

院內結核病感控的新進展 Advance in Hospital Infection Control for Tuberculosis

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Outlines

- Cases
- Risk factors of tuberculosis in Taiwan
- Advance in Hospital Infection Control for Tuberculosis

Case I

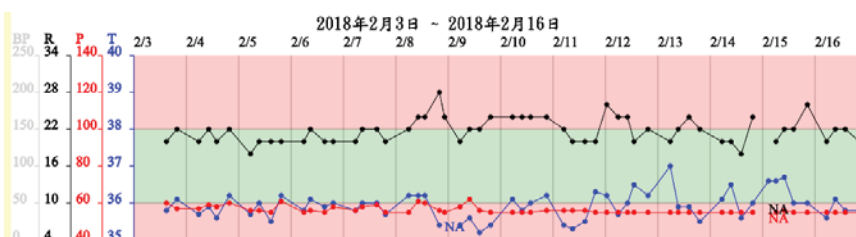
- An 85-year-old man
 - Type II diabetes mellitus
 - Parkinson's disease
 - Dementia
- ER visit
 - accidentally fell down and hit the buttock last night





Case I

- Decreased appetite (+), weight lose (+, 7 kg in 3 months), night sweating (+, for several weeks) , cough (-), chest pain (-), sputum (-)



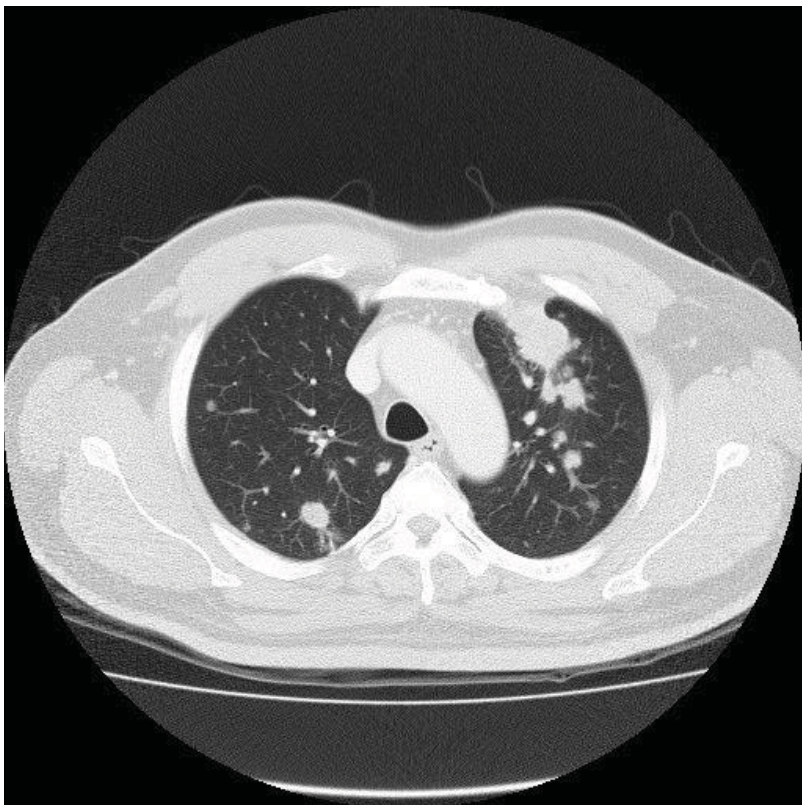
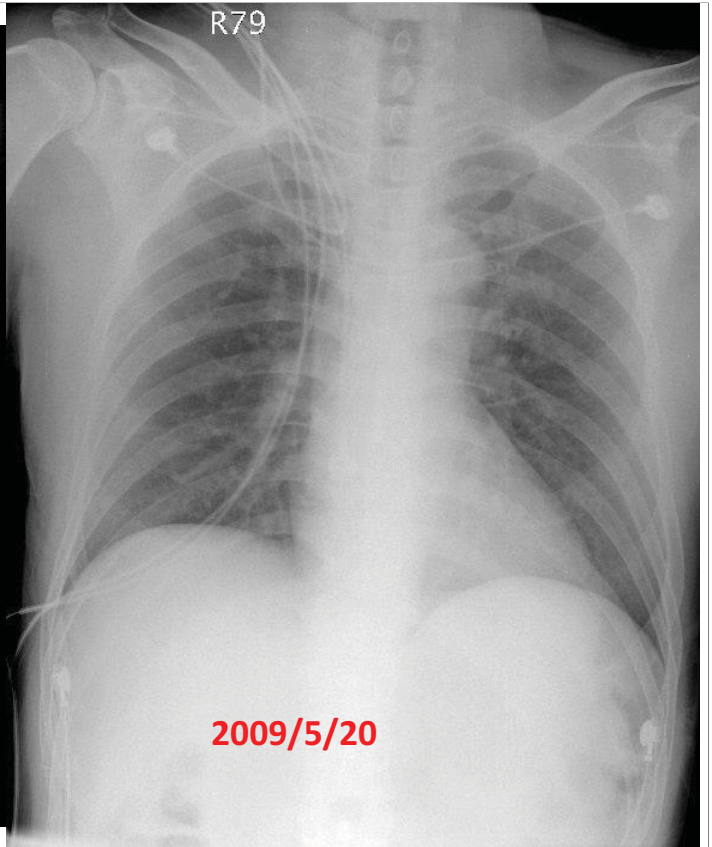
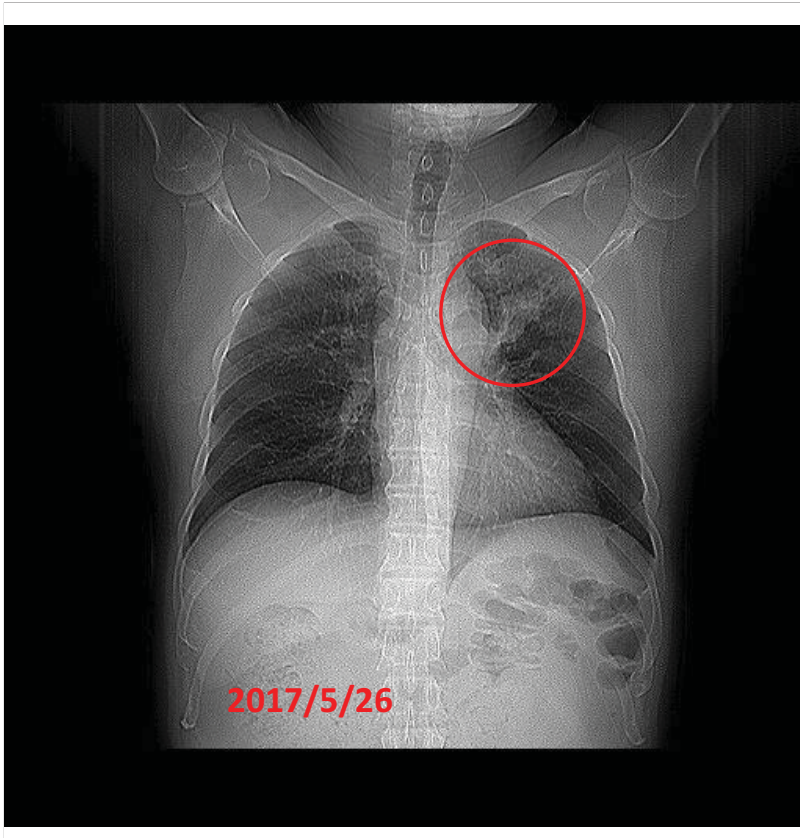
2018/2/4 sputum AFS: Positive 2+
Culture: *M. tuberculosis*

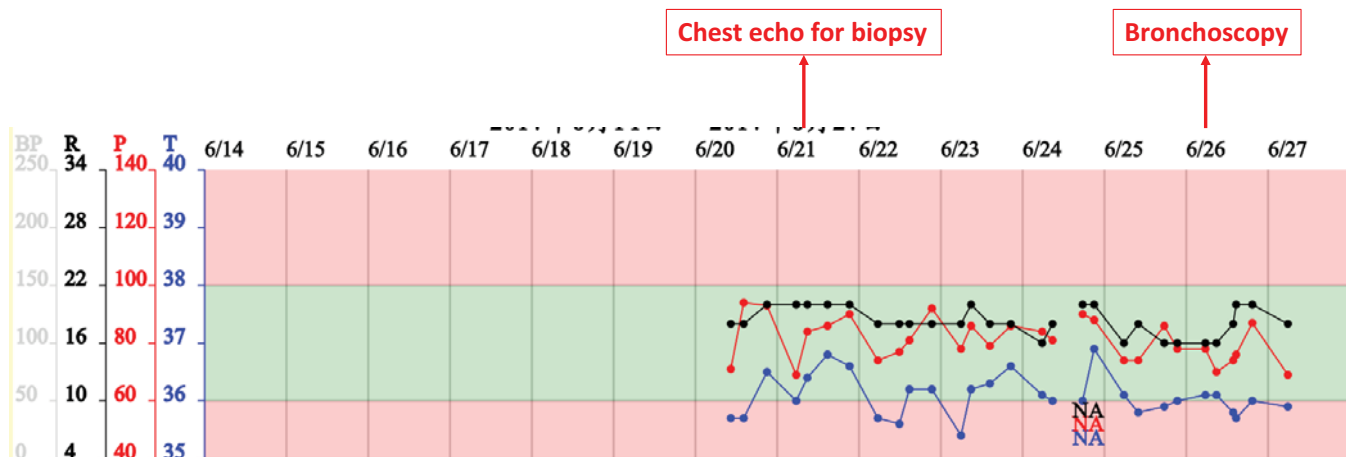
Case II

- 61-year-old man
 - Coronary artery disease, one-vessel-disease, complicated with anterior ST-elevation myocardial infarction, Killip I, status post percutaneous transluminal coronary angioplasty with stenting in the left anterior descending artery on 2009/05/18
 - Type 2 DM under insulin, poorly controlled

Case II

- 5/26 NTUH oncology OPD
 - **Abnormal chest X-ray** was told during health checkup in Hospital A
 - Suspicion of **lung cancer, stage IV**, was told in Hospital A
 - There were no cough, no fever, and no weight loss.
- 5/20 NTUH admission to oncology Ward





Study results

- Pathology
 - Lung, upper lobe, **caseating granulomatous inflammation**
- Sputum AFS x3: negative
- Bronchial lavage: **TB PCR positive**

Case III

- A 79-year-old man
 - Hypertension
 - Diabetes mellitus, type II
 - Dyslipidemia
 - Benign prostate hyperplasia
 - Reflux gastritis

Case III

- 2019/9/10 Orth OPD
 - Pain at lateral aspect of right thigh for 1 week
 - No definite preceding trauma or fall
 - No significant pain at lower back
 - Mild discomfort at right buttock
 - Limping while walking due to pain

9/10



Case III

- 2019/9/10 Orth OPD
 - Pain at lateral aspect of right thigh for 1 week
- 2019/9/24 Orth OPD
 - Pain at lateral aspect of right thigh for 3 weeks
 - WBC 6150 (Seg **87.2%**, Lym 11.5%), Hb 11.6, MCV 86 uL, Plt 258K
 - ALP 63, LDH 163, Cr 1.1, CRP **4.01**, ESR **66**

9/24



9/10



Case III

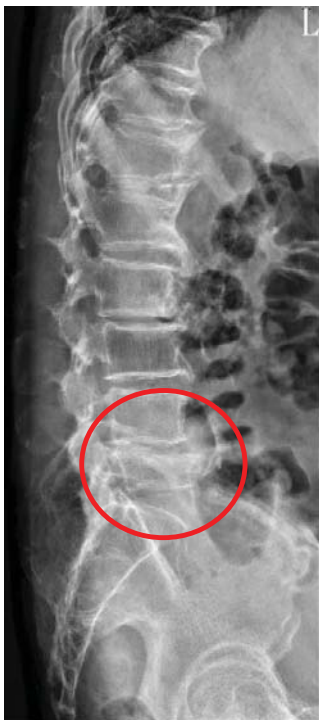
- 2019/9/29 MRI Without Contrast--L Spine
 - (1) Lumbar spondylosis with moderate to severe central canal stenosis at the L2-L3 level, severe central canal stenosis at the L3-L4-L5 levels, and right foraminal stenosis at the L4-L5 level, causing right L4 (mild) and bilateral L5 nerve root compression.
 - (2) Subacute compression fracture at the L5. Subchondral edema at lower portion of the L4.

Case III

- 2019/10/7
 - Admission for the operation



10/7 Admission

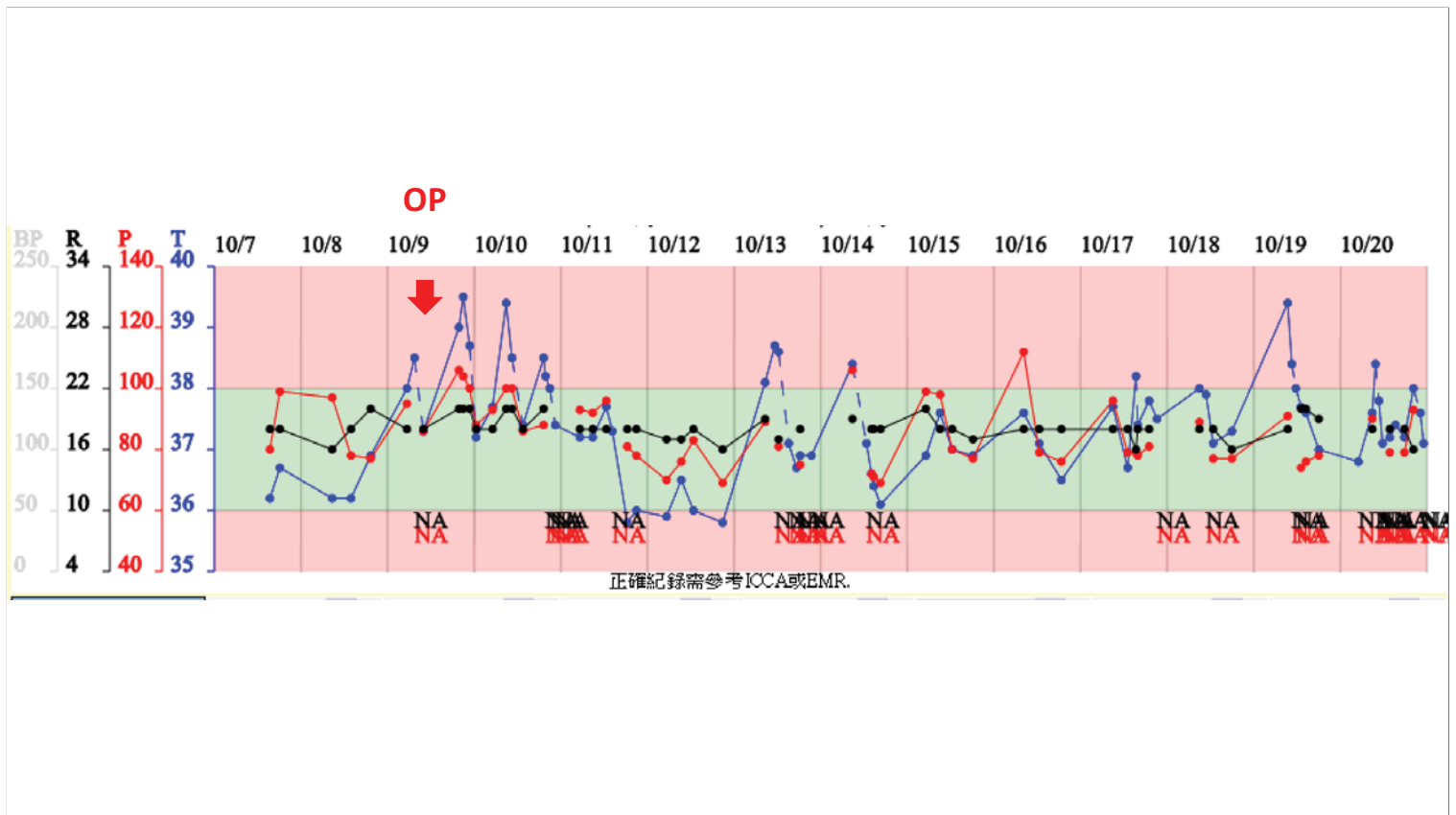


9/24 OPD



9/10 OPD





Case III

- 2019/10/9
 - Pre-operative diagnosis
 - L4 and L5 osteomyelitis with pathologic fracture of L5
 - Lumbar spondylosis with spinal canal stenosis, L3-L5
 - Post-operative diagnosis
 - L4 and L5 osteomyelitis with pathologic fracture of L5
 - Lumbar spondylosis with spinal canal stenosis, L3-L5, operated

Case III

- Pathology of OP specimen
 - Bone, spine, L4/L5, excision, **osteomyelitis**
 - Microscopically, it shows fragmented bone and cartilage tissue with necrotizing debris surrounded by histiocytes and lymphocytes. Shadow cells are present.
 - **AFS** shows positive of few **rod-like bacteria**. PAS and GMS demonstrate no fungal hyphae or cocci.
 - It is compatible with osteomyelitis.
- Acid-fast stain of his sputum
 - I: **Positive** → Negative TB PCR
 - II: Negative
 - III: Negative
- TB culture of his sputum
 - ***M. tuberculosis*** x III
- TB culture of his surgical specimen
 - ***M. tuberculosis***



Persons using assistive technology might not be able to fully access information in this file. For assistance, please send e-mail to: mmwrq@cdc.gov. Type 508 Accommodation and the title of the report in the subject line of e-mail.

Nosocomial Transmission of *Mycobacterium tuberculosis* Found Through Screening for Severe Acute Respiratory Syndrome --- Taipei, Taiwan, 2003

The emergence of severe acute respiratory syndrome (SARS) has highlighted the importance of hospital infection-control programs (1). Prevention of *Mycobacterium tuberculosis* transmission also requires effective infection control in health-care facilities (2,3). In Taipei, Taiwan, an area with moderate to high incidence of tuberculosis (TB) (50--74 cases per 100,000 population), health-care workers (HCWs) are at increased risk for *M. tuberculosis* (Taiwan Center for Disease Control, unpublished data, 2002). In April 2003, SARS-related screening in a hospital in Taipei resulted in the detection of suspected TB among HCWs. This report summarizes how SARS screening led to the discovery of 60 cases of TB. HCWs in Taiwan should remain vigilant for cases of TB so persons suspected of having TB are evaluated and treated promptly.

Nosocomial transmission of TB

- Apr 2003
 - An health-care workers (HCWs) was screened for SARS symptoms (fever, cough, and shortness of breath)
 - CXR: pleural effusion
 - Pleural biopsy culture: *M. tuberculosis*
 - TB screening of close co-workers → **6** additional cases of pulmonary TB

MMWR 2004; 53: 321–2.

Nosocomial transmission of TB

- Jun – Jul 2003
 - Hospitalwide screening of HCWs → **28** (2%) of 1409 with TB
- Oct – Nov 2003
 - A repeat hospitalwide screening of 1463 HCWs → additional **29** cases of TB
 - 5 were later found not to have TB after reinterpretation of their chest radiographs
 - **Another** HCW developed TB lymphadenitis
 - $7+28+29-5+1=$ **60** HCWs

MMWR 2004; 53: 321–2.

Nosocomial transmission of TB

- Review of patient records
 - An elderly patient had spent **12 weeks** on **floor A** without respiratory isolation before AFS-positive pulmonary TB was diagnosed in **May 2003**.
 - The patient's hospital course was complicated, eventually requiring **continuous ventilator support** and **frequent endotracheal suctioning**.
- Isolates from this patient matched the **genotype** of the **seven** culture-positive HCWs, **five** of whom (including the first diagnosed HCW) worked on **floor A**.

MMWR 2004; 53: 321–2.

Number of health-care workers (HCWs) surveyed and number with tuberculosis (TB) diagnosed by hospital floor and unit

Floor	Unit	No. HCWs	Dx TB, N	%	Odds ratio	95% CI
Floor A	Pulmonary	77	28	36	47.3	23.4 – 95.4
Floor B	Intensive care	57	6	11	9.7	2.9 – 22.0
Floor C	Radiology	84	4	5	4.1	1.6 – 16.8
Floor D	Dialysis	186	5	3	2.6	0.9–7.2
Remaining floor		1172	14	1	Reference	

MMWR 2004; 53: 321–2.

Effect of Types of Contact and Living Conditions on the Likelihood of Contagion from Common Bacterial and Viral Respiratory Tract Pathogens

Variable	Bacteria	<i>Mycobacterium tuberculosis</i>	Influenzavirus <i>risk of contagion</i>	Rhinovirus, RSV*	Other Viruses
Type or location of contact					
Casual social contact	Low	Low	Moderate	Low	Moderate
School, workplace	Moderate	Moderate	High	Low	Low
Bar, social club	High	High	High	Low	Low
Travel tour	Moderate	Moderate	High	Low	Low
Dormitory	Moderate	High	High	Moderate	Moderate
Home	High	High	High	Moderate	High
Special conditions					
Loss of air circulation	Moderate	High	High	None	Low

Musher DM, et al. N Engl J Med 2003; 348: 1256-66

院內接觸者

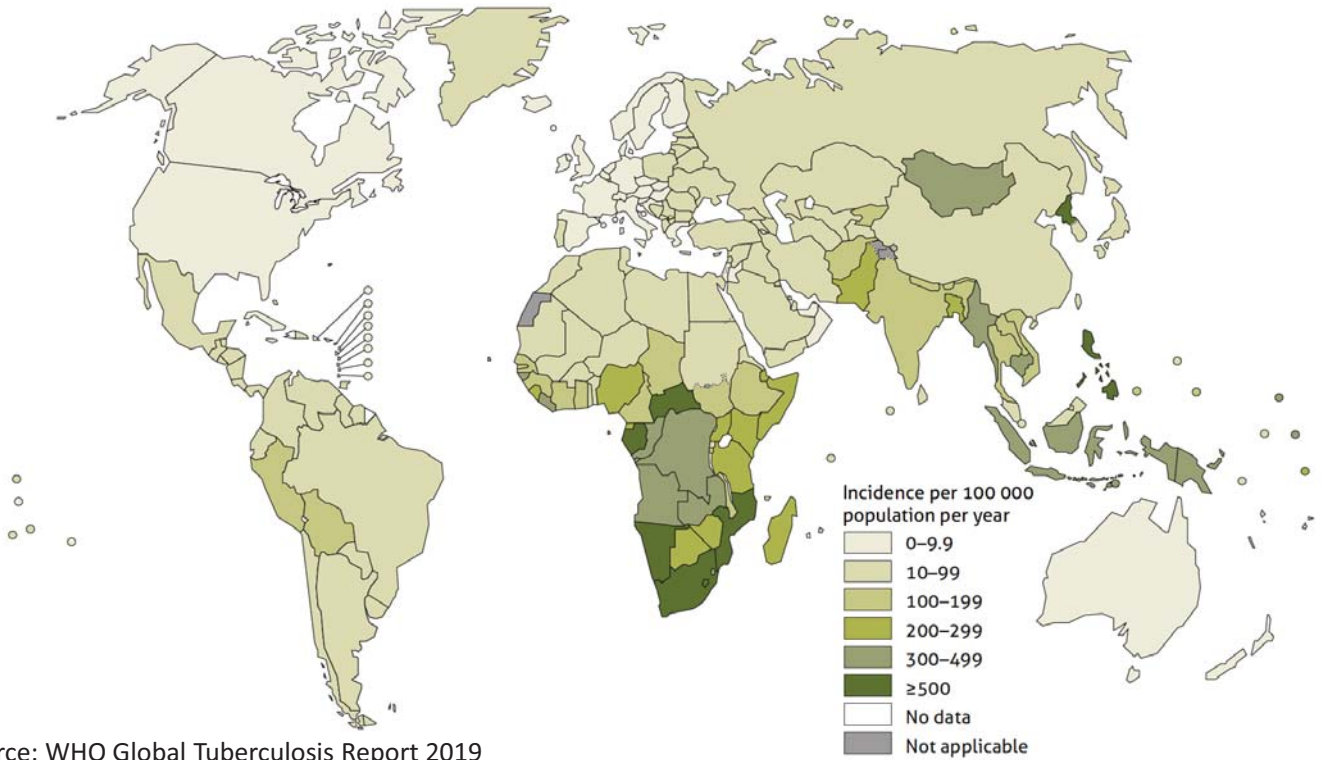
• 院內接觸者定義

- 指標個案(住院病患, Index case)未配戴**外科口罩**，同病室的其他病人、家屬及醫療照護工作人員，未配戴**N95口罩**以上等級防護裝備下，與指標個案接觸**一天內8小時(含)以上**，或於指標病人可**傳染期間**累積**40小時**者。

• 指標個案若符合下列條件之一，醫院須進行院內接觸者疫調：

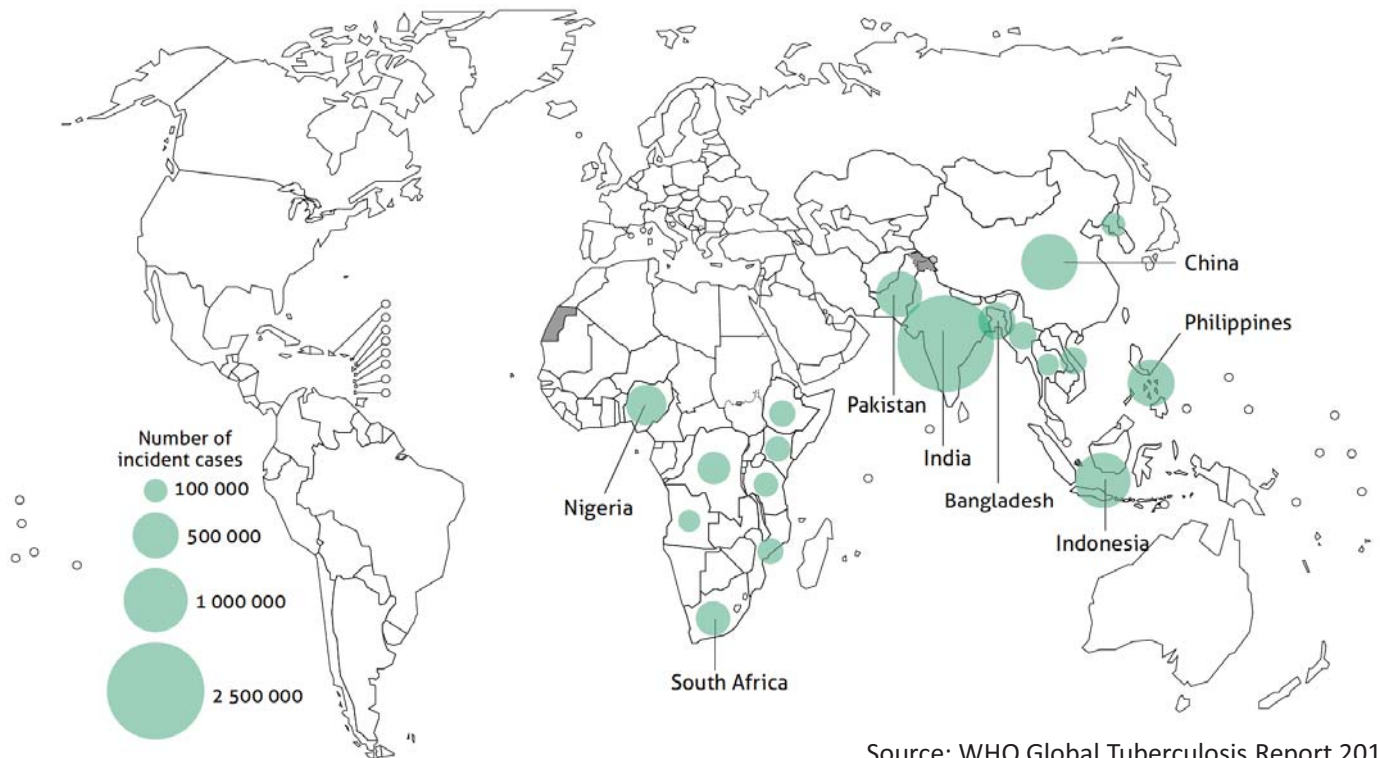
- (一)痰抹片**陽性**且鑑定為**MTB肺結核**個案。
- (二)痰抹片**陰性**但**培養**鑑定為**結核分枝桿菌**病人，且個案於住院期間曾進行會**產生飛沫微粒之醫療處置**(aerosol generating procedures)。
- (三)**多重抗藥性結核**病個案。

Estimated TB incidence rates, 2018 西元2018年結核病發生率



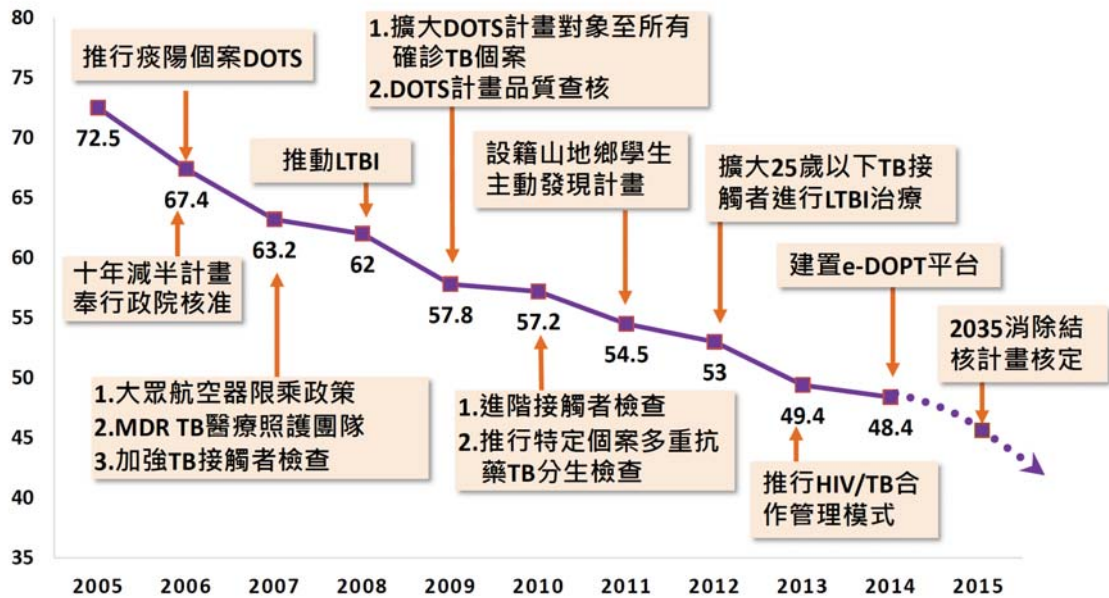
Source: WHO Global Tuberculosis Report 2019

Estimated TB incidence in 2018, for countries with at least 100 000 incident cases 西元2018年結核病新案



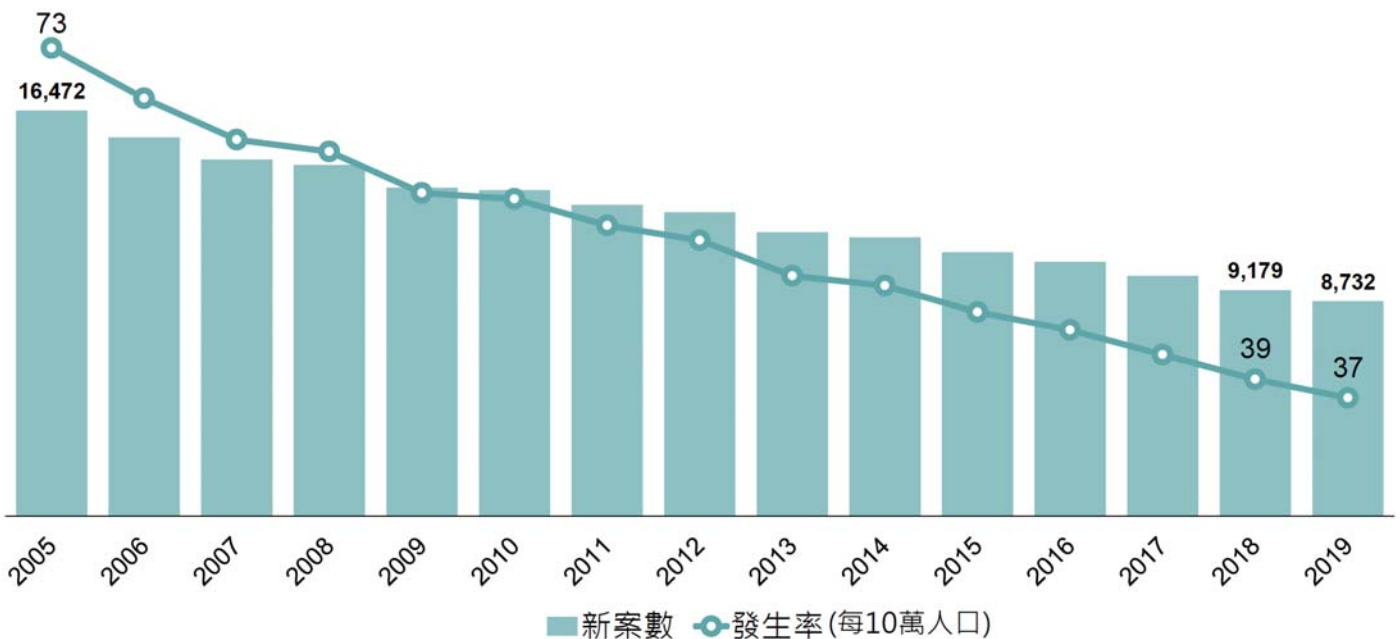
Source: WHO Global Tuberculosis Report 2019

我國結核病政策推動



Source: <https://www.cdc.gov.tw/Uploads/100c2c39-d5b3-4bfa-815f-0baf7404e43f.pdf>

全國結核病發生率

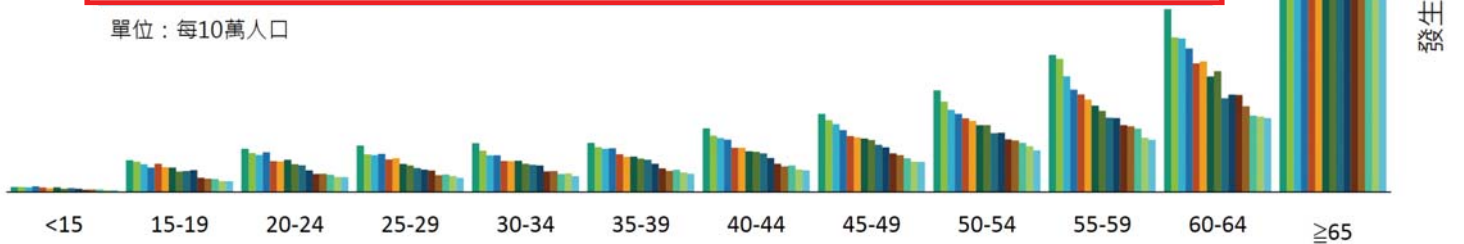


Source: <https://www.cdc.gov.tw/Uploads/100c2c39-d5b3-4bfa-815f-0baf7404e43f.pdf>

結核病年齡別發生率(2005-2019)

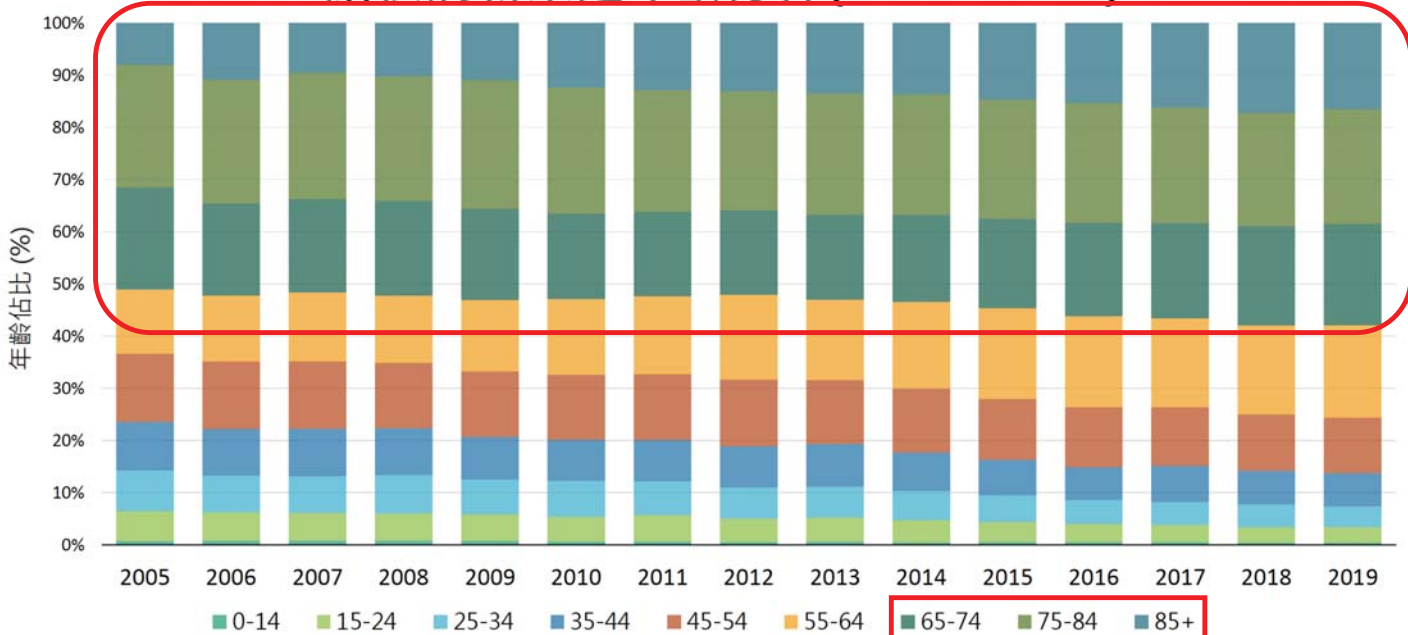
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
<15	3.5	3.5	3.3	4	3.2	2.6	3.3	2.2	2.7	2.2	1.5	1.7	1.6	1.2	1.2
15-19	22.7	21.7	19.9	17.5	20.2	17.7	17.5	14.6	14.9	15.6	10.2	9.5	9.2	7.7	7.6
20-24	31	27.9	26.5	28.4	22	21.8	23	19.9	19.1	15.4	12.9	13	12.3	10.7	10.6
25-29	33.2	26.9	26.4	27.3	23.3	24.2	20	19	17	16	15.3	11.9	12.5	11.4	10
30-34	34.9	29.6	26.3	26.2	22.2	22.1	22.3	20.1	19.3	18.9	14.7	14.9	12.8	13.3	11.3
35-39	35.1	32	31	31.2	27.1	25.2	25.3	23.8	23	20.2	16.9	15	15.9	14	13
40-44	45.5	40.3	38.6	37.5	31.6	31.7	29.1	28.8	27.6	24.3	20.1	18.3	19.0	16.1	15.5
45-49	56	51.4	48.5	44.3	40	39.1	38.2	37.2	33.8	31.9	27.6	26.4	24.1	21.7	21.5
50-54	72.8	64.8	58.8	55.9	52.7	50.9	47.9	47.8	42.2	42.4	37.7	36.9	35.2	32.7	29.8
55-59	98.3	95.5	83	73.4	69.9	66.2	61.9	58.1	53.3	53	47.8	47.1	45.3	38.8	37.3
60-64	131.2	110.8	110	102.9	92.2	93.7	82.8	86.6	67.2	69.8	69.6	61.5	54.8	54.1	53
≥65	385	356.5	323	314	291.3	283.1	263.5	250.5	230.9	220	208.3	191.3	173.4	159.2	143.7

單位：每10萬人口



Source: <https://www.cdc.gov.tw/Uploads/100c2c39-d5b3-4bfa-815f-0baf7404e43f.pdf>

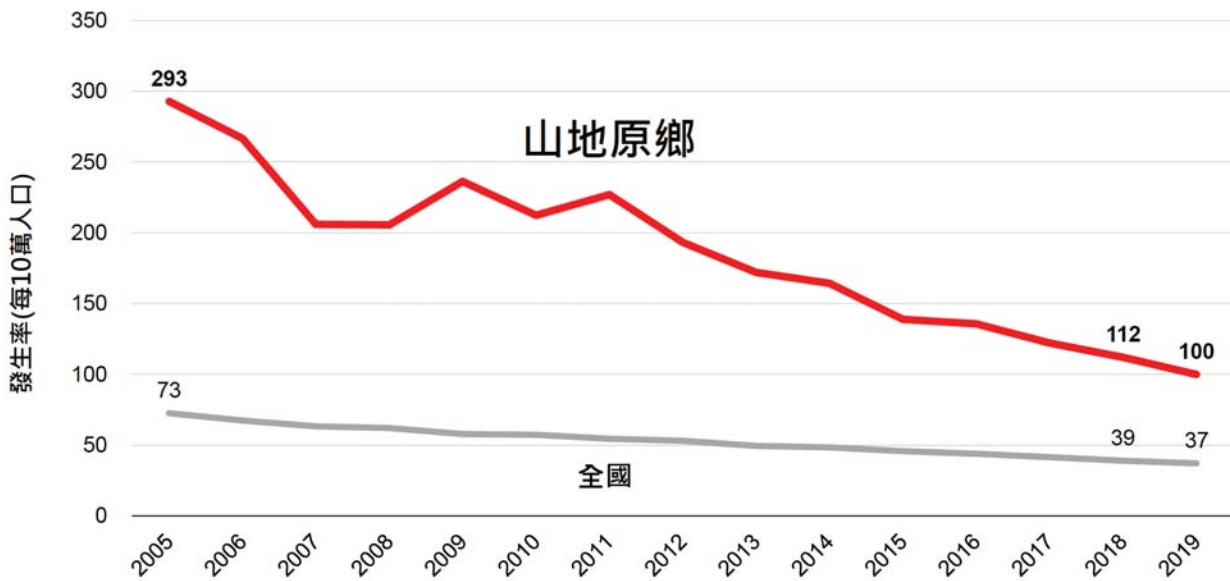
結核病新案之年齡分佈(2005-2019)



Source: <https://www.cdc.gov.tw/Uploads/100c2c39-d5b3-4bfa-815f-0baf7404e43f.pdf>


65歲以上個案占所有個案近60%

山地原民鄉結核病發生率



Source: <https://www.cdc.gov.tw/Uploads/100c2c39-d5b3-4bfa-815f-0baf7404e43f.pdf>

原鄉計畫全面執行

 2020年目標

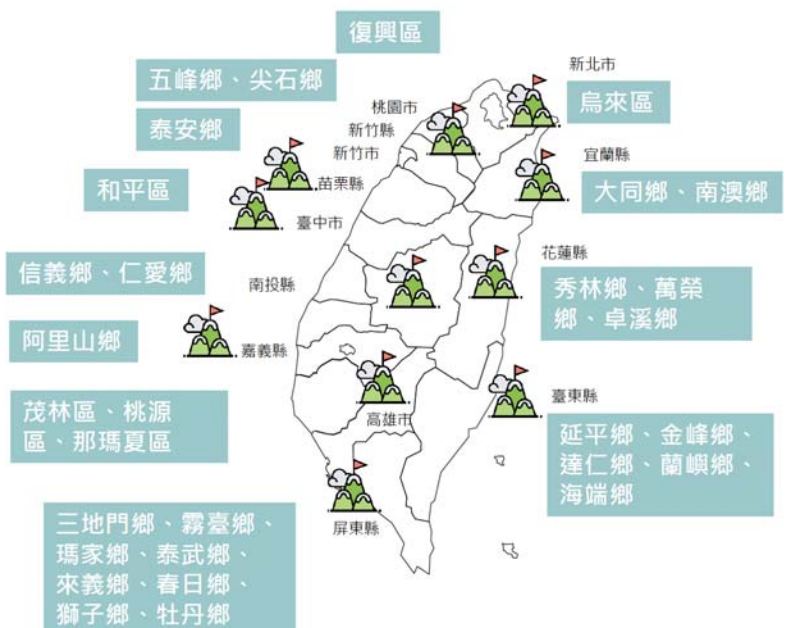
55%

35-64歲
3年篩檢率

50%

65歲以上
每年篩檢率

- 增加合作醫療院所，擴大服務涵蓋範圍
- 強化X光異常送驗結核菌分子檢驗機制



Source: <https://www.cdc.gov.tw/Uploads/100c2c39-d5b3-4bfa-815f-0baf7404e43f.pdf>

結核病接觸者檢查規範



為強化並督導接觸者追蹤工作，自2007年7月1日起由公務預算支付接觸者檢查之部分負擔費用。

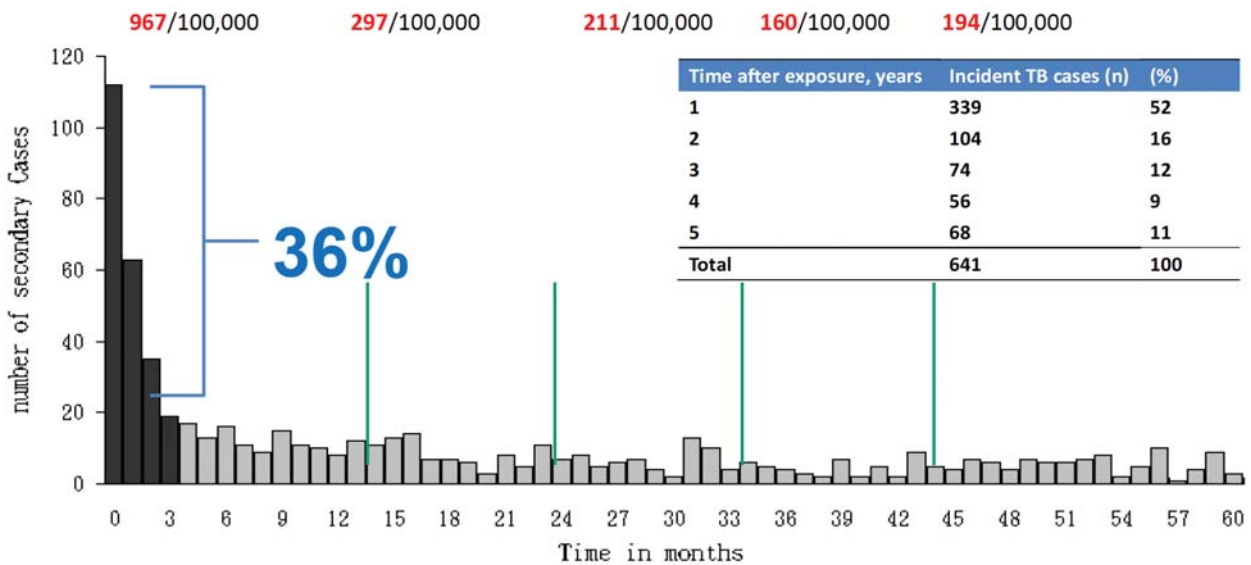
檢查對象

- 與確診之結核病個案共同居住者
- 與結核病個案於可傳染期間一天內接觸8小時以上或累積達40(含)小時以上之接觸者
- 其它專案

Source: <https://www.cdc.gov.tw/Uploads/100c2c39-d5b3-4bfa-815f-0baf7404e43f.pdf>

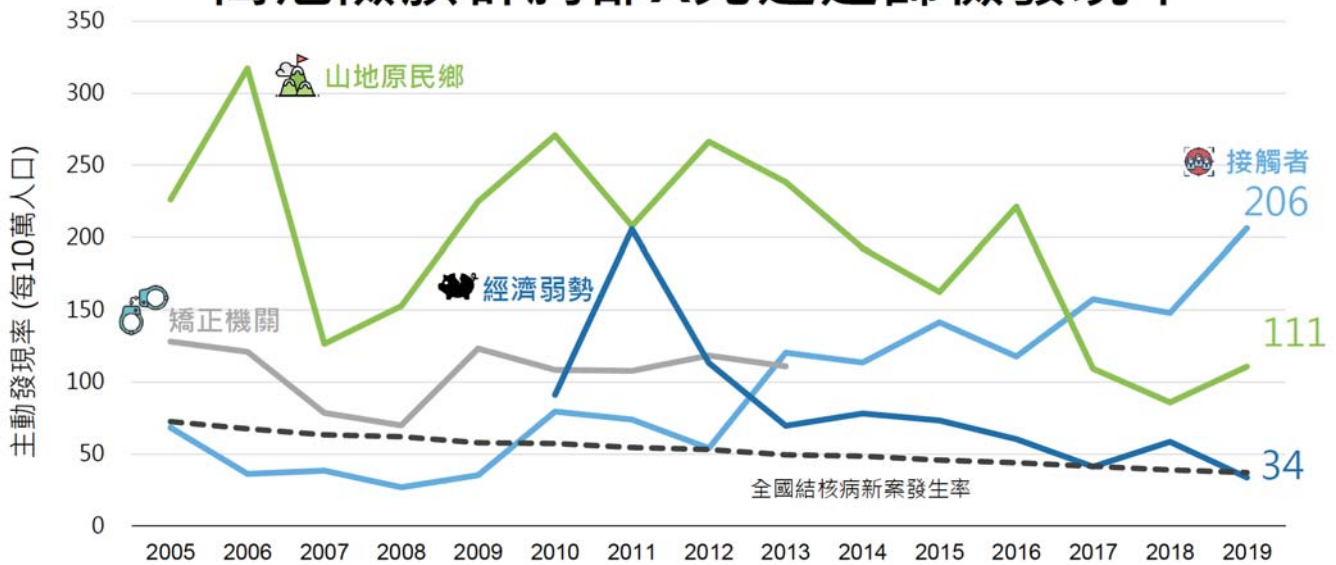
接觸者發病為一般民眾發病的8 - 240倍

結核病接觸者追蹤5年發病率



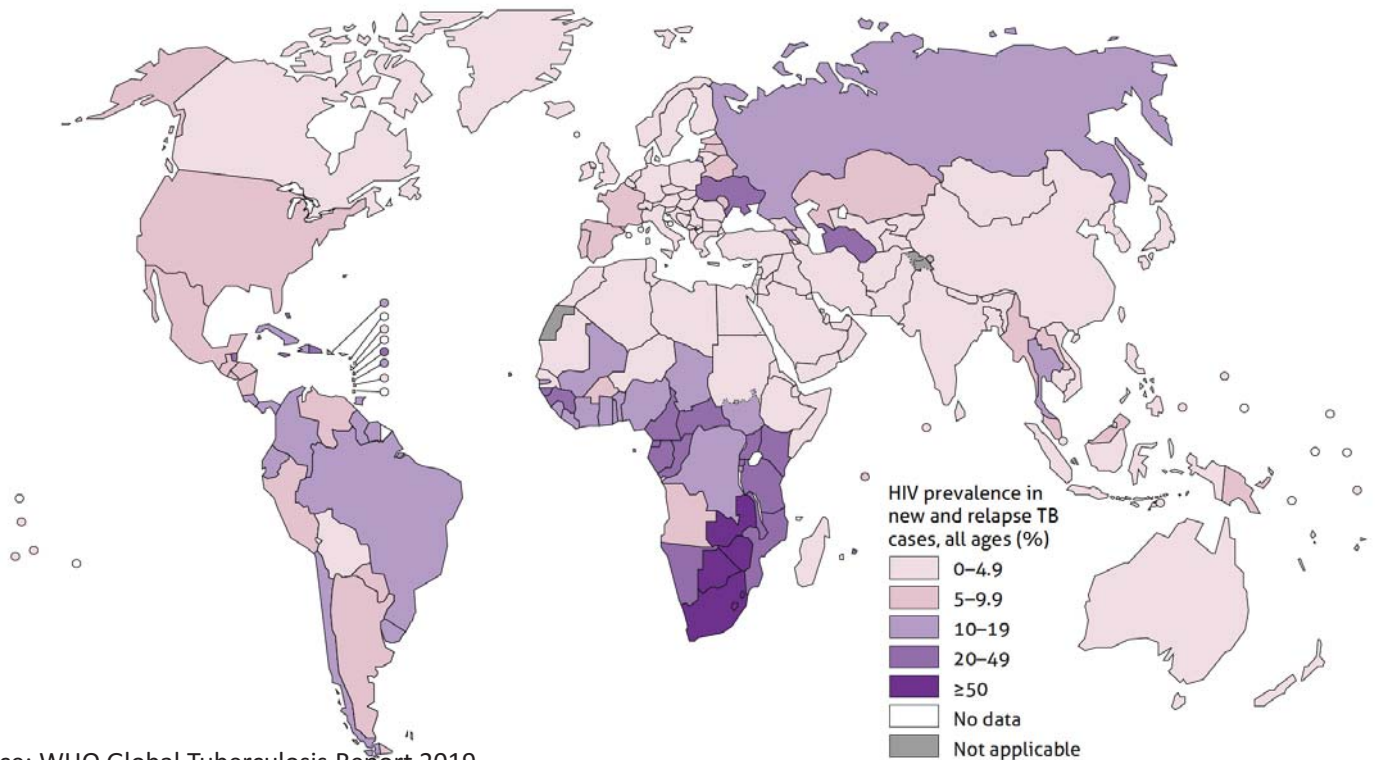
Timing of diagnosis of 641 coprevalent and incident TB cases following diagnosis in the index case during 60-month follow up. **The black bar reveals coprevalent cases found directly by contact investigation.**

高危險族群胸部X光巡迴篩檢發現率



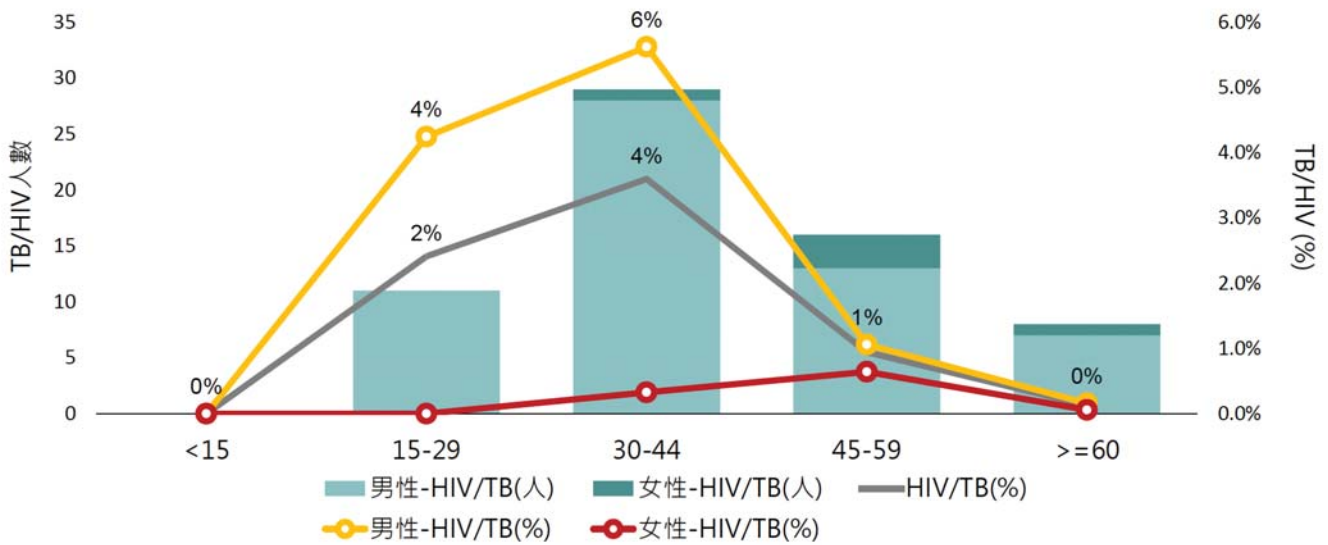
Source: <https://www.cdc.gov.tw/Uploads/100c2c39-d5b3-4bfa-815f-0baf7404e43f.pdf>

Estimated HIV prevalence in new and relapse TB cases, 2018



Source: WHO Global Tuberculosis Report 2019

結核病各年齡層新案之HIV感染比率

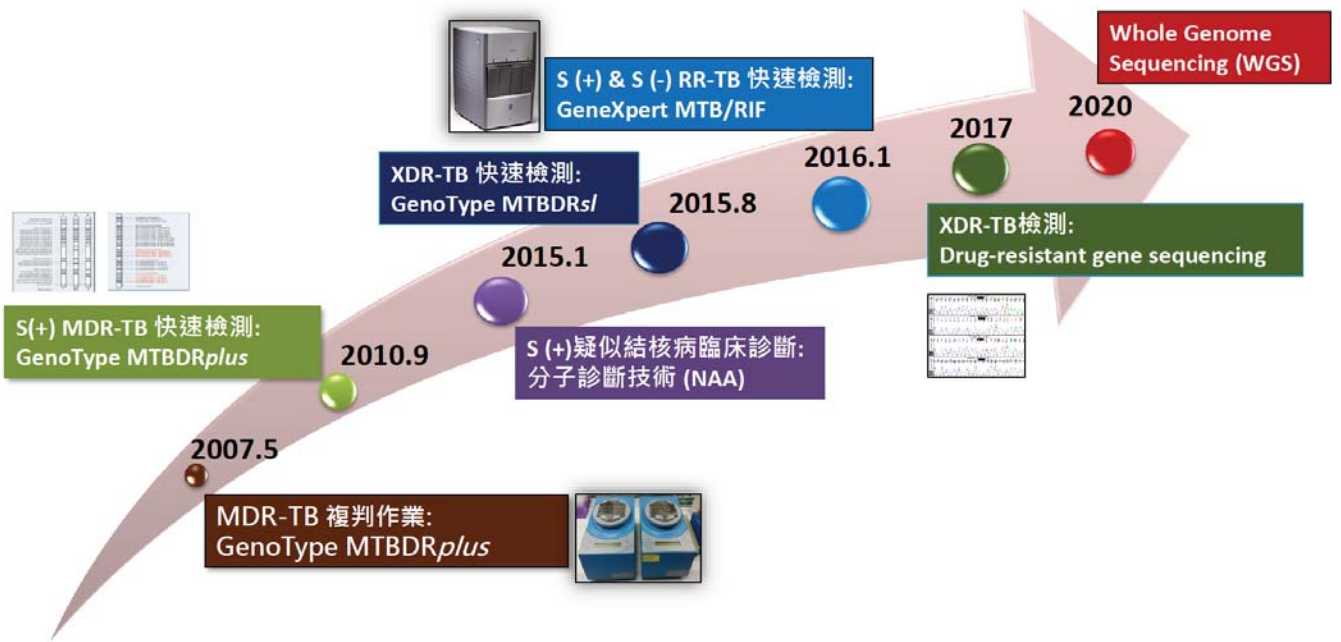


2018年TB新案中HIV個案數64人(HIV/TB比率：0.7%·男性0.9%·女性0.2%)
 15-49歲TB新案中HIV個案數48人(HIV/TB比率：2.9%·男性4.6%·女性0.2%)

合併潛在性疾病的TB風險：台灣的資料

	發生率	相較於一般族群的風險
HIV	64-440	1.4-9.6
矽肺症/塵肺症	473	10.3
糖尿病	128	2.8
慢性腎衰竭/透析族群	141.8	3.1
腫瘤壞死因子阻斷劑使用者 (TNF-alpha blocker users)	600	13.1
器官/骨髓移植	500-688	10.9-15.1
胃癌 (含胃切除及化學治療)	523	11.4
血液腫瘤	120	2.6

WHO推薦新檢驗技術之引進



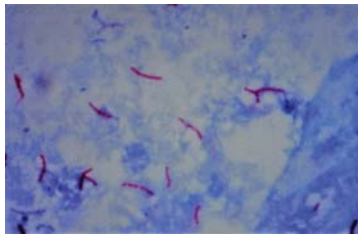
抗酸菌的鏡檢 -- 抗酸菌染色

- 顯微鏡鏡檢
 - 是實驗室能**最早**且**最快**發現抗酸菌的方法
 - 能迅速確認是否被感染，提供作為**初步診斷**結核菌感染的參考
 - 能監測病人接受**藥物治療**進行的狀況
 - 於確認培養出的菌落為分枝桿菌
- 經由染色的抹片鏡發現抗酸菌
 - 每mL中約需有**5000-10000**隻抗酸菌
- 經由培養發現抗酸菌
 - 每mL檢體中只需**10-100**隻活抗酸菌

抗酸菌的鏡檢 -- 抗酸菌染色

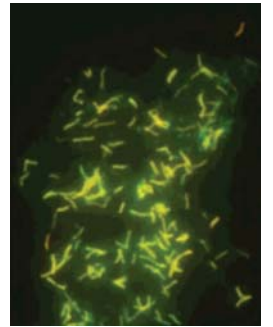
- Ziehl-Neelsen 染色法 (複紅染色)

- 800 倍至1000 倍鏡檢
- 至少要觀察300 個視野，都不見抗酸菌，才能報告為陰性反應。
- 將抗酸菌於藍色背景下染成紅色菌體
- 所需時間：4分鐘



- 螢光抗酸菌染色

- 250 倍至450 倍鏡檢
- 視野較複紅染色抹片廣 (約4-10 倍)
- 將抗酸菌於黑色或暗紅色背景下染成具黃色光的菌體
- 所需時間：30-60 秒



抗酸菌的鏡檢 -- 抗酸菌染色

- In 2011, World Health Organization (WHO) recommends switching conventional to fluorescence microscopy
- Whether introduction of these more sensitive diagnostic tools reduces the risk of nosocomial TB transmission?

Aim

- To assess whether switching from **conventional microscopy** to a more sensitive rapid diagnostic tool (**fluorescent microscopy**) improves early detection and prompt isolation of hospitalized patients with undiagnosed TB

Sun HY, et al. PLoS One 2020

Methods

- Study period
 - Period 1: Jan 1 – Dec 31, **2001**
 - **conventional** microscopy with **Ziehl-Neelsen** staining,
 - represented the baseline situation before 2003 SARS outbreak
 - Period 2: Jan 1 – Dec 31, **2014**
 - after full switching to **fluorescent** microscopy with **auramine-rhodamine** staining and the quality assurance program

Sun HY, et al. PLoS One 2020

Methods

- Study setting

- A medical center with a 2,200-bed capacity providing both primary and tertiary referral care
- **3,454,724** outpatient visits and **91,645** admissions in **2014**
 - nearly **2-fold** than that in 2001

Sun HY, et al. PLoS One 2020

Tuberculosis control practices, 2001–2014

- Enhanced contact investigation
 - Annual chest X-ray for HCWs
 - TB case managers
 - Contact tracing
- Improvements in laboratory diagnosis
 - timely results of AFS, TB cultures, identification, drug susceptibility, **fluorescent microscopy**, text messages, Capilia
- Expansion of isolation facilities
 - **48** respiratory isolation rooms in 2001 to **86** respiratory isolation rooms in 2014

Sun HY, et al. PLoS One 2020

Tuberculosis control practices, 2001–2014

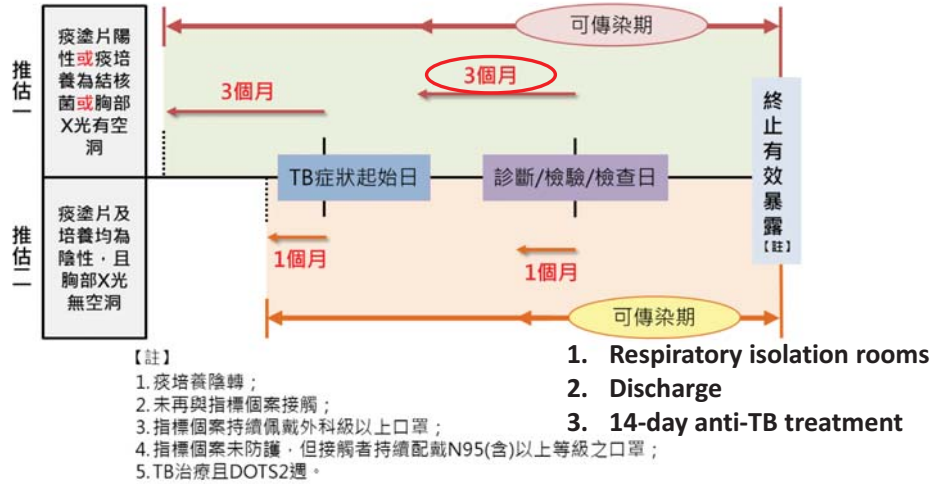
- Enhanced contact investigation
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- Expansion of isolation facilities
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Methods

- Study population
 - Hospitalized patients with **culture-confirmed** pulmonary TB in **25 wards/units** in 2001 and 2014
- Comparison
 - The **duration** from **admission/arrival** to **respiratory isolation** in 2001 and 2014
 - Cox regression
 - used to adjust for effects of **covariates**
 - Causal mediation analysis
 - Used to identify the effect mediated by improved **smear detection rate**

圖 1. 結核病個案可傳染期計算方式

可傳染期的定義



結核病治療指引 第六版

Methods – Definitions I

• Time to respiratory isolation

• The zero time

- the date of **admission to the hospital** or the date of **arrival to emergency department (ER)**

• The end of follow-up

- the date when the patients was sent to **a respiratory isolation room** (event),
- the date of **discharge** (from hospital or ER) before respiratory isolation can be implemented (censored)
- the date of **14-day anti-TB treatment completion** (censored), or the date of mortality due to any cause (censored)

Methods – Definitions II

- For patients with **multiple admissions** or **multiple positive sputum cultures**
 - only the admission with or following **the first positive sputum culture** (the index culture) was used to calculate the Kaplan-Meier estimates for time to respiratory isolation.
- **Total non-isolated infectious patient-days** in hospital
 - each TB case/patient was considered infectious from **3 months** prior to **the first positive** sputum culture
 - unless being put in **a respiratory isolation room** or had already received **a 14-day course** of at least two in vitro active anti-tuberculous agents after the last positive sputum culture

Methods – Definitions III

- For those who had **multiple hospitalization** or had ever been **transferred between wards/units** before being diagnosed with pulmonary TB or adequately treated
 - all hospitalizations or stay in **each ward/unit** were counted in the calculation of total infectious patient-days

Methods – Definitions IV

- **Typical** presentations of pulmonary TB
 - a prolonged **cough** for >3 weeks
 - **clinical suspicion** of pulmonary TB based on **chest radiography**, such as cavitary pulmonary lesions, upper lobe diseases, or miliary lesions
 - already received a **confirmed diagnosis** of pulmonary TB by a positive sputum culture of *Mycobacterium tuberculosis*, positive acid-fast stain (AFS), or positive TB PCR, before the hospitalization

Methods – Definitions V

- **TB-related** hospitalization
 - the chief complaint suggested **an infectious etiology** or
 - the admission was for **inpatient TB treatment**
- **Comorbidity-related** hospitalization
 - admitted for management of **acute complications of non-infectious diseases**
 - such as myocardial infarction, pulmonary edema, malignancy, or acute exacerbation of chronic lung diseases
- Identification of TB cases
 - a computerized registry of **Mycobacteriology Laboratory**, verified in each case with **review of medical records**

Results

- The number of hospitalized patients with culture-confirmed pulmonary TB
 - 180 of 403 (45%) in 2001
 - TB incidence in Taiwan in 2001: 72⁺/10⁵
 - 81 of 301 (27%) in 2014
 - TB incidence in Taiwan in 2014: 48.4/10⁵

Characteristics of hospitalized patients with culture-confirmed pulmonary tuberculosis

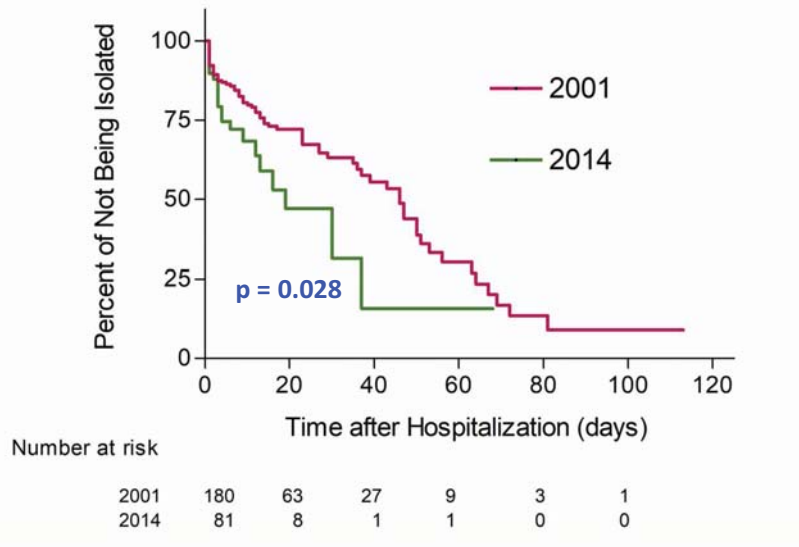
Variables	2001	2014	P value
Number of patients	180	81	
Age (years), mean (SD)	63.0 (20.7)	66.1 (19.8)	0.271
Men, n (%)	126 (70.0)	60 (74.1)	0.501
Positive sputum smear, N (%)	41 (22.8)	39 (48.1)	<0.001
Sputum TB-PCR performed, n/N (%)	4/41 (9.8)	37/39 (94.9)	<0.001
Negative sputum smear, N (%)	139 (77.2)	42 (51.9)	<0.001
Sputum TB-PCR performed, n/N (%)	25/139 (18.0)	8/42 (19.0)	0.876
Available sputum TB PCR data, N (%)	29 (16.1)	45 (55.6)	<0.001
Positive TB-PCR, n/N (%)	14/29 (48.3)	40/45 (88.9)	<0.001
Patients with cavitory pulmonary lesions, n (%)	30 (16.8) ^a	11 (13.6)	0.515
Positive sputum smear, % (n/N)	43.3 (13/30)	81.8 (9/11)	0.029
Patients with non-cavitory pulmonary lesions, n (%)	149 (83.2) ^a	70 (86.4)	0.515
Positive sputum smear, % (n/N)	28 (18.8)	30 (42.9)	<0.001

Patients without typical presentations, n (%)	119 (66.1)	48 (59.3)	0.286
Positive sputum smear, % (n/N)	14.3 (17/119)	27.1 (13/48)	0.051
Hospitalization due to comorbidity, n (%)	69 (38.3)	31 (38.3)	0.992
Positive sputum smear, % (n/N)	14.5 (10/69)	25.8 (8/31)	0.173
Non-chest/ID specialty attending doctors, n (%)	124 (68.9)	57 (70.4)	0.810
Fluoroquinolone exposure within 6 months, n (%)	32 (17.8)	16 (19.8)	0.703
Underlying diseases, n (%)			
Hypertension	52 (28.9)	28 (34.6)	0.357
Diabetes mellitus	39 (21.7)	26 (32.1)	0.071
Malignancy	45 (25.0)	17 (21.0)	0.481
Chronic lung disease	53 (29.4)	6 (7.4)	<0.001
Chronic kidney disease	9 (5.0)	3 (3.7)	0.886
Congestive heart failure	9 (5.0)	4 (4.9)	0.983
Liver cirrhosis	8 (4.4)	1 (1.2)	0.343
Transplantation	4 (2.2)	2 (2.5)	0.903
HIV infection	1 (0.6)	1 (1.2)	0.525
Immediate respiratory isolation ^b , n (%)	11 (6.1)	23 (28.4)	<0.001
Non-isolated infectious duration, median (IQR), days	12.5 (6.8–28.3) days	3.0 (0–8.0) days	. <0.001 ^c

Results

- **Time to respiratory isolation: 2001 vs. 2014**
 - The median non-isolated infectious duration
 - decreased from **12.5** in 2001 to **3** days in 2014 (P<0.001)

Kaplan-Meier estimates for time to respiratory isolation of hospitalized patients with tuberculosis, 2001 vs. 2014.



Factors associated with **prompt respiratory isolation** (Model 1: 2014 vs. 2001; Model 2: The effects of positive sputum acid-fast smear and TB-PCR; Model 3: The effect of physician alertness)

Variables	Univariable analysis		Multivariable analysis		P value	aHR (95% CI) (Model 3) ^a	P value	
	HR (95% CI)	P value	aHR (95% CI)(Model 1)	P value				
2014 vs. 2001	2.4 (1.6–3.6)	<0.001	4.7 (2.7–8.2)	<0.001	2.0 (1.2–3.4)	0.006	2.7 (1.7–4.3)	<0.001
Men vs. Women	0.9 (0.6–1.3)	0.578						
Cavitary lung lesions	2.8 (1.9–4.1)	<0.001	2.0 (1.3–3.1)	0.001	1.7 (1.1–2.6)	0.022	1.8 (1.2–2.9)	0.007
Positive sputum smear	5.5 (3.8–8.0)	<0.001			3.2 (2.1–4.9)	<0.001	3.6 (2.3–5.5)	<0.001
Sputum TB-PCR test								
Done vs. Not done	0.3 (0.2–0.5)	<0.001			1.5 (0.9–2.4)	0.094		
Duration from hospital visits to the date of index culture (days)	0.96 (0.94–0.98)	<0.001					0.98 (0.96–0.99)	0.004
Lack of typical clinical presentations	0.2 (0.2–0.3)	<0.001	0.4 (0.2–0.6)	<0.001	0.3 (0.2–0.5)	<0.001	0.3 (0.2–0.5)	<0.001
Fluoroquinolone use	0.8 (0.5–1.2)	0.239						
Hospitalization for comorbidities	0.4 (0.3–0.6)	<0.001	0.5 (0.3–0.7)	<0.001	0.6 (0.4–0.9)	0.025		

Results

• Effect of fluorescent microscopy

- Switching to auramine-rhodamine staining with fluorescent microscopy doubled the overall positive sputum smear rate from **22.8%** (2001) to **48.1%** (2014) ($P < 0.001$), particularly in patients with **non-cavitary** lung lesions (**18.8%** to **42.9%**, $P < 0.001$)
- Cox regression analyses
 - a **positive sputum smear** was associated with an **earlier respiratory isolation** (aHR **3.2**, 95% CI 2.1–4.9, $P < 0.001$)
- Causal mediation analyses
 - the two-fold **higher sputum smear detection rate of fluorescence** microscopy **doubled** the likelihood of **early respiratory isolation** (odds ratio [OR] for natural indirect effect mediated by improved sputum smear detection rate: **1.8**, 95%CI 1.3–2.5, $P < 0.001$)

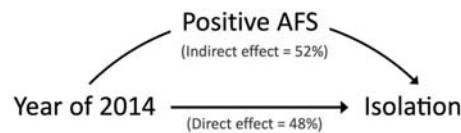
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Factors associated with **prompt respiratory isolation** (Model 1: 2014 vs. 2001; Model 2: The effects of positive sputum acid-fast smear and TB-PCR; Model 3: The effect of physician alertness)

Variables	Univariable analysis		Multivariable analysis		aHR (95% CI) (Model 2)		aHR (95% CI) (Model 3) ^a	
	HR (95% CI)	P value	aHR (95% CI)(Model 1)	P value		P value		P value
2014 vs. 2001	2.4 (1.6–3.6)	<0.001	4.7 (2.7–8.2)	<0.001	2.0 (1.2–3.4)	0.006	2.7 (1.7–4.3)	<0.001
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Sputum TB-PCR test								
Done vs. Not done	0.3 (0.2–0.5)	<0.001			1.5 (0.9–2.4)	0.094		
Duration from hospital visits to the date of index culture (days)	0.96 (0.94–0.98)	<0.001					0.98 (0.96–0.99)	0.004
Lack of typical clinical presentations	0.2 (0.2–0.3)	<0.001	0.4 (0.2–0.6)	<0.001	0.3 (0.2–0.5)	<0.001	0.3 (0.2–0.5)	<0.001
Fluoroquinolone use	0.8 (0.5–1.2)	0.239						
Hospitalization for comorbidities	0.4 (0.3–0.6)	<0.001	0.5 (0.3–0.7)	<0.001	0.6 (0.4–0.9)	0.025		

Causal mediation analyses of the effect **attributable to switching** from conventional to fluorescence microscopy



	OR	95% CI	p
Indirect Effect	1.82	(1.32-2.50)	<0.001
Direct Effect	3.80	(1.60-9.02)	0.002
Total Effect	6.90	(2.78-17.10)	<0.001
Percentage of Mediation		52.50%	

Results

- **Alertness of physicians**

- measured by **duration from patient arrival to physician's ordering** of smear or culture, also improved from 2001 to 2014 (median: **5** vs. **2** days, $P < 0.001$)

- **Cox regression analysis**

- physician **alertness** was also associated with **earlier respiratory isolation** (aHR 0.98 for each additional day before physician ordering TB smear/culture, 95% CI 0.96–0.99, $P = 0.004$)

- **Causal mediation analyses**

- improved physician alertness increased the likelihood of **early respiratory isolation** by **1.3-fold** (OR for natural indirect effect mediated by early ordering of smear/culture: 1.3, 95% CI 1.02–1.5, $P < 0.001$)

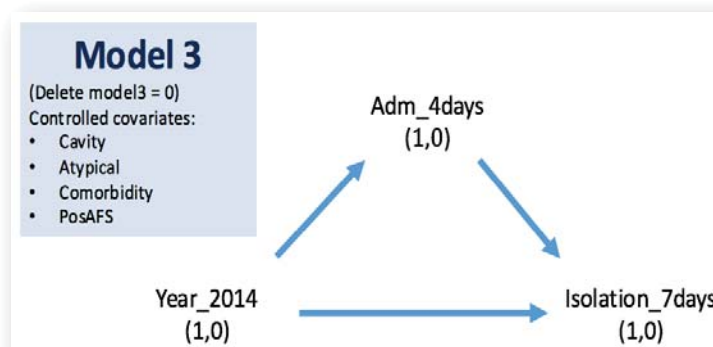
Non-isolated infectious duration of hospitalized patients (at the first admission after the index culture)

	2001, median (IQR)	2014, median (IQR)	<i>P</i> value
All tuberculosis patients			
Kaplan-Meier estimate for time-to-respiratory isolation (discharge before isolation was treated as censored), days	46 days	19 days	0.028
Non-isolated infectious duration, median (IQR), days	12.5 (6.8-28.3) days	3.0 (0-8.0) days	<0.001 ^a
From hospital <u>visits</u> ^b to the index culture <u>date</u> ^c , median (IQR), days	5 (2-13) days	2.0 (1.0-5.9) days	<0.001
From sampling to the report of positive smear, mean (IQR), days	1-2 days	1 (1.1-1.6) days	–
From taking TB culture to the report of culture, mean (IQR), days	6-8 weeks	25.7 (18.0-29.1) days	–

Factors associated with prompt respiratory isolation (Model 1: 2014 vs. 2001; Model 2: The effects of positive sputum acid-fast smear and TB-PCR; **Model 3: The effect of physician alertness**)

Variables	Univariable analysis		Multivariable analysis		aHR (95% CI) (Model 2)	P value	aHR (95% CI) (Model 3) ^a	P value
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Causal mediation analyses of the effect mediated by **the higher rate of early ordering** (less than 4 days after admission) of smear/culture in 2014



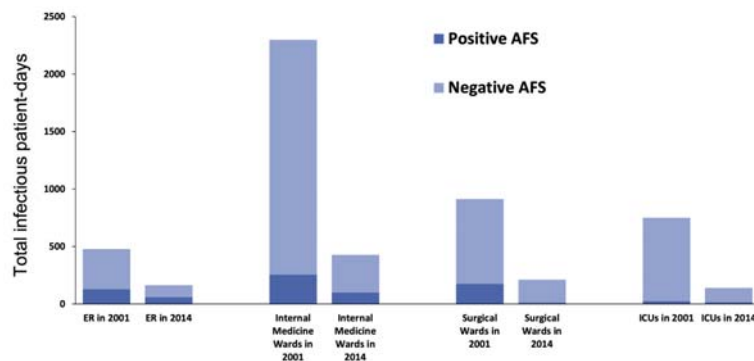
Summary of Effects						
	Estimate	Standard Error	Wald 95% Confidence Limits		Z	Pr > Z
Odds Ratio Total Effect	5.3349	2.8321	-0.2159	10.8857	1.88	0.0596
Odds Ratio Controlled Direct Effect (CDE)	4.2449	2.2567	-0.1782	8.6680	1.88	0.0600
Odds Ratio Natural Direct Effect (NDE)	4.2449	2.2567	-0.1782	8.6680	1.88	0.0600
Odds Ratio Natural Indirect Effect (NIE)	1.2568	0.1221	1.0175	1.4961	10.29	<.0001
Total Excess Relative Risk	4.3349	2.8321	-1.2159	9.8857	1.53	0.1259
Excess Relative Risk Due to CDE	1.3798	1.1814	-0.9357	3.6952	1.17	0.2428
Excess Relative Risk Due to NDE	3.2449	2.2567	-1.1782	7.6680	1.44	0.1505
Excess Relative Risk Due to NIE	1.0900	0.7381	-0.3567	2.5367	1.48	0.1397
Percentage Mediated	25.1447	9.7520	6.0311	44.2583	2.58	0.0099
Percentage Due to Interaction	62.2466	13.5842	35.6220	88.8711	4.58	<.0001
Percentage Eliminated	68.1701	15.4350	37.9179	98.4222	4.42	<.0001

Results

- **Total non-isolated infectious patient-days per year**

- 2001
 - a total of **4,778** infectious patient-days in hospital (582 from smear-positive patients, 4,196 from smear-negative patients)
- 2014
 - the total non-isolated infectious patient-days in hospital decreased by **69%**, to **1,502** infectious patient-days (229 from smear-positive patients and 1,273 from smear-negative patients)
- Improvement occurred over all types of wards/units, including ER, internal medicine wards, surgical wards, and intensive care units

Total non-isolated infectious patient-days from hospitalized patients with culture-confirmed tuberculosis, 2001 vs. 2014



Conclusions

- **Highly sensitive rapid diagnostic tools** could substantially **improve** timing of respiratory isolation and **reduce risk** of nosocomial TB transmission in high TB risk settings.
- **Lack of typical presentations** and **hospitalization due to comorbidities** continued to be main reasons of delayed isolation.
- Studies will be required to assess whether **routine sputum smear** or **TB-PCR** of **all hospitalized patients** with cough or abnormal chest radiograph is effective in overcoming these remaining barriers

Take Home Messages

- 肺結核診斷的困難
 - Admission for comorbidities (Case I and III)
 - Atypical presentations (Case II and III)
- 破解之道
 - 提高警覺 (不要忘記看胸部X光，無論住院主訴為何)
 - 高風險(年紀大，糖尿病，免疫不全)的病患，未確診的胸部病兆，同步檢查 acid-fast stain and TB cultures
 - 必要時先隔離，檢查陰性後再解除