Outlines

- Introduction
- Case demo – TB & NTM
- Epidemiology
- Diagnosis
- Treatment
- Outcome
- Transmission

TB Incidence

New Cases / Incidence rate
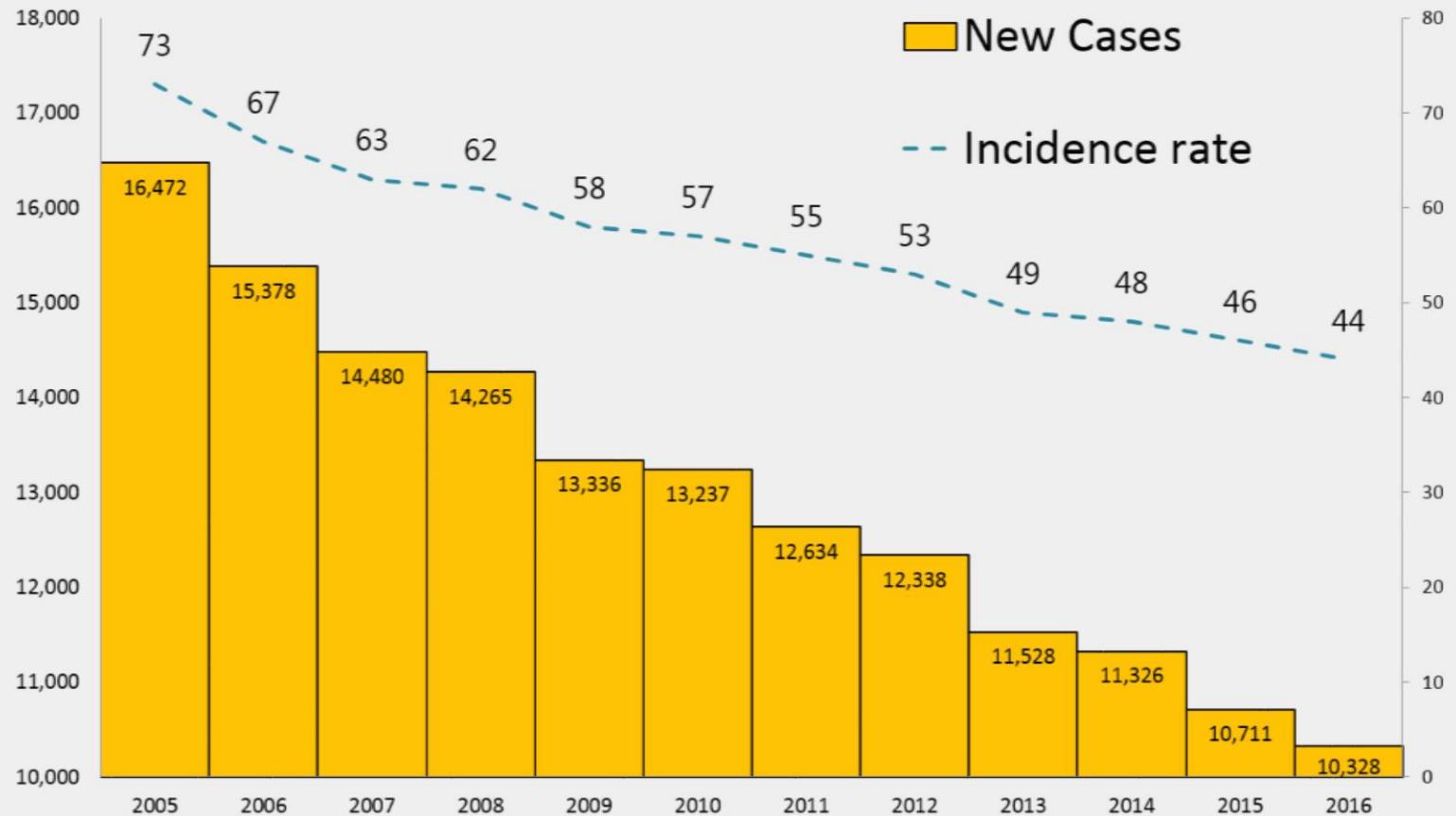
Year	New Cases	Incidence rate
2005	16,472	73
2006	15,378	67
2007	14,480	63
2008	14,265	62
2009	13,336	58
2010	13,237	57
2011	12,634	55
2012	12,338	53
2013	11,528	49
2014	11,326	48
2015	10,711	46
2016	10,328	44

Taiwan CDC website

A case admitted to your ICU

S/C: mixed flora

A case admitted to your ICU

S/C: mixed flora; AFS 2+Mtb

TB/NTM epidemiology in ICU

- **<u>TB in ICU</u>**
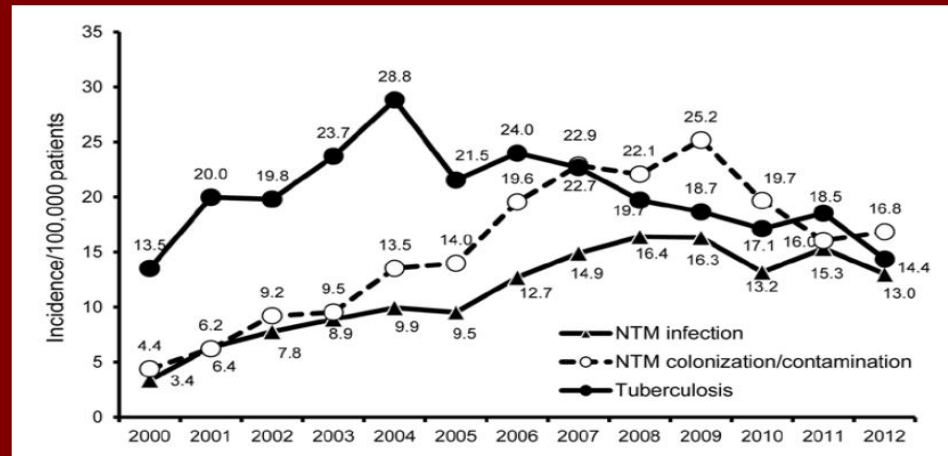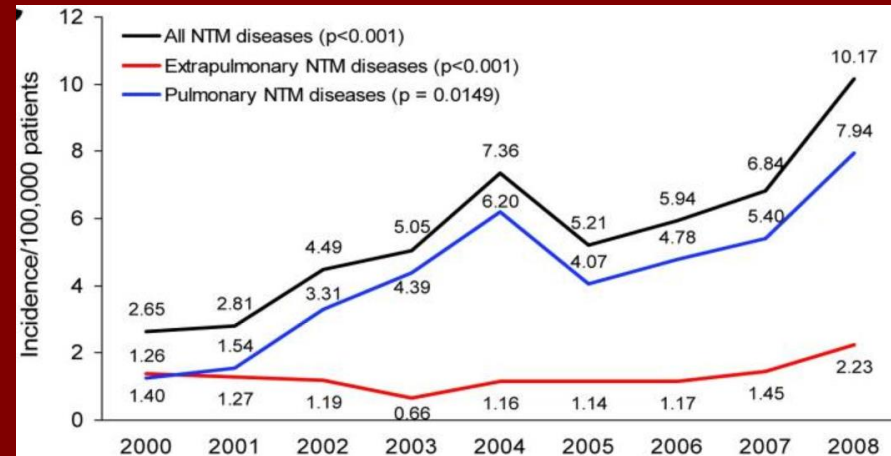
- 46 TB / 341 susp PTB / 2309 ICU South Africa

  = 2%   ~ *Gregory L Calligaro, Lancet Respir Med* 2015; 3: 621–30
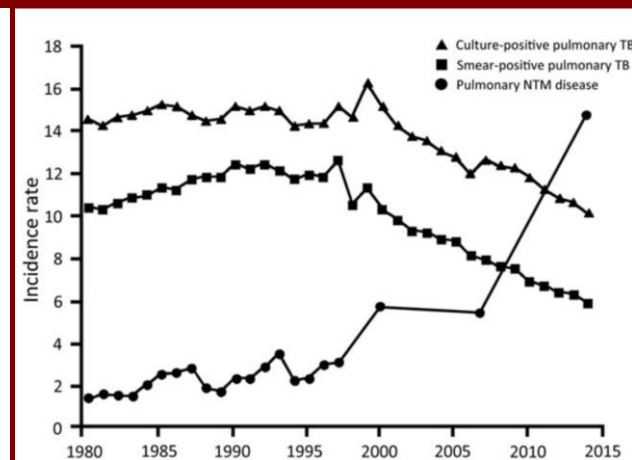
- 9 in 187 ARDS in 984 RICU admissions, India

  = 5% of ARDS, 0.9% of RICU
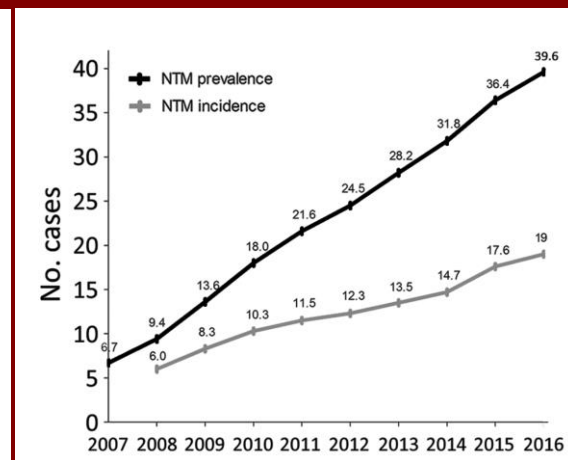
  ~ Ritesh Agarwal, ICM 2005, 31:1284–1287

NTM肺部疾病，在全球都快速的增加

可能的原因目前正熱烈的被討論中
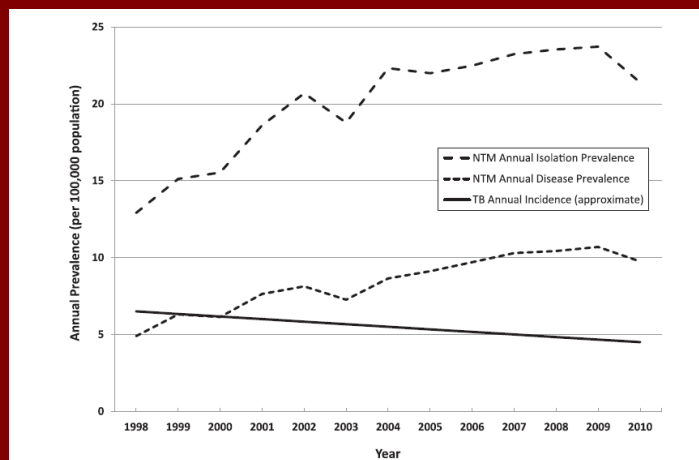
NTM in ICU

54 y/o male

Known for MAC-LD for years, s/p treatment but refractory

Sputum AFS 1-3+

S/C: **MAC** x 5 sets

NTM in ICU
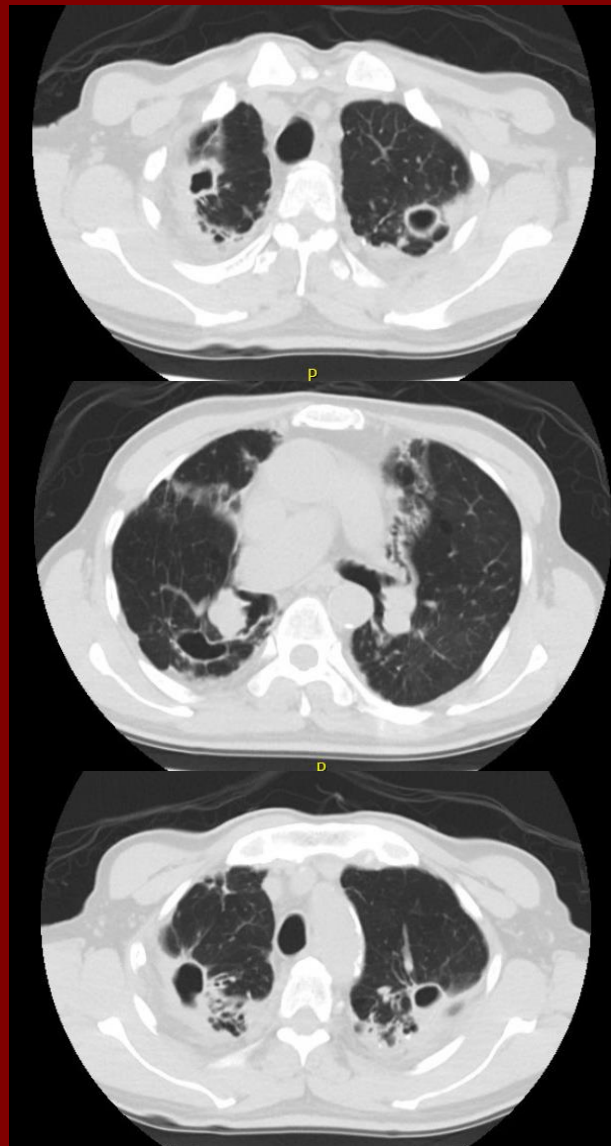
TB/NTM epidemiology in ICU

- **NTM in ICU**

  - 47 NTM-LD / 169 (+)culture / 2,866 had done culture / 5,378 ICU-patients, Taiwan

  = 0.9%
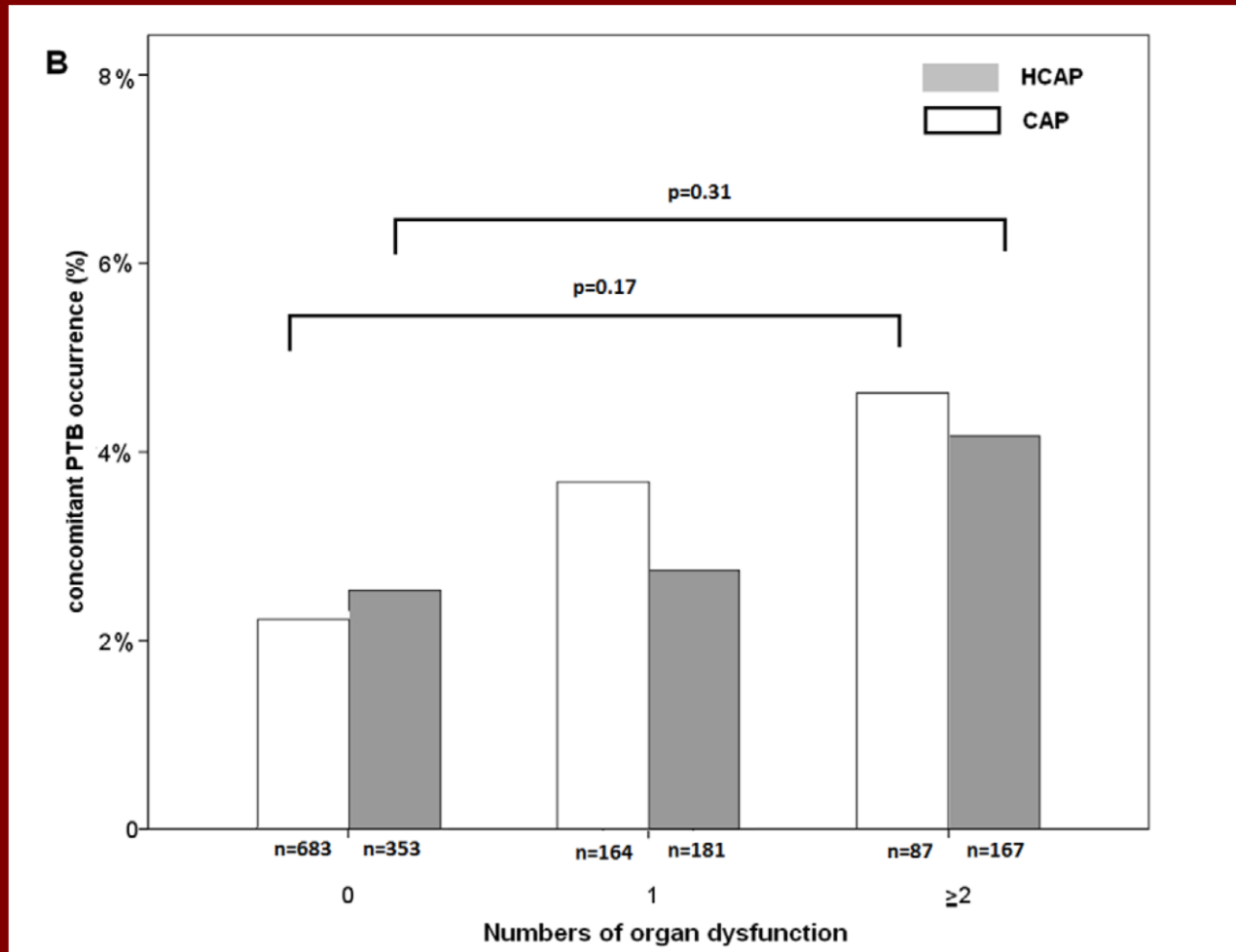
~Shu CC, ICM 2008

TB in CAP and HCAP

Feng JY, et al. PLoS ONE 7(5): e36832.

Outlines

- Introduction
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- **Diagnosis**
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- Outcome
- Transmission

Diagnosis, not easy in ICU

Radiology: typical and atypical

Microbiology: Role of PCR

Challenge : delay diagnosis

Radiological pattern D/D

Hashemian, Int J mycobact 2015 4, 233238
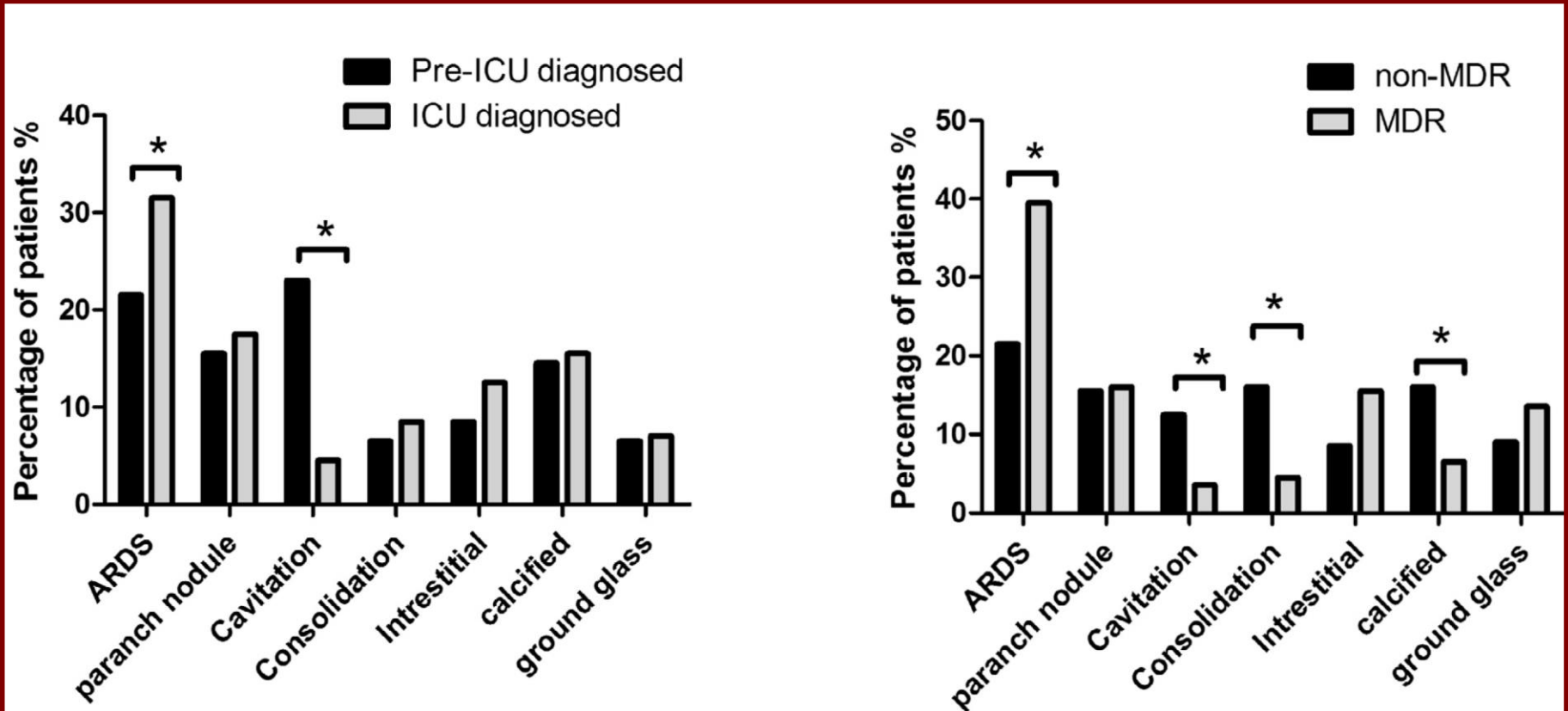
TB Case, CXR typical / atypical

AFS 3+Mtb

AFS 2+Mtb

NTM Case, CXR typical / atypical

MAC, bleeding

MAB, High fever

AFS / Culture
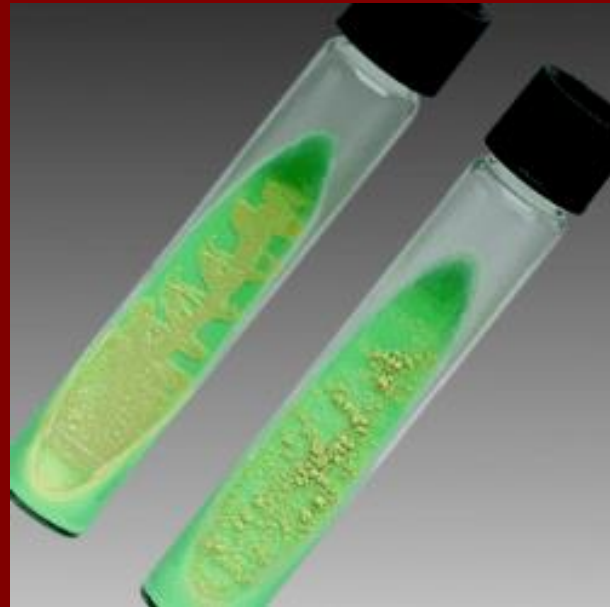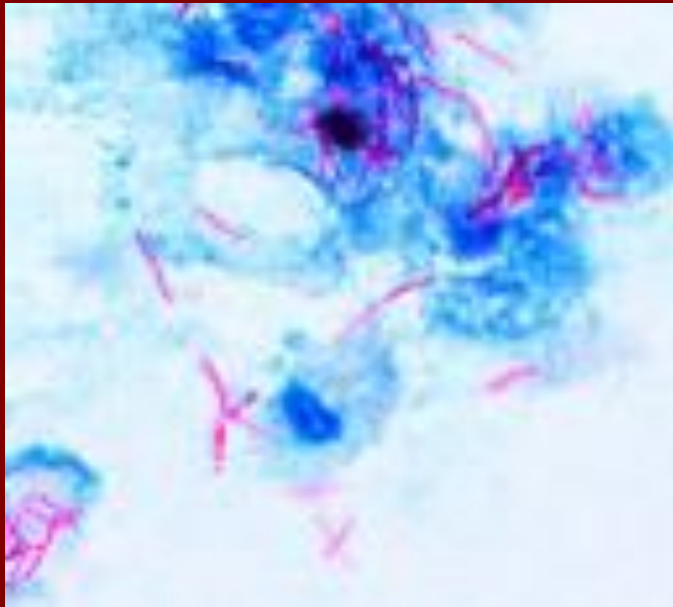
TB diagnosis

- **Microbiology**
- culture positive
- AFB smear +, and TB PCR +

- **<u>Clinical</u>** / image / pathology plus treatment response

TB case

- AFS 2+, PCR +

Recent **milestones** in diagnosis of TB

- Mycobateria growth indicator tube (MGIT)

Shorten waiting time from 4-6 weeks to 1-3 weeks

- Nucleic acid amplification test (NAAT)

Helpful for smear positive patient
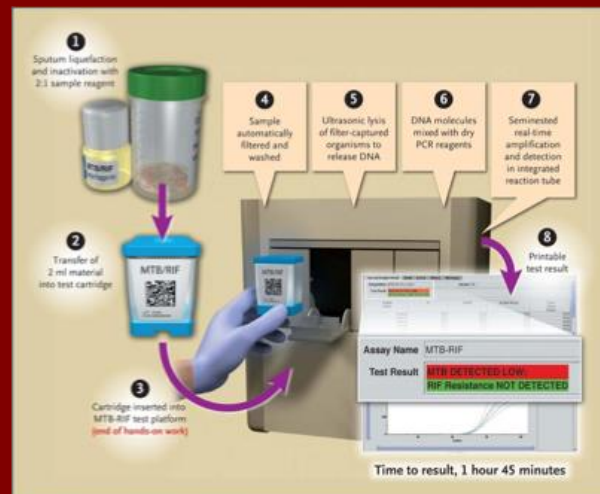
For NTM

- Old TB, 2 yrs ago, s/p tx
- Cough with hemosputum x 2 mons
- Sputum AFS:

1+, 3+, 4+

For NTM
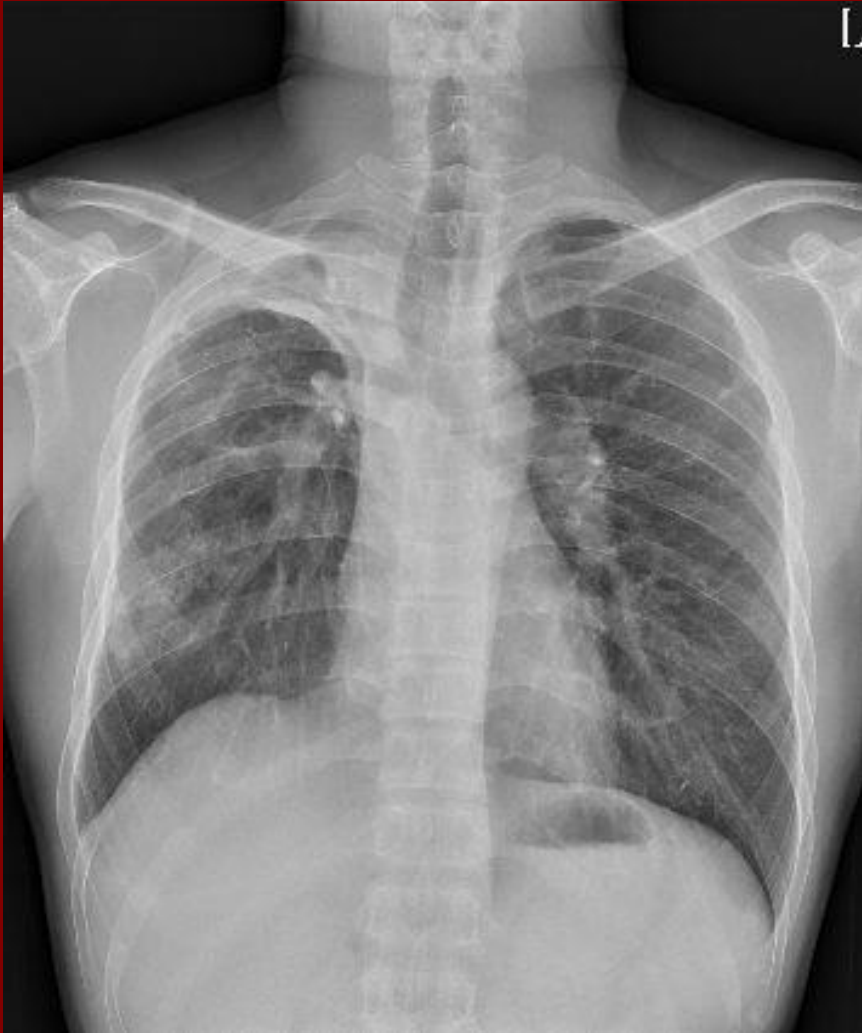
- Old TB, 2 yrs ago, s/p tx
- Cough with hemosputum x 2 mons
- Sputum AFS: 1+, 3+, 4+

- PCR: neg

- Cult: MACx III

結核診治指引第6版
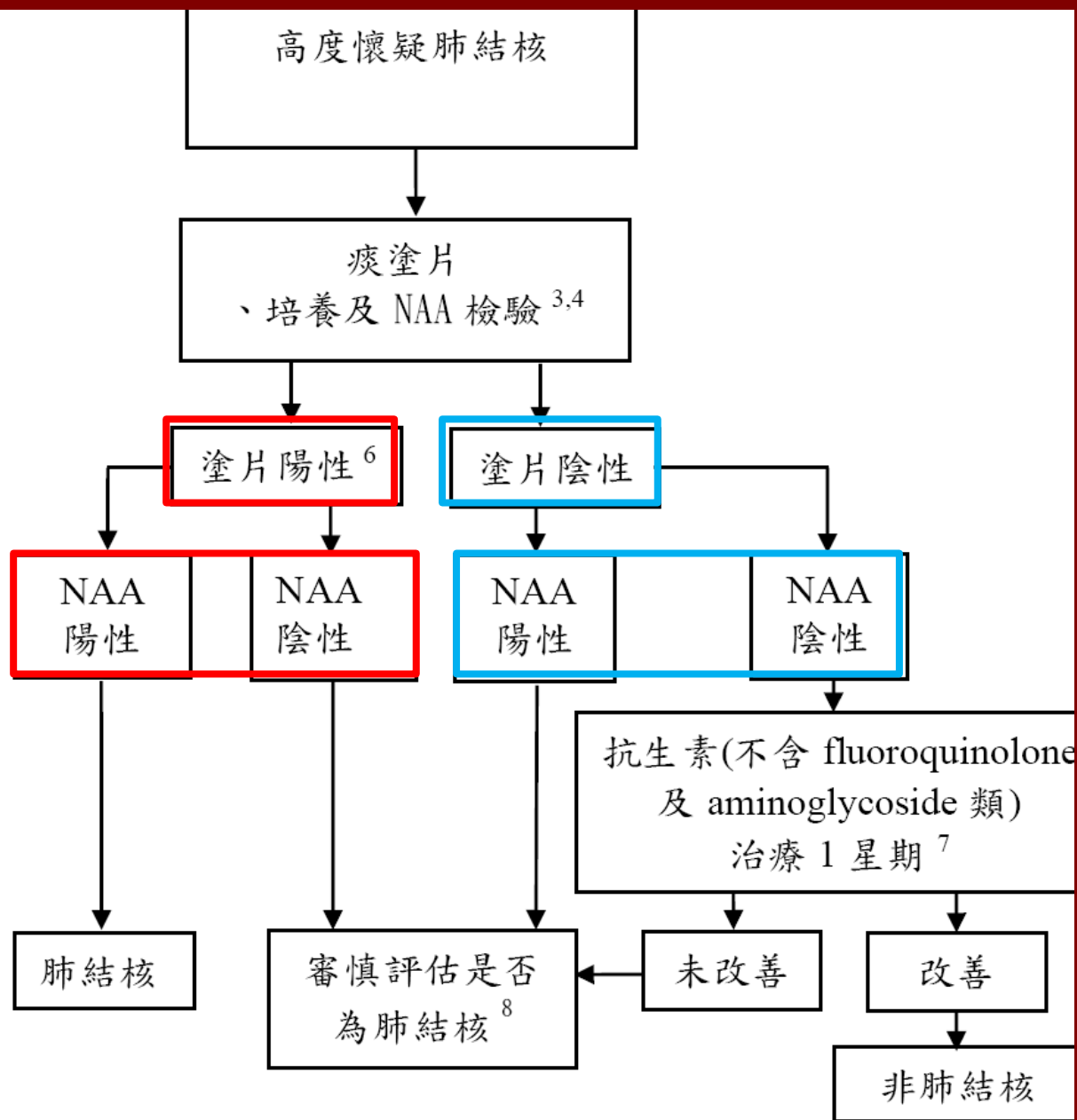
PCR efficacy

分子診斷技術 - 注意事項

- 現階段仍**無法取代**傳統之塗片、培養與藥物敏感度試驗

- Sm+: NTM漸多，NAA比起塗片有較高的陽性預測值 (>95% in smear positive state)

- Sm-: NAA 提早診斷TB, but not 100%

AFS vs PCR for dx

Gregory L Calligaro, Lancet Respir Med 2015; 3: 621–30

AFS vs PCR for dx

AFS vs PCR

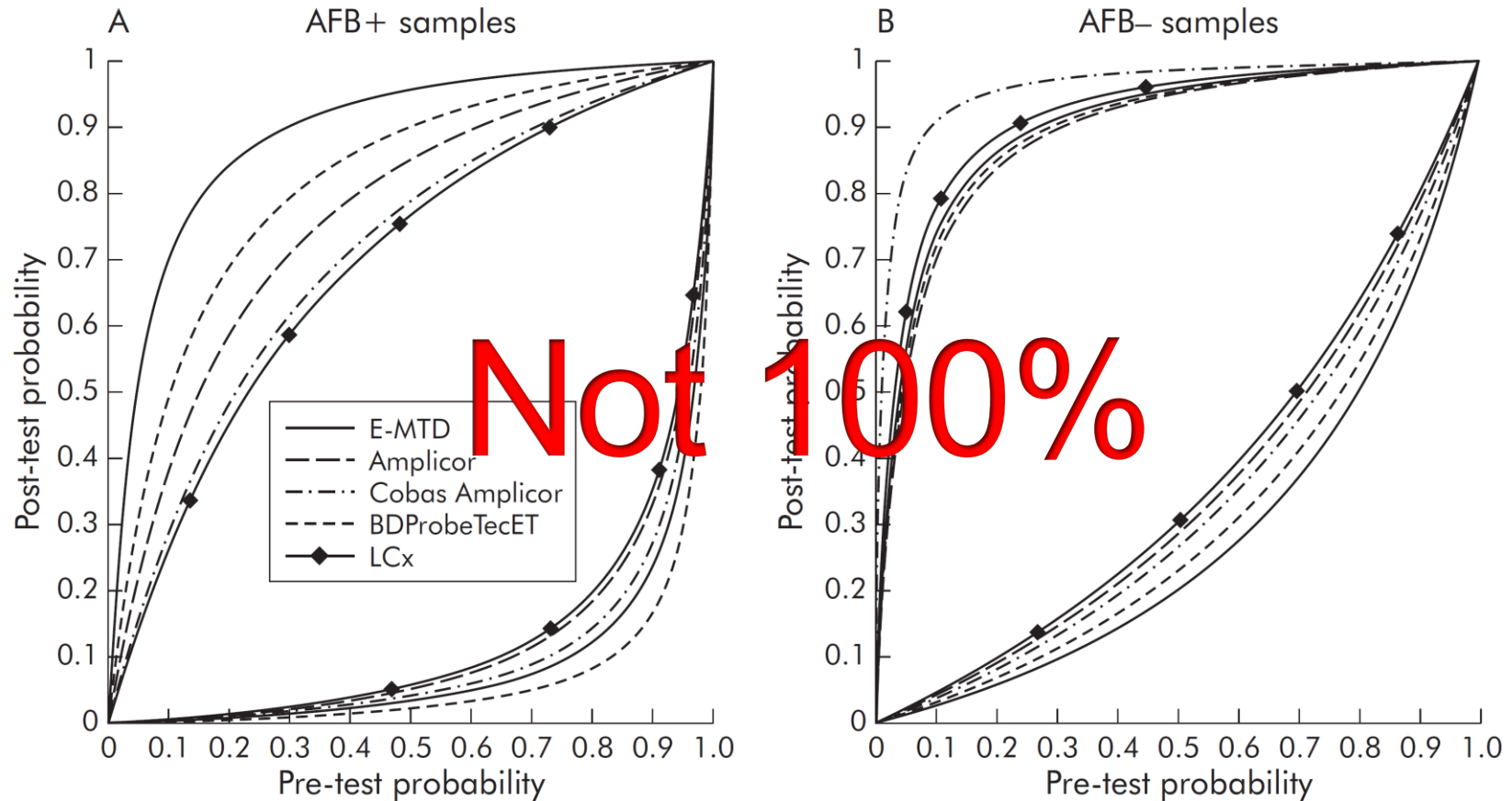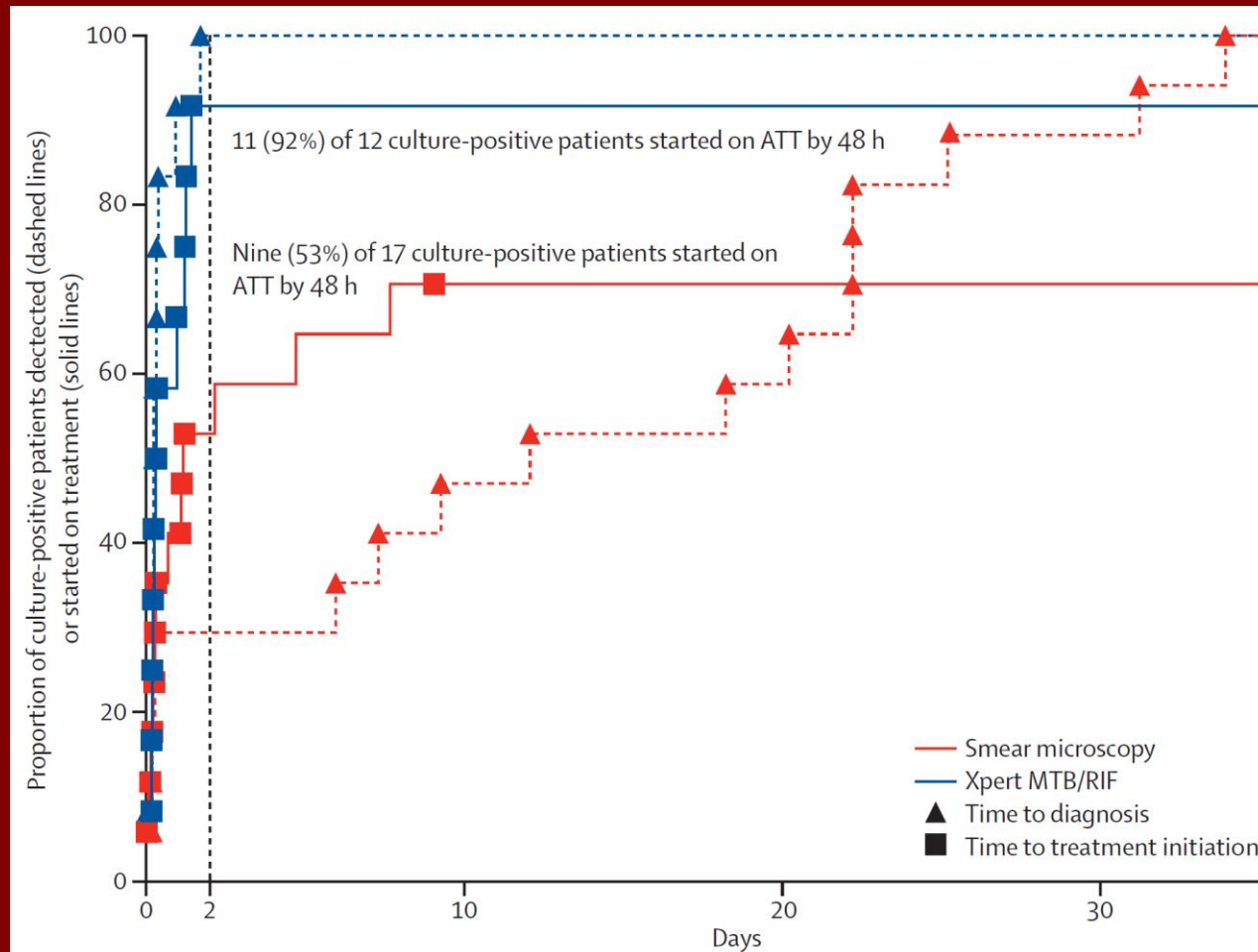|	Smear microscopy (n=115)	Xpert MTB/RIF (n=111)	p value*
Primary outcome			
Culture-positive patients started on treatment by 48 h	9/17 (53%)	11/12 (92%)	0·043
Secondary outcomes			
Time to diagnosis (days)	12·1 (0·3–22·2)	0·2 (0·2–0·3)	0·0004
Time to treatment (days)	0·7 (0·2–2·2)	0·3 (0·2–1·2)	0·4788
ICU length of stay (days)	8 (4–20)	10 (4–24)	0·3301
Hospital length of stay (days)	15 (8–29)	17 (10–36)	0·2196
Duration of mechanical ventilation (days)	6 (3–14)	7 (4–15)	0·3350
Duration of inotrope use (days)	2 (1·5–5·0)	3 (2·0–5·0)	0·2849
ICU mortality	39/115 (34%)	30/111 (27%)	0·261
In-hospital mortality	41/115 (36%)	34/111 (31%)	0·423
28-day mortality	39/115 (34%)	30/111 (27%)	0·2611
90-day mortality	48/115 (42%)	36/111 (32%)	0·1478
Other tuberculosis diagnosis and treatment-related outcomes			
Patients started on antituberculous treatment	16/115 (14%)	24/111 (22%)	0·129
Culture-positive patients started on treatment	12/17 (71%)	11/12 (92%)	0·354
Empirical treatment overall	9/16 (56%)	4/24 (17%)	0·015
Empirical treatment in culture-positive individuals	5/16 (31%)	0/11	0·046
Patients with culture-positive tuberculosis not receiving treatment	5/17 (29%)	1/12 (8%)	0·354

Delay diagnosis worsens outcome

Symptom duration at treatment initiation — Number of organ failures (OF)
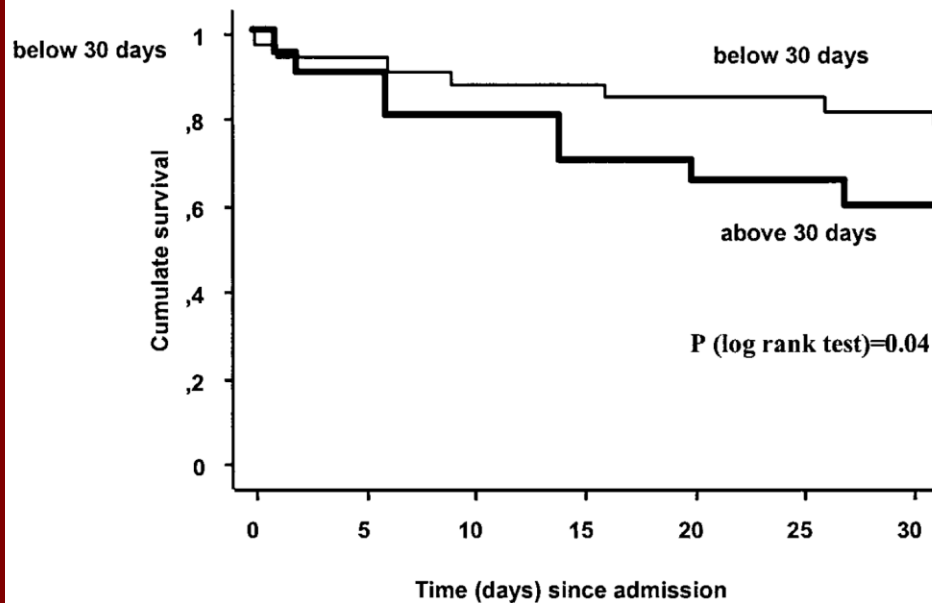
Zahar ICM 2001, 27 :513-520
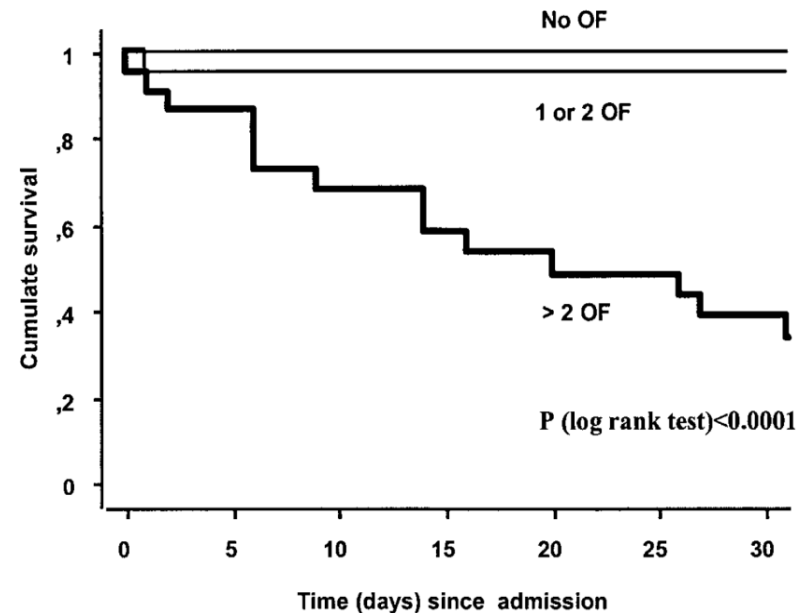
What is diagnosis criteria for NTM-LD?

NTM-LD, 2007 ATS guideline

Clinical

Typical image

Microbiology

Exclusion

Diagnosis criteria

- ## ATS criteria 2007

TABLE 3. CLINICAL AND MICROBIOLOGIC CRITERIA FOR DIAGN[OSIS ... BACTE]RIAL LUNG DISEASE*

Clinical (both required)

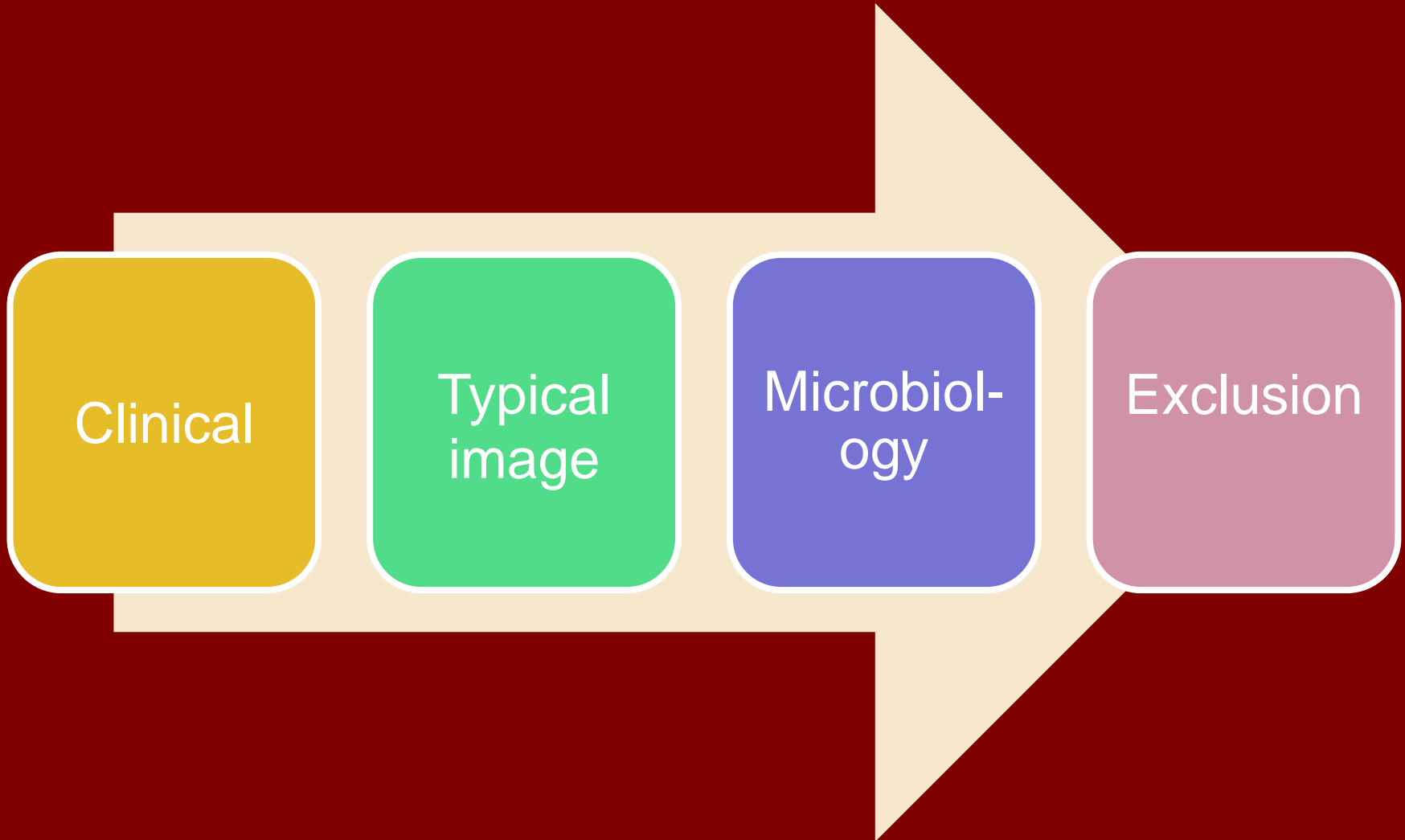1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules (A, I)*

and

2. Appropriate exclusion of other diagnoses (A, I)

Microbiologic

1. Positive culture results from at least two separate expectorated [sputum samples. If the results from the initial sputum samples are] nondiagnostic, consider repeat sputum AFB smears and cultures (C, III).

or

2. Positive culture result from at least one bronchial wash or lavage (C, III)

or

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM (A, II)

4. Expert consultation should be obtained when NTM are recovered that are either i[nfrequently encountered or usually represent en]vironmental contamination (C, III)

5. Patients who are suspected of having NTM lung disease but do not meet the d[iagnostic criteria should be followed until the diagn]osis is firmly established or excluded (C, III)

6. Making the diagnosis of NTM lung disease does not, *per se*, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients (C, III)

* For evidence quality, *see* Table 1.

Annotations (callouts): Routine CT or CXR? · Role of bronchoscopy? · Pathology? TB or NTM · When to start tx?

Griffith D.E., Am J Respir Crit Care Med 2007; 175: 367–416

American Thoracic Society Documents

An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases

David E. Griffith, Timothy Aksamit, Barbara A. Brown-Elliott, Antonino Catanzaro, Charles Daley, Fred Gordin, Steven M. Holland, Robert Horsburgh, Gwen Huitt, Michael F. Iademarco, Michael Iseman, Kenneth Olivier, Stephen Ruoss, C. Fordham von Reyn, Richard J. Wallace, Jr., and Kevin Winthrop, on behalf of the ATS Mycobacterial Diseases Subcommittee

November 2017 Volume 72 Supplement 2

Thorax
An international journal of RESPIRATORY MEDICINE

BRITISH THORACIC SOCIETY GUIDELINES FOR THE MANAGEMENT OF NON-TUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE (NTM-PD)

British Thoracic Society
NTM Guideline Development Group

thorax.bmj.com   BMJ

- **recommendation**

▸ In the absence of robust evidence to support an alternative definition and due to the clinical and research benefits of having a uniform definition, use of the ATS/IDSA 2007 definition of NTM-pulmonary disease is recommended. **(Grade D)**

Griffith DE. *Am J Respir Crit Care Med* 2007;175:367-416.
Haworth CS. Thorax. 2017 ;72(Suppl 2):ii1-ii64

Clinical relevance of NTM in ICU
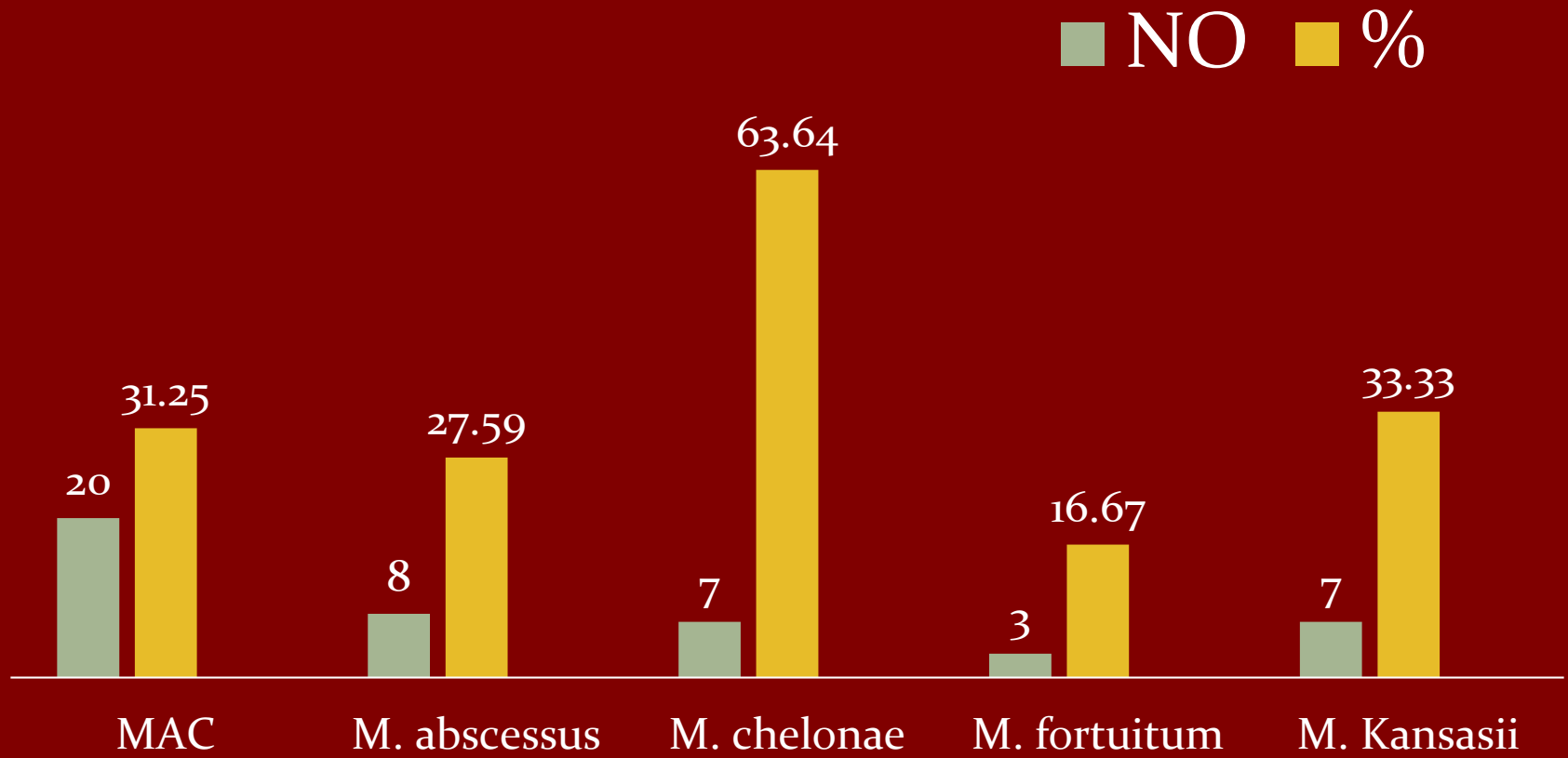
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Treatment tricks in ICU patients

- TB
  - Tolerance
  - FQ use
  - Corticosteroid

- NTM
  - Timing to start treatment
  - Adverse effect

Tolerance

Table 4 Reasons for withdrawal of anti-tuberculosis drugs

Reason for drug withdrawal	n	%
Liver dysfunction	71	42.5%
Drug allergy	25	15.0%
Thrombocytopenia	25	15.0%
Disease deterioration	12	7.2%
Renal dysfunction	10	6.0%
Use of voriconazole	7	4.2%
Convulsions	4	2.4%
Gastrointestinal bleeding	2	1.2%
Economic reasons	2	1.2%
Based on resistance to the drug	1	0.6%
Malignant arrhythmia	1	0.6%
Psychiatric symptoms	1	0.6%
Unclear	6	3.6%
Total	167	100.0%

147 (45.9%) drug withdrawal

Tolerance

147 (45.9%) drug withdrawal

Table 3 Frequencies of anti-tuberculosis drug use and withdrawal

Drug	Use of drug (n)	Withdrawal of drug (n)	Rate of withdrawal (%)
Isoniazid	293	76	25.9%
Rifampicin	197	82	41.6%
Ethambutol	258	42	16.3%
Pyrazinamide	135	40	29.6%
Quinolones	217	24	11.1%
Rifapentine	60	25	41.7%
Others	55	8	14.6%

Factors for withdrawal drug

Table 5 Logistic regression analysis of factors independently associated with anti-tuberculosis drug withdrawal

Variable	Odds ratio	95% confidence interval	P
APACHE-II score > 18 points	2.10	1.32–3.33	0.002
COPD (yes vs. no)	1.91	1.03–3.56	0.04
Hemoglobin level (continuous)	0.99	0.98–0.997	0.01

COPD chronic obstructive pulmonary disease

FQ saving time for severe pneumonia in ICU

Tseng YT, et al., *Critical Care* 2012, **16**:R207
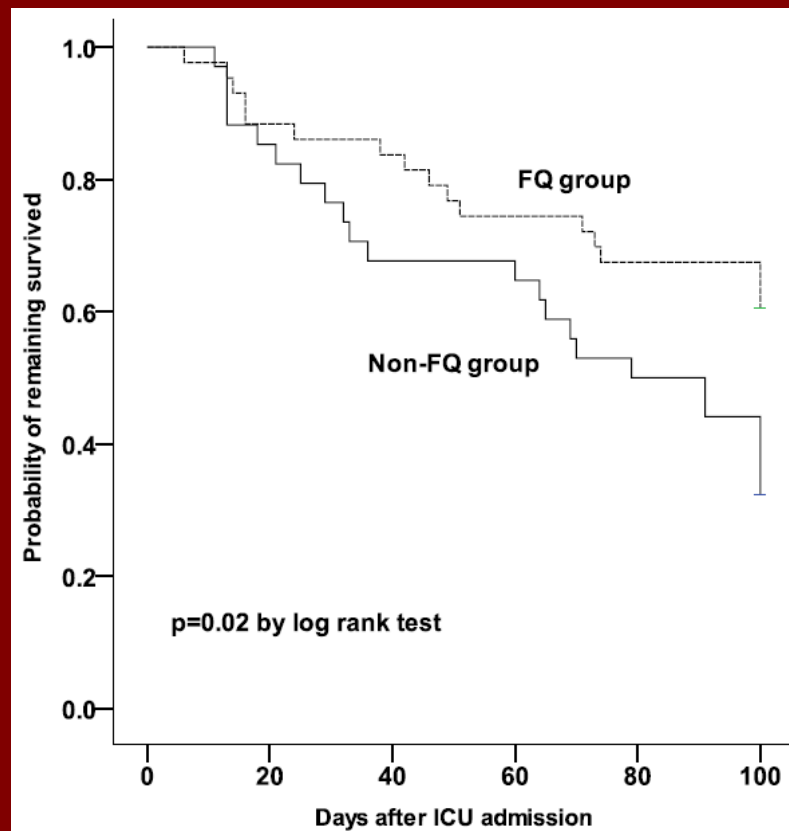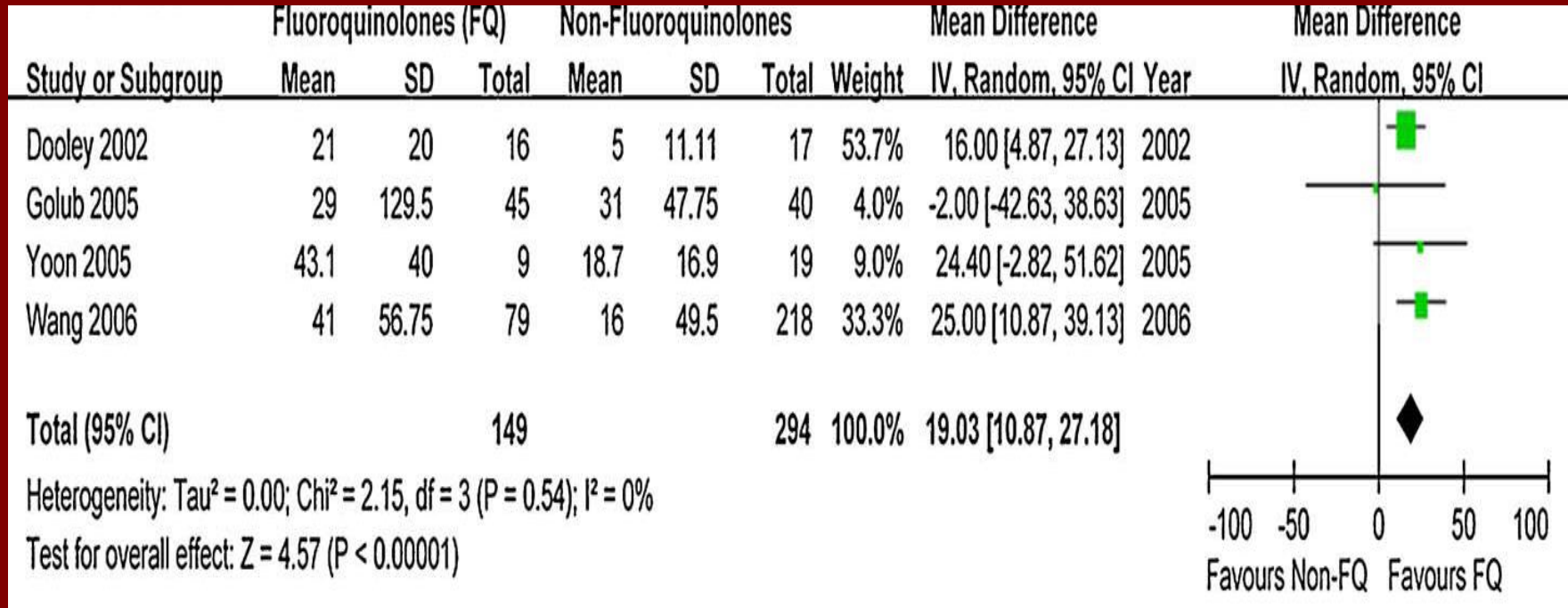
Diagnosis Delay

FQ Resistant MTB

A: Nil

B: FQ <10d, <60d before TB diagnosis

C: FQ <10d, >60d before TB diagnosis

D: FQ >10d, <60d before TB diagnosis

E: FQ >10d, >60d before TB diagnosis

Rose A, Am J Respir Crit Care Med 2009; 180: 365–70

Corticosteroids on Pulmonary Tuberculosis with resp. failure

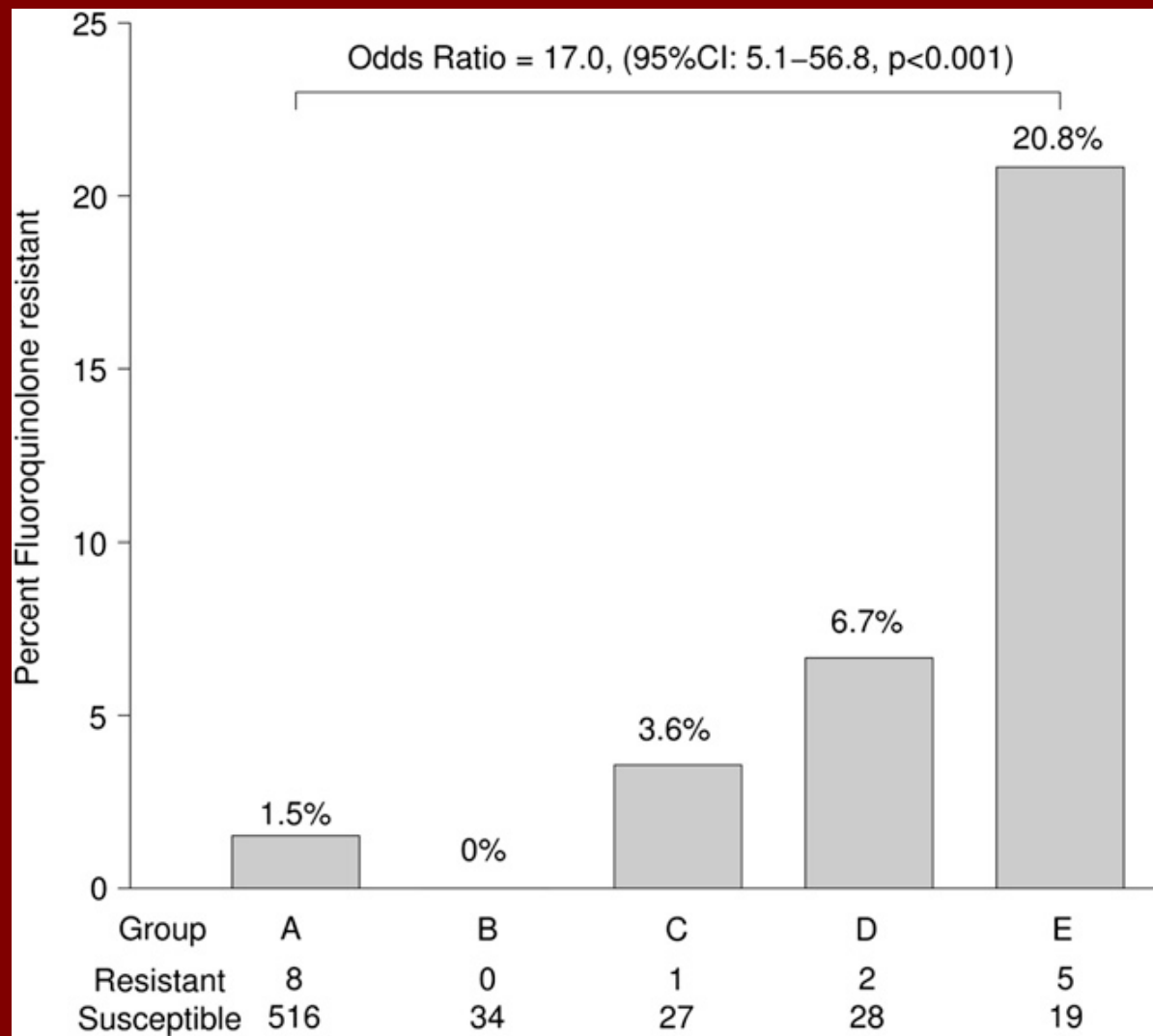**Table 3. Analysis of Steroid Treatment Related to 90-Day Mortality in the Study Patients**

Analysis	90-Day Mortality	P Value
Crude OR (95% CI)	0.94 (.46–1.92)	.875
Adjusted OR (95% CI)[a]	0.46 (.18–1.19)	.110
Adjusted OR by IPTW (95% CI)	0.47 (.22–0.98)	.049

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; OR, odds ratio.

[a] Adjusted for variables, including Acute Physiology and Chronic Health Evaluation (APACHE) III score, Sequential Organ Failure Assessment (SOFA) score, shock, mechanical ventilation, and multiorgan failure.

NTM-LD, Difficult diagnosis

- Clinical problem: true disease or false? treat or not?
- Diagnosis not equal to start treatment

Table 3 Treatment and outcome

	Cavitary TB-LD	NTM-LD			p value*
		Cavitary	Bronchiectatic	Consolidative	
Patient no.	180	62	134	56	
Anti-mycobacterial treatment	179 (99%)	40 (65%)	49 (36%)	12 (21%)	<0.001
Treat as TB		17	18	4	
Treat as NTM		23	31	8	
Number of effective drugs		2.1 [0.8]	1.9 [0.8]	2 [0.7]	
Days from index sample collection to treatment[a]	7.4 [11.5]	37.4 [90.1]	41.1 [69.0]	24.7 [30.0]	<0.001
Within 2 weeks	142 (79%)	22 (35%)	26 (16%)	4 (7%)	<0.001
6-month mortality rate	20 (11%)	5 (8%)	6 (3%)	14 (25%)	<0.001

Shu CC, et al., Lung (2011) 189:467–474
van Ingen, et al., Thorax 2009;64:502-506.

ADR for NTM-LD treatment

In MAC-LD treatment,

- hepatotoxicity 19.5%, 55 days
- leucocytopaenia 20.0%, 41 days
- thrombocytopaenia 28.6%, 61.5 days
- cutaneous reactions 9.3%, 30 days
- ocular toxicity 7.7%, 278 days
- increase in serum creatinine 12.4%, 430.5 days

Timing to treat NTM-LD

It's ART.

Usually start treatment when

- Initial cavitation
- Critical/acute illness direct due to NTM-LD (rare)
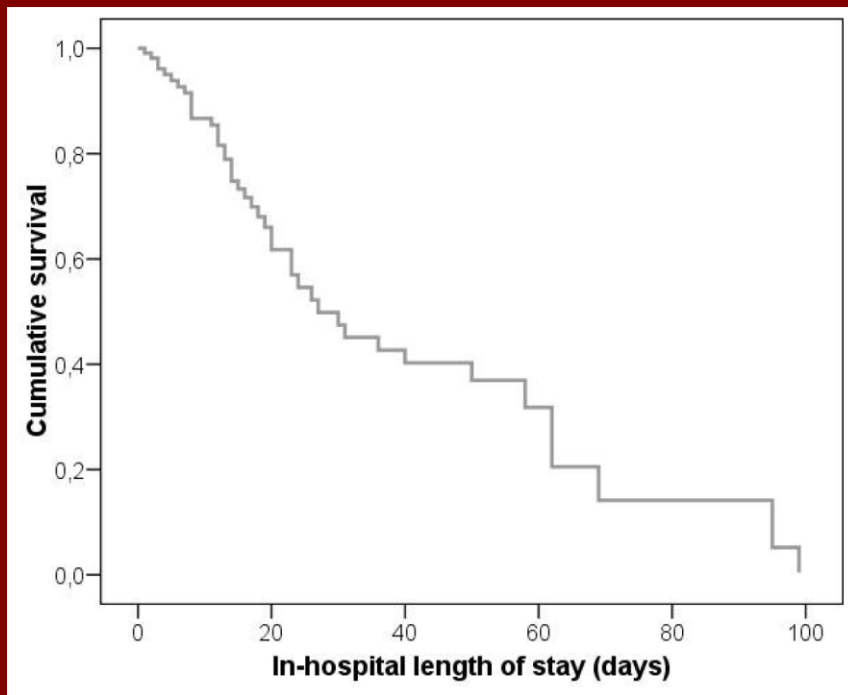- Progression under observation

Outcome

Survival / MV dependent

Overall mortality for TB in ICU

- Overall, **44 (65.7%)** patients died
- 38 (56.7%) died in ICU
- 6 (8.9%) died in ward

Silva et al. BMC Infectious Diseases 2010, 10:54

Factors associated with mortality for active pulmonary TB requiring ICU

Table II. Multivariate logistic regression analysis of predictors of in-hospital mortality.

Variable	p-value
Age	0.699
Ischaemic heart disease	0.999
Low albumin	0.033*
APACHE II score	0.722
Shock	0.821
Disseminated intravascular coagulation	0.119
Multiorgan failure	0.147

*p < 0.05 was considered statistically significant. APACHE: Acute Physiology and Chronic Health Evaluation

Factors for in-hospital mortality
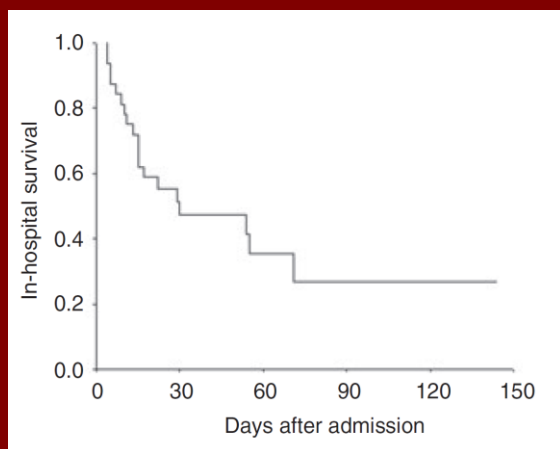
Table 3 Factors contributing to in-hospital mortality in the Cox proportional hazard model

Variable	No. of patients	Hazard ratio (95% confidence interval)	*P*-value
Tuberculous-destroyed lungs	4	6.61 (1.21–36.04)	0.029
Sputum AFB smear ≥3+	16	2.00 (0.59–6.75)	0.264
Multidrug-resistant tuberculosis	2	2.65 (0.28–25.33)	0.397
APACHE II score ≥ 20	8	4.90 (1.43–16.80)	0.012
Sepsis	16	5.84 (1.63–20.95)	0.007
Multiple organ failure	7	0.60 (0.14–2.60)	0.495

AFB, acid-fast bacilli; APACHE II, Acute Physiology and Chronic Health Evaluation II.

NTM-LD outcome in ICU

~Shu CC, ICM 2008
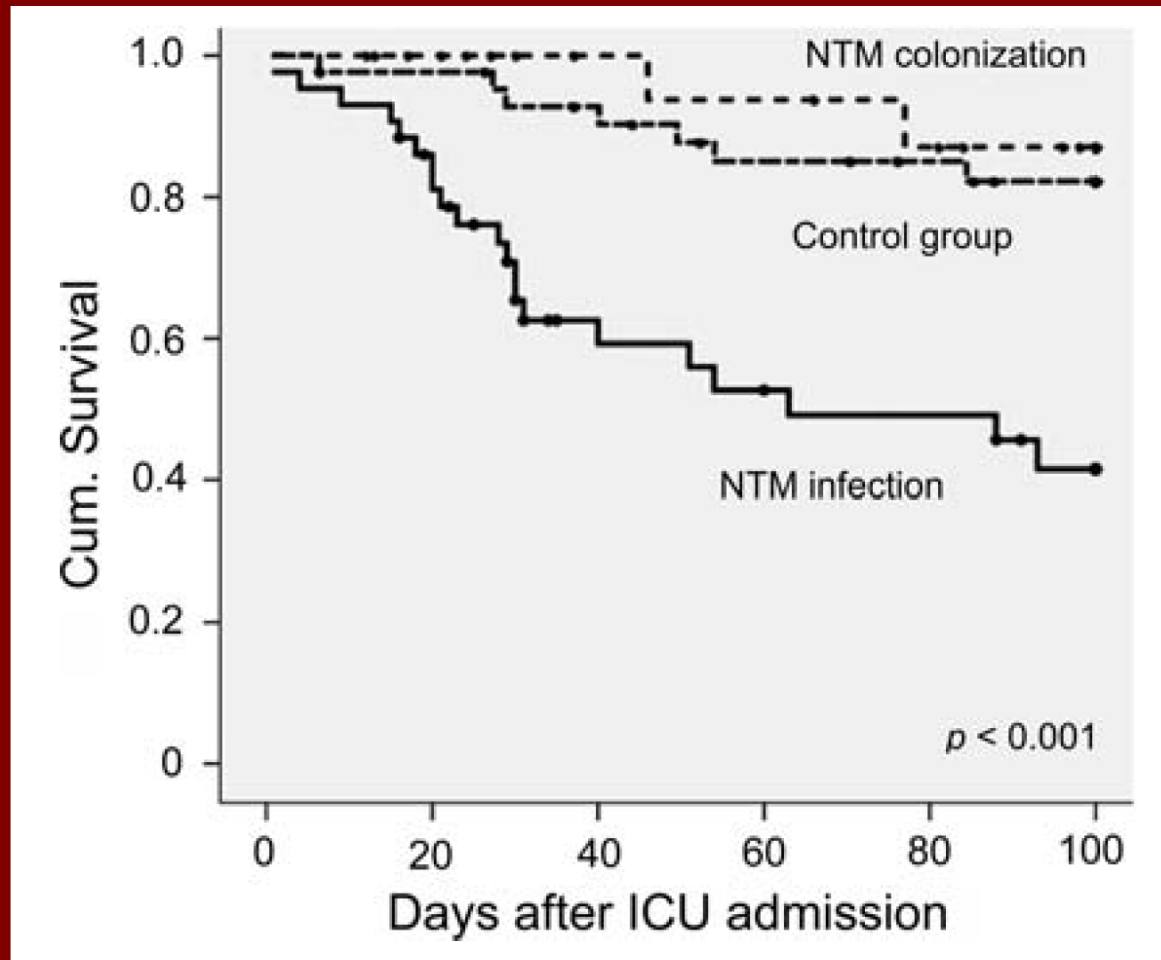
Mortality

Table 3 Outcome of patients

	NTM infection		NTM colonization All ($N = 24$)	Control All ($N = 43$)
	Untreated ($N = 22$)	Treated ($N = 21$)		
Weaning rate	8 ($n = 19$, 42%)	6 ($n = 16$, 38%)	9 ($n = 18$, 50%)	27 ($n = 37$, 73%)
MV day: days ± SD	6.25 ± 3.1	10.2 ± 10.2	16.0 ± 9.6	11.33 ± 12.3
ICU-mortality*	5 (26%)	6 (29%)	2 (8%)	2 (5%)
ICU-stay: days ± SD	21.4 ± 15.7	22.4 ± 16.4	20.7 ± 19.3	18.0 ± 15.2
Survived: days ± SD	22.7 ± 16.4	18 ± 11.4	17 ± 14.8	18.0 ± 15.3
Dead: days ± SD	17.0 ± 13.7	33.3 ± 22.5	61 ± 21.2	18.1 ± 15.1
100-days mortality*	10 (45.6%)	10 (47.6%)	2 (8.3%)	6 (14%)

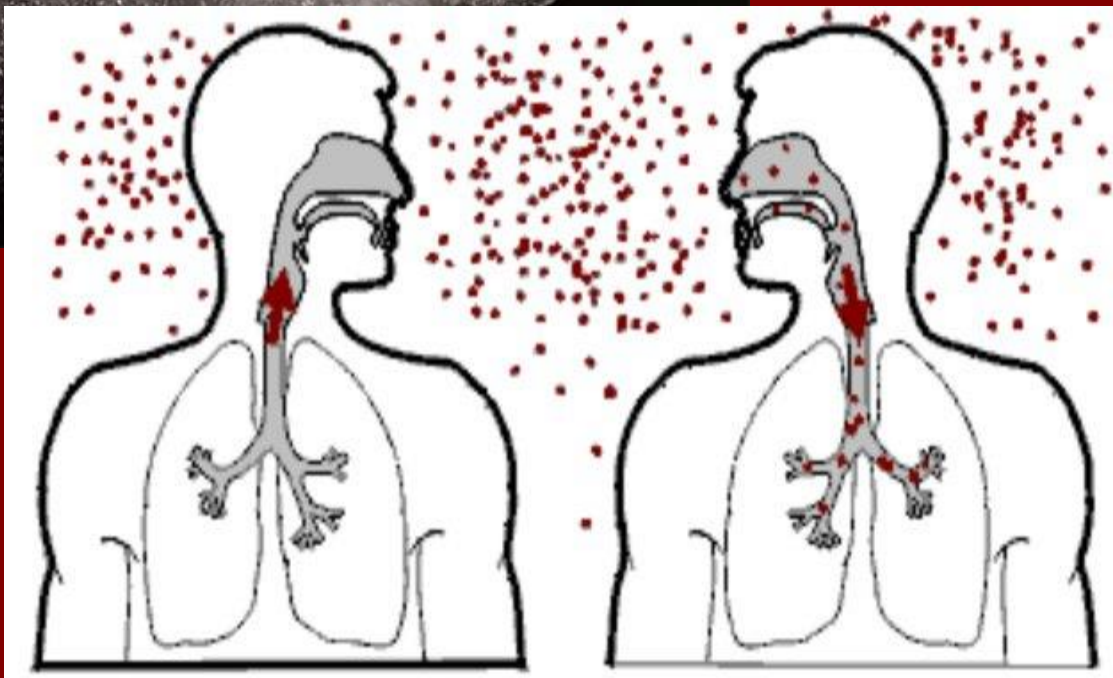Data are no. (%), unless otherwise indicated

ICU intensive care unit; *MV* mechanical ventilation; *NTM* nontuberculous mycobacteria

* Significant difference ($P < 0.05$) between NTM infection, NTM colonization and control groups

~Shu CC, ICM 2008

Transmission

- Outbreak?
- Contamination?

TB/NTM是透過空氣傳染

Isolation strategy for TB

- Smear+ or Culture +
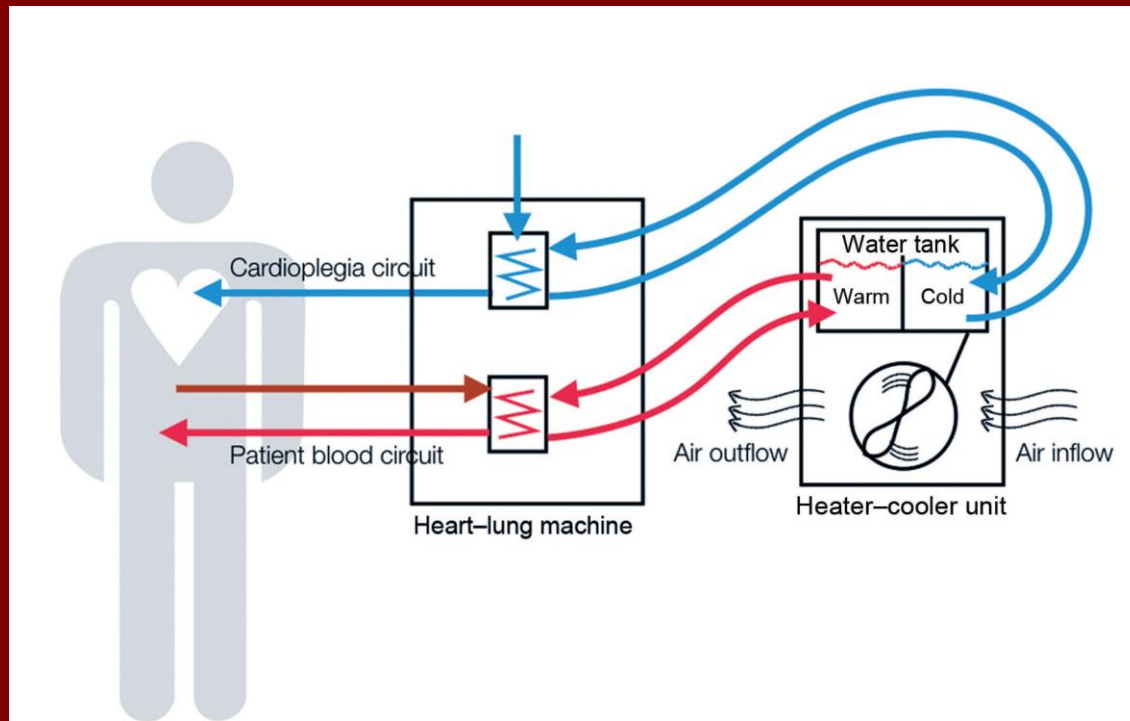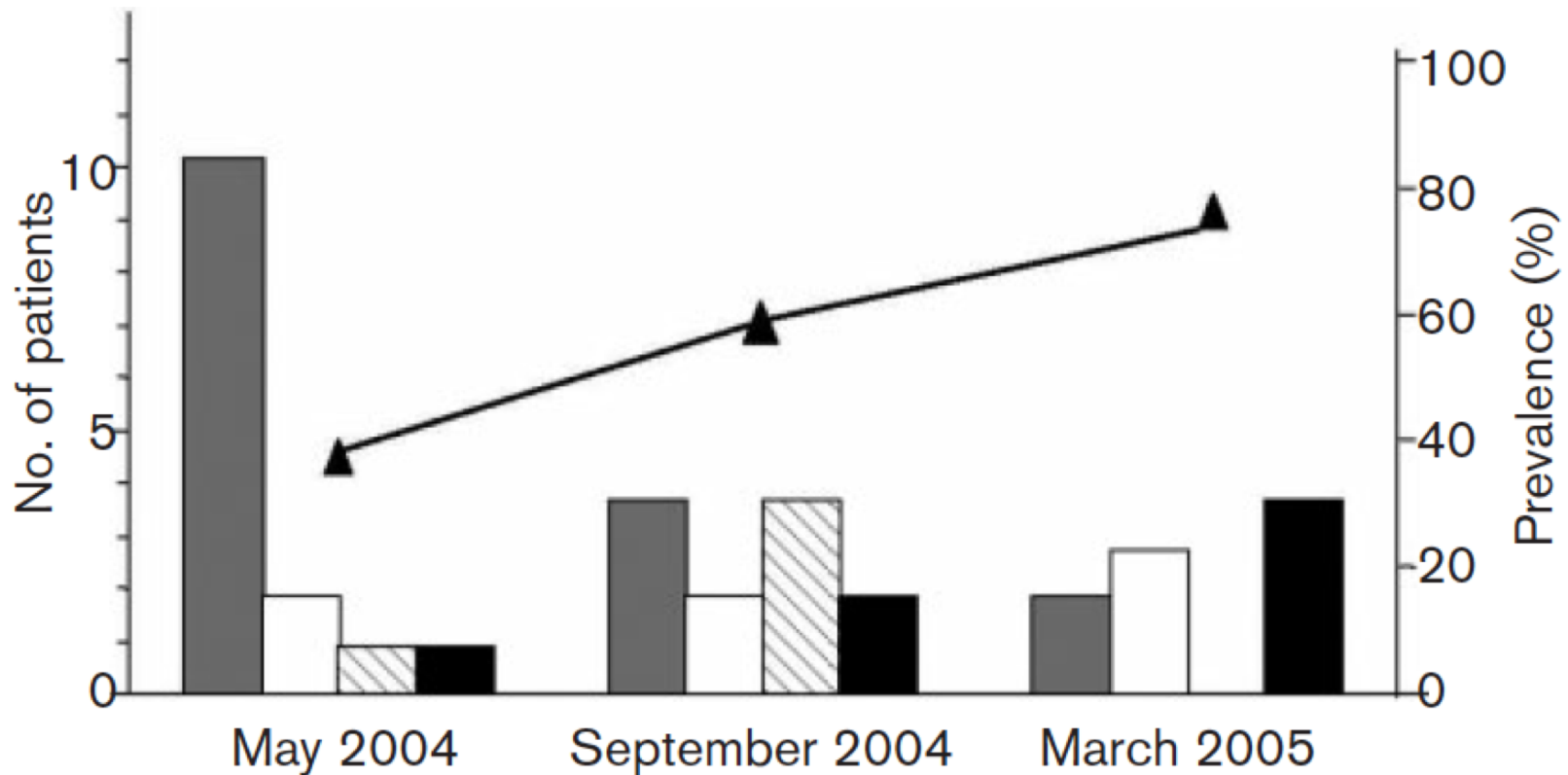 and
- Treatment < 14 days

How about NTM?

Not known for person to person transmission! **?**

Heater–cooler units (HCUs)
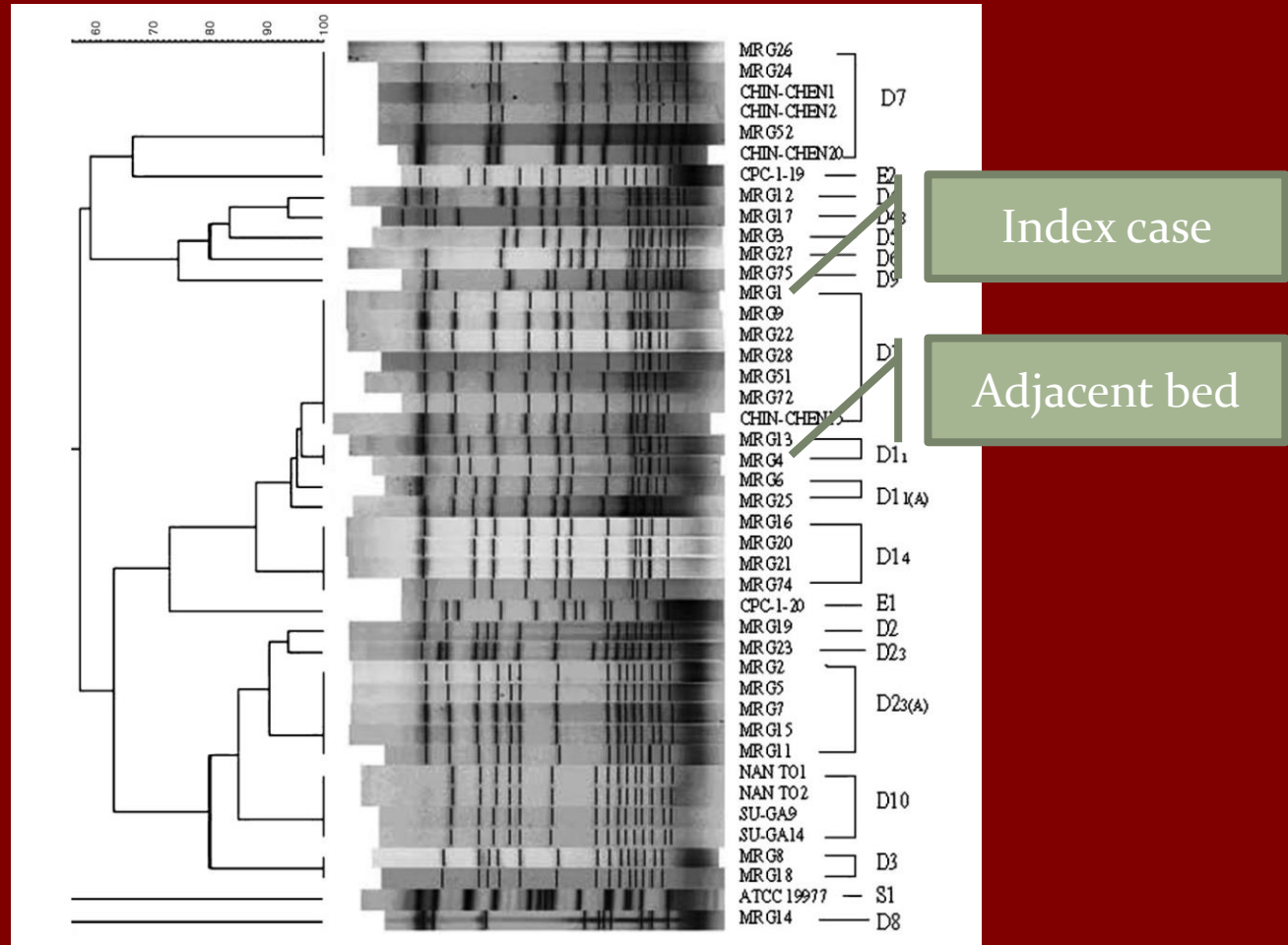
- Heater–cooler units (HCUs) were recently identified as a source of *M. chimaera* **infections** in open-chest heart surgery patients

Sommerstein R, Emerg Infect Dis 2016 Jun;22(6):1008-13.

New insight in Taiwan RCC

New worry in Taiwan RCC

Index case

Adjacent bed

Huang WC et al. J Med Microbiol 2010

New worry in Taiwan RCC

Other hospital

Index case

New p't

Huang WC et al. J Med Microbiol 2010
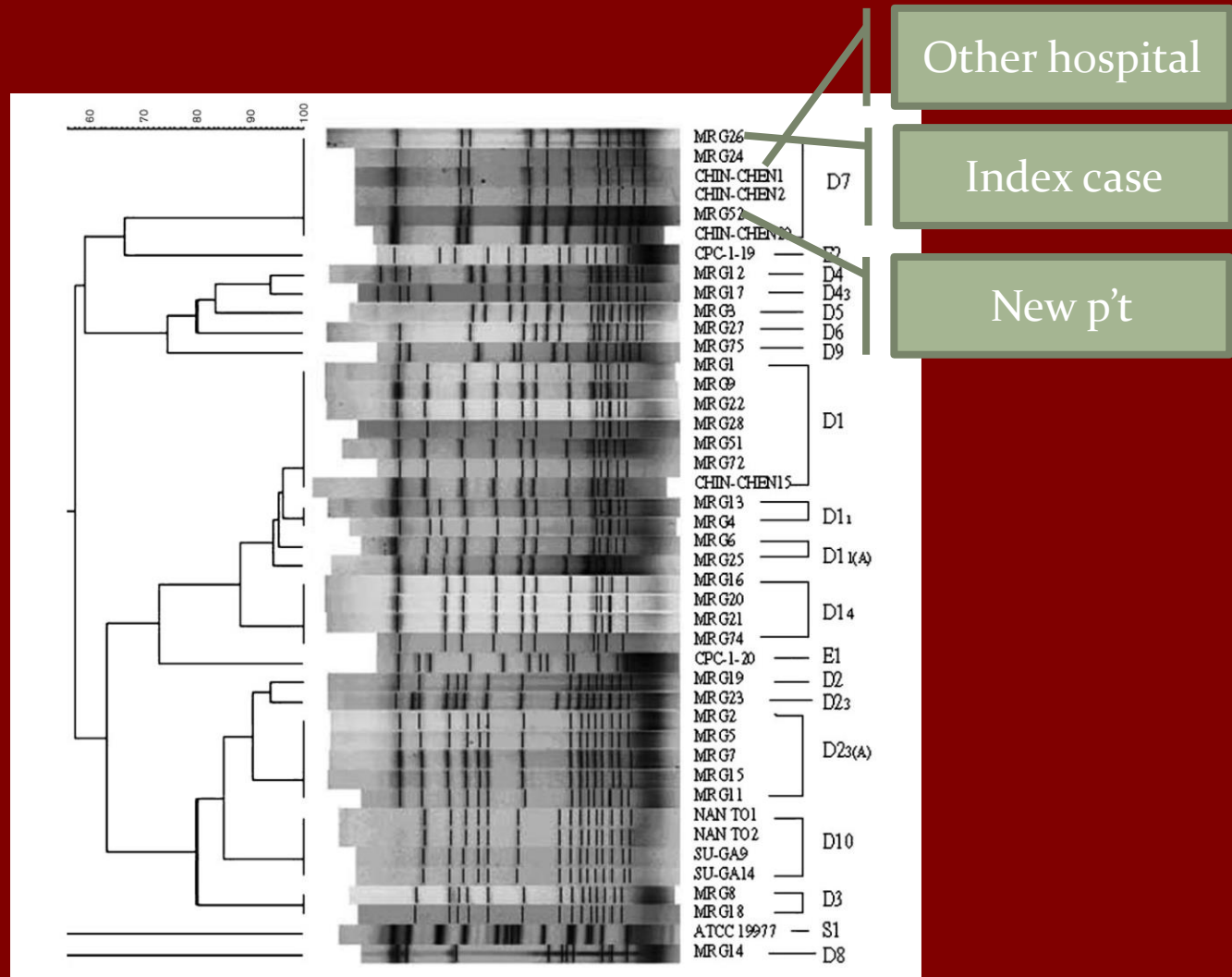
RCW

- 72 patients

- Culture positive for *M. abscessus* increased from
  15.3% (11/72) on D1 to
  30.6% (22/72) at M3 and
  38.9% (28/72) at M6.

- Two *M. abscessus* subspecies *abscessus* isolates obtained from different patients had **identical** randomly amplified polymorphic DNA pattern

Lee MR, Futrure Microbiol 2016;11(4):491-500.

Take Home message

- **TB/NTM** is **not uncommon** pen in ICU **.**

- Difficult in **early diagnosis** and treatment based on CXR. **AFS, PCR, and clinical feeling** help a lot.

- Treatment of **FQ empirically** or **corticosteroid adjunctively** are still questionable.

- **Prognosis** is usual not good and **early treatment** might favor survival.

- **Transmission** within ICU might exist, diagnosis and strain identification as well source control are important to emphasize.

由衷的感謝

- 感謝**大家**的聆聽與指教
- 感謝**學會**邀請 和 **師長**的推薦
- 台大**胸腔科**大家庭 和 **整合醫學科**

台大醫院胸腔內科全體同仁合影 101.03.28 攝於景福園