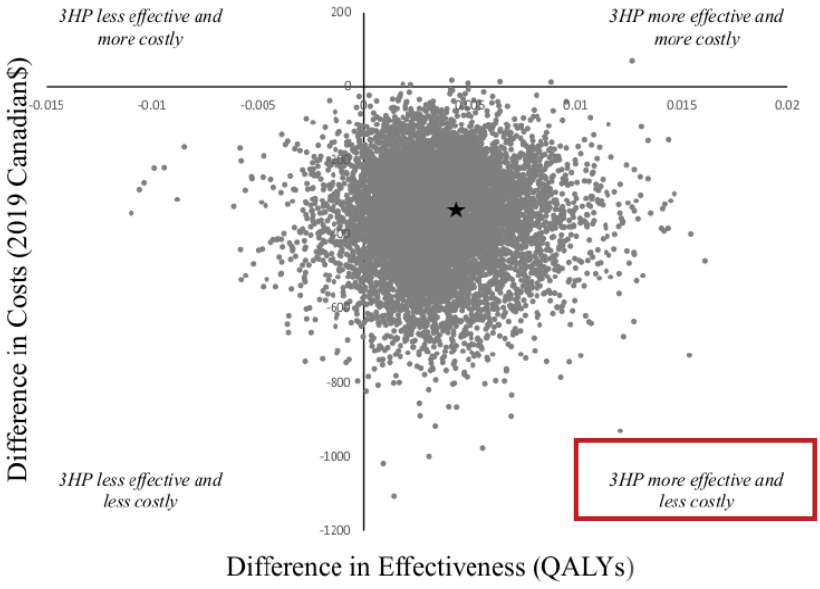


J Antimicrob Chemother 2019; 74: 218–227

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.

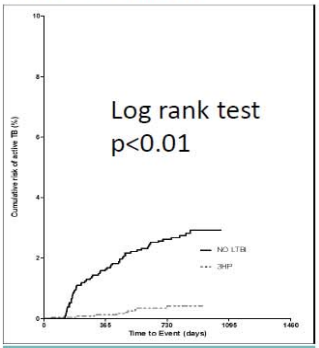


Pease C, et al. BMJ Open 2021;11:e047514.

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)

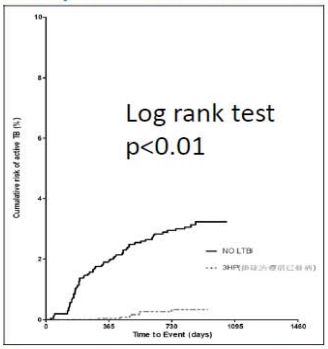
	發生率 (人年)	RR	95%CI		發生率 (人年)	RR	95%CI
3HP 未曾接受治療	0.18 1.35	0.13	(0.07-0.27)	3HP 9H	0.18 0.28	0.64	(0.27-1.52)

LTBI 接觸者接受治療的保護力約87%



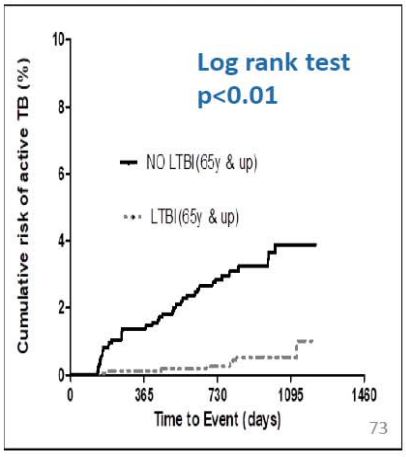
3HP vs. 未治療

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%



INH or RPT induced 3HP related SDR ? Still uncertain !

- Unpredictable systemic drug reaction occurred in 3.8%-10% of 3HP

Table S3. Drug re-challenge in participants who received 3HP and developed a systemic drug reaction (SDR) in the PREVENT TB study

First Drug re-challenge			Second Drug re-challenge		
First drug	Number re-challenged	Tolerated	Second drug	Number re-challenged	Tolerated
INH	20	Yes (n=3) (15%)	---	0	--
		No (n=17) (85%)	RPT[c]	5	Yes (n=3) (60%)
					No (n=2) (40%)
RPT	51	Yes (n=36) (71%)	INH	12	Yes (n=2) (17%)
					No (n=10) (83%)
		No (n=15) (29%)	INH	7	Yes (n=3) (43%)
					No (n=4) (57%)
INH + RPT	2	Yes (n=0)			
		No (n=2) (100%)			
Total	73	Yes (n=39) (53%)		24	Yes (n=8) (33%)

N. Engl. J.Med. 2011, 365, 2155–2166
Tuberculosis 2018, 111, 121–126
Clin. Infect. Dis. 2015, 61, 527–535
WHO. Global Tuberculosis Report 2020

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

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:

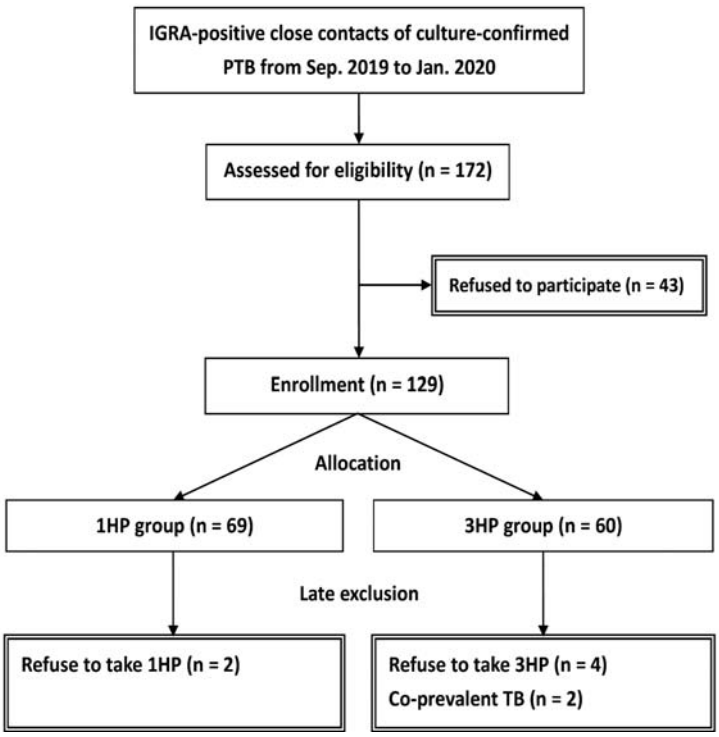
1. ADRs: flu-like symptoms, Hepatotoxicity
2. treatment completion
3. plasma drug levels
4. risk factors of SDR

Number needed: 245 * 2

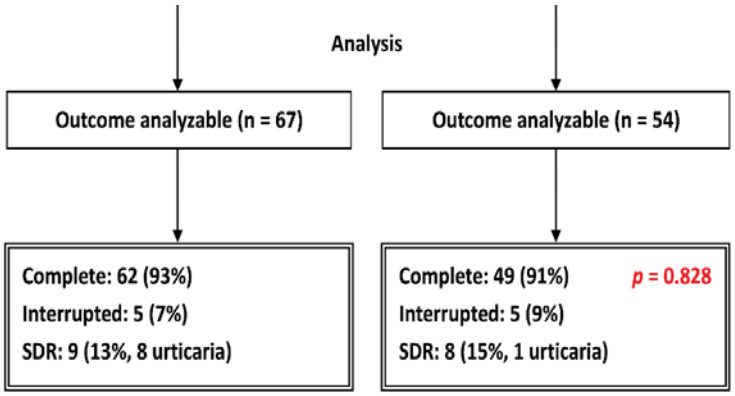
Study period: 2019 – 2022

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	



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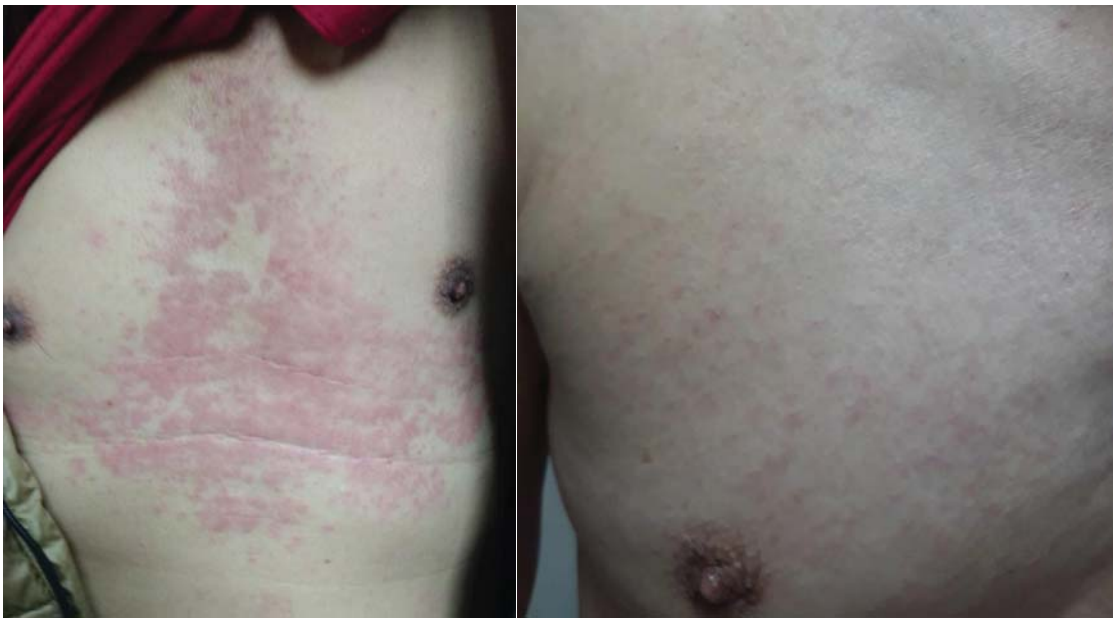
The details of ADRS in 1HP group and 3HP group

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

Unpublish data

52 year-old male, post 14th dose1HP



Maculopapular eruption, not very itching

Unpublish data

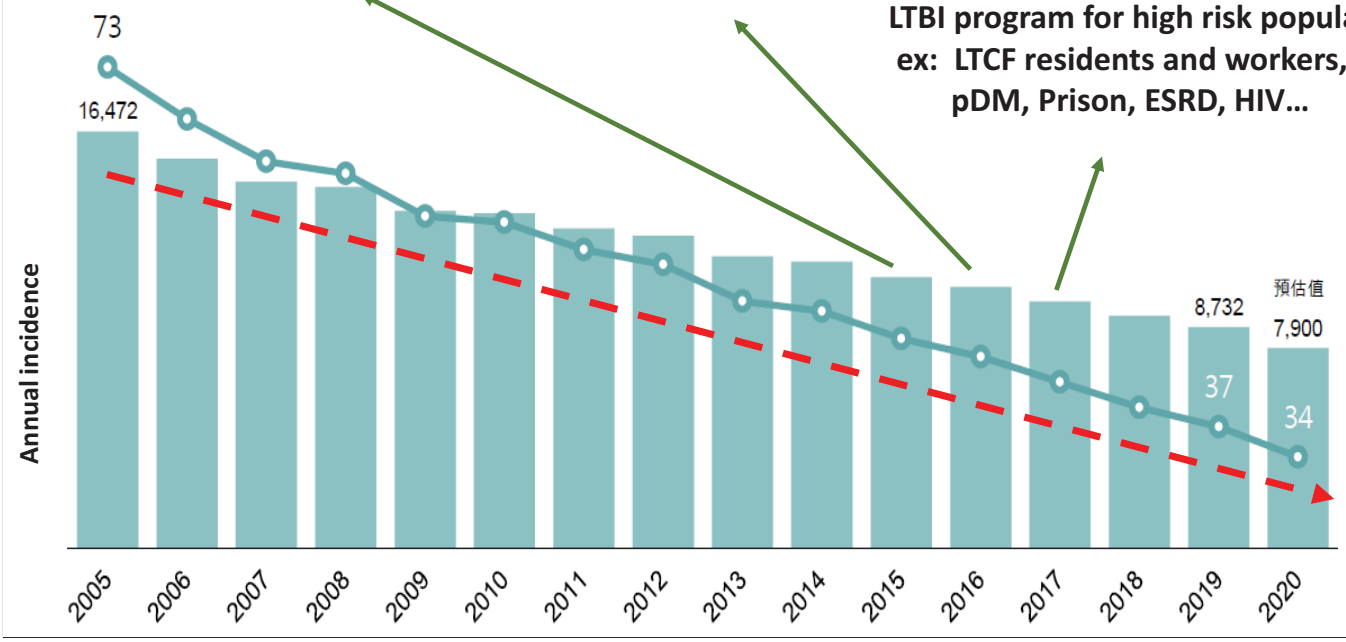
Thank You

LTBI Intervention in Taiwan : since 2014

IGRA/TST/9H for all aged contact
eDOT initiation

IGRA/3HP & 9H for all aged contact

LTBI program for high risk population
ex: LTCF residents and workers,
pDM, Prison, ESRD, HIV…



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 Metabolic Enzyme Genetic Polymorphisms associated with ADRs

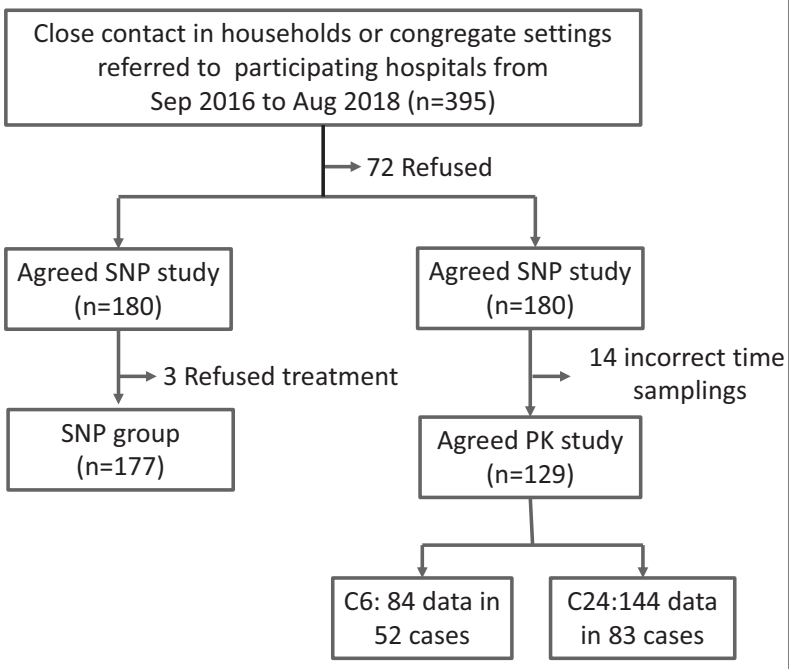
- A multicenter observational study
  - 377 close contacts aged >12 years receiving 3HP
  - February 2017 - October 2018.
  - Mean age was 45.7 years
  - 208 participants (55.2%) were women,
  - 144 participants (38.2%) had comorbidities
  - 184 (48.8%) developed ADRs
    - Grade 1: 77.68%
    - Grade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

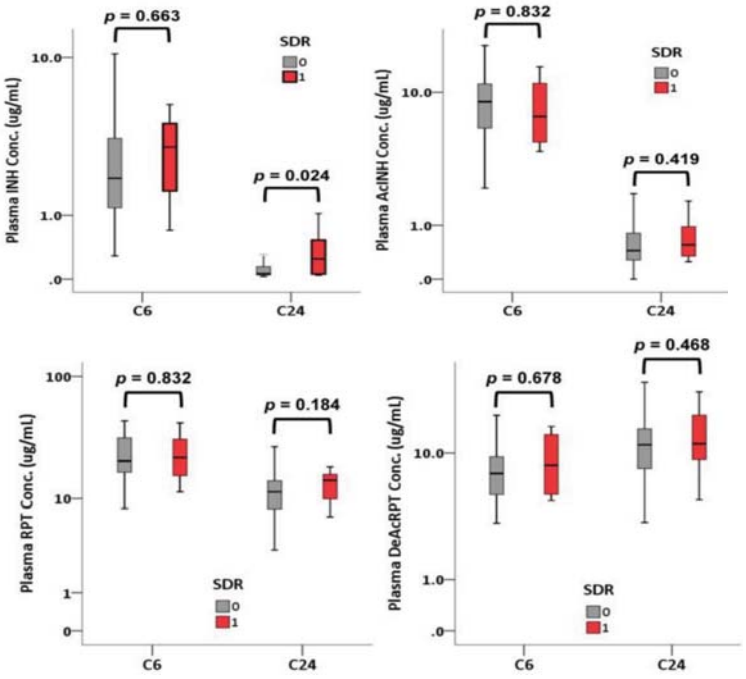
J. Clin. Med. 2019, 8, 812

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



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

J. Clin. Med. 2019, 8, 812