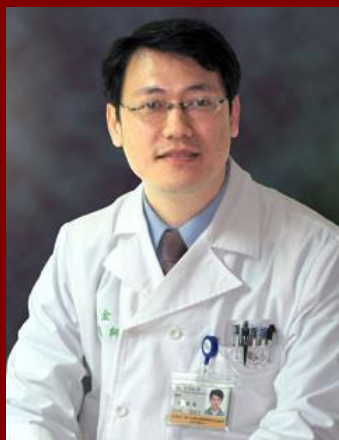


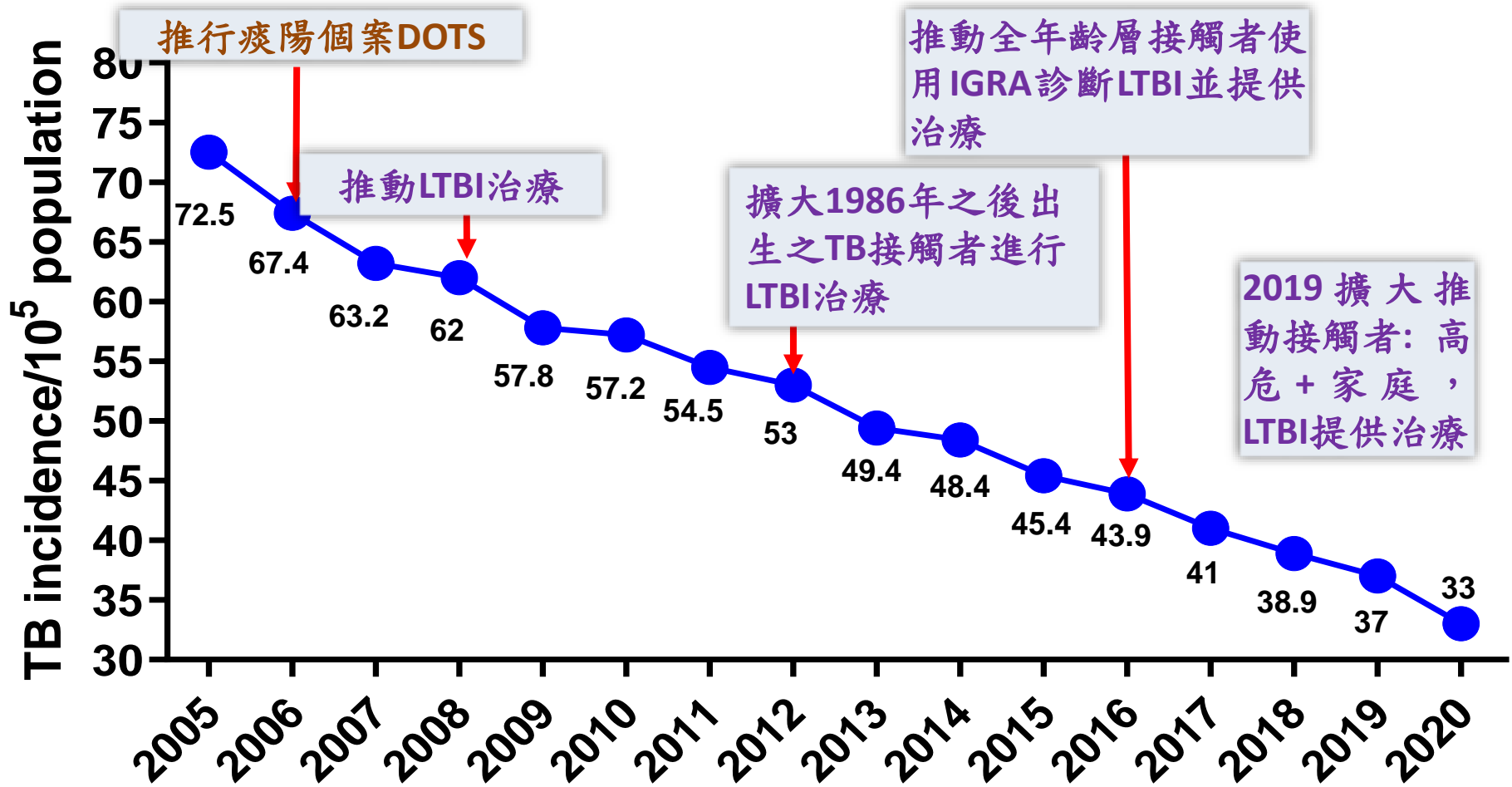


洗腎腎友和腎移植病人的 結核病防治實務



- 樹金忠
- 台大醫院 內科部
整合醫學科
- ccshu@ntu.edu.tw

結核病政策現況



End TB Strategy Post-2015 Era

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.



From WHO website

<http://www.who.int/tb/strategy/end-tb/en/>

好還要更好，TB烏托邦

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

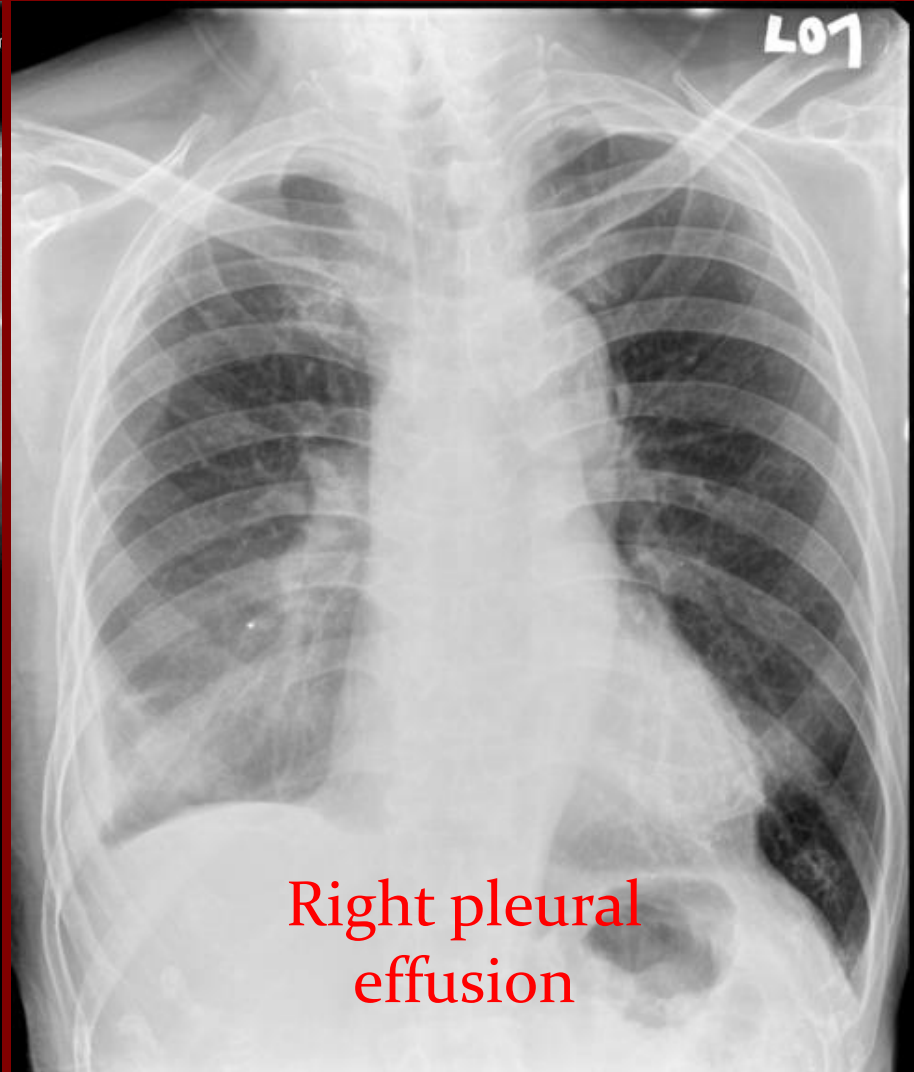
Outline

- Active TB in 洗腎和腎移植
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 - LTBI在洗腎和腎移植的治療實務

腎衰竭跟腎移植病人在TB防治 重要性?



Active Case Finding



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.

CKD vs TB incidence

- NTUH, 2008-2014 data

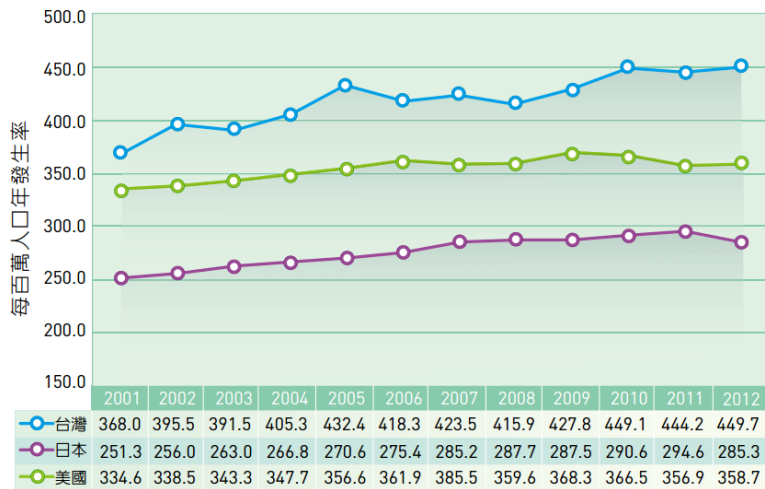
Table 2 Incidence rates of tuberculosis (TB) (*N* = 289,579, TB events = 1012)

Variable	TB events	N	Follow up (years/person)	Follow up (person-years)	Incidence rate (per 100,000 person-years)	Hazard Ratio	(95%CI)	<i>P</i> -value
Kidney function								
CKD nil or stage 1	362	129421	3.99	516,705.16	70.06	Reference		
CKD stage 2	395	128248	4.33	555,749.96	71.08	1.024	(0.888, 1.182)	0.7408
CKD stage 3a	120	17228	4.15	71,566.72	167.68	2.404	(1.956, 2.956)	< 0.0001
CKD stage 3b	64	7116	3.92	27,917.47	229.25	3.273	(2.509, 4.270)	< 0.0001
CKD stage 4	37	3449	3.52	12,133.22	304.95	4.317	(3.078, 6.054)	< 0.0001
CKD stage 5	22	2500	2.52	6298.52	348.88	4.852	(3.154, 7.464)	< 0.0001
Long-term dialysis	10	1579	3.61	5694.64	175	2.493	(1.330, 4.673)	0.0044
Kidney transplant	2	38	3.68	139.93	1429.33	20.575	(5.147, 82.239)	< 0.0001

Abbreviation: *CKD* Chronic kidney disease

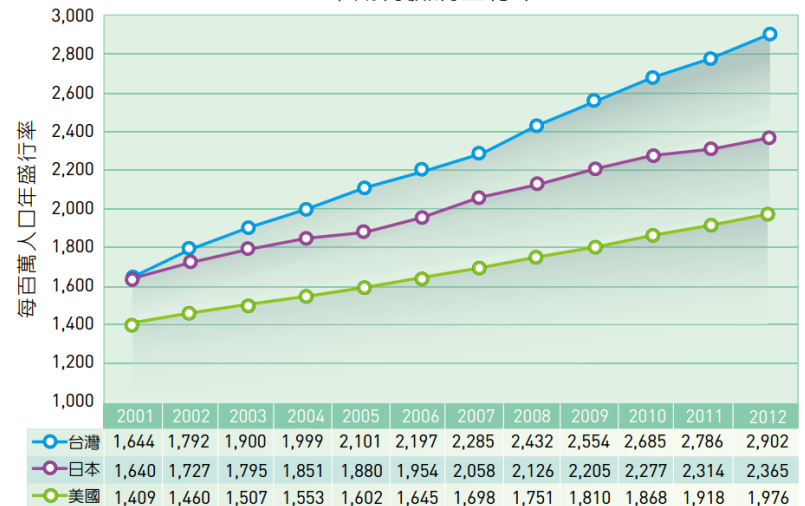
台灣末期腎臟病 (ESRD) 發生率/盛行率

末期腎臟病發生率



資料來源：美國腎臟資料系統 (USRDS)

末期腎臟病盛行率



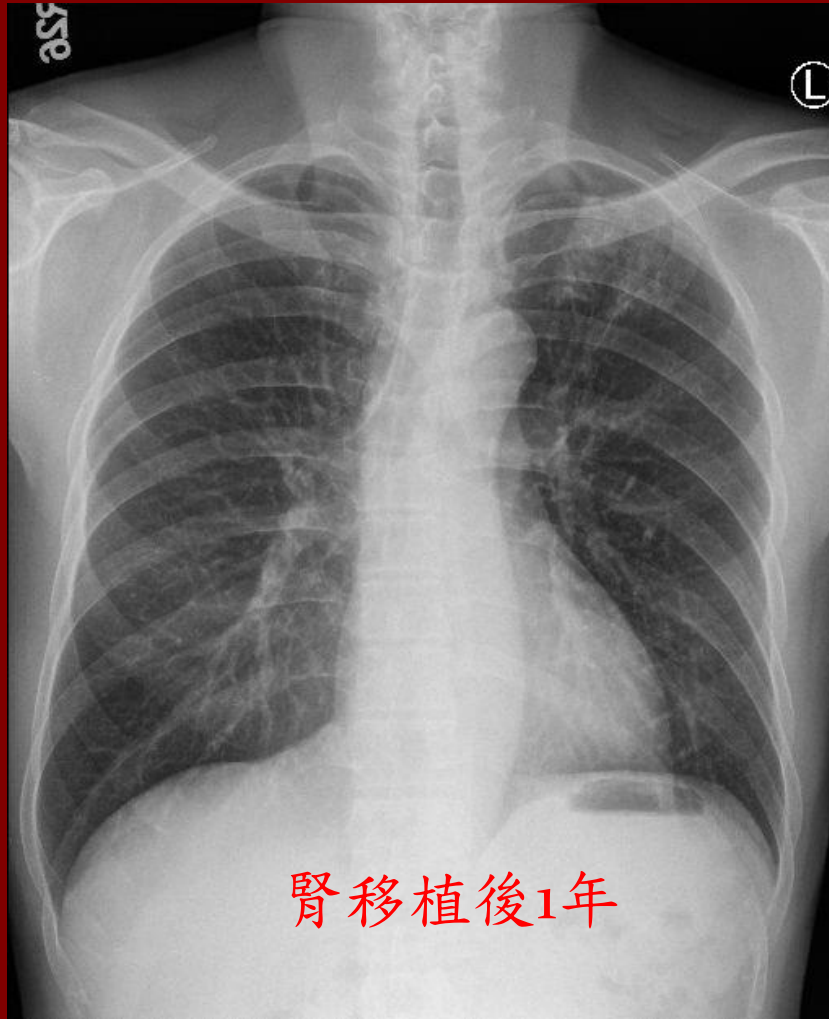
資料來源：美國腎臟資料系統 (USRDS)

移植成果



A TB case in kidney transplant

- 移植前評估, IGRA: strong positive



腎移植後1年

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

NTUH data

- NTUH, 2008-2014 data

Table 2 Incidence rates of tuberculosis (TB) (*N* = 289,579, TB events = 1012)

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Abbreviation: *CKD* Chronic kidney disease

Outcome - Mortality

1.7%

TB directed death

25.6%

nonTB directed death

Dialysis

6.1 ~ 8.9%

Kidney transplant

Chou K.J., Nephron 2001;88:138–143
Bai KJ, Respirology, 2017 Jul;22(5):991-999

Liu J, BMC Infect Dis. 2014 Jul 11;14:387
Canet E. Nephrol D 2011 Nov;26(11):3773-8

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



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



Outline

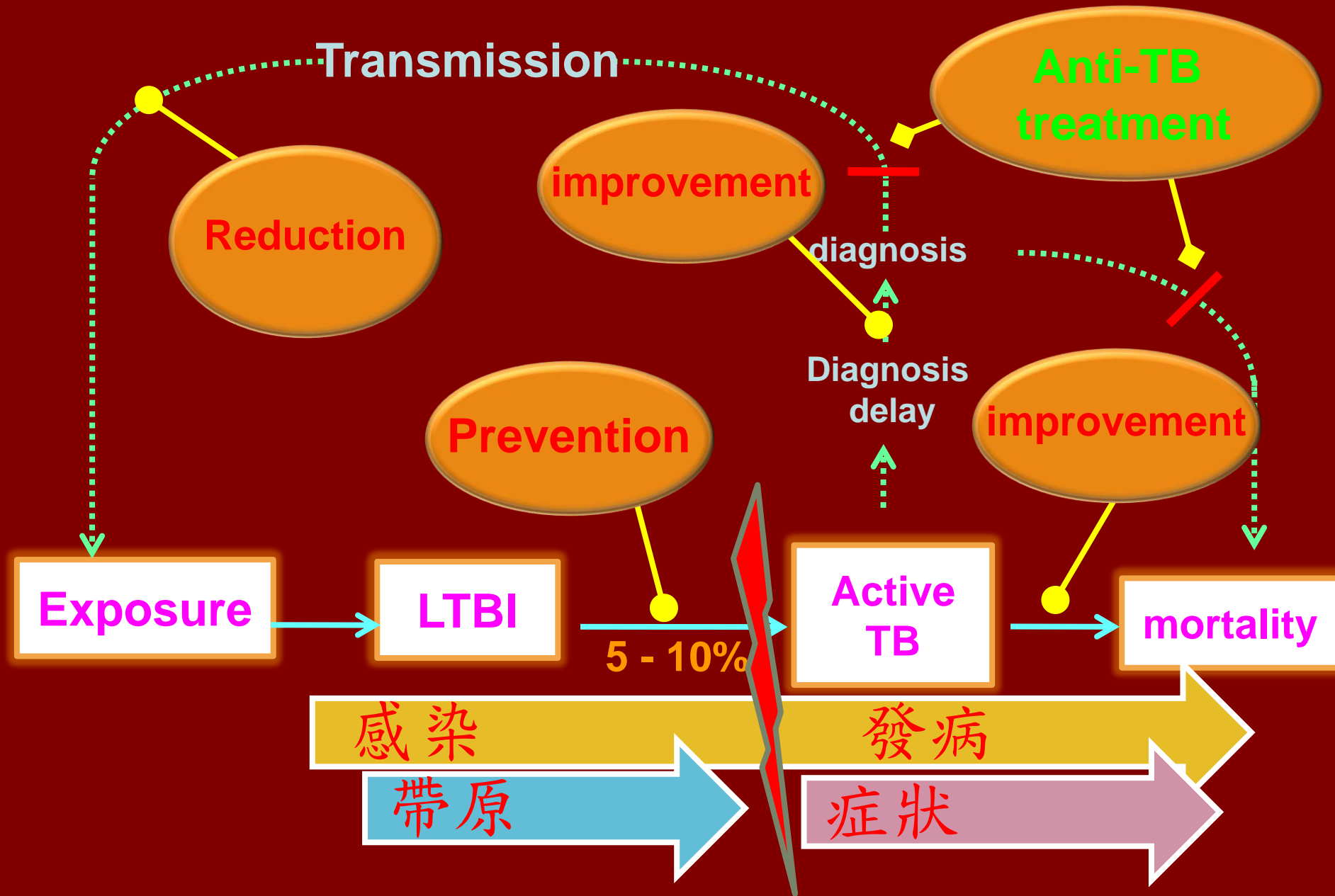
- Active TB in 洗腎和腎移植
- TB prevention 在洗腎和腎移植角色
- LTBI 防治在洗腎和腎移植病人策略
 - LTBI在洗腎和腎移植的診斷
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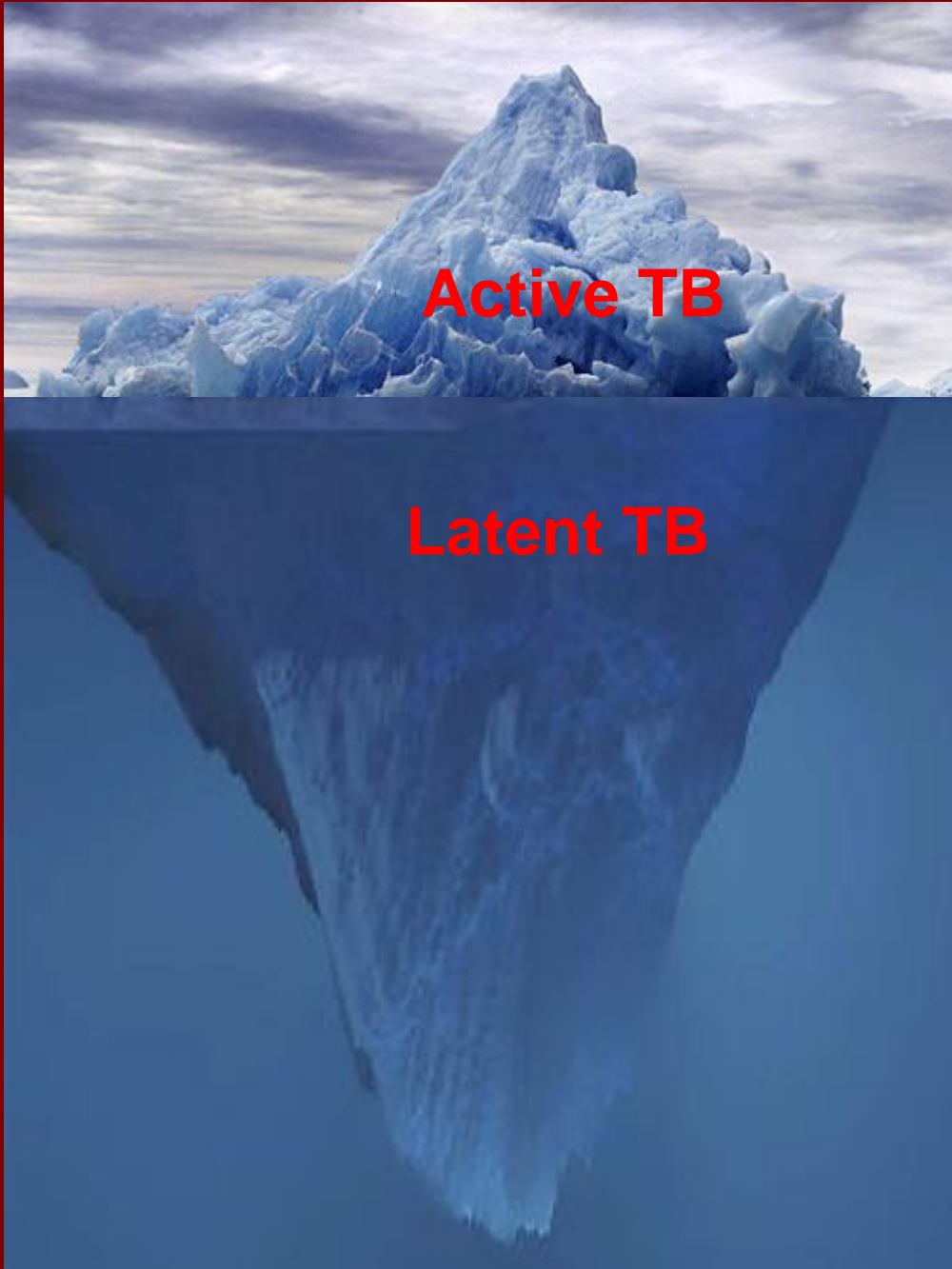
LTBI防治的重要性?

病病病
未欲已
醫醫醫
醫醫醫
上中下



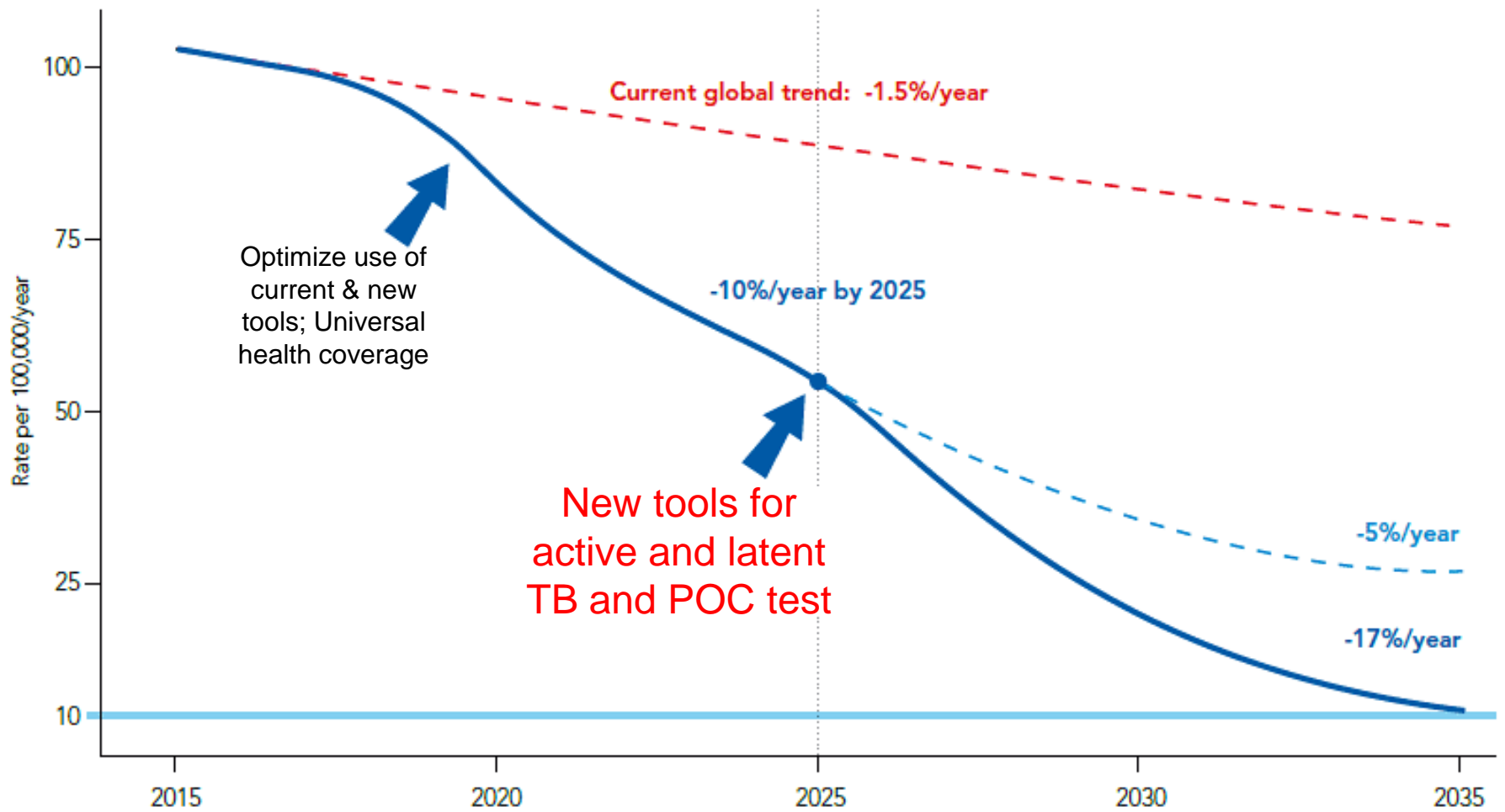
Nature course of TB





Active TB

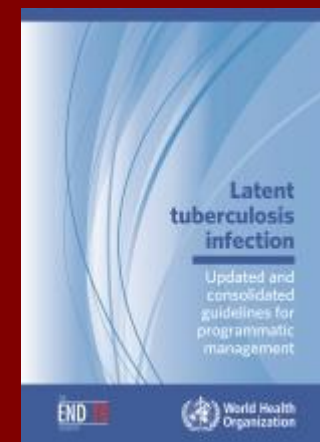
Latent TB



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 hematologic transplantation
 - patients with silicosis.

(Strong recommendation)



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
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American Transplant Society (recipient) ³⁹	2011	—	—	All transplant candidates should be screened with TSS or IGRA
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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.

肺結核高風險群 洗腎病友免費篩檢



2018，00市開始

- 00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

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

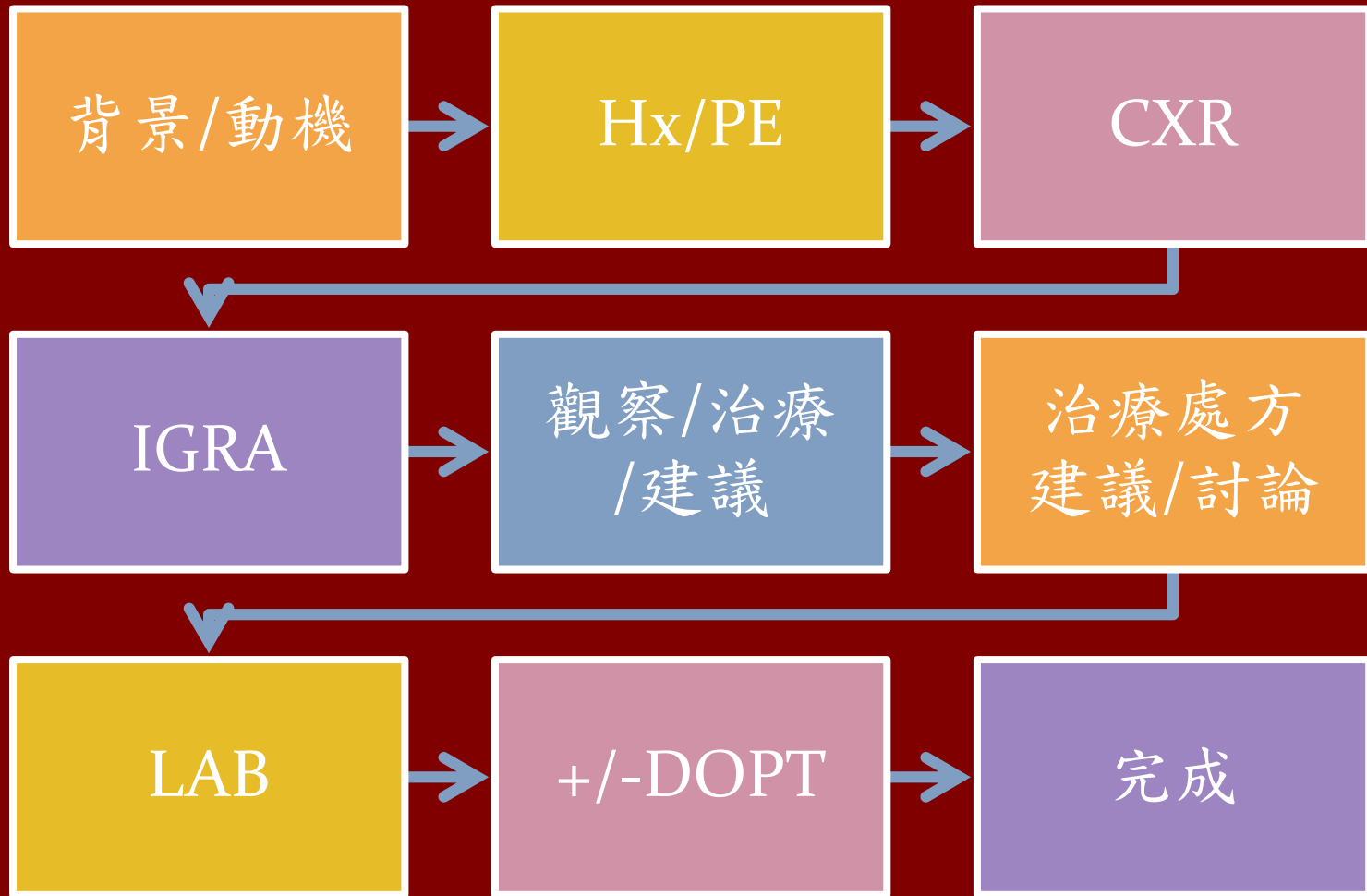
LTBI in 洗腎和腎移植

- LTBI 在洗腎和腎移植的診斷
- LTBI 在洗腎和腎移植的治療實務

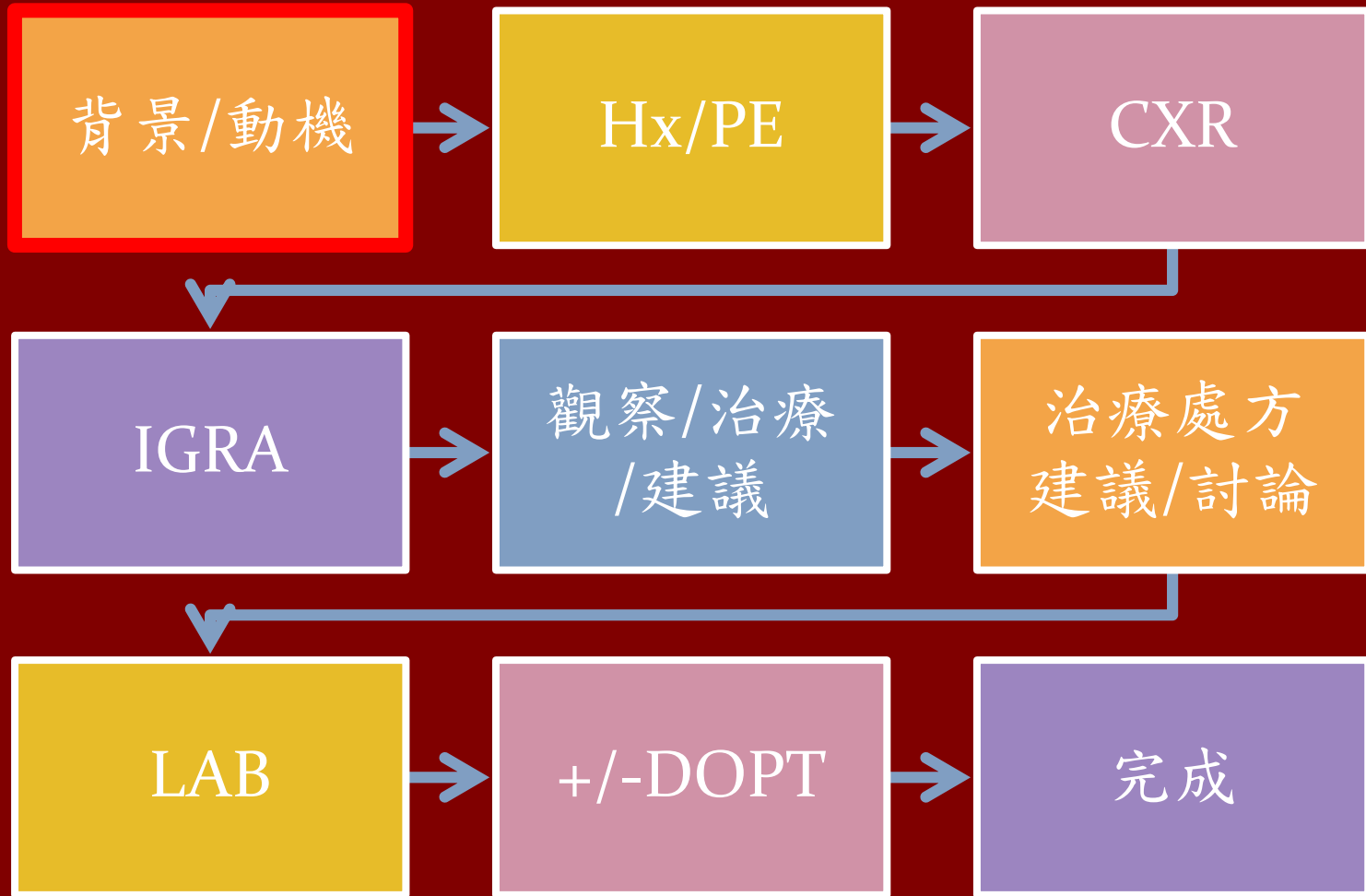


Others?

建議流程



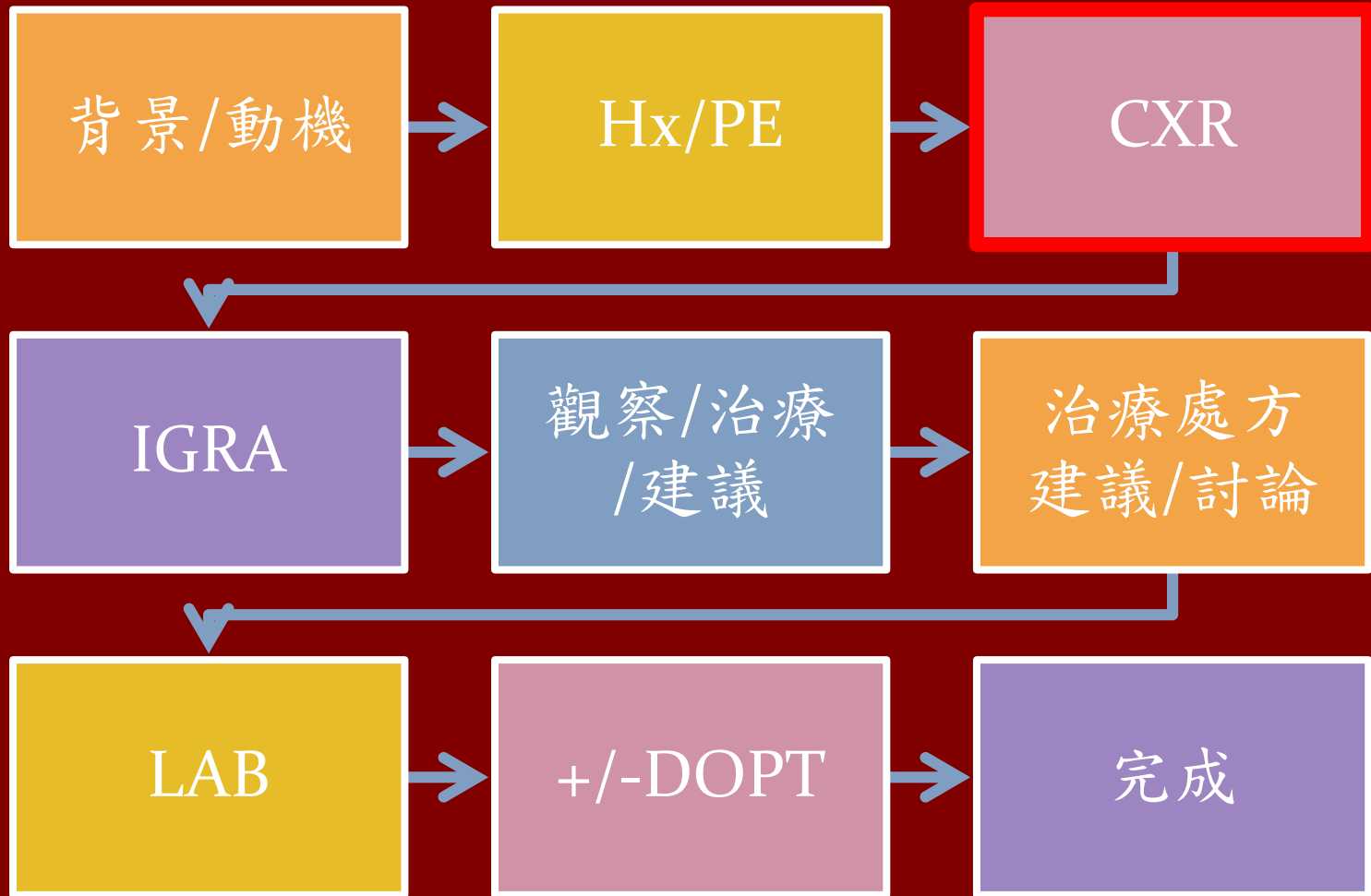
建議流程



解釋說明比用藥重要



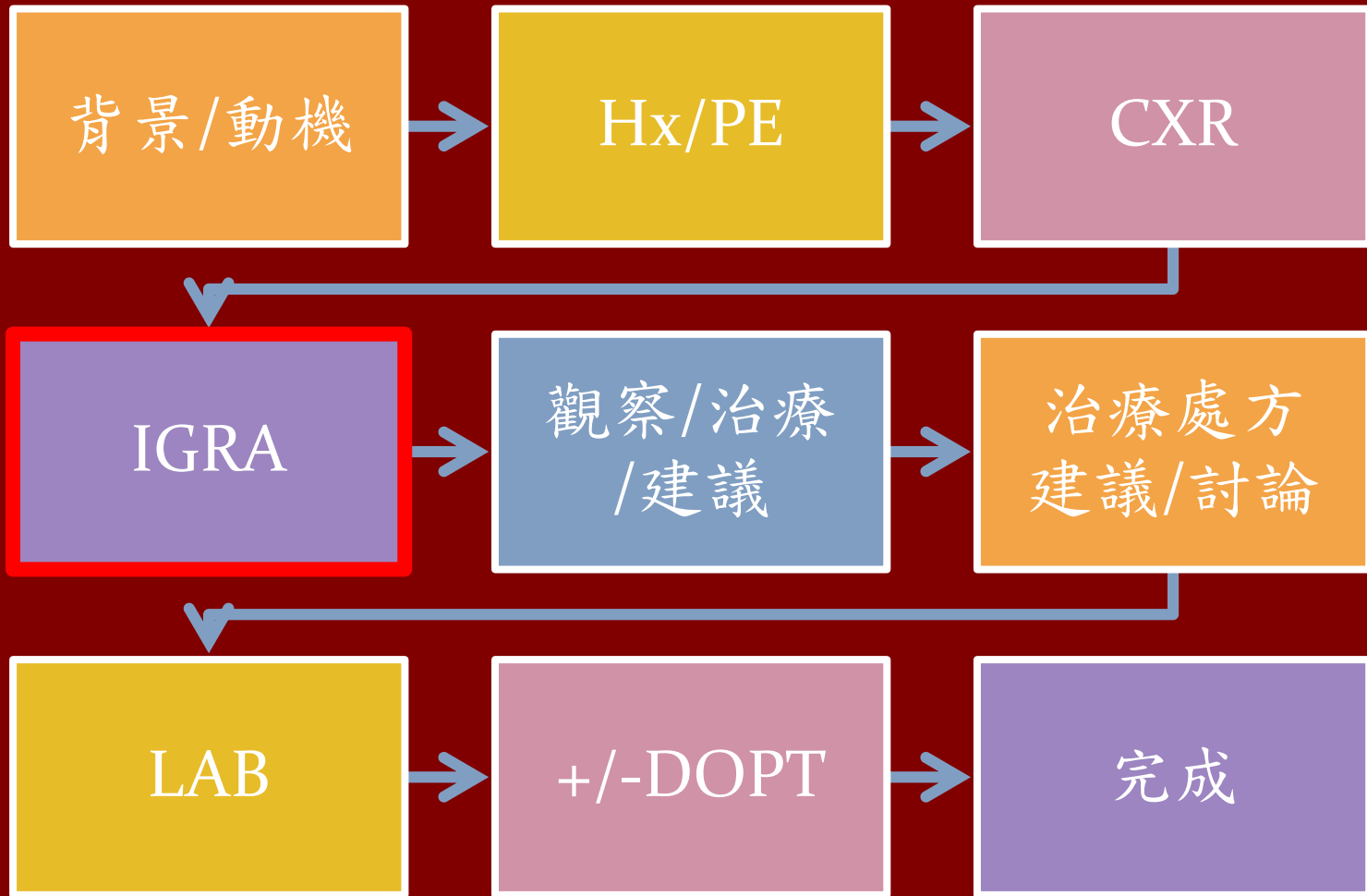
建議流程



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,並排除活動性結核。
- 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

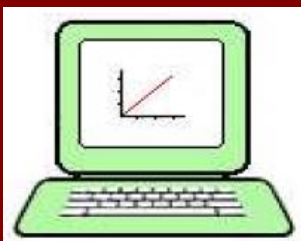
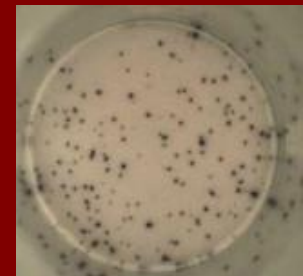
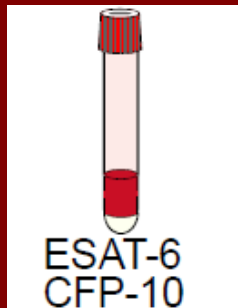
In tube

In culture plate










IFN-gamma assay

ELISA

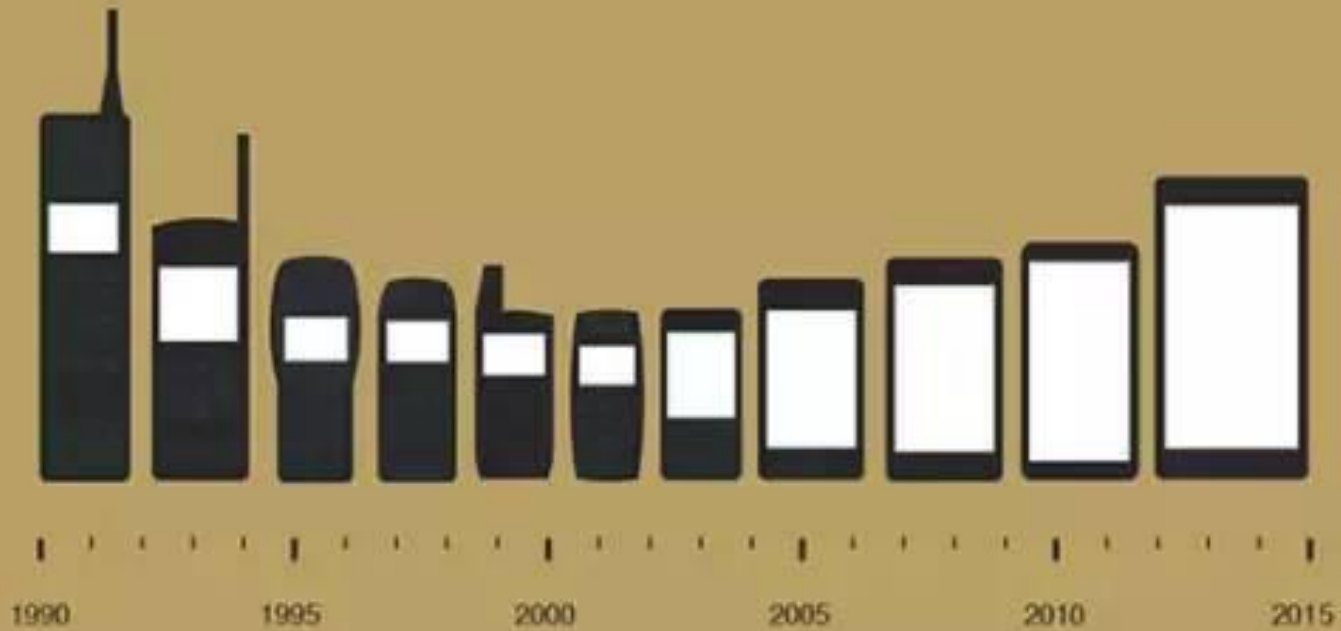
ELISpot



診斷方式的比較

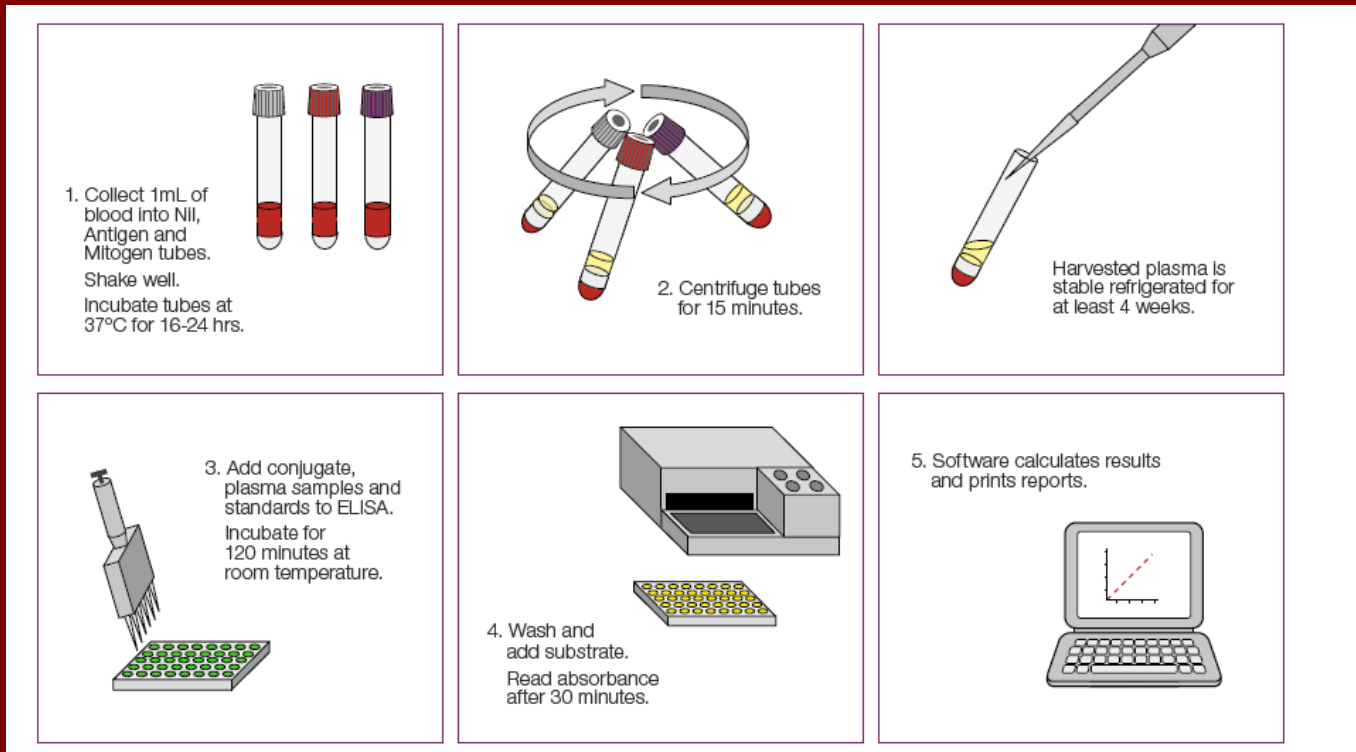
	皮膚結核菌素測驗	丙型干擾素釋放試驗
1. 價格	便宜 	昂貴
2. 普及性	取得易 	普及增加中
3. 抗原專一性	不專一，易交叉反應	較專一 
4. 檢測需返診	需要	不需 
5. 免疫不全患者，是否容易偽陰性	易	有對照組 
6. 副作用	皮膚潰爛	抽血 
7. Booster effect	有	無 
8. 人為判讀誤差	有	無 
9. 文獻佐證	充足 	<2歲，目前文獻不足

進化史



Detection of LTBI

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

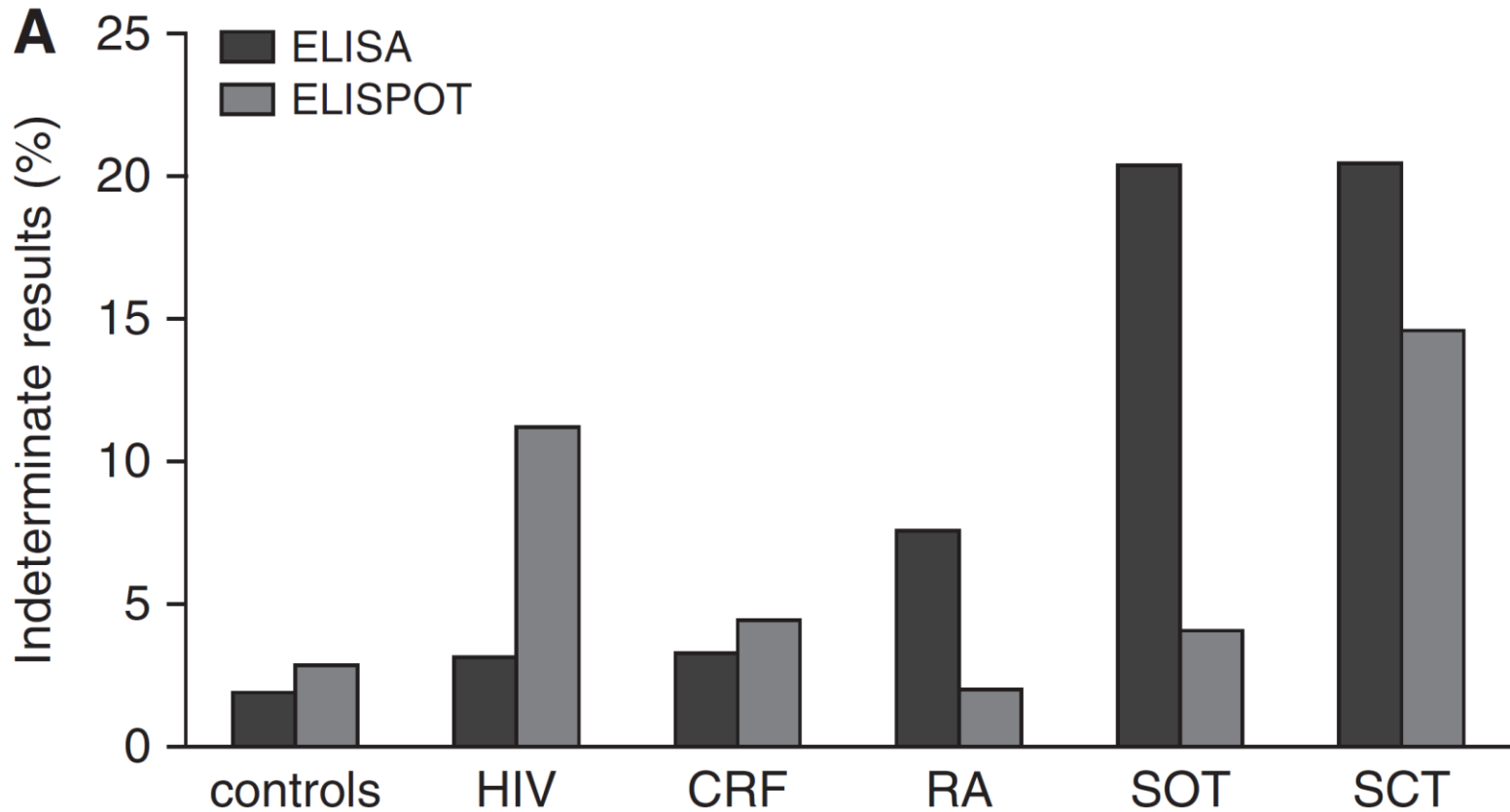


Antigens: IGRA vs. TST

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

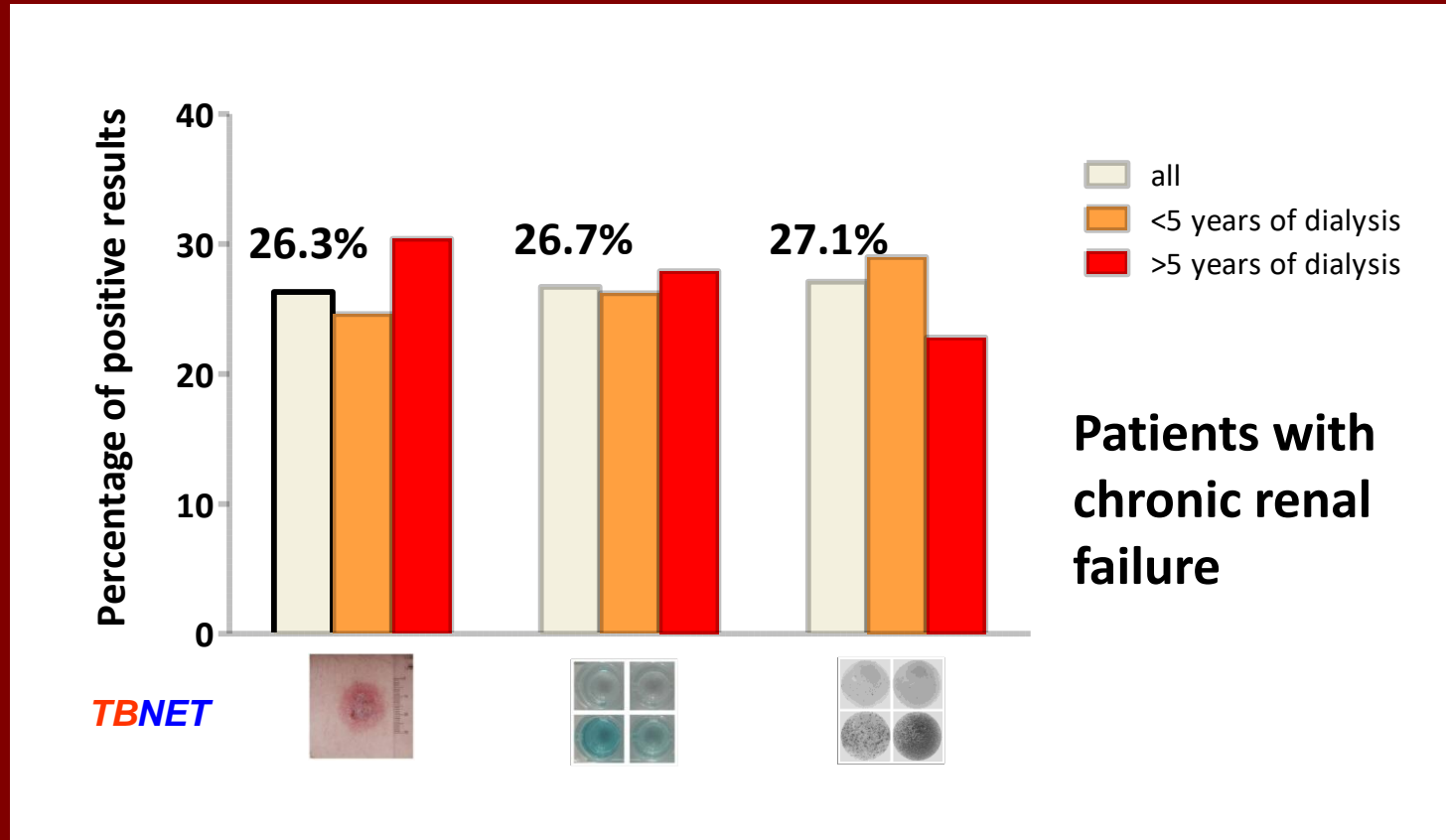
Tuberculosis Complex	ESAT-6	CFP-10	TB7.7	Environmental Strains	ESAT-6	CFP-10	TB7.7
M tuberculosis	+	+	+	M abcessus	-	-	-
M africanum	+	+	+	M avium	-	-	-
M bovis	+	+	+	M branderi	-	-	-
BCG substrain				M celatum	-	-	-
gothenburg	-	-	-	M chelonae	-	-	-
moreau	-	-	-	M fortuitum	-	-	-
tice	-	-	-	M gordonii	-	-	-
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



LTBI在洗腎病人中多嗎？

Similar percentages of positive test results in all assays in **CRF**



QFT+ in dialysis patients

- IGRA-positive rate is reportedly around 21-40%.
- The predictors of IGRA-positivity in dialysis population are old age, smoking, and prior TB.

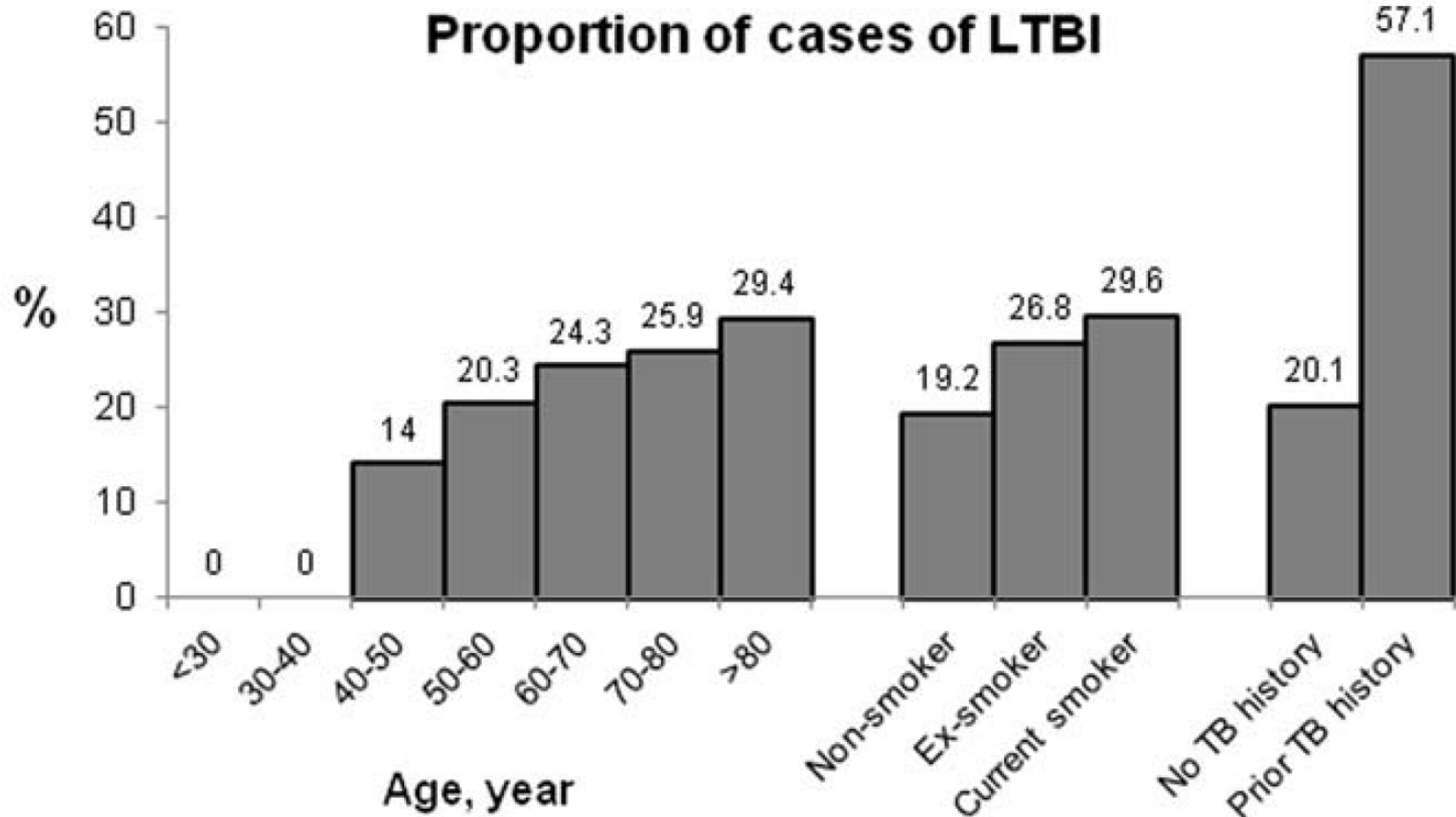
Triverio et al., Nephrol Dial Transplant 2009. 24: 1952-1956.

Lee et al., Infection 37: 96-102

Lee et al., Clin J Am Soc Nephrol 5: 1451-1457

Shu et al. PLoS ONE 7(8): e42592

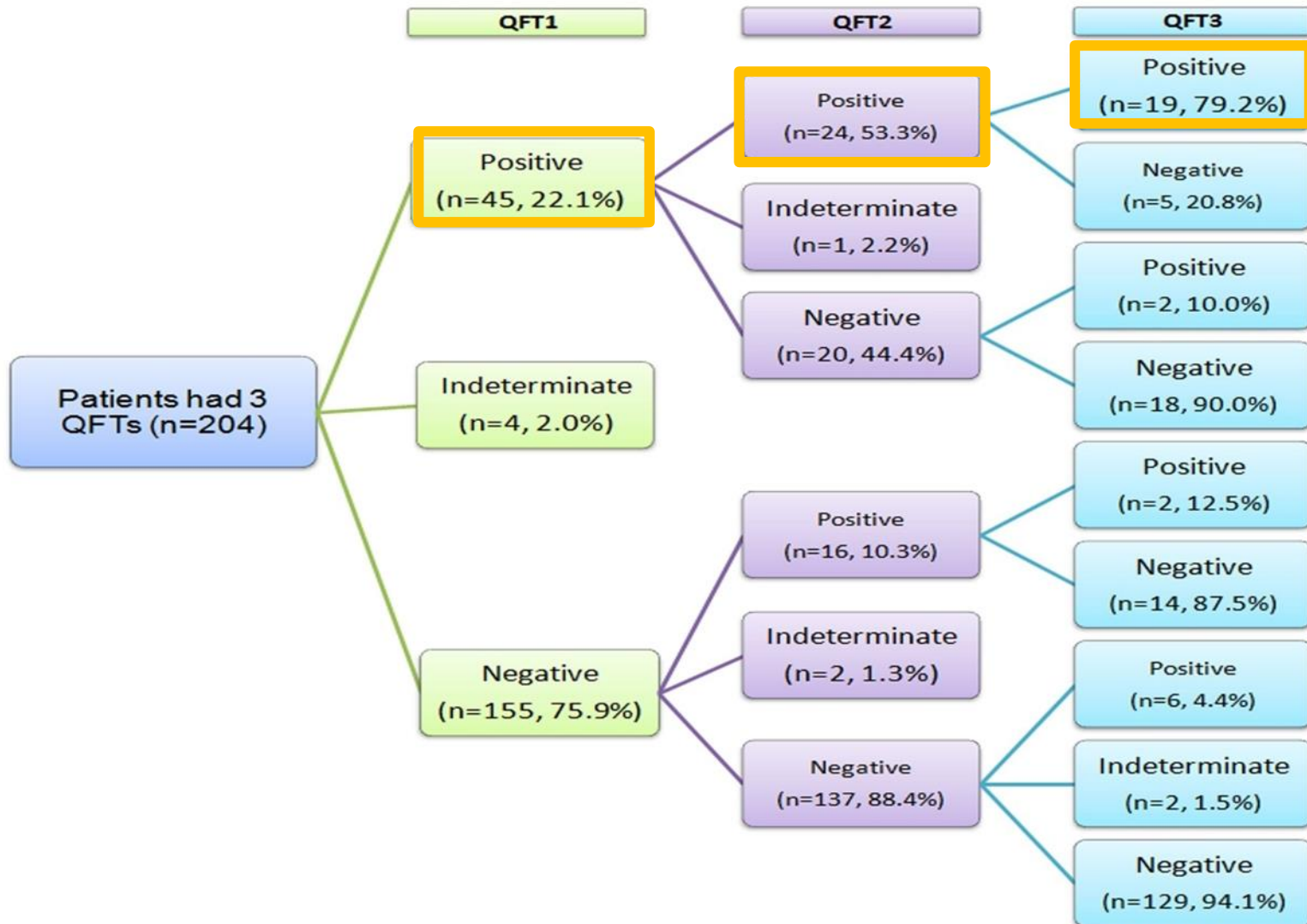
QFT (+) in dialysis (NTUH)



一年完整追蹤QFT的病患

- Total: 204 (HD 173, PD 31)
- 男: 女 = 55% : 45%
- 平均年齡: 61.2歲 (SD: 12.5)
- Dialysis duration: 4.7年(SD: 3.8)
- DM:23%, Cancer: 7%, old TB: 3%
- 初次LTBI: 22.1%

Serial Follow-up



Clinical characteristics

Table 1 Baseline clinical characteristics of patients according the dynamic pattern of QuantiFERON-TB Gold In-Tube (QFT-GIT) response.

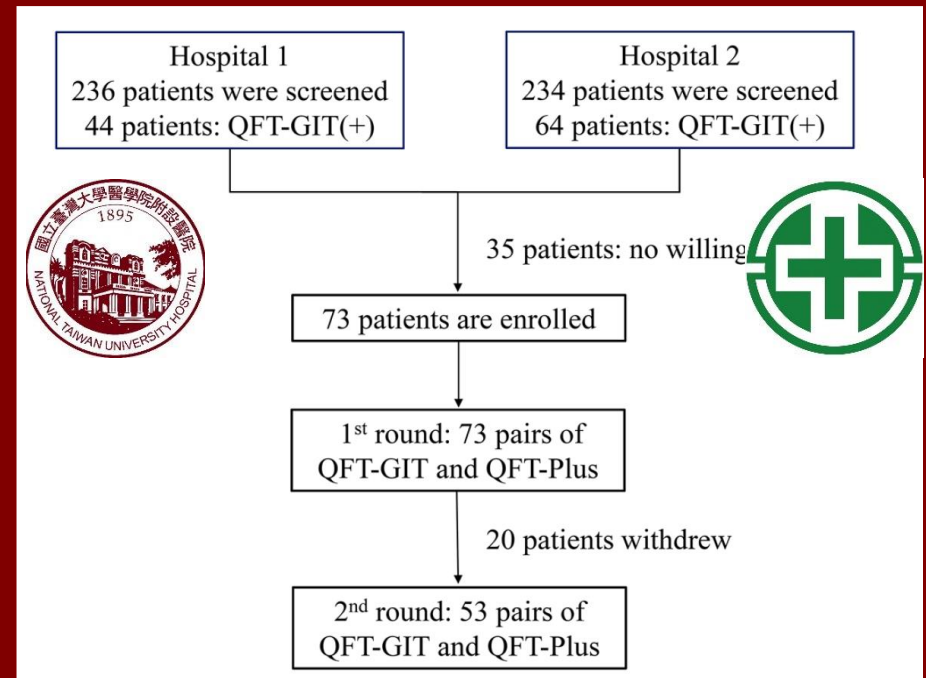
	Complete cases (n = 204)	Reverters ^a (n = 25)	Persistent positive (n = 19)	Converters ^a (n = 22)	Persistent negative (n = 129)
Age, year	61.2 (12.5)	62.4 (11.2)	63.7 (9.9)	62.8 (12.6)	59.7 (13.0)
Male sex	112 (55%)	14 (56%)	14 (74%)	11 (50%)	69 (54%)
Current smoker	14 (7%)	4 (16%)	2 (11%)	2 (9%)	6(5%)
Dialysis age, year	4.7 (3.8)	5.1 (4.1)	4.1 (3.4)	4.1 (3.4)	4.6 (3.64)
Malignancy	15 (7%)	1 (4%)	1 (5%)	0	12 (9%)
Diabetes mellitus	46 (23%)	5 (20%)	7 (37%)	7 (32%)	24 (19%)
Prior TB history	7 (3%)	1 (4%)	2 (11%)	2 (9%)	2 (2%) [#]
Hemoglobin, g/dL	10.3 (1.7)	10.7 (1.2)	10.8 (1.5)	10.0 (1.4)	10.1 (1.8)
Serum albumin, g/dl	3.92 (0.37)	4.00 (0.19)	3.98 (0.37)	3.91 (0.38)	3.91 (0.39)
QFT-GIT1 response, ^b IU/ml	0.40 (0.23)	0.67 (0.54)	2.85 (3.55) ^{##}	0.04 (0.11)	0.02 (0.06)
Presence of symptoms ^c	24 (12%)	2 (8%)	3 (16%)	1 (5%)	18 (14%)
Any radiological lesion	78 (38%)	7 (37%)	5 (20%)	23 (55%)	49 (38%)

QFT-GIT, QuantiFERON-TB Gold In-Tube test; TB, tuberculosis.

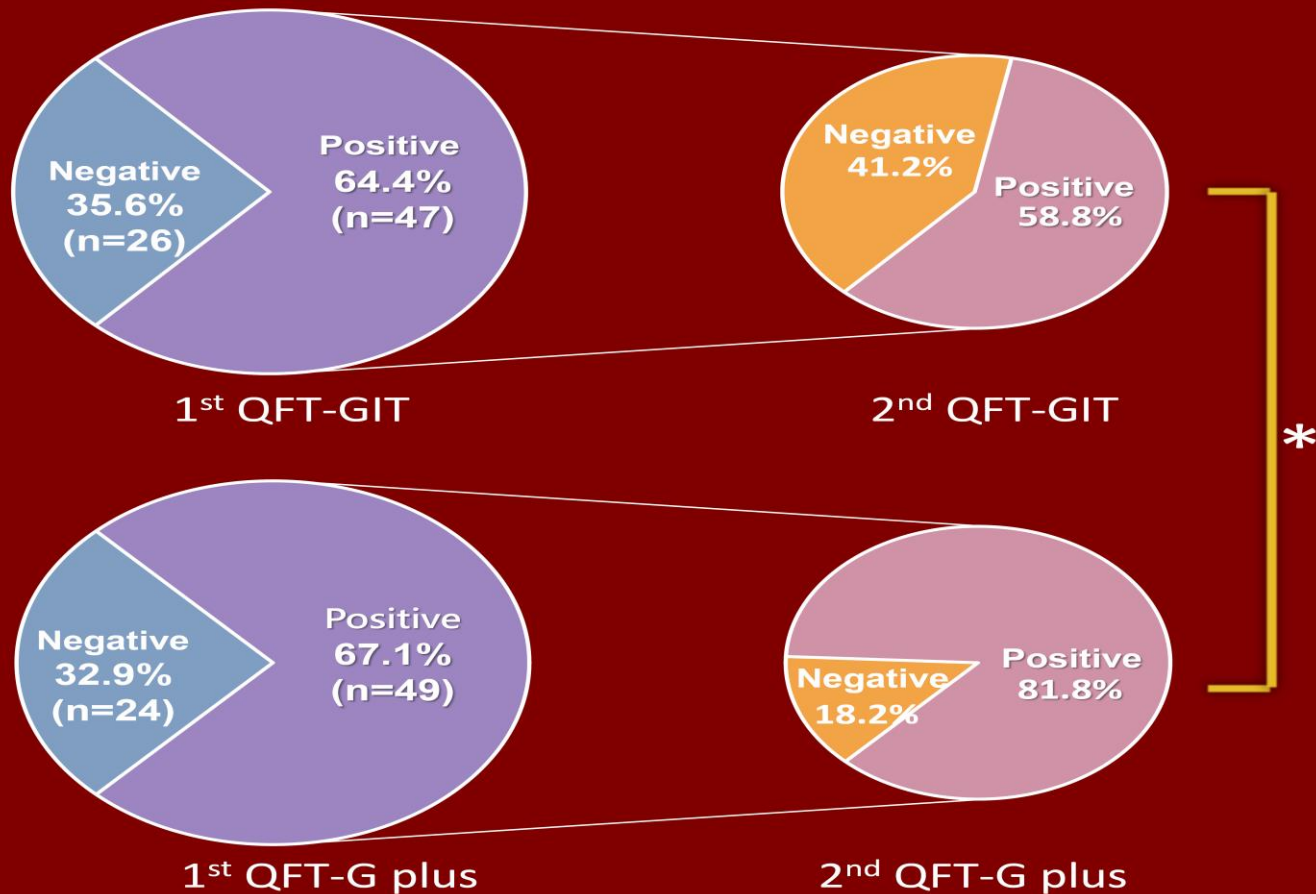
Data are no. (%) or mean (standard deviation) except median (inter-quartile range) in QFT-GIT response.

To compare the LTBI assay in **results persistency**

- **Unmet needs:** High negative conversion rate of LTBI assay (**40-50%**) in dialysis population
- To compare QFT-GIT with QFT-plus (new assay)
- Endpoint: positive consistency



To compare the LTBI assay in **results persistency**



LTBI 在移植前後的人多嗎？

Current recommendations

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
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World Health Organization ³⁶	2015	—	Screen all dialysis patients with TST or IGRA	Screen all transplant candidates with TST or IGRA

**Only candidate
but not recipients**

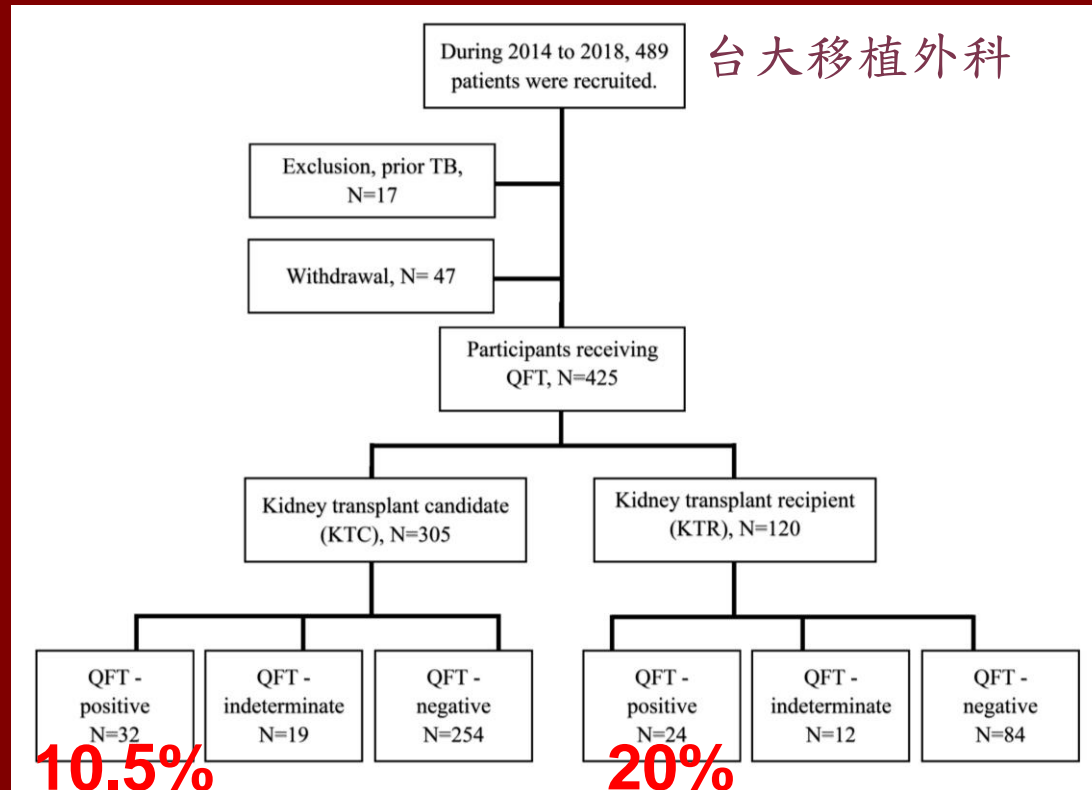
CKD, chronic kidney disease; IGRA, interferon gamma release assay; TST, tuberculin skin test.

LTBI in kidney transplant recipients (KTR)

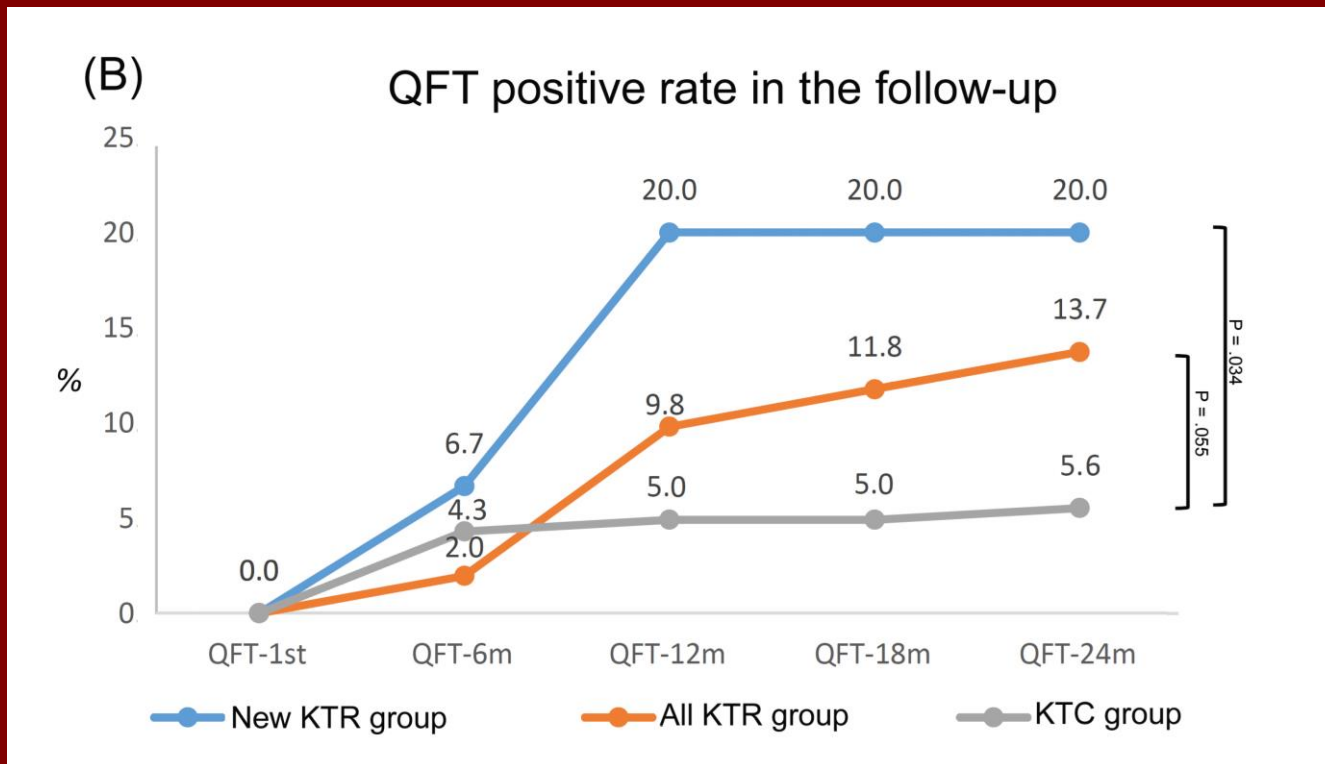
- Problem: What's LTBI status in **kidney transplant recipients**.
- Unmet needs:
No reports for LTBI in kidney transplant recipients

Specific Aims: To investigate prevalence of incidence of LTBI in KTR

Flow chart of enrollment



Incidence of LTBI among KTR



Multivariable analysis for LTBI in KTR

Characteristics	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age, years	1.028 (1.001–1.055)	.046	1.027 (1.000–1.055)	.050
BCG scar ^a				
0	Reference		Reference	
1	0.213 (.072–.633)	.005	0.199 (.065–.608)	.005
≥2	0.198 (.060–.654)	.008	0.175 (.051–.598)	.005
Current dialysis mode				
No dialysis	Reference		...	
Peritoneal dialysis	0.637 (.290–1.398)	.260	...	
Hemodialysis	1.028 (.533–1.982)	.934	...	
KTR compared with KTC group	2.133 (1.196–3.802)	.010	1.904 (1.031–3.516)	.040
KTR, liver donor vs deceased donor	0.986 (.425–2.284)	.973	...	
Donor, ABO, incompatible vs compatible	3.060 (.910–10.294)	.071	...	
DSA, presence vs absence	3.214 (1.299–7.954)	.012	8.242 (1.249–54.399)	.028

Clinical Infectious Diseases

MAJOR ARTICLE



Latent Tuberculosis Infection Increases in Kidney Transplantation Recipients Compared With Transplantation Candidates: A Neglected Perspective in Tuberculosis Control

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洗腎病人的LTBI後續發病多嗎？

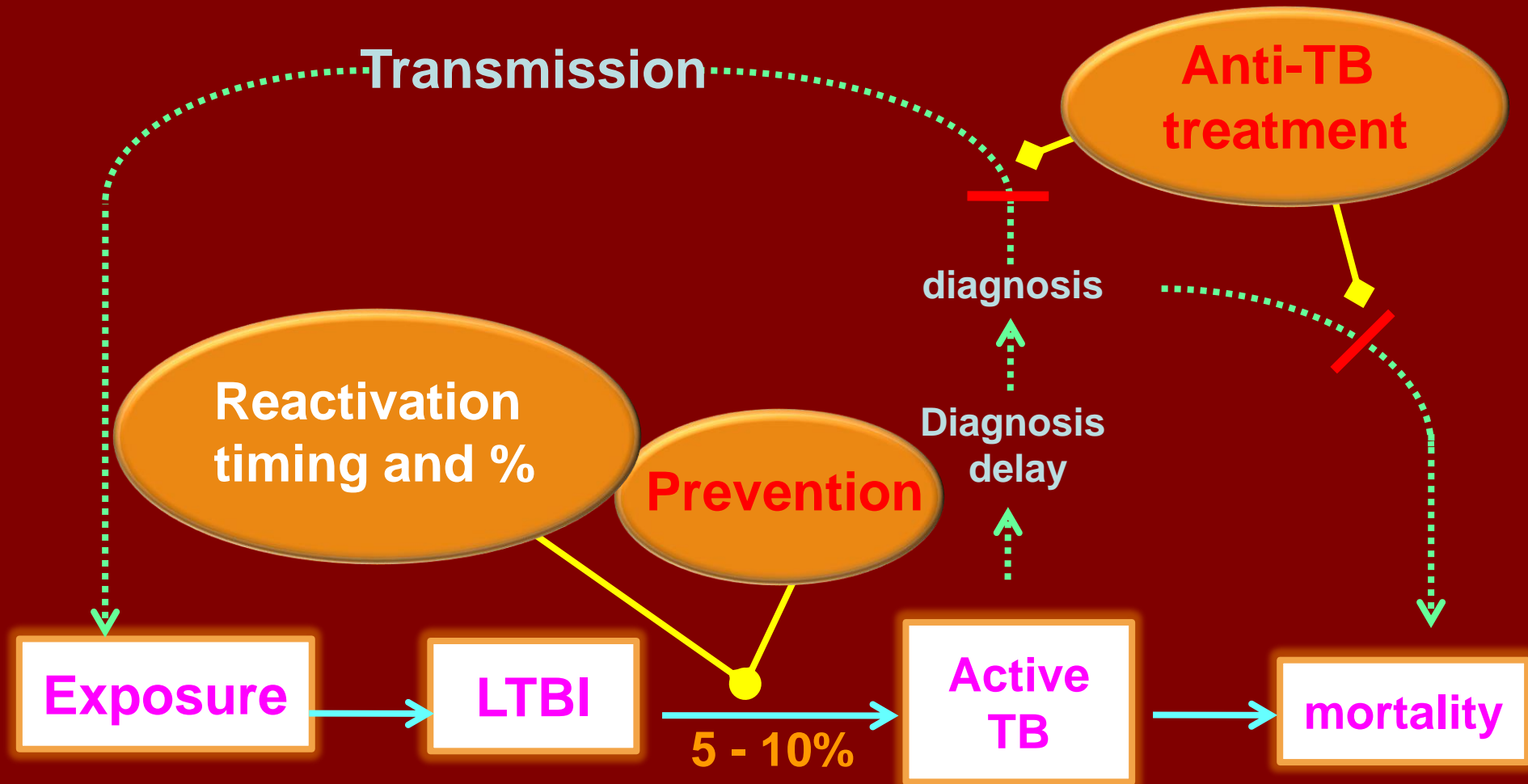
潛伏感染



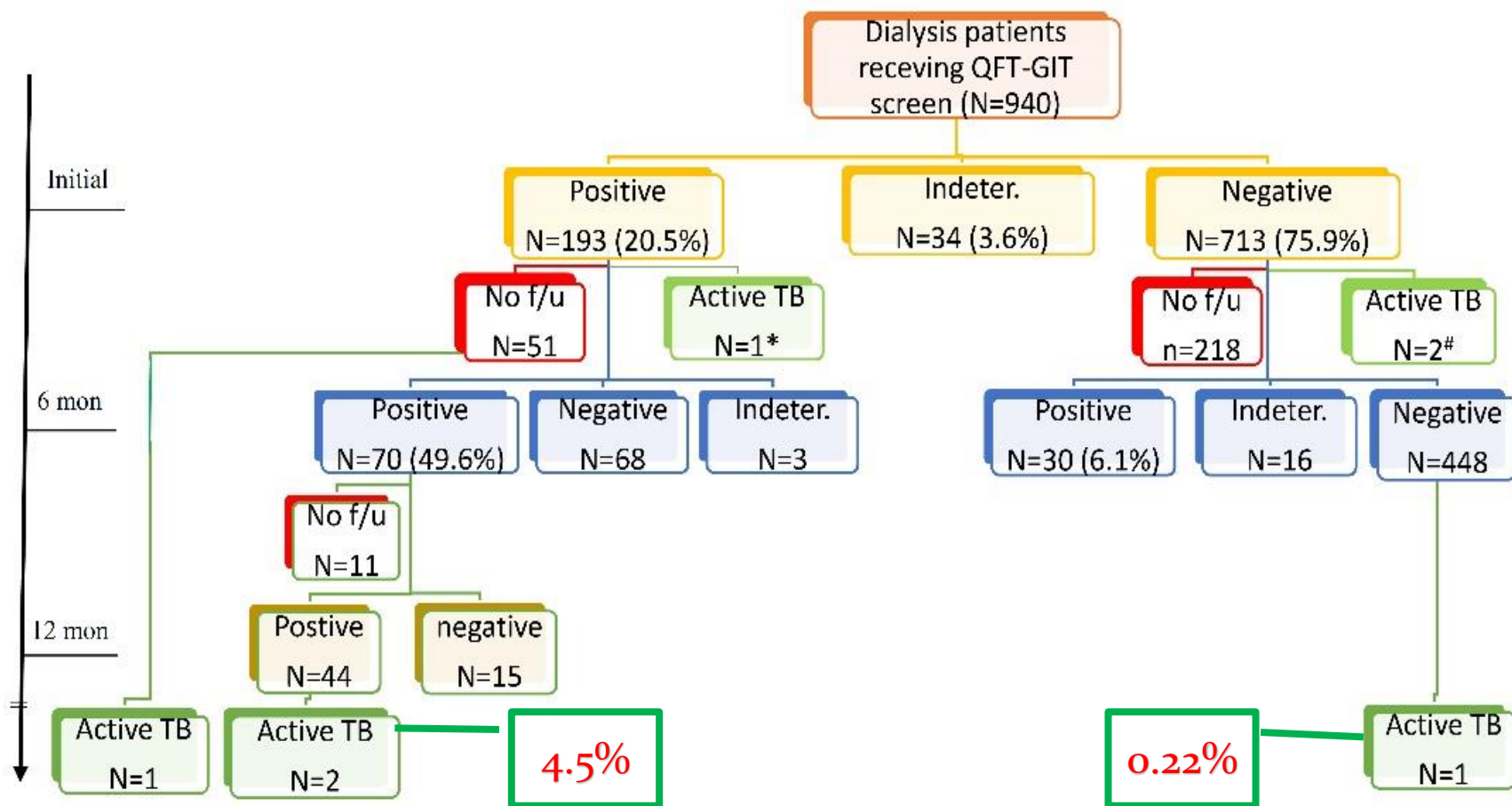
活動性結核

?

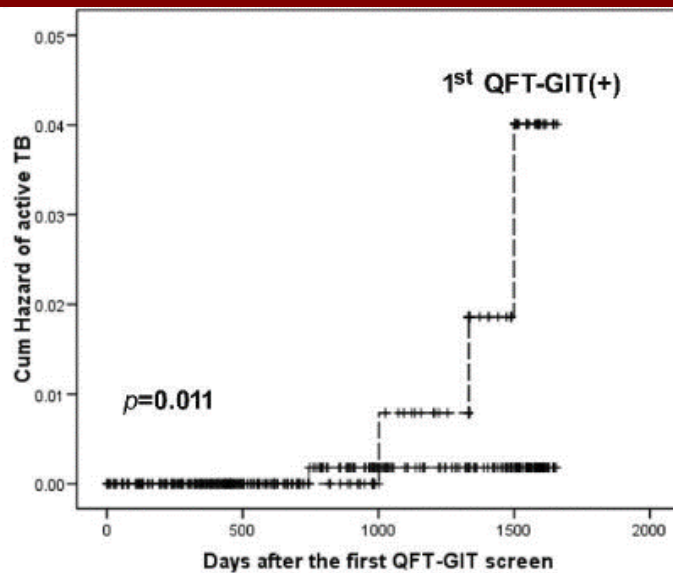
Question



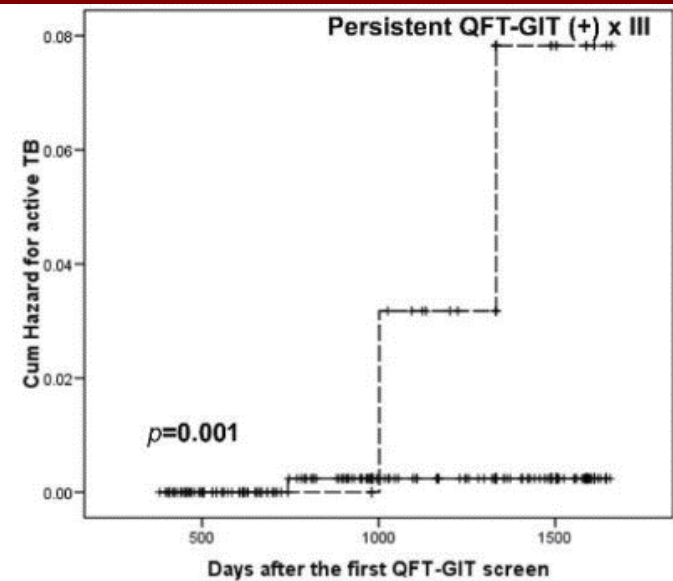
Flow chart of case follow-up



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



QFT-GIT (+) no.:	193	173	149	51
The remaining no.:	747	594	512	210



QFT-GIT (+) x III no.:	44	41	39	10
The remaining no.:	484	459	398	137

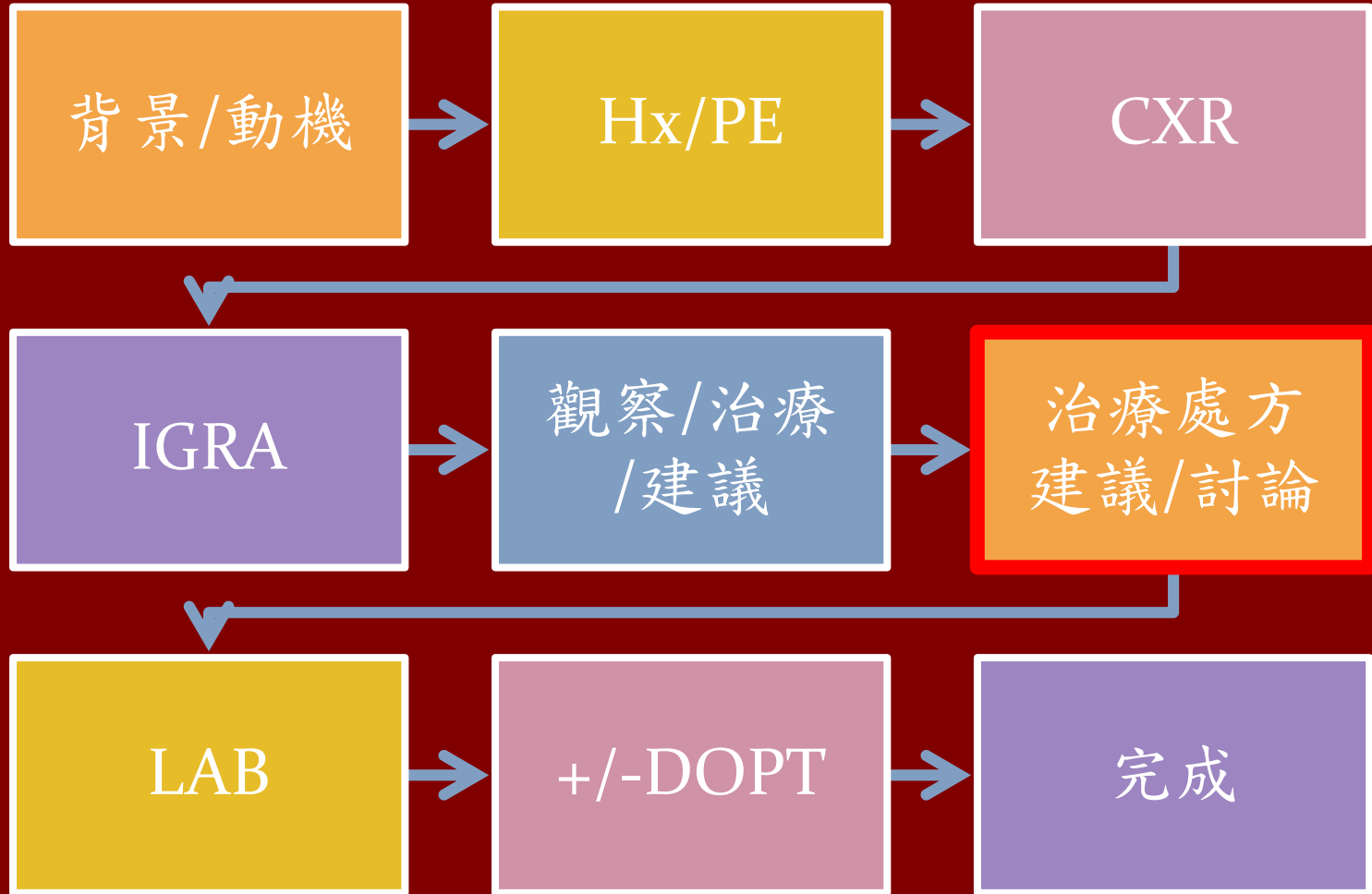
Probability of incident TB in dialysis

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*	P
	Data	No.	No.	%	HR (95% CI)	
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

腎移植LTBI後續發病多嗎？

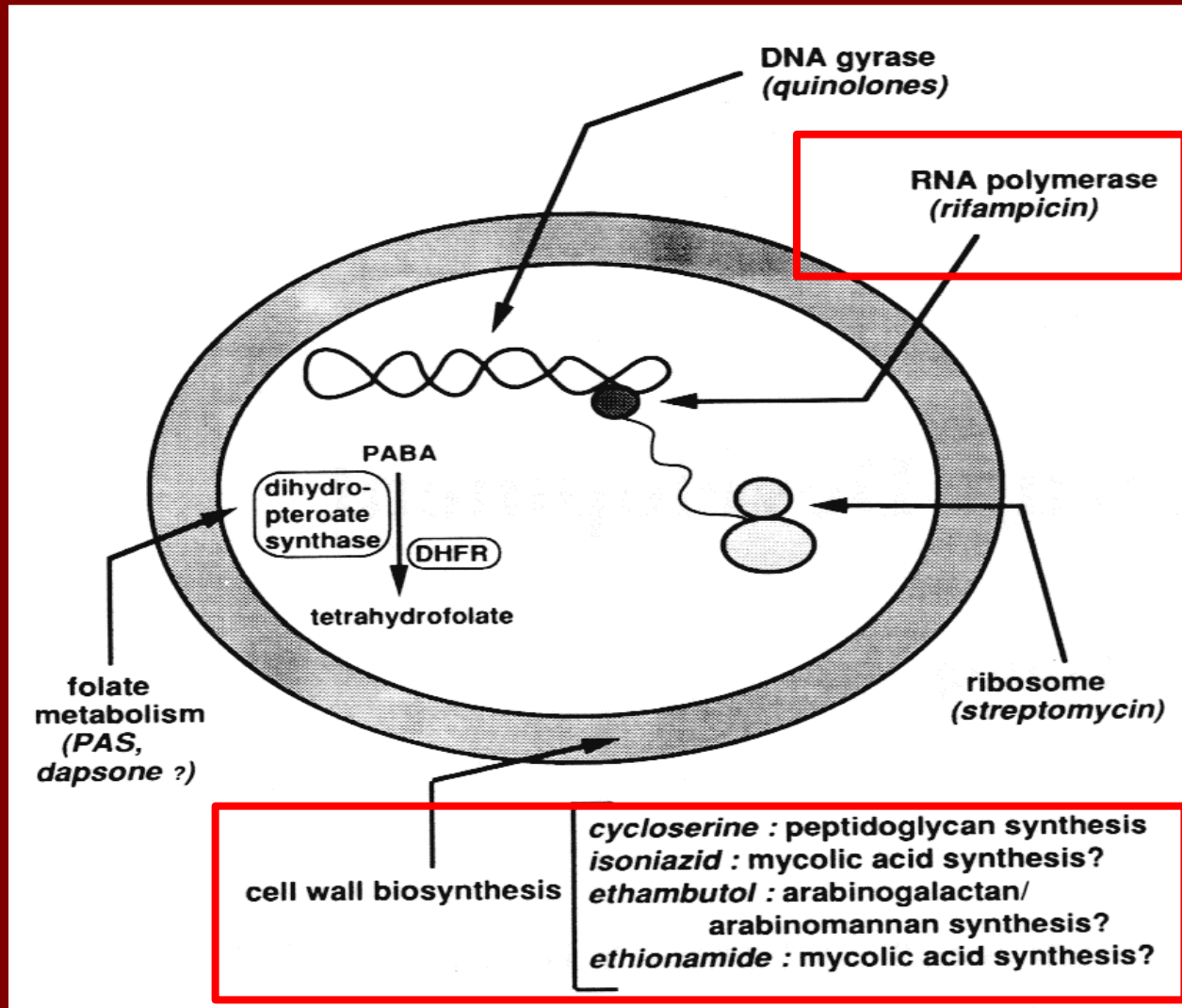
建議流程



LTBI 目前的治療處方

Regimen	內容
9H	每日 isoniazid 共9個月
3HP	一周一次，高劑量 isoniazid 和 Rifapentine，共12周
4R	每日 rifampin 共4個月
3HR	每日 isoniazid 和 Rifampin，3個月
1HP	每日一般劑量 isoniazid 和 Rifapentine，共1個月
6FQ	每日 FQ，共6個月

Site of drug action



治療的處方有那些？



∅ 12 mm

9H

每日三顆, 9個月

3X270

=810



3HP

每次9顆, 12次

9X12

= 108



藥量



3HR

最少每次2顆,
90次

2X90
= 180



4R

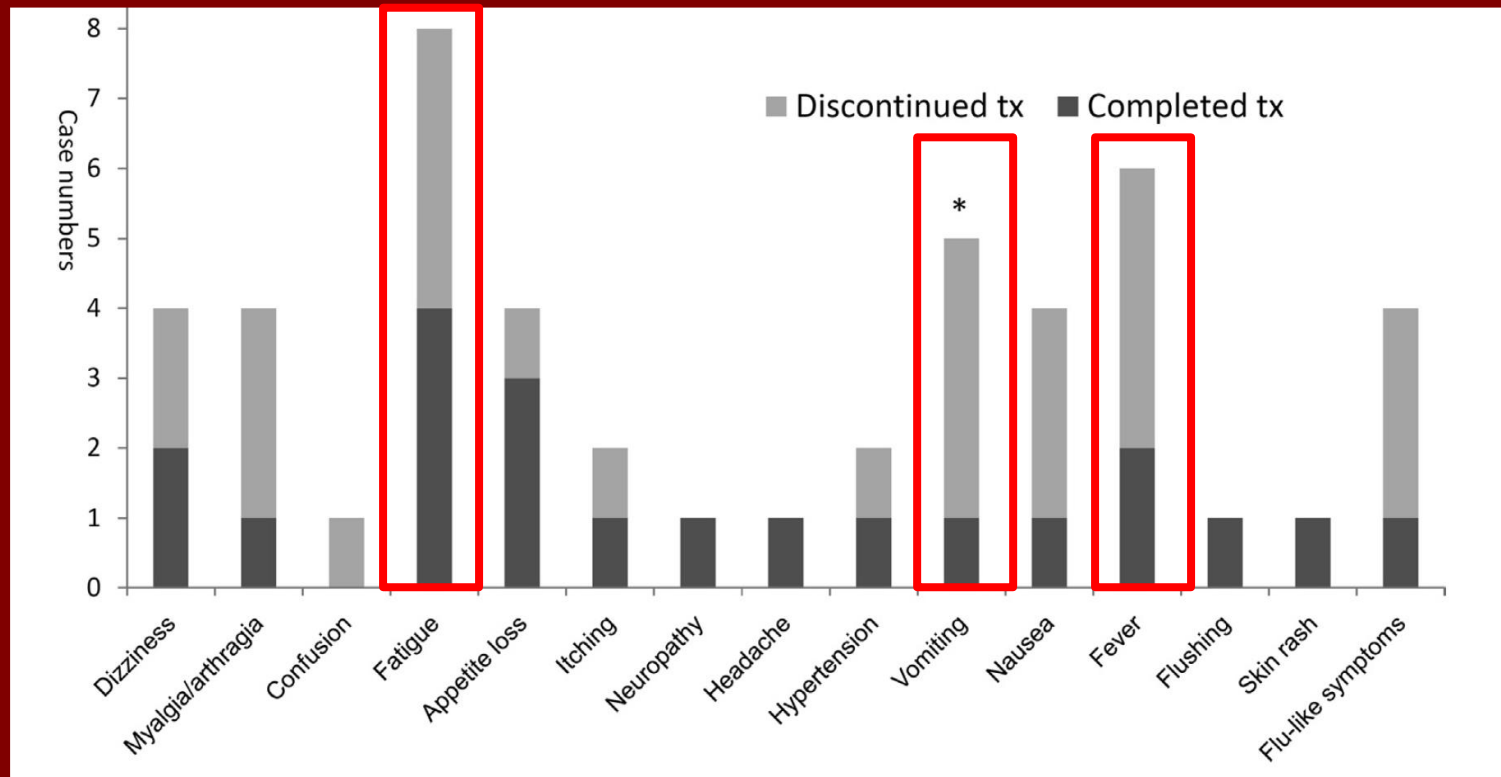
每次4顆,
120次

4X120
= 480

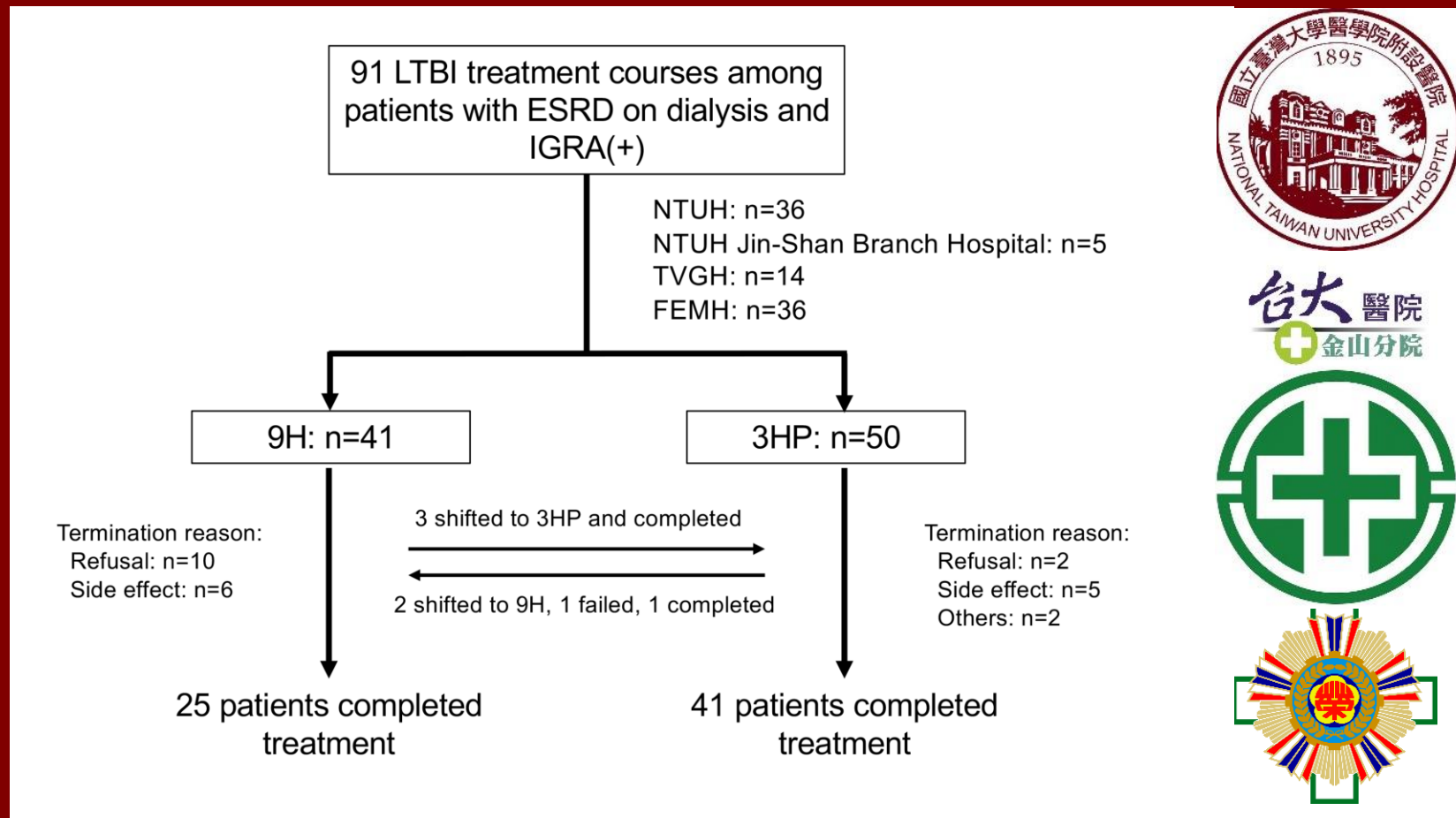
3HP vs 9H in CKD

3HP AE

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



Treatment regimen for dialysis patients



Treatment regimen for dialysis patients

Table 3. Logistic regression models for treatment termination

Variables	Crude OR	95% CI	P	Adjusted OR	95% CI	P
3HP vs. 9H	0.39	0.15–0.99	0.049	0.17	0.04–0.69	0.013
Age over 60	0.58	0.23–1.49	0.259			
Male	1.30	0.47–3.56	0.616			
Active smoking	1.60	0.55–4.66	0.392			
Diabetes mellitus	2.08	0.78–5.54	0.141			
Peritoneal dialysis	1.79	0.46–6.94	0.401			
≥ Grade 2 ADE	2.82	1.00–7.96	0.050	6.67	1.66–26.80	0.008
Eosinophils* <349/μl	reference					
Eosinophils* 350-699/μl	>100		0.999			
Eosinophils* ≥700/μl	>100		0.999			

Abbreviations: ADE, adverse drug event; CI, confidence interval; OR, odds ratio; 3HP, three-month weekly rifapentine plus isoniazid; P, p value; 9H, nine-month daily isoniazid

*Laboratory test obtained at 2 weeks after initiating LTBI treatment. Eosinophil count cutoff was based on 2 times the normal upper limit value.

Only variables with P < 0.1 in univariate regression are included in the multivariate model.



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

3HR vs 9H in Kidney transplant receipts

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

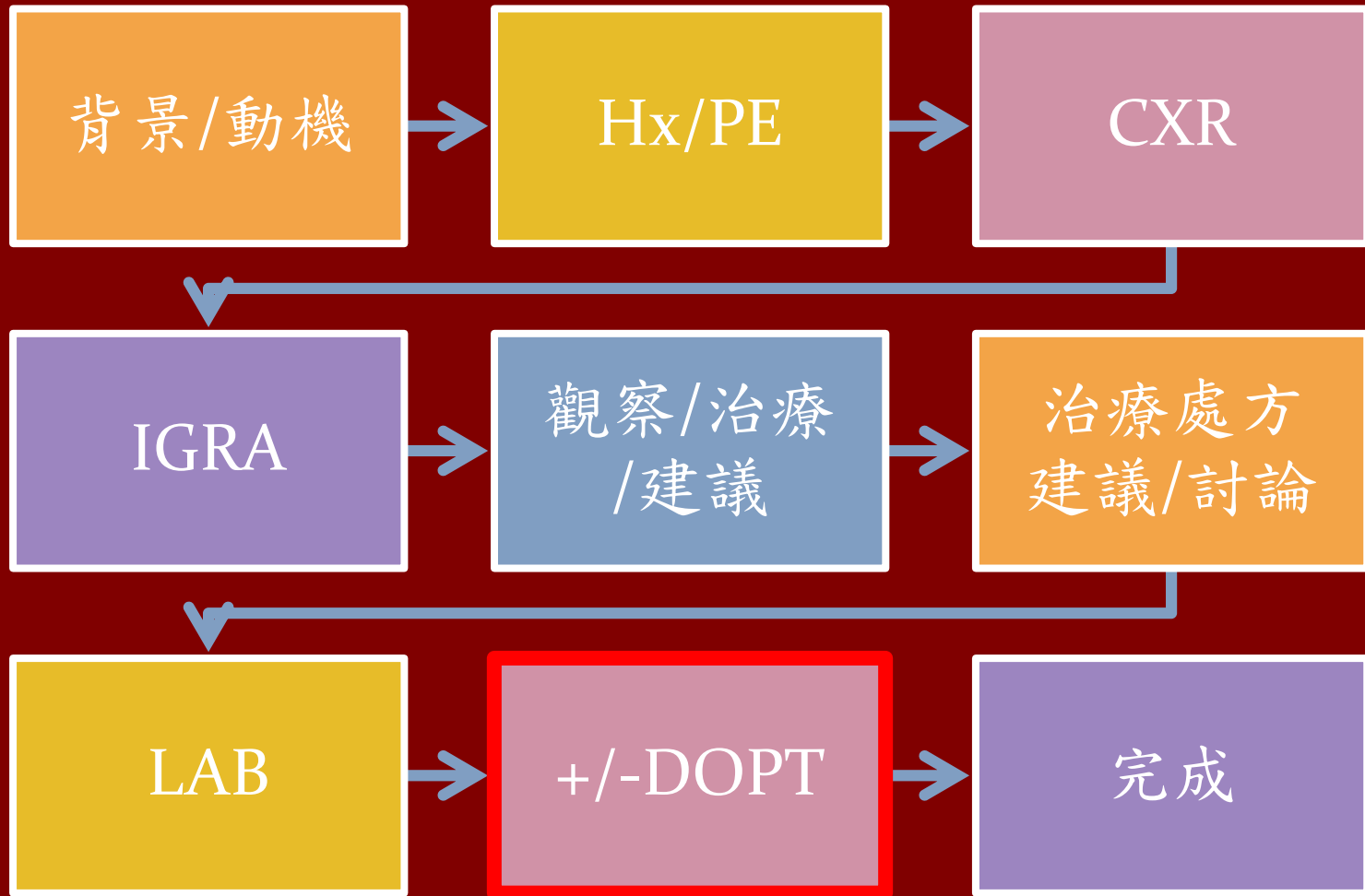
Worry
malaise (Taxi
driver)

?

Worry

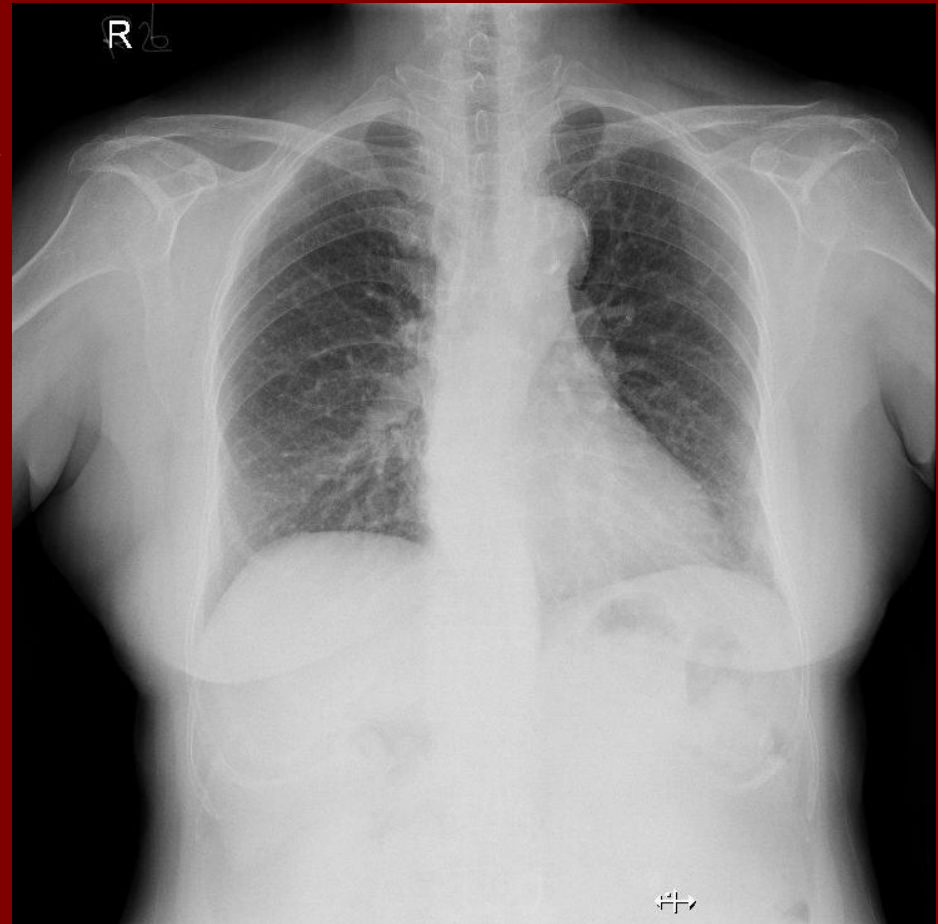
D-D: drug-drug

建議流程



A case received 3HP/3HR

- 了解背景與**動機**重要
- **AE**與失落相關



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

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)

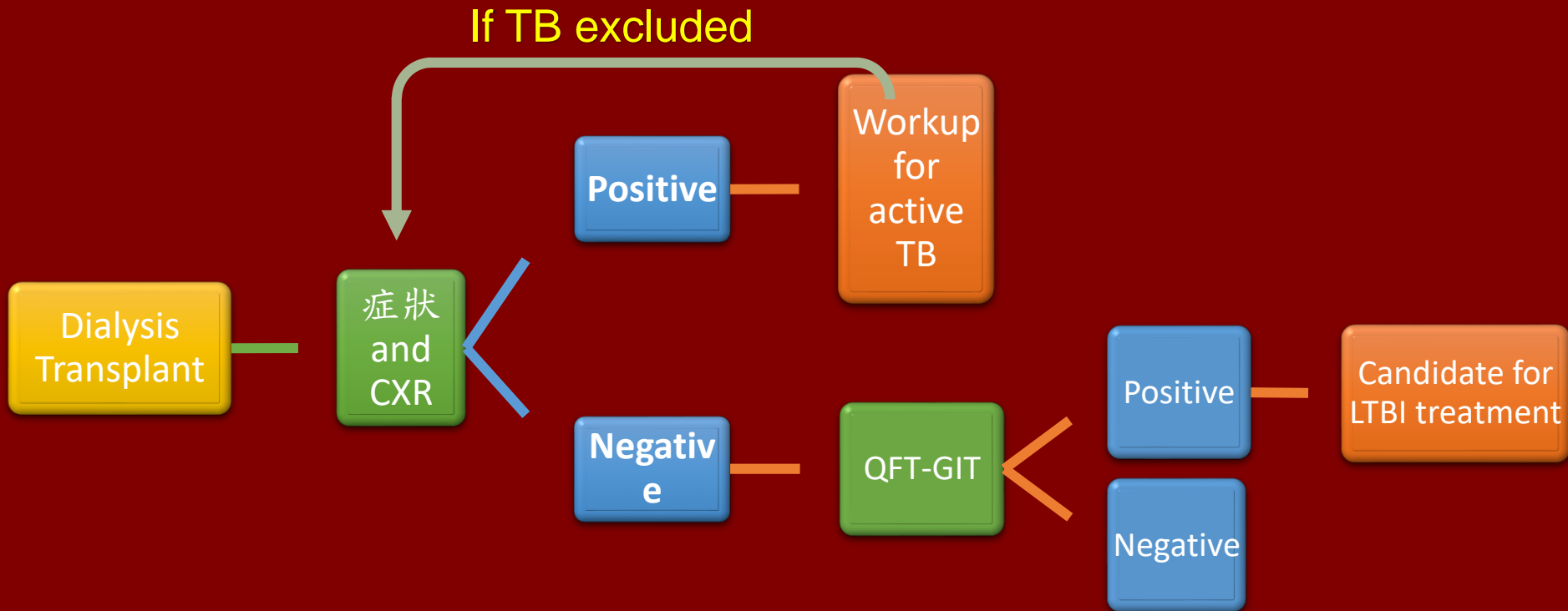
Kim S.H, American Journal of Transplantation 2011; 11: 1927–1935

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

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

S. Vikrant, Transpl Infect Dis 2005; 7: 99-108

LTBI篩檢的流程



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)

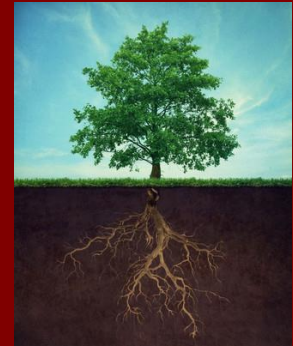


治療時要注意的事

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

心得分享

- 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

- 感謝傳染病防治研究及教育中心舉辦與邀請
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