



腎衰竭與腎移植病人的LTBI防治



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Outline

- Active TB in 洗腎和腎移植
- TB prevention 在洗腎和腎移植角色
- LTBI 防治在洗腎和腎移植病人策略
 - LTBI在洗腎和腎移植的診斷
 - LTBI在洗腎和腎移植的治療實務

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1. 為何要針對腎衰竭跟腎移植病人作TB防治?



Active TB in dialysis patients

300/10⁵

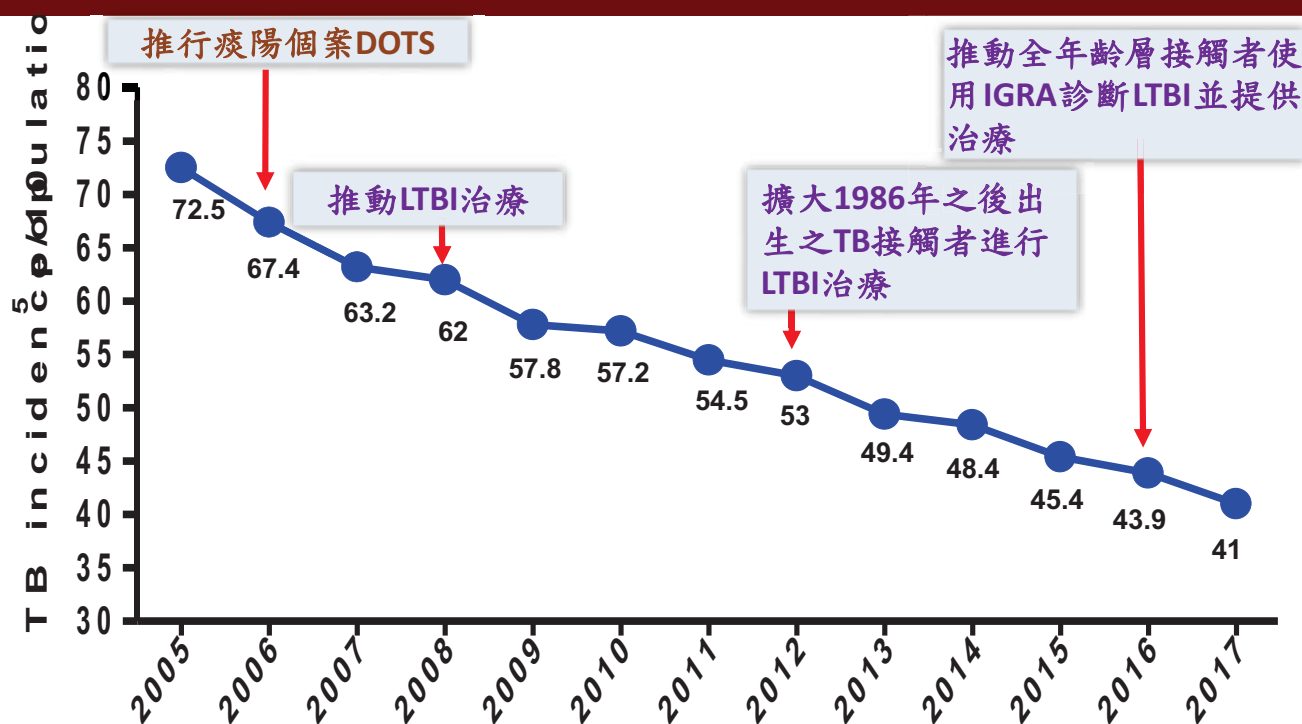
台灣年發生率
(健保資料庫文獻)

10-20倍

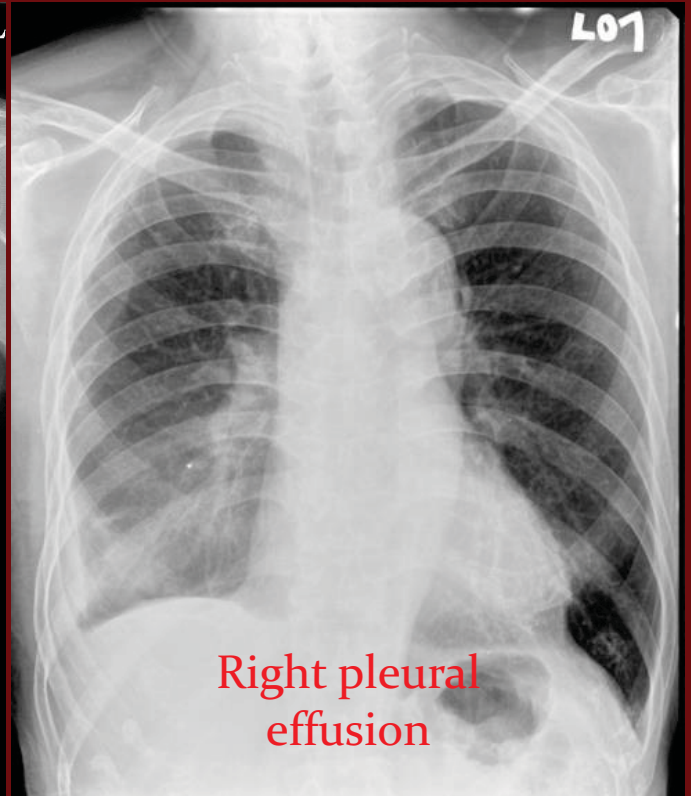
與一般人發生率比較

Li S.Y., Clin Microbiol Infect 2011; 17: 1646-1652
Lundin et al, Am J Med. 1979 ;67:597-602
Lui SL, et al, Am J Kidney Dis. 2001 Nov;38(5):1055-60.
Kazancioglu R et al., Hemodial Int. 2010 Oct;14(4):505-9.

結核病政策現況



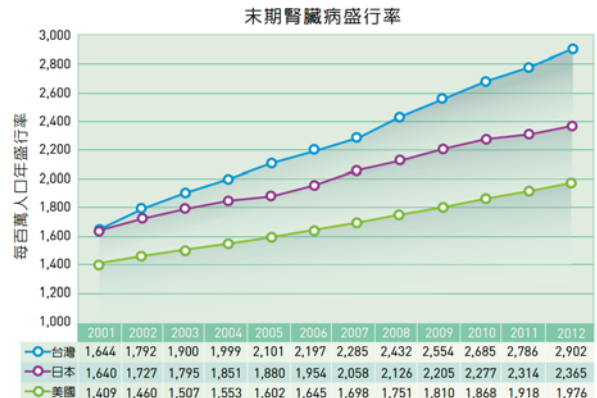
Active Case Finding



台灣末期腎臟病 (ESRD) 發生率/盛行率



資料來源：美國腎臟資料系統 (USRDS)



資料來源：美國腎臟資料系統 (USRDS)

移植成果



Active TB in Kidney Transplant patients

506/10⁵

發生率

7倍

與一般人發生率比較

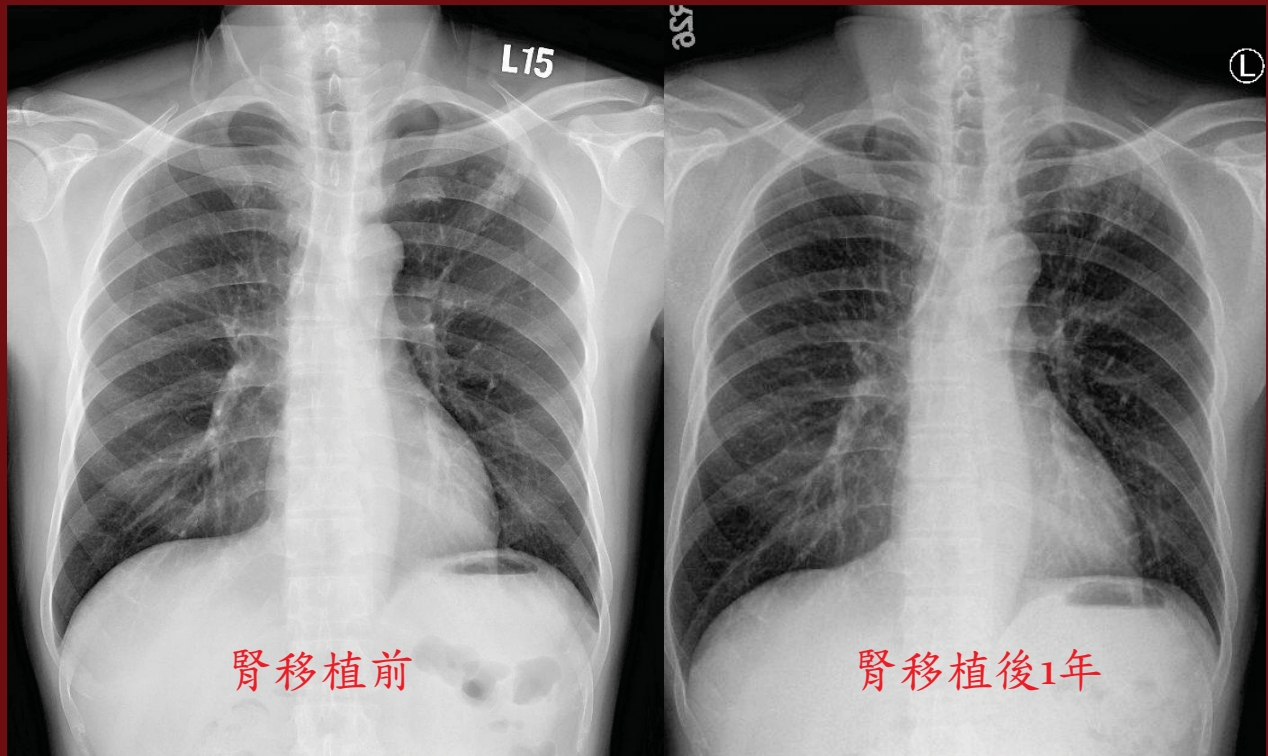
20 月

移植後20個月發生

IQR 5.0-70.0 月

A TB case in kidney transplant

- 謝00先生, IGRA: strong positive



Clinical Features of active TB

- An **insidious** or **atypical** symptoms
- More **extra-pulmonary** presentation

→ **Delay** diagnosis

→ increase **mortality**

Chou KJ, *Nephron* 2001;88:138 – 143

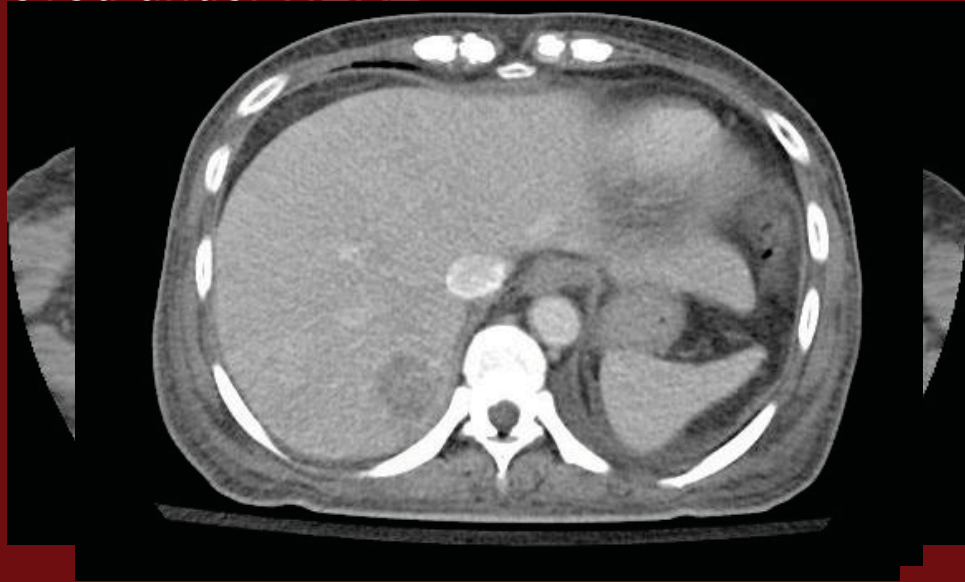
Venkata RK, *Clin Nephrol* 2007; 67: 217-220.

Fang HC. *Int J Tuberc Lung Dis* 2004; 8: 92-97.

Torre-Cisneros J, *Clin Infect Dis* 2009; 48: 1657-1665.

A TB case in ESRD status

- 劉00女士
 - A ESRD case, neck & mediastinal LAP + liver tumor
 - ⇒ All biopsies showed granulomatous inflammation
 - ⇒ Improved under HERZ



Outcome - Mortality

1.7%

TB directed death

25.6%

nonTB directed death

Dialysis

6.1 ~ 8.9%

Kidney transplant

1. 為何要針對腎衰竭跟腎移植病人作TB防治?

- 免疫力低下，易發生結核
- 發生時不典型，預後較差
- 藥物耐受性差



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2. LTBI防治的重要性?

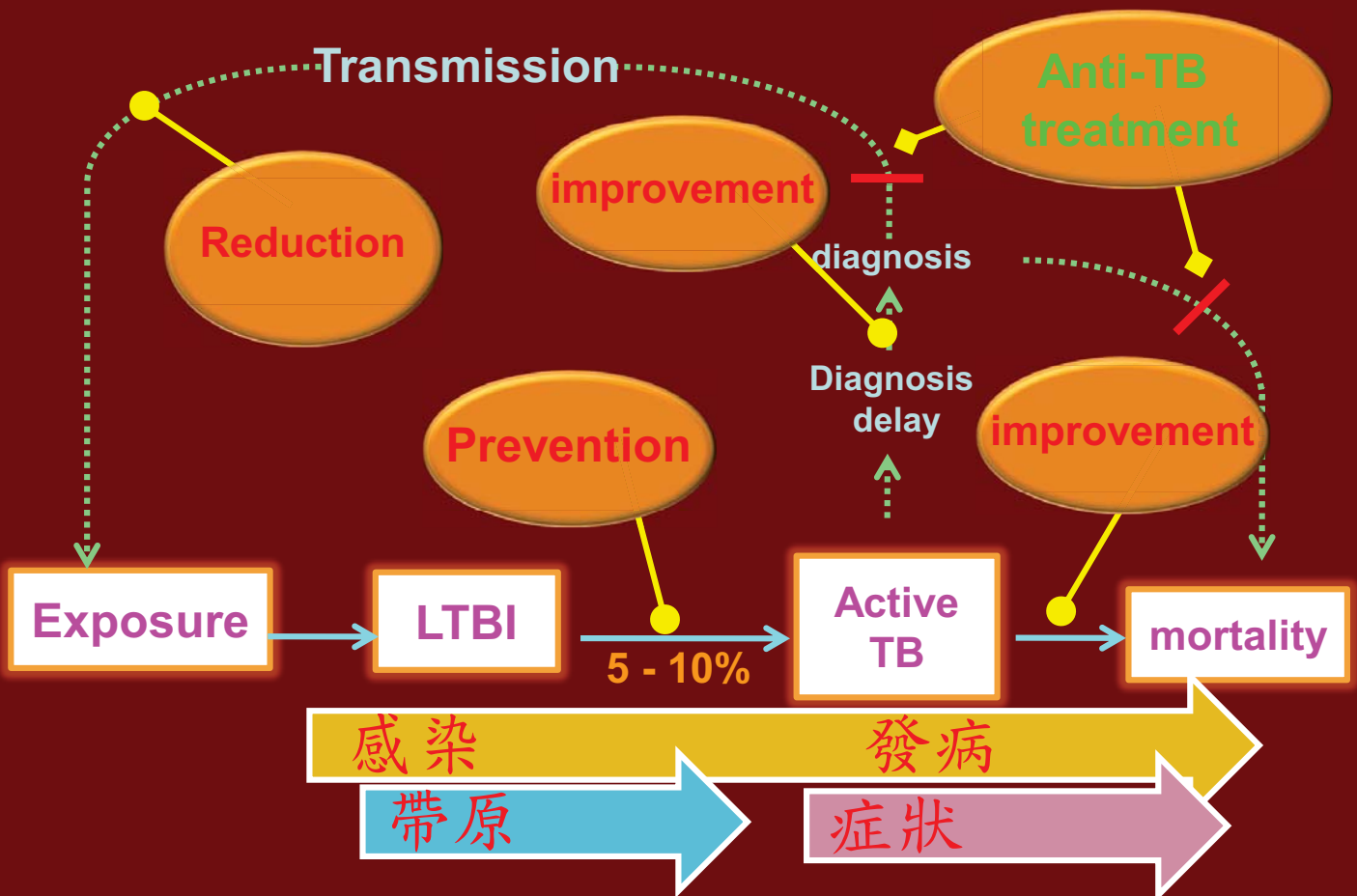
病未病
病欲病
病已病

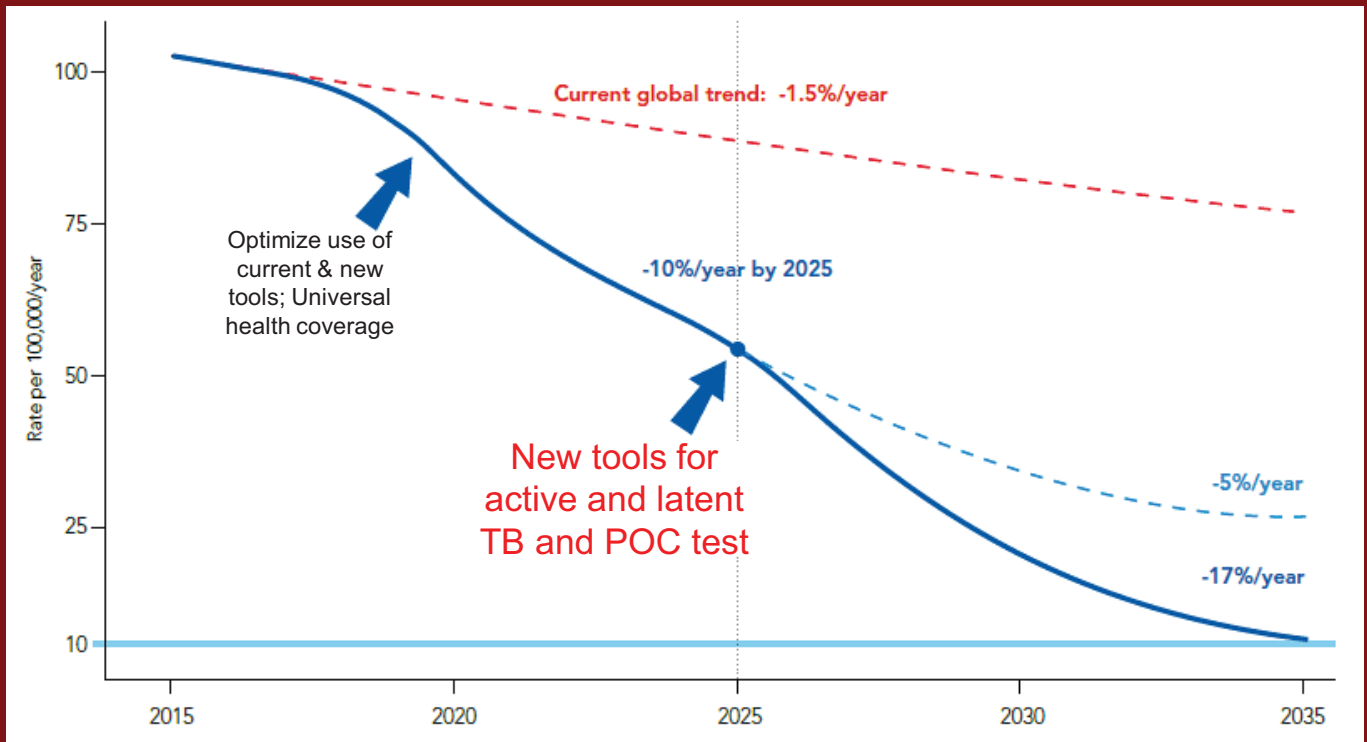
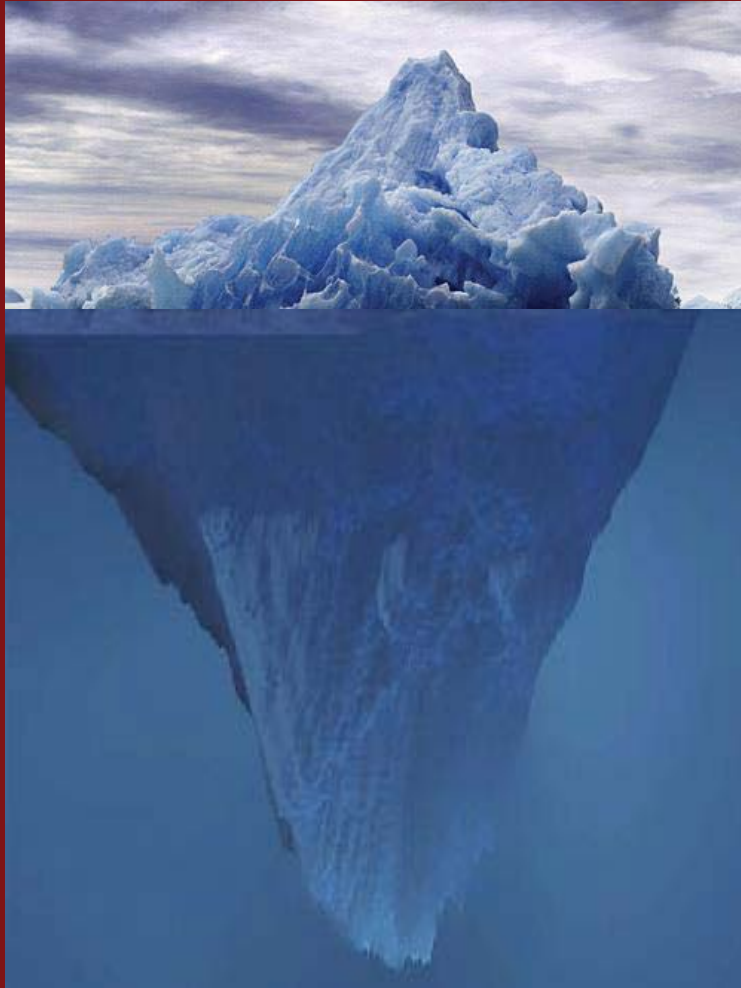
醫醫醫
醫醫醫
醫醫醫

上中下



Nature course of TB





預防治療，是一人的效果嗎？



世界未來結核病政策

Vision

A world free of TB. Zero deaths, disease and suffering due to TB.

Goal

End the global tuberculosis epidemic.

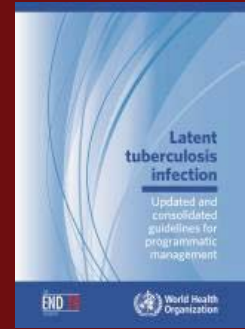
Indicators

- 95% reduction by 2035 in number of **TB deaths** compared with 2015.
- 90% reduction by 2035 in **TB incidence** rate compared with 2015.
- Zero TB-affected families facing **catastrophic costs** due to TB by 2035.



WHO LTBI GUIDELINE

- Systematic testing & treatment of LTBI for
 - contacts of pulmonary TB cases,
 - people living with HIV,
 - patients initiating anti-TNF treatment,
 - **patients receiving dialysis,**
 - **organ or haematologic transplantation**
 - patients with silicosis.(Strong recommendation)



問題1

- 下列何種族群**“不是”**列為WHO要LTBI篩檢治療的高風險族群？
 - 1、洗腎族群
 - 2、準備要移植的病人
 - 3、結核接觸者
 - 4、控制良好的糖尿病病人



各國的建議

Table 1 | Tuberculosis screening guidance for chronic kidney disease populations

Society	Year	CKD	Dialysis	Transplant
American Thoracic Society ³⁷	2000	—	TST for immune compromised. No specific recommendations for dialysis	TST for immune compromised. No specific recommendations for transplant candidates
American Transplant Society (donor) ³⁸	2012	—	—	All living donors should be screened with a TST or IGRA
American Transplant Society (recipient) ³⁹	2011	—	—	All transplant candidates should be screened with TSS or IGRA
British Thoracic Society ²⁹	2010	CKD patients should receive a TB risk assessment and if appropriate an IGRA	All dialysis patients should receive a TB risk assessment and, if appropriate, an IGRA	All transplant candidates should be screened with an IGRA
Canadian Thoracic Society ⁴⁰	2014	—	TST or IGRA recommended for immune compromised. No specific recommendations for dialysis	TST or IGRA recommended for immune compromised. No specific recommendations for transplant candidates
Canadian Transplant Society ⁴¹	2005	—	—	All transplant candidates should be screened with TST
European Centre for Disease Prevention and Control ⁴²	2011	—	IGRA with concurrent TST for immune compromised. No specific recommendations for dialysis patients	IGRA with concurrent TST for immune compromised. No specific recommendations for transplant candidates
National Institute for Health and Clinical Excellence ⁴³	2011	—	IGRA or IGRA and concurrent TST for immune compromised. No specific recommendations for dialysis	IGRA or IGRA and concurrent TST for immune compromised. No specific recommendations given for transplant candidates
World Health Organization ³⁶	2015	—	Screen all dialysis patients with TST or IGRA	Screen all transplant candidates with TST or IGRA

CKD, chronic kidney disease; IGRA, interferon gamma release assay; TST, tuberculin skin test.

Romanowski K et al., 2016 Jul;90(1):34-40.

肺結核高風險群 洗腎病友免費篩檢



2018，新北市開始

- 新北市2017年度的資料顯示：
 - 腎友TB發病 **888/10⁵** 人年
 - 是一般人的 **23** 倍

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LTBI in 洗腎和腎移植

- LTBI在洗腎和腎移植的診斷
- LTBI在洗腎和腎移植的治療實務

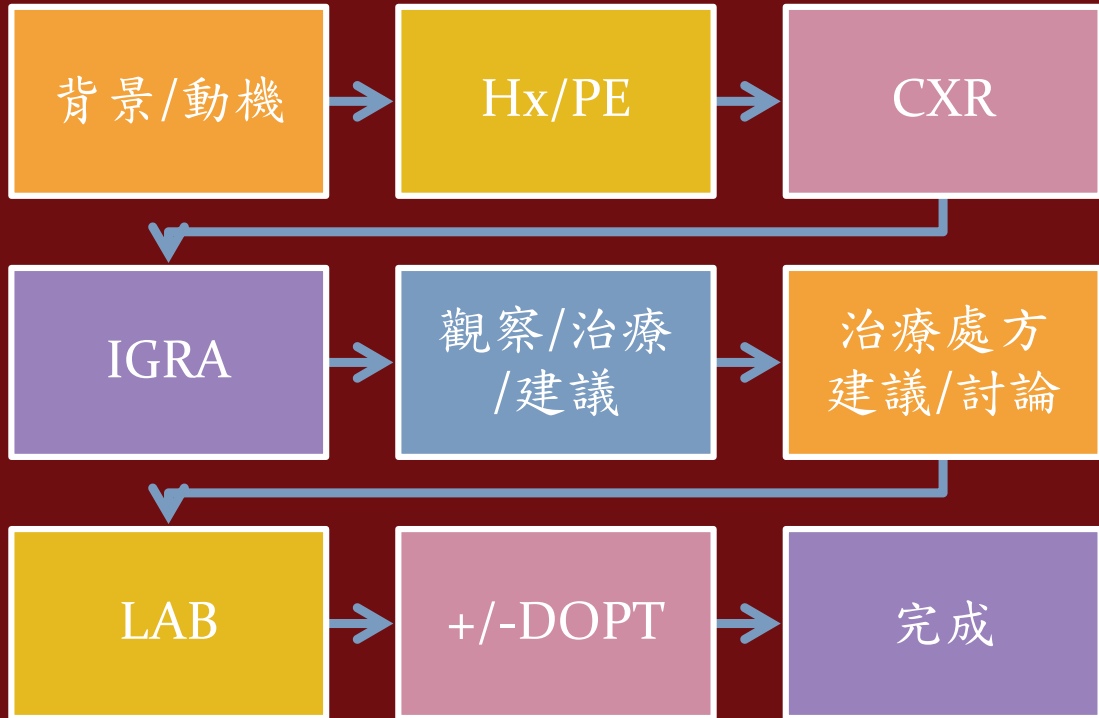
Others?

問題2

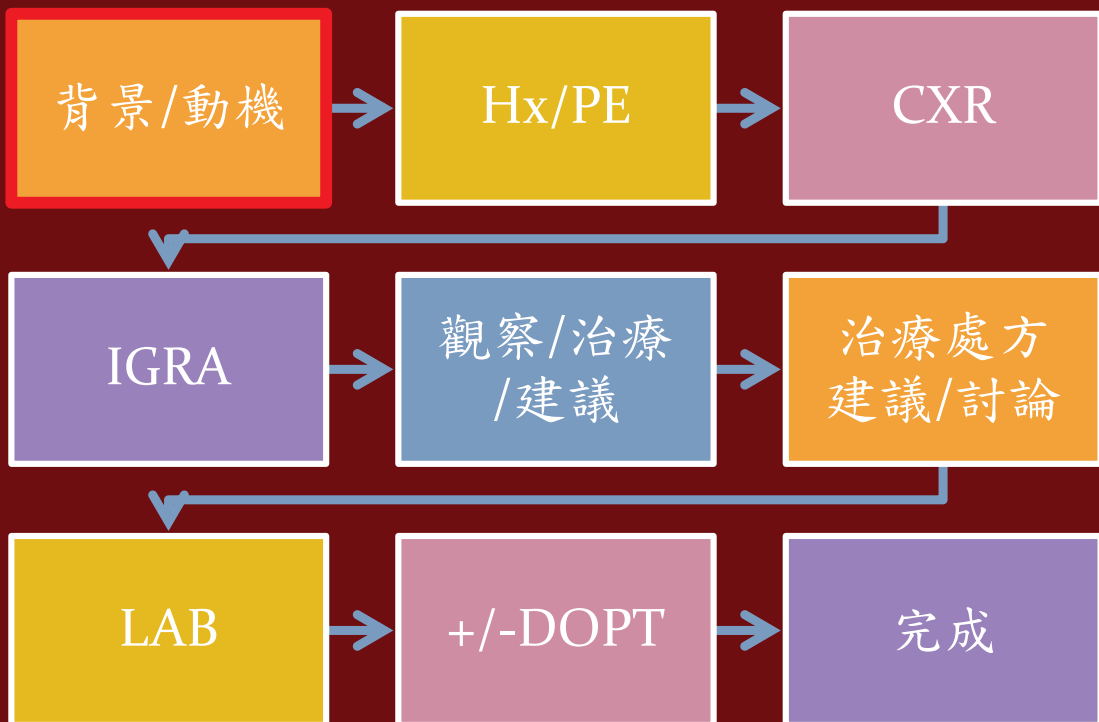
- 下列是LTBI診治重點，以下何者為“非”？
 - 1、陽性就要治療
 - 2、討論病人的動機與意願
 - 3、治療時要注意是否有副作用產生
 - 4、要先排除活動性結核



建議流程



建議流程



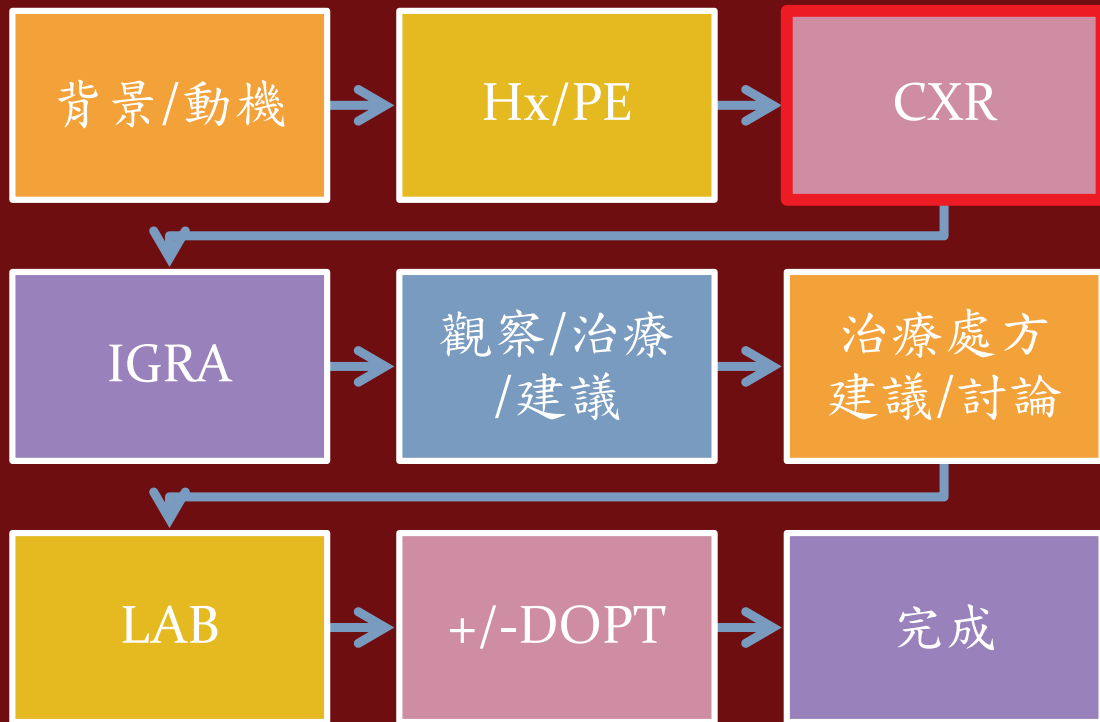
解釋說明比用藥重要



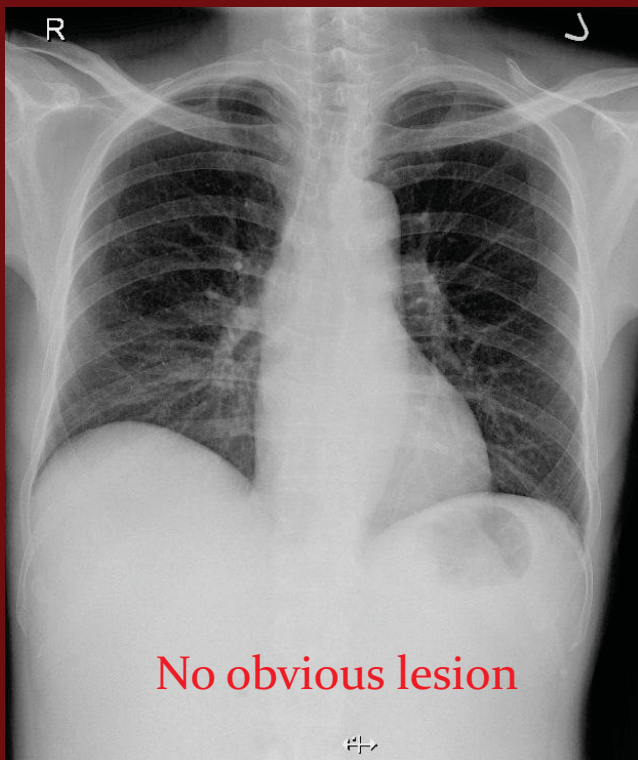
FAQ

- 緊張型 – 會不會傳染？
- 散漫型 – 沒感覺！會跟著你一生
- 拒絕型 – 吃藥聽起來很恐怖
- 忙碌型 – 在拼指考，沒空！

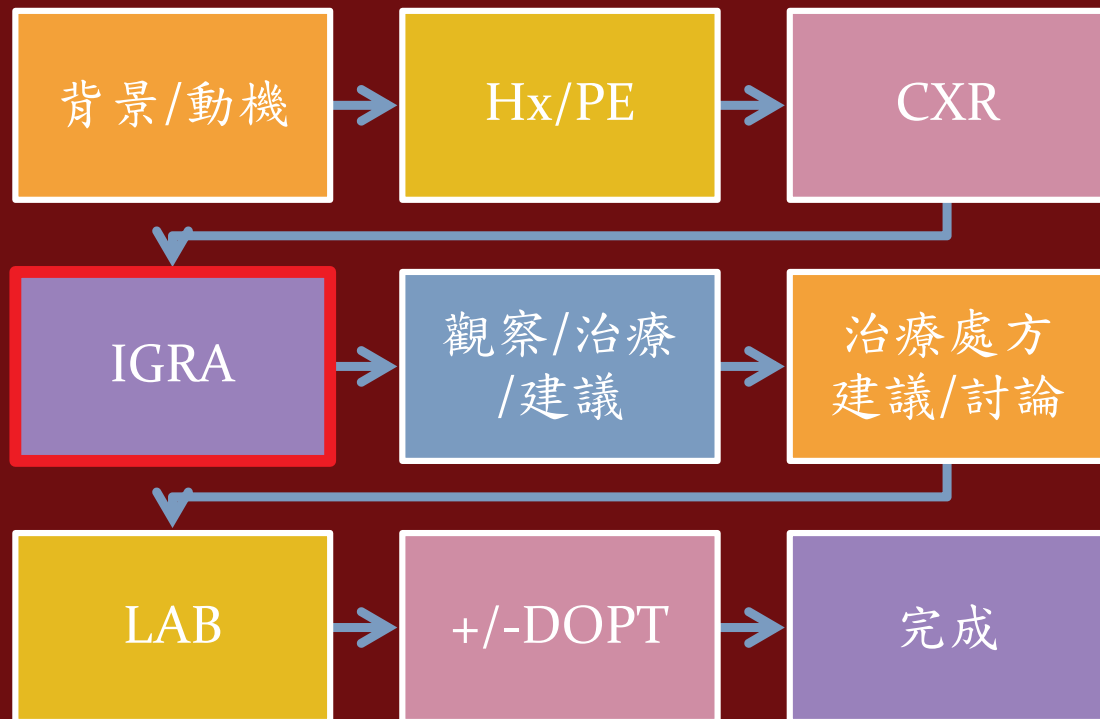
建議流程



排除active TB



建議流程



如何診斷潛伏結核感染/帶原

- 診斷方式:偵測對結核菌抗原有**免疫反應**
- 目前這類間接的診斷方法，大致上有兩種。
 - Tuberculin skin test (TST)
皮膚結核菌素測驗
 - Interferon-gamma release assay (IGRA)
丙型干擾素釋放試驗

皮膚結核菌素測驗

- 已經被使用超過一個世紀
- 觀察對皮內注射結核菌素後48到72小時後的延遲性過敏反應



丙型干擾素釋放試驗

克肺癆

T-Spot

抽血

In tube

Isolating PBMC

Stimulation by TB antigen in 37 °C

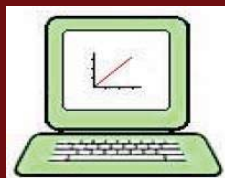
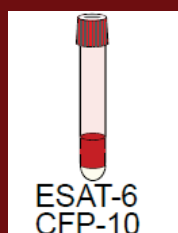
In tube

In culture plate

IFN-gamma assay

ELISA

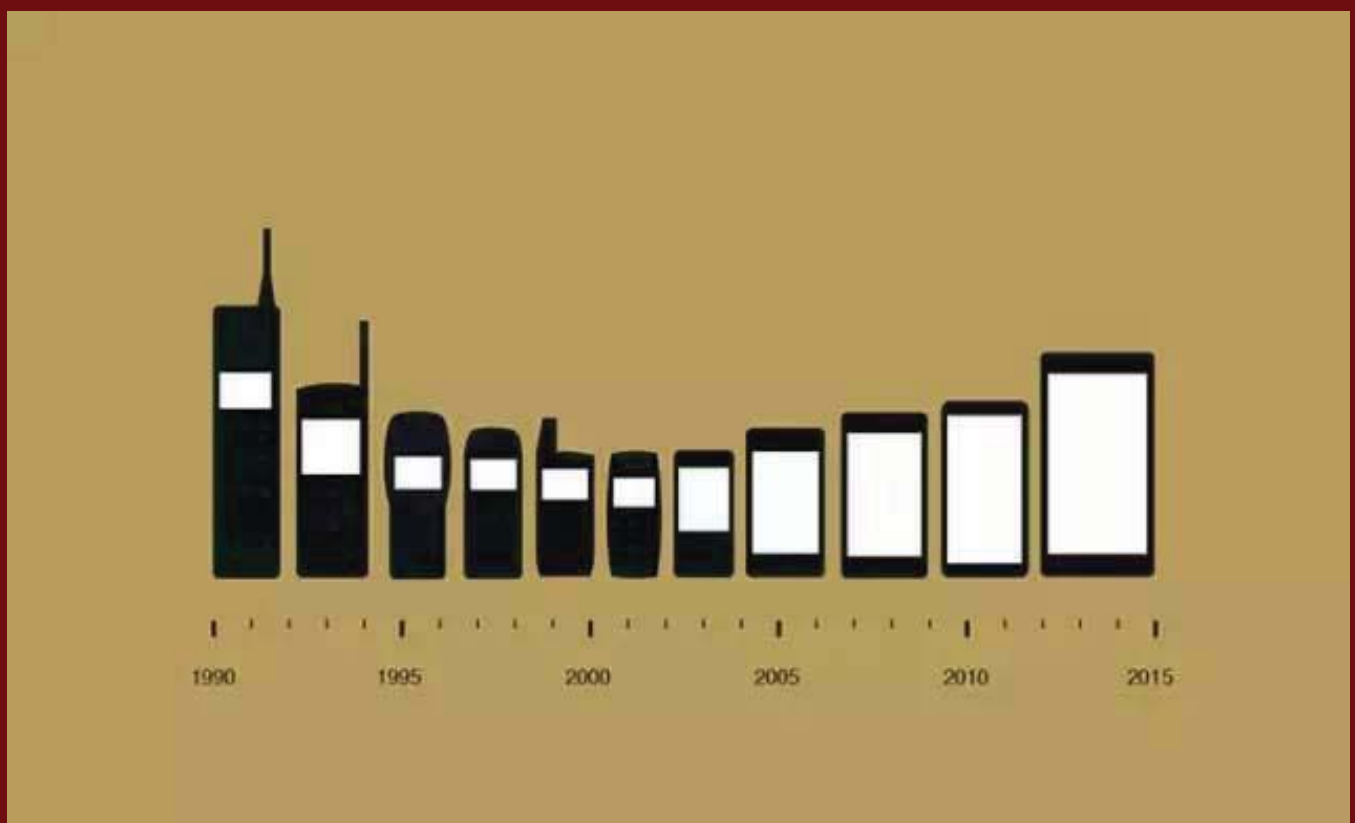
ELISpot



診斷方式的比較

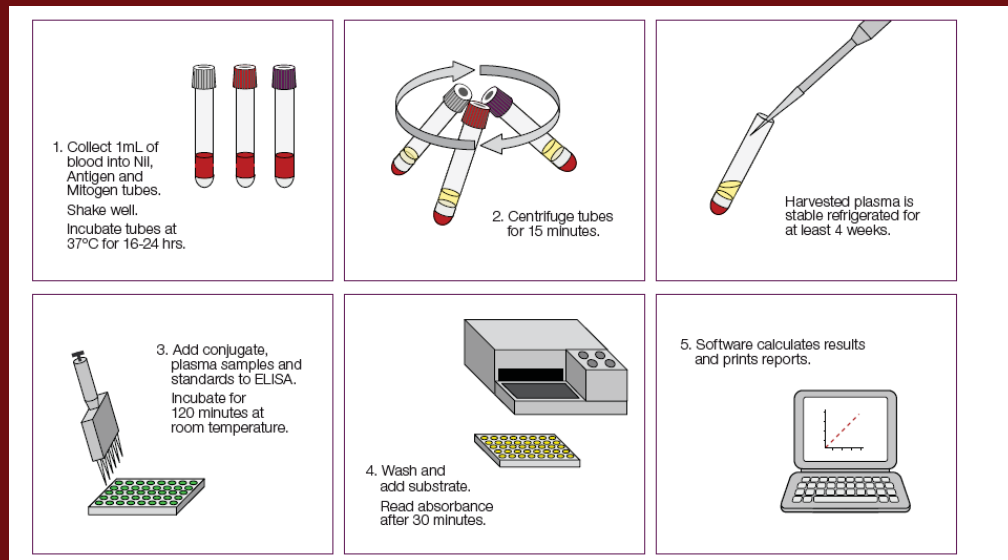
	皮膚結核菌素測驗	丙型干擾素釋放試驗
1. 價格	便宜 勝	昂貴
2. 普及性	取得易 勝	不普及
3. 抗原專一性	不專一，易交叉反應	較專一 勝
4. 檢測需返診	需要	不需 勝
5. 免疫不全患者，是否容易偽陰性	易	有對照組 勝
6. 副作用	皮膚潰爛	抽血 勝
7. Booster effect	有	無 勝
8. 人為判讀誤差	有	無 勝
9. 文獻佐證	充足 勝	<5歲，目前文獻不足

進化史



Detection of LTBI

- interferon-gamma release assay (IGRA) such as the QuantiFERON®-TB Gold in tube (QFT-GIT)

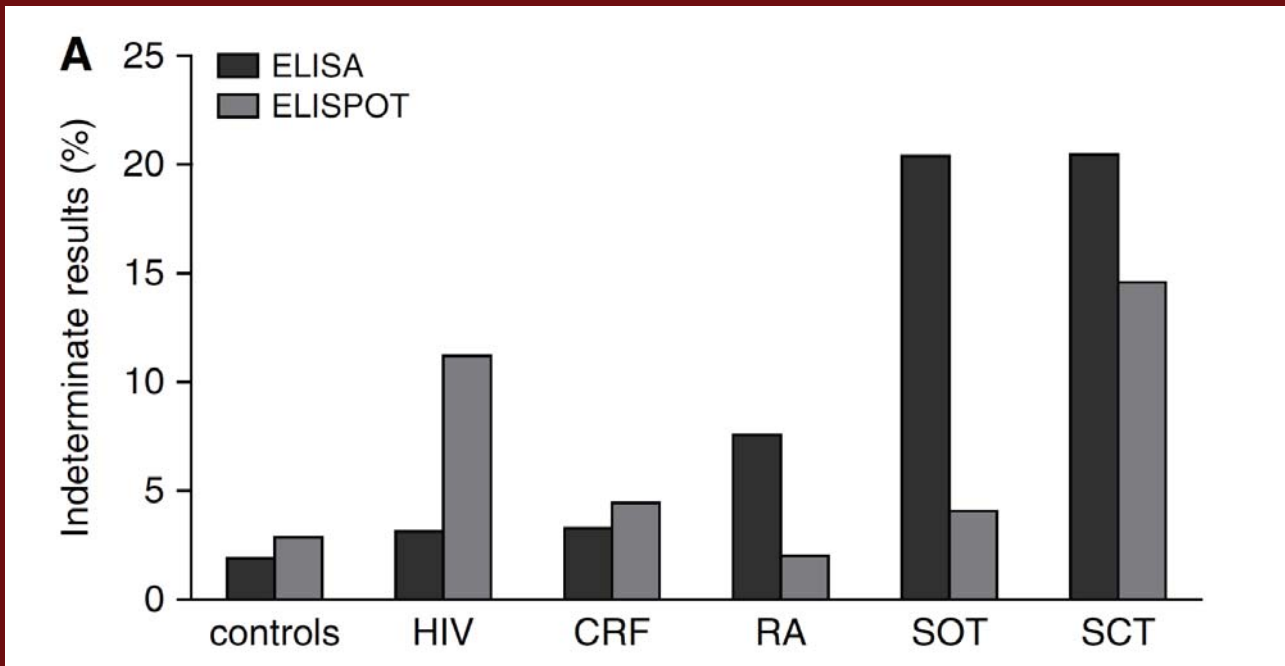


Antigens: IGRA vs. TST

- TST: purified protein derivative
- IGRA: Proteins from *region of difference-1 (RD-1) gene* that is not present in BCG sub-strain

Tuberculosis Complex	ESAT-6	CFP-10	TB7.7	Environmental Strains	ESAT-6	CFP-10	TB7.7
M tuberculosis	+	+	+	M abcessus	-	-	-
M africanum	+	+	+	M avium	-	-	-
M bovis	+	+	+	M branderi	-	-	-
BCG substrain				M celatum	-	-	-
gothenburg	-	-	-	M chelonae	-	-	-
moreau	-	-	-	M fortuitum	-	-	-
tice	-	-	-	M gordonii	-	-	-
tokyo	-	-	-	M intracellulare	-	-	-
danish	-	-	-	M kansasii	+	+	-
glaxo	-	-	-	M malmoense	-	-	-
montreal	-	-	-	M marinum	+	+	-
pasteur	-	-	-	M oenavense	-	-	-
				M scrofulaceum	-	-	-
				M smegmatis	-	-	-
				M szulgai	+	+	-
				M terrae	-	-	-

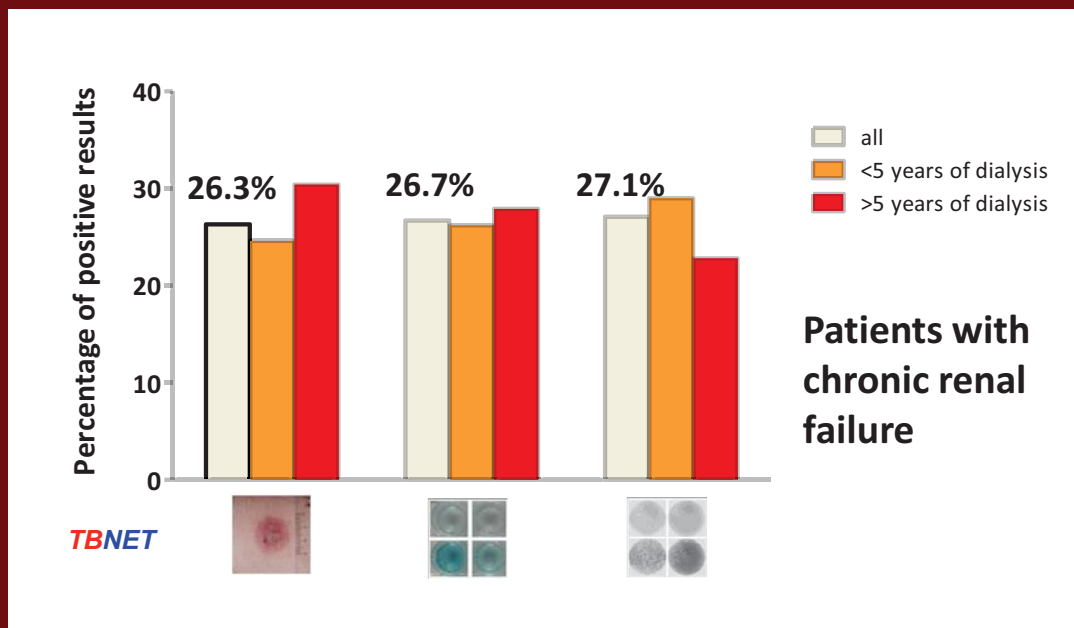
洗腎/腎移植病人的IGRA



Sester M, Am J Respir Crit Care Med 2014 Nov 15;190(10):1168-76

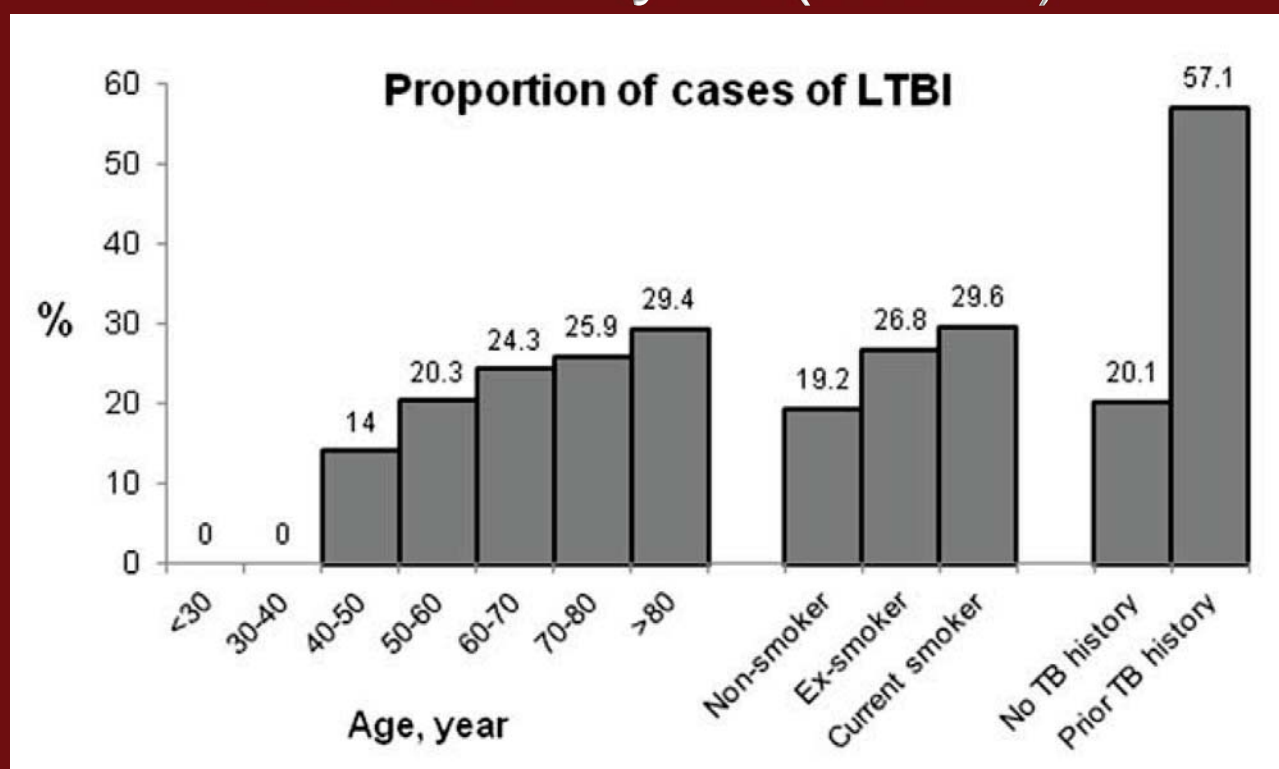
LTBI在洗腎病人中多嗎?

Similar percentages of positive test results in all assays in CRF

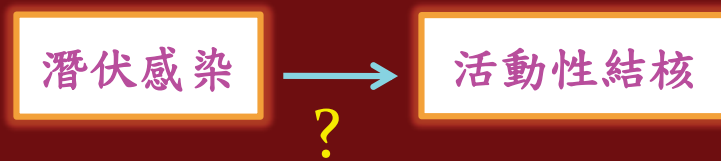


Sester M, Am J Respir Crit Care Med 2014 Nov 15;190(10):1168-76

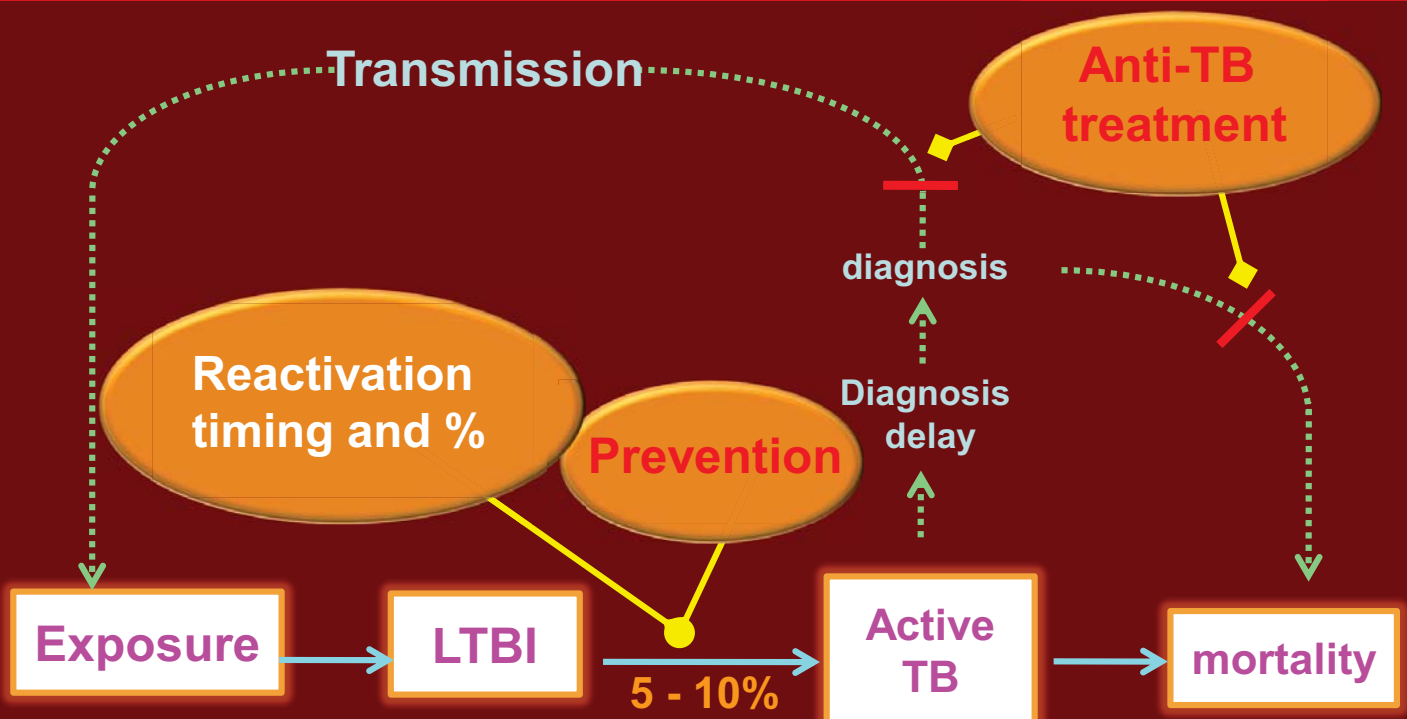
LTBI in dialysis (NTUH)



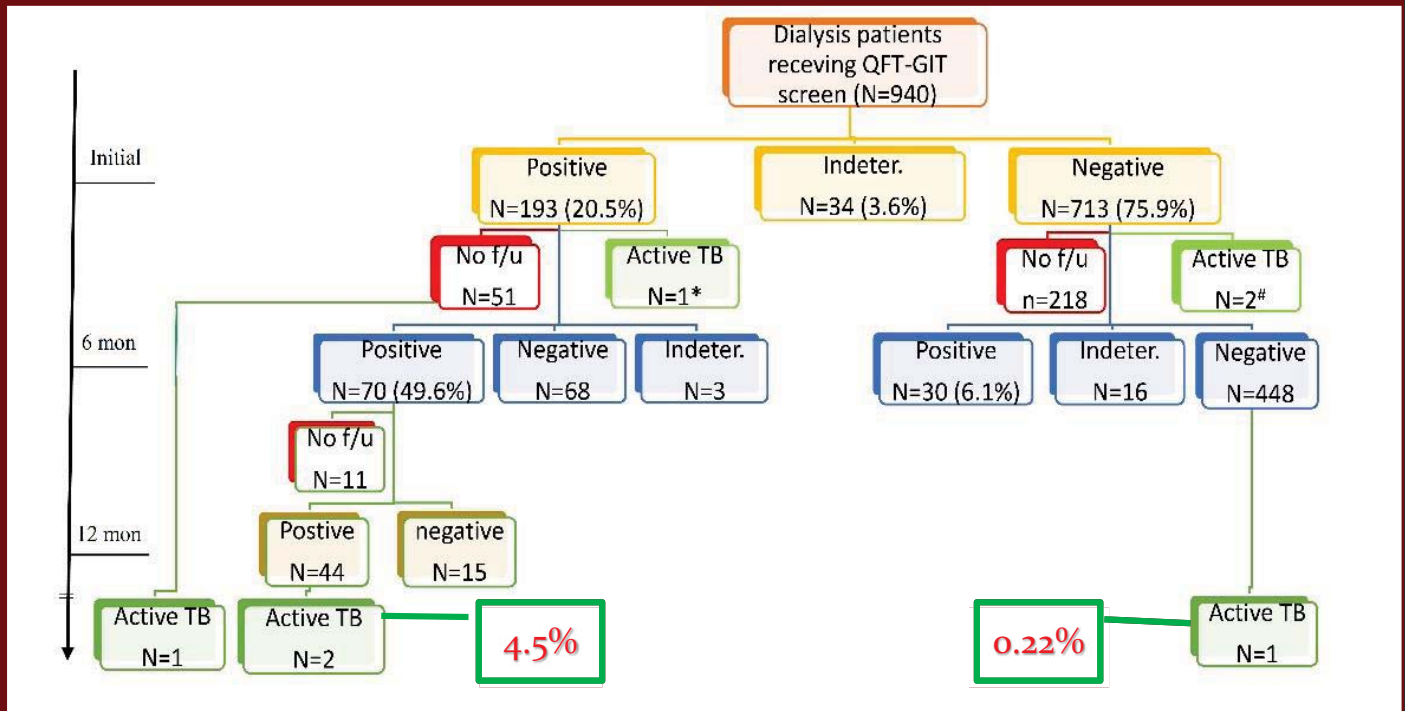
洗腎病人的LTBI後續發病多嗎？



Question

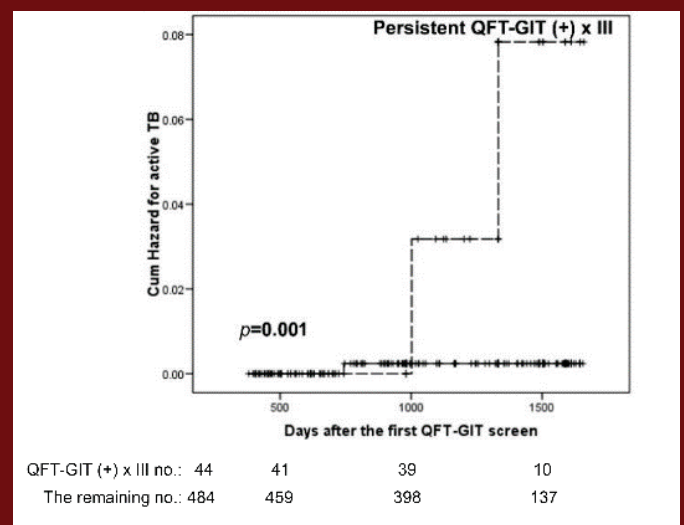
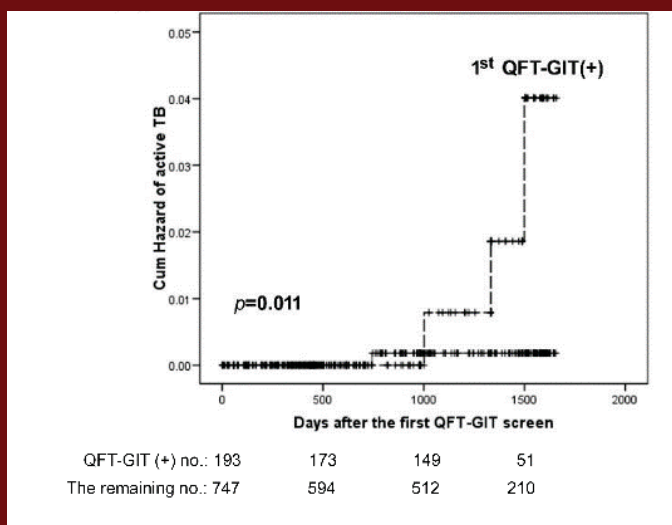


Flow chart of case follow-up



Shu CC. Medicine 2016 95(22):e3813

KM curves of incident tuberculosis by different status of QFT-GIT results in dialysis patients



Shu CC. Medicine 2016 95(22):e3813

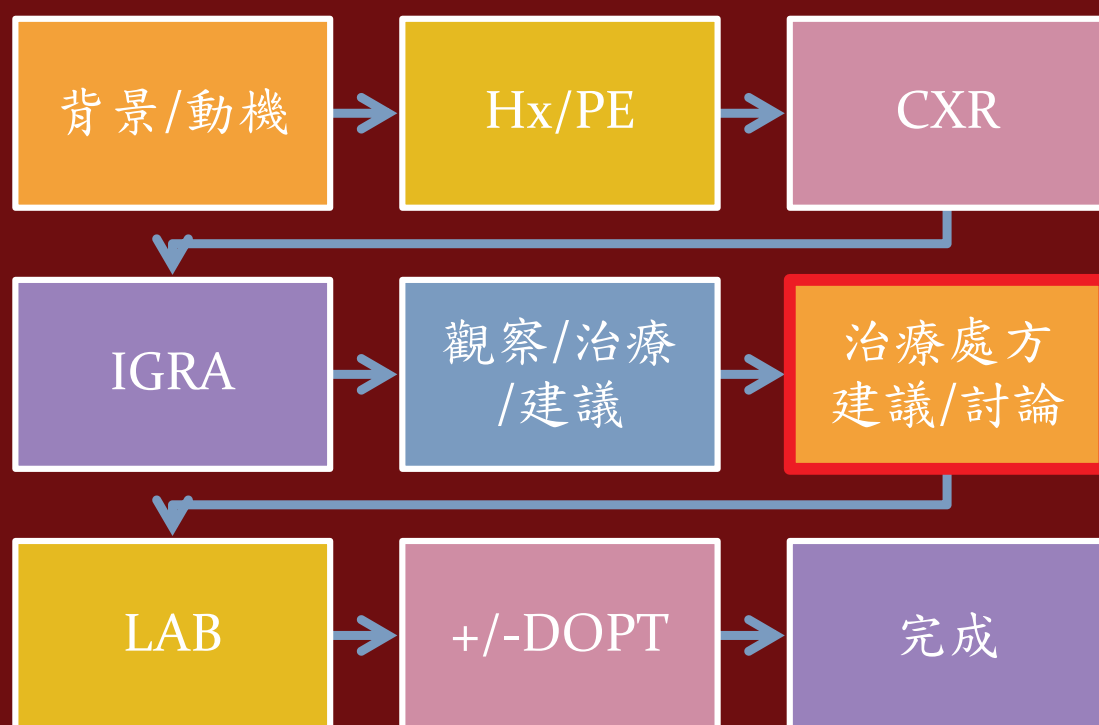
Probability of incident TB in dialysis

TABLE 3. Cox Proportional-hazards Model for Tuberculosis Risk Among Dialysis Patients, by Different quantiFERON-TB Gold In-tube (QFT-GIT) Results

Characteristics	Assay Results		TB		Multivariate With Forward Factor Selection*	
	Data	No.	No.	%	HR (95% CI)	P
First QFT-GIT	Negative	747	1	0.1	1	—
	Positive	193	3	1.6	10.38 (1.08–99.91)	0.043
First QFT-GIT, Strong (+) [†]	Low (+) or negative	834	2	0.2	1	—
	Strong (+)	106	2	1.9	7.54 (1.05–53.91)	0.044
First and second QFT-GIT, Both (+)	Not both (+)	584	1	0.2	1	—
	Both positive	70	2	2.9	14.44 (1.31–159.25)	0.029
First to third QFT-GIT, All (+)	Not all (+)	484	1	0.2	1	—
	All positive	44	2	4.5	20.29 (1.84–223.83)	0.014

Shu CC. Medicine 2016 95(22):e3813

建議流程



治療的處方有那些?



9H (56%)

每日三顆, 9個月

3X270

=810



3HP (44%)

每次9顆, 12次

9X12

= 108



不適用3HP處方者

Ineligible Patients

孕婦 (或準備懷孕的婦女)

Pregnant and those expecting to become pregnant during treatment

指標個案為INH或RMP抗藥

Source case is INH or RMP resistant

未滿2歲之兒童

< 2 years of age

PRECAUTIONS

- 接受ARTs治療之HIV感染者 (protease inhibitors的濃度會被影響)
- 2-11歲兒童(建議處方為9H, 欲使用3HP請參考劑量建議)
- 正在使用coumadin, methadone, phenytoin

Dialysis / Kidney Transplant

Worry
hepatitis

3HP

Worry D-D
interaction

9H

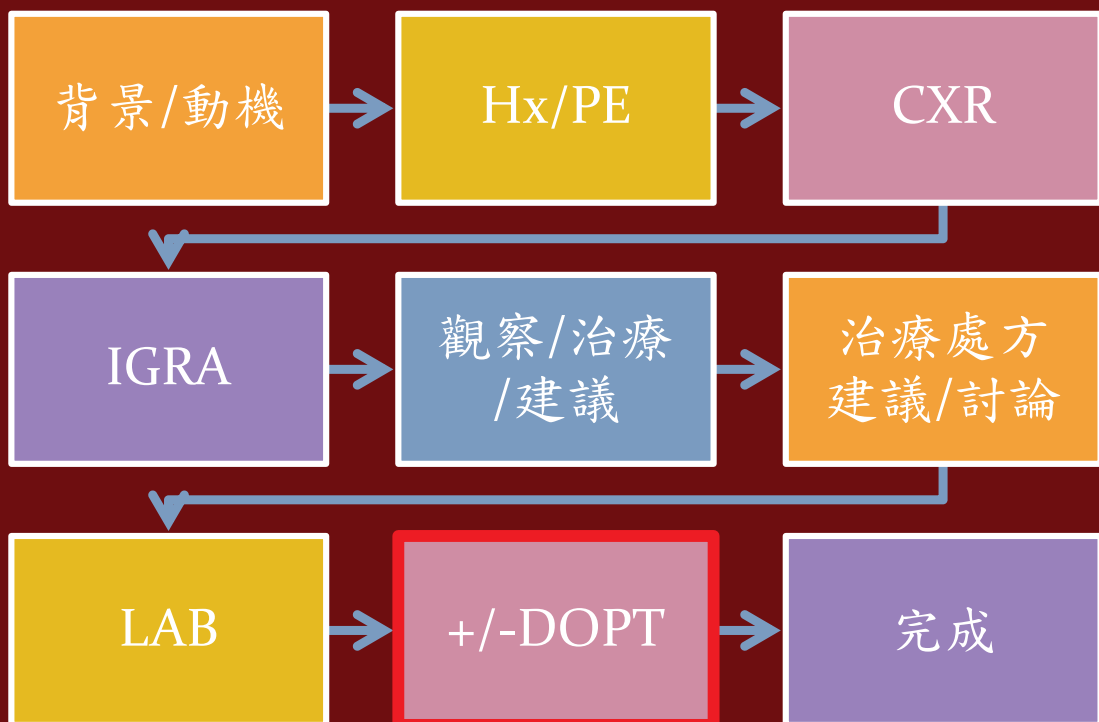
Worry
malaise (Taxi
driver)

?

Worry

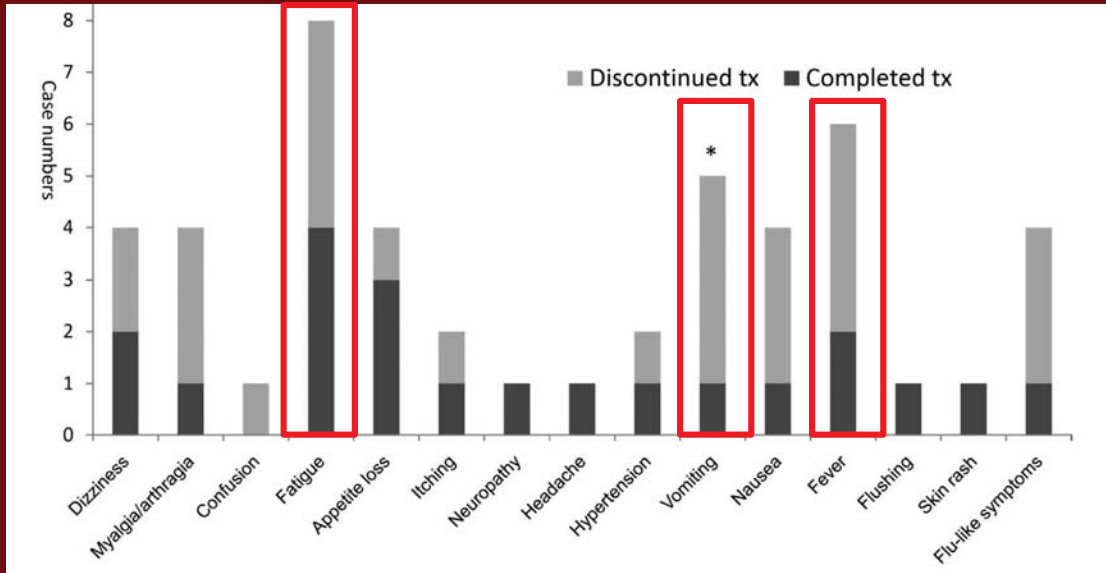
D-D: drug-drug

建議流程



3HP AE

- Eighteen of 26 (69.2%) patients had AEs. The most common AEs were fatigue, fever and vomiting



Lin SY. J Microbiol Immunol Infect. 2018 Jun [Epub ahead of print]

病人的副作用如何?

	3HP	9H	p value
Discontinuing	20%	46%	0.192
Due to drug AE	20%	8%	0.035
Due to poor compliance	0%	38%	0.035
≥ Grade 2 AE	80%	7%	<0.001
≥ Grade 3 AE	20%	8%	0.035

AE的詢問

- 忍耐型: “還好”，就是.....
- 抱怨型: 樹醫師，那個.....
- 主觀
- 客觀
- 評估對其生活功能的影響
- 是否能用藥物或吃藥習慣改善

CTCAE 參考

等級	等級				
	1	2	3	4	5
腸胃不適 (abdominal pain, fullness)	輕度，不需藥物治療	中度，影響日常生活	重度，影響自我照顧功能	-	-
噁心	仍能進食	進食顯著下降，無體重減輕或脫水	須管灌、住院、靜脈補充營養	-	-
嘔吐	不需處理	門診 IV 補水或需藥物治療	須管灌、住院、靜脈補充營養	有生命危險	死亡
食慾下降	食慾不良	進食減少、無體重減輕	需要管灌或全身性營養注射	有生命危險需緊急處理	死亡
皮膚癢	輕微或局部，使用皮膚藥物處理	廣泛癢灶，需口服藥物，輕度影響日常生活	廣泛癢灶，影響自我照顧功能，需使用全身性類固醇或免疫抑制藥物	-	-
皮疹，過敏反應	不需使用全身性藥物	需使用口服藥物	氣管攣縮，血管水腫、過敏性低血壓，需住院治療，使用 IV 藥物	有生命危險需緊急處理	死亡
發燒	38-39°C	39.1-40°C	>40°C (<24hr)	>40°C (>24hr)	死亡

通則

不影響日常生活

需藥物或影響生活

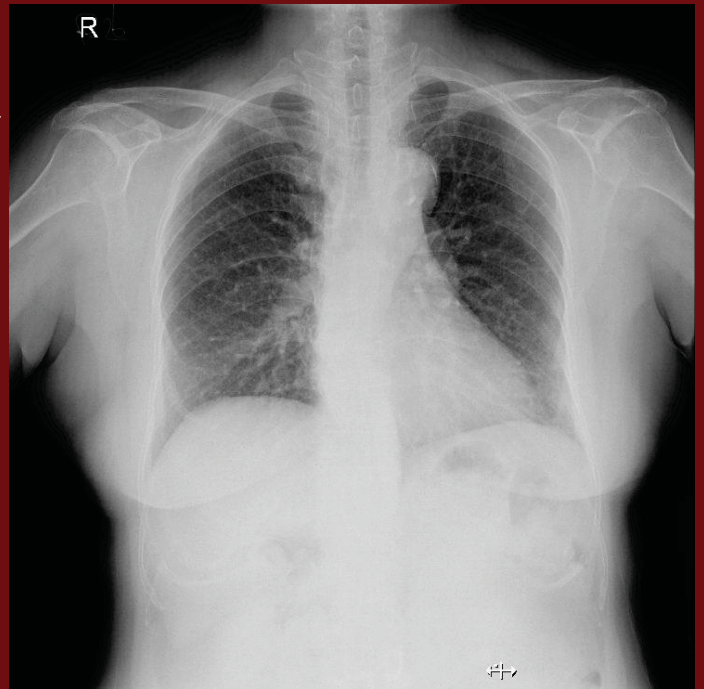
需住院或影響自我照顧

有危險

死亡

A case received 3HP

- 了解背景與**動機**重要
- **AE**與失落相關



The reduction of LTBI therapy

有治療的發生結核的相對風險**下降**

- **6% vs 0%** (2 yrs) by LTBI tx in Kidney transplant ($p < 0.001$, in Korea)

Kim S.H, American Journal of Transplantation 2011; 11: 1927 - 1935

- The risk ratio of INH vs. control group for development of TB in dialysis was

0.40 (95% [CI], 0.17~0.92; $P=0.032$).

The reduction of LTBI therapy

有治療的發生結核的相對風險下降

- <5 yr, 94% protection
- 5-12 yrs, 78% protection
- 13-17 yrs, 89% protection
- 13-29 yr, 90% protection
- ≥30 yr, 73% protection

CDC data

問題3

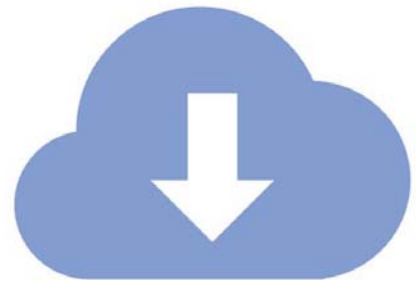
- 下列是LTBI治療過程，以下何者為“是”？
 - 1、建議開立連續處方箋，便民便己
 - 2、速克伏 (3HP) 只需吃12次，不用都治
 - 3、副作用很少，不用追蹤
 - 4、9H療程久，療程中需鼓勵病人，強調說明完治的重要性



TAIWAN CDC

智慧關懷卡

smart card

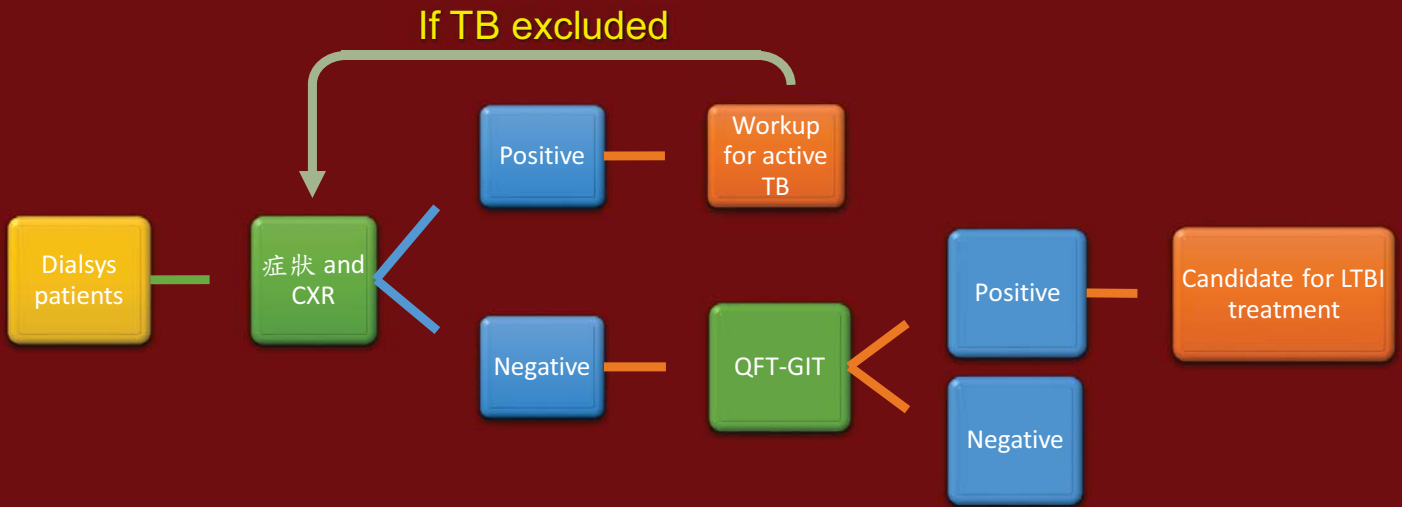


UP
GRADE



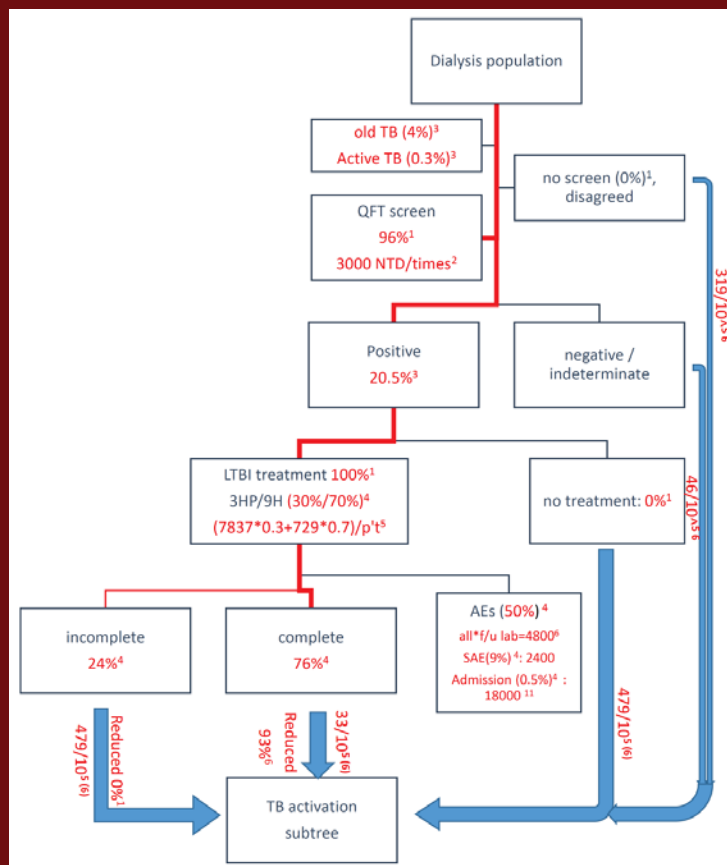
LTBI在洗腎病人篩檢的流程與 成本效益

LTBI screen Strategy



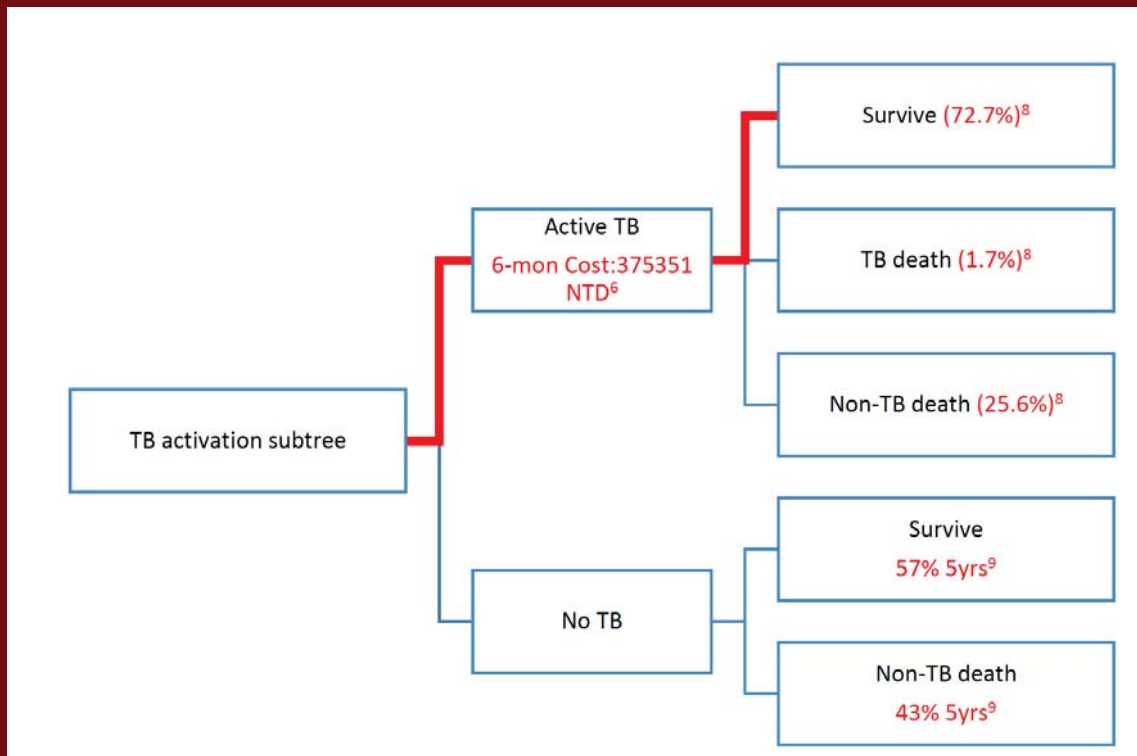
Shu CC. Medicine 2015 95(22):e3813

Cost-Effectiveness of preventing LTBI



Shu CC
Preliminary data

Cost-Effectiveness of preventing LTBI



Shu CC, Preliminary data

全面篩檢治療的CEA

- Cost: Screen + Treatment + AE related fee
- Saving: reduction of TB cost
- Year of life lost: TB related death
- Year of life disability: TB related disability

Save 1 DALY = 654,456 NTD (1-2 GDP in Taiwan)



Shu CC, Preliminary data

治療時要注意的事

- Drug related side effect in 3HP
- Drug adherence in 9H
- Drug-Drug Interaction
- DOPT and hot-line contact are thoughtful.

Take home message

- 洗腎 / 腎移植是結核的高風險，從LTBI防治作起，才能從**根**處理
- LTBI的解釋，是開始LTBI診斷前最重要的步驟
- LTBI的診斷，目前成人使用的是IGRA，在洗腎/腎移植是可信賴的
- LTBI的治療，選擇3HP或9H各有各的好壞處。
- 使用3HP需特別注意AE的關懷，9H則是遵醫囑性。



感謝

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謝謝聆聽
敬請指教

