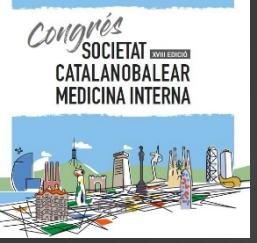


Infecciones por micobacterias no tuberculosas

José Antonio Martínez

Servicio de Enfermedades Infecciosas
Hospital Clínic de Barcelona

Donohue MJ, et al. *Increasing prevalence rate of nontuberculous mycobacteria infections in five states, 2008-2013.* Ann Am Thorac Soc 2016;13:2143-50.

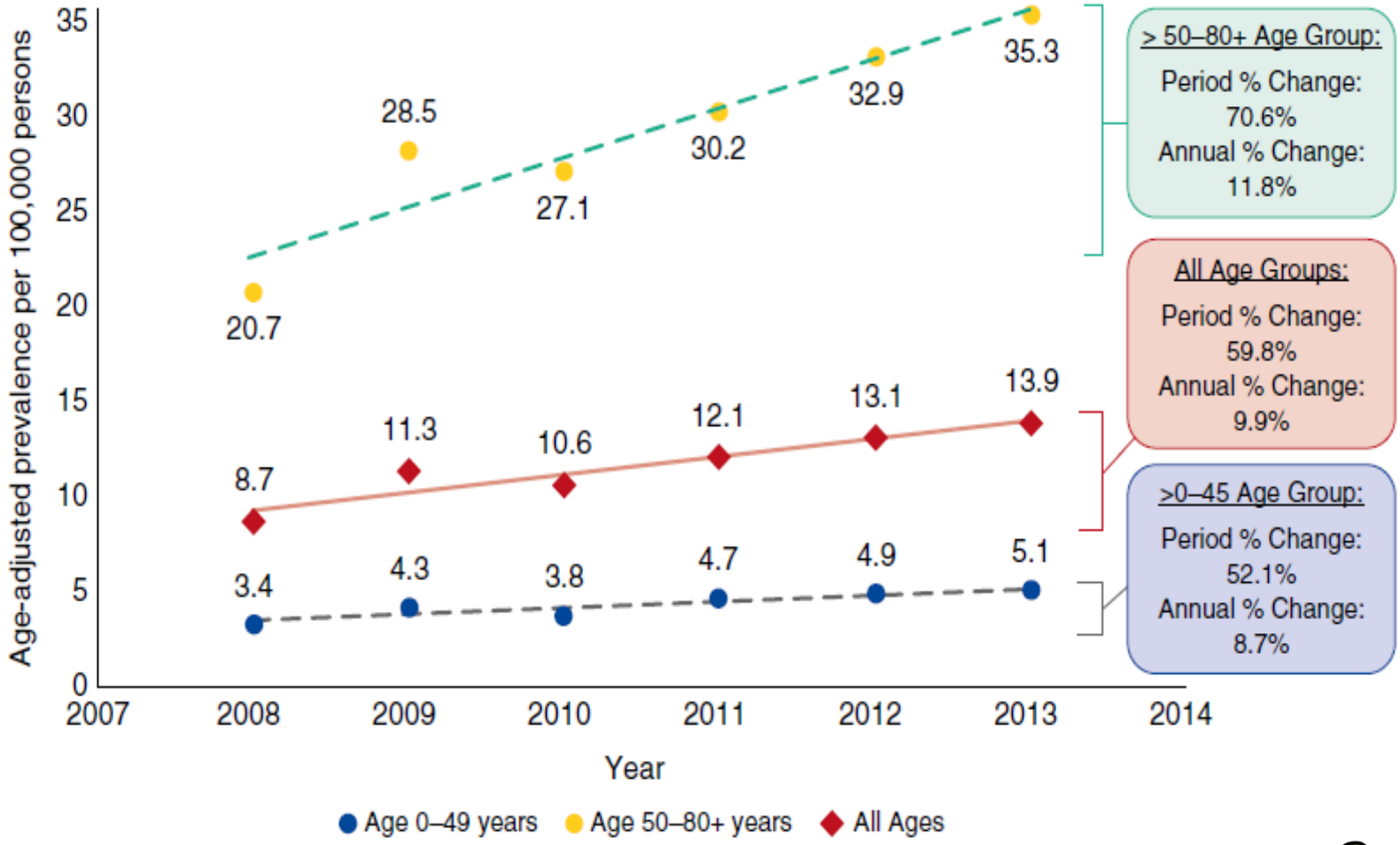
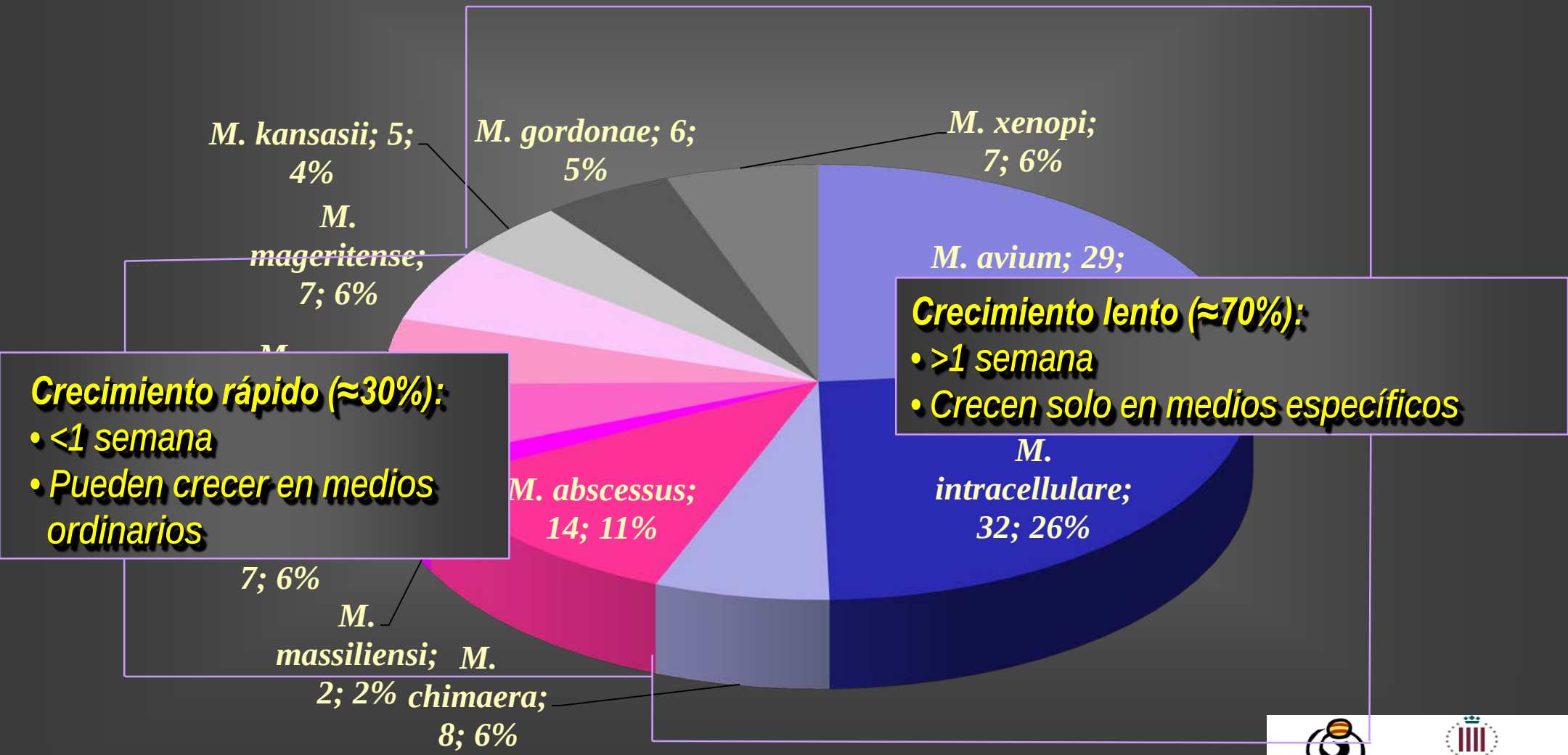


Figure 2. The average age-adjusted annual prevalence of nontuberculous mycobacteria case rate per 100,000 persons. change from 2008 to 2013.

Micobacterias no tuberculosas. Hospital Clínic de Barcelona 2013-2016.



Crecimiento rápido (≈30%):
- <1 semana
- Pueden crecer en medios ordinarios

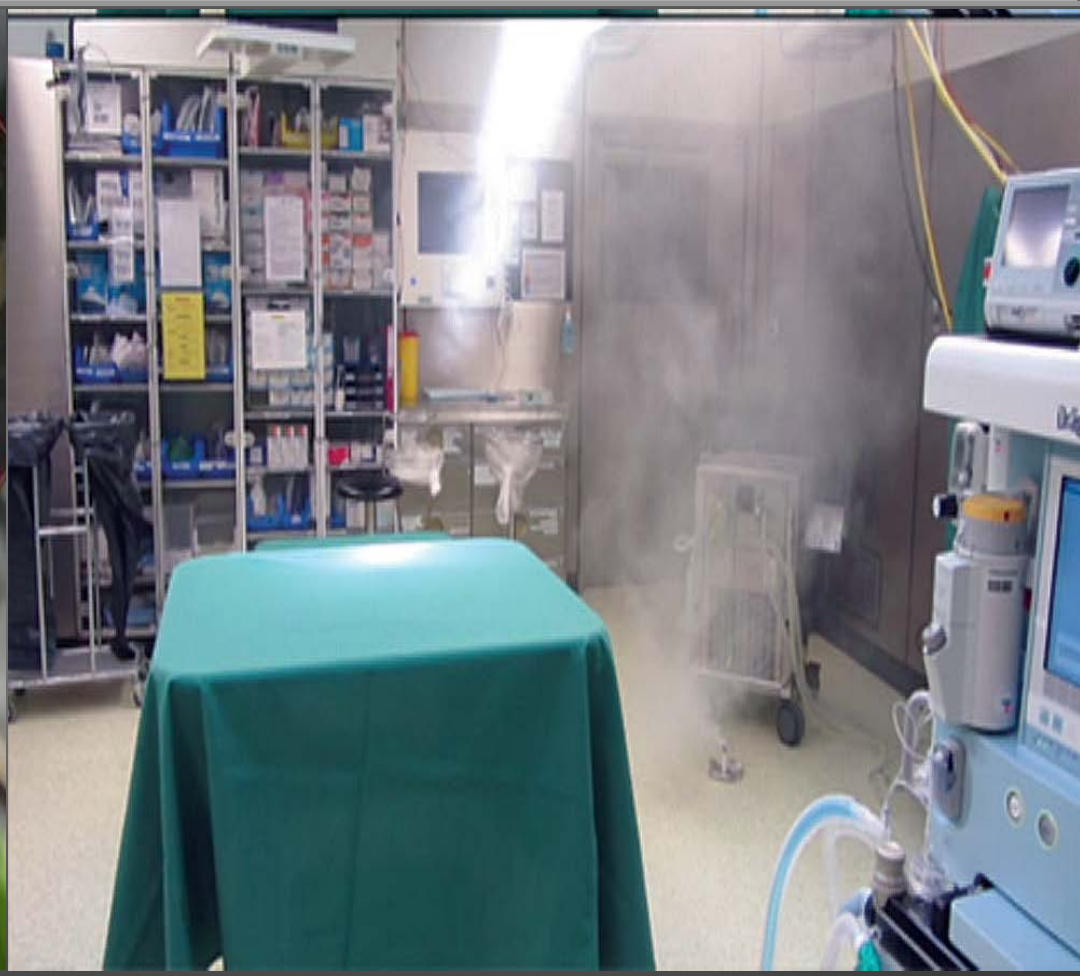
Crecimiento lento (≈70%):
- >1 semana
- Crecen solo en medios específicos

Falkinham JO, et al. Current epidemiologic trend of the nontuberculous mycobacteria (NTM). Curr Environ Health Rpt 2016;3:161-7.

Table 2 Environmental sources of nontuberculous mycobacteria (NTM)

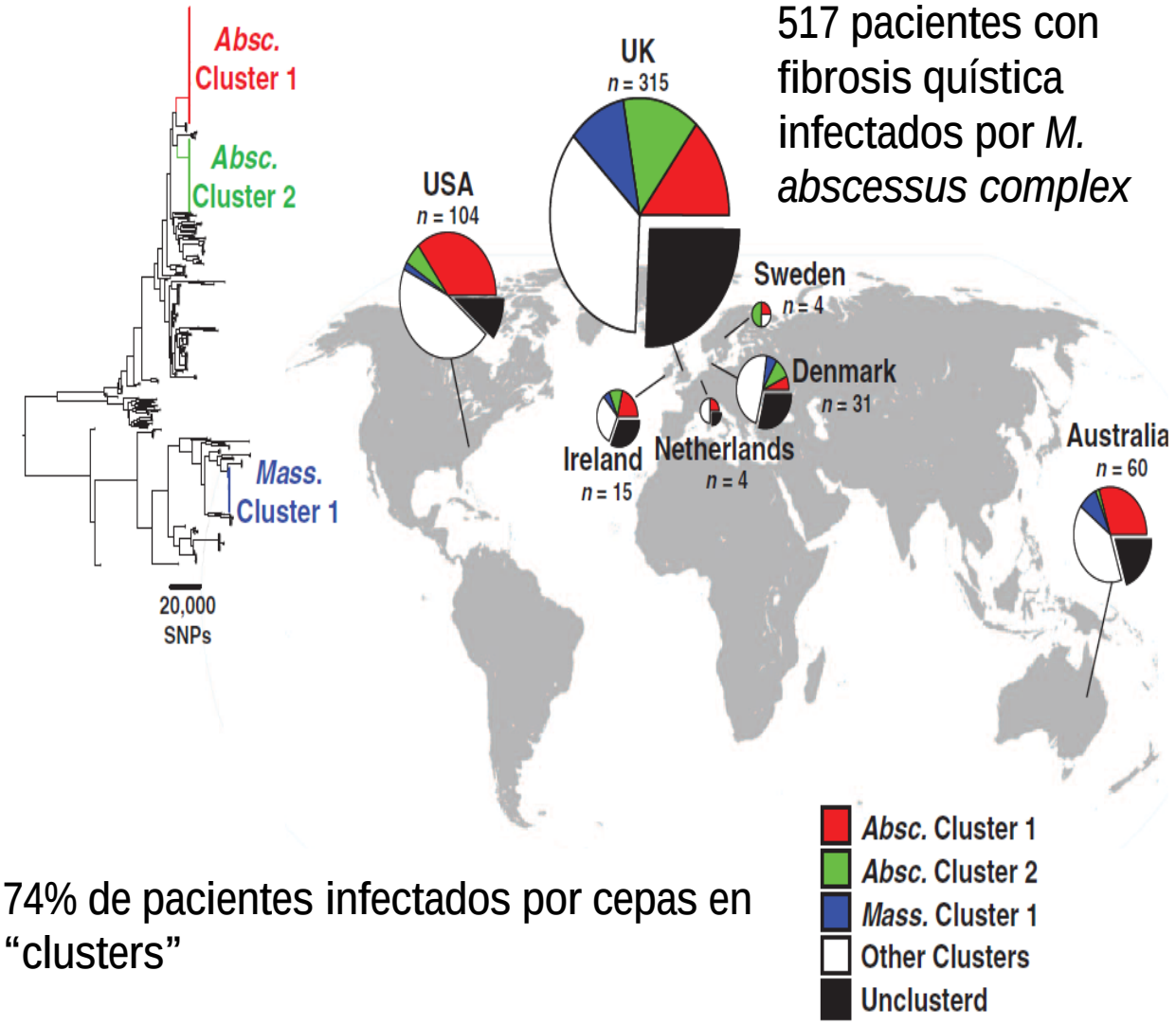
Peat-rich soils	10^6 UFC/cm^2
Drainage water from peat-rich soils	
U.S. coastal swamp soils, waters, and sediments	
Natural streams, rivers, ponds, and lakes	
Drinking water distribution systems	10^2-10^3 UFC/mL
Premise (hospitals, homes, apartments) plumbing	
Instruments with water reservoirs (humidifiers, heater-coolers)	
Refrigerator water, taps, and ice	
Shower aerosols	
Spas and hot tubs	
Biofilms in all the above	10^4 UFC/cm^2

Biopelículas de M. chimaera en máquinas de calentamiento-enfriamiento y aersolización en quirófanos



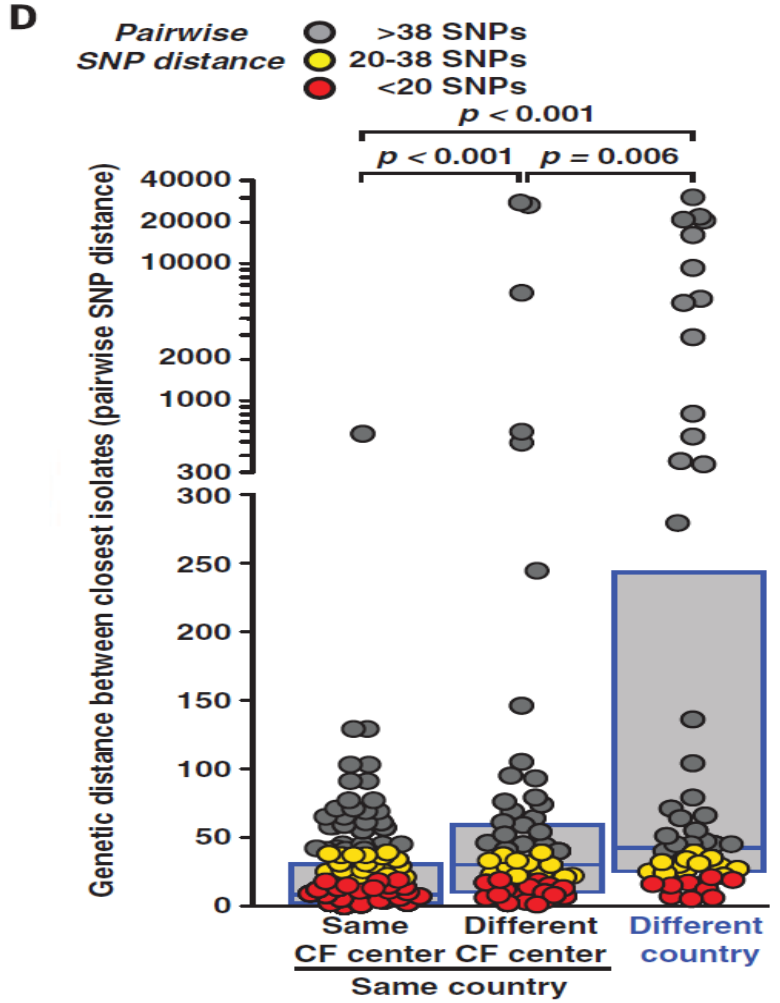
La práctica totalidad de los aislados de pacientes infectados son genéticamente idénticos a los aislados de un tipo particular de máquina de calentamiento-enfriamiento y de fuentes ambientales del lugar de fabricación (van Ingen J et al. Lancet Infect Dis 2017;17:1033-41)

Bryant JM, et al. *Emergence and spread of a human-transmisible multidrug-resistant nontuberculous mycobacterium*. Science 2016;354:751-7.



517 pacientes con fibrosis quística infectados por *M. abscessus complex*

74% de pacientes infectados por cepas en "clusters"



Maurer JP, et al. *Erm(41)-dependent inducible resistance to azithromycin and clarithromyin in clinical isolates of Mycobacterium abscessus. J Antimicrob Chemother 2014;69:1559.*

Table 1. Clarithromycin and azithromycin DST results of *M. abscessus* complex and *M. chelonae* clinical isolates

	MIC range (mg/L)			Median MIC (mg/L)		
Species/antibiotic	day 3	day 7	day 12	day 3	day 7	day 12
M. abscessus subsp. *abscessus*						
clarithromycin (*n*=21)	<0.5–8	<0.5–256	32 to >256	0.5	32	256
azithromycin (*n*=21)	<0.5–256	64 to >256	256 to >256	4	>256	>256
M. abscessus subsp. *bolletii*						
clarithromycin (*n*=16)	1–4	32–256	256 to >256	1	128	256
azithromycin (*n*=16)	2–128	256 to >256	>256	32	>256	>256
M. abscessus subsp. *massiliense*						
clarithromycin (*n*=10)	<0.5	<0.5–2	<0.5–4	<0.5	<0.5	<0.5
azithromycin (*n*=10)	1–4	2–8	2–32	4	8	8
M. chelonae						
clarithromycin (*n*=22)	<0.5–1	<0.5–2	<0.5–4	<0.5	<0.5	1
azithromycin (*n*=22)	<0.5–16	1–16	2–32	2	8	16

Shown are MICs for isolates with a wild-type *rrl* gene. *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii* isolates carried an inducible Erm(41) methylase (all T28 sequevars).

La tasa de conversión del esputo en pacientes con infección pulmonar tratados con un régimen a base de claritromicina ***es ≈88% en M. masiliense, frente a ≈25% en M.*** *abscessus con Erm(41) funcional (Koh WJ. Am J Respir Crit Care Med 2011;183:405)*

Inmunocompetencia

Linfadenitis localizada (niños <8 años)

MAC (70-80%), M. haemophilum, M. scrofulaceum, M. kansasii, M. malmoense, M. lentiflavum

Cutánea u osteoarticular localizada

- C. rápido: M. fortuitum, M. chelonae, M. abscessus, M. immunogenum, M. wolinskyi (trauma, cirugía cosméticos o estéticos, prótesis)
- M. marinum, M. ulcerans

Diseminada y endocarditis poscirugía cardíada, dispositivos (marcapasos, DF)

- M. chimaera (contaminación máquinas calentadoras-enfriadoras en cirugía cardíaca)
- Crecimiento rápido

Respiratoria (75-90%)

- EPOC, bronquiectasias, corticoides inhalados
- Bajo peso, anomalías esqueléticas
- Reflujo
- Neoplasia respiratoria
- Artritis reumatoide

MAC, M. abscessus, M. kansasii, M. xenopi, M. malmoense, M. szulgai

Inmunodepresión

- Inmunodeficiencia primaria
- Autoanticuerpos anti-IFN-γ
- VIH <100 CD4
- Trasplante órgano sólido o precursores hematopoyéticos
- Corticoides, inmunosupresores, biológicos (anti-tnf)

Diseminada multiorgánica

MAC (90%), M. genavense, M. simiae, M. haemophilum (VIH); M. abscessus (Ac anti-IFN- γ)

Cutánea diseminada

M. chelonae, M. abscessus y otros c. rápido

Bacteriemia relacionada con catéter

M. mucogenicum, M. fortuitum, M.abscessus, M. chelonae, otros c. rápido (M. neoaurum, M. bacteremicum)

Caracteristicas de los pacientes con MNT en secreción respiratoria

• Edad media, años	56-67
• Mujeres, %	38-55
• Comorbilidad, %	73-92
- Respiratoria	33-76
- Diabetes, insuf. renal, cardiopatia	10-18
- Alcoholismo	11
- Cáncer	9-25
- Corticoides/inmunosupresores	6-26
- Trasplante	5-6
- VIH	4-6
- Patología esofágica (reflujo)	10

Evidencia clínica y radiológica de infección (enfermedad pulmonar): 25-50%

van Ingen J et al. Thorax 2009;64:502. Marras TK et al. Lung 2010;188:289. Andrejak C et al. Am J Respir Crit Care Med 2010;181:514. Prevots DR et al. Am J Respir Crit Care Med 2010;182:970. Kotilainen H et al. Scand J Infect Dis 2013;45:194.

Prevots DR, et al. Epidemiology of human pulmonary infection with non-tuberculous mycobacteria: a review. Clin Chest Med 2015;36:13-34.

Host factors		
Lung cancer (neoplasms of larynx, trachea, and bronchus)	3.4 (7)	Disease
COPD	2–10 (7) (18) (27)	Disease
Bronchiectasis	44–187.5 (7) (22)	Disease (coding) (7) Disease (validated microbiologic surrogate) (20)
Thoracic skeletal abnormalities	5.4 (18)	Disease
Low body weight	9.09* (18)	Disease
Rheumatoid arthritis	1.5 (7),1.9# (25) – undefined (26)	Disease
Immunomodulatory drugs/anti-TNF agents	1.3- Undefined (OR=infinity) (18) anti-TNF agents 2.2 (79) Others 1.6–2.9 (79)	Disease
Steroid use	8 (18) 1.6 (79)	Disease
Gastro-esophageal reflux disease	5.3# (27) 1.5* (25)	Disease

EPOC sin corticoides inhalados: OR 7,6 (3,4-16,8)
EPOC con corticoides inhalados: OR 29,1 (13,3-63,8)
No asociación con asma y corticoides inhalados

Andrejak C et al. Thorax 2013;68:256

Haworth CS et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 2017;72:iii1-ii-64

Box 1 Clinical and microbiological criteria for diagnosing non-tuberculous mycobacterial lung disease (modified with permission from Griffith *et al*[1])

Clinical (both required)

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules.
   and
2. Appropriate exclusion of other diagnoses.

Microbiological

1. Positive culture results from at least two separate expectorated sputum samples; if the results are non-diagnostic, consider repeat sputum AFB smears and cultures.
   or
2. Positive culture results from at least one bronchial wash or lavage.
   or
3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathological features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture-positive for NTM.

Cite: Griffith DE, Aksamit T, Brown-Elliott BA, *et al*. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;175:367–416.
The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.
AFB, acid-fast bacilli; NTM, non-tuberculous mycobacteria

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[1] (see box 1). (Grade D)

Good practice point

✓ The management of coexisting lung conditions/infections should be optimised before ascribing clinical decline to NTM-pulmonary disease.

¿Qué criterios radiológicos?

- Bronquiectasias difusas y bronquiolitis (nódulos < 1 cm múltiples y patrón de "árbol en gemación")

- Cavidades

- Consolidación
- **Nódulos ≥ 1 cm**

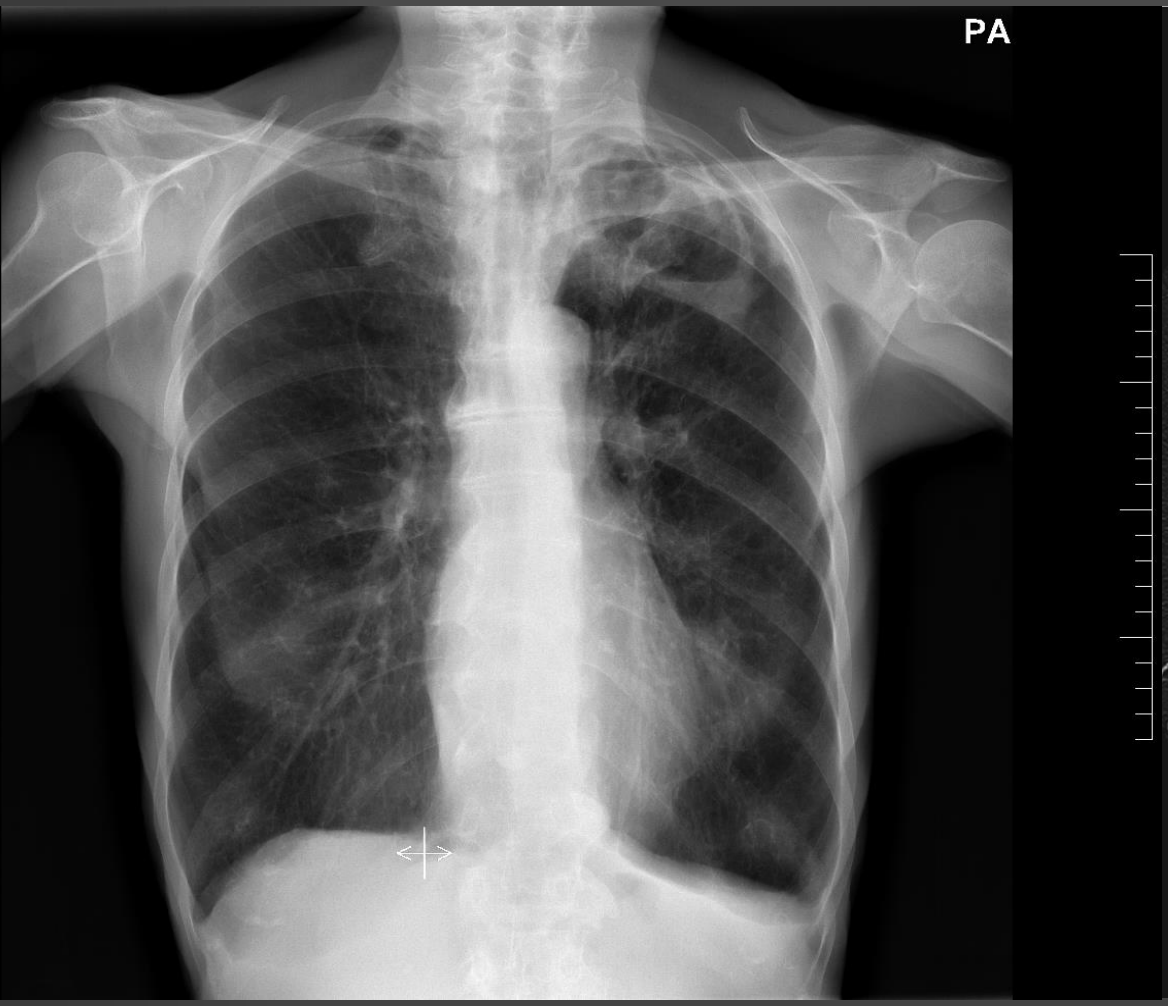
Forma nodular bronquiectásica

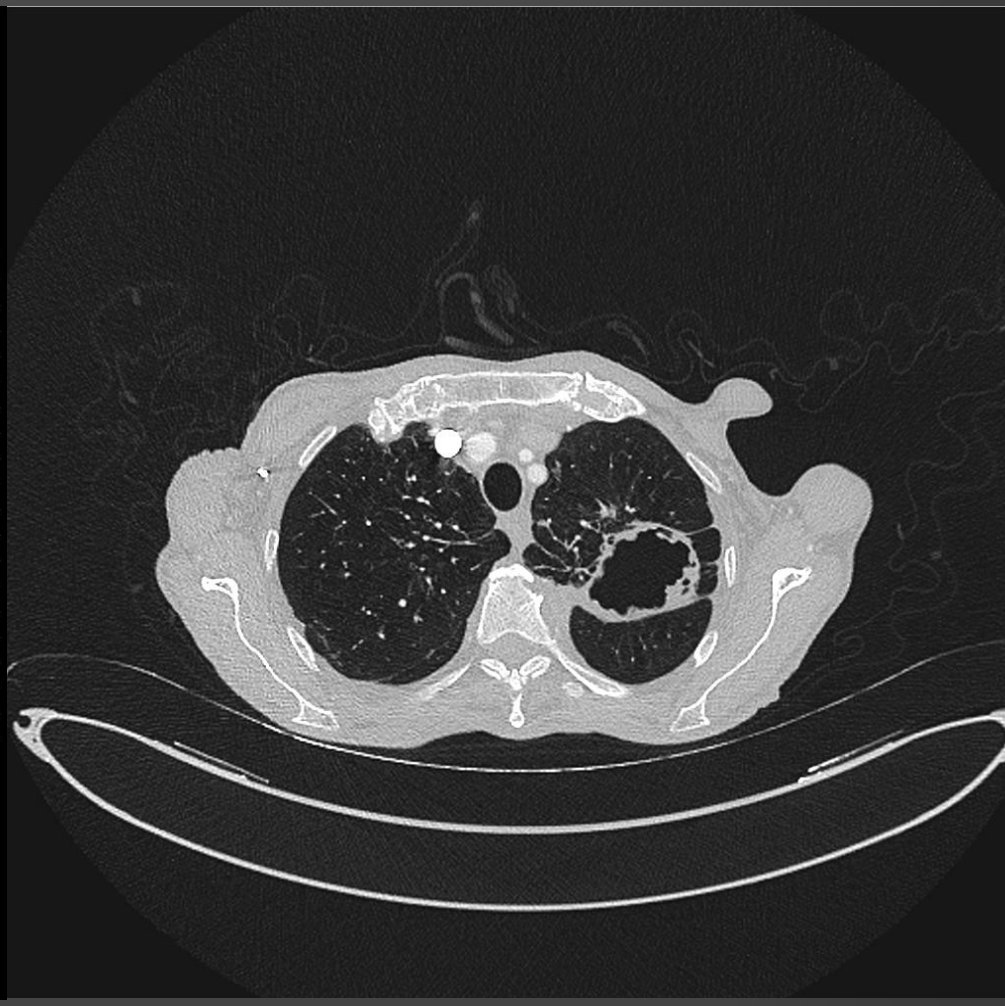
- *Mujeres >50 años*
- *Predominio en LM y língula*
- *No patología broncopulmonar previa*

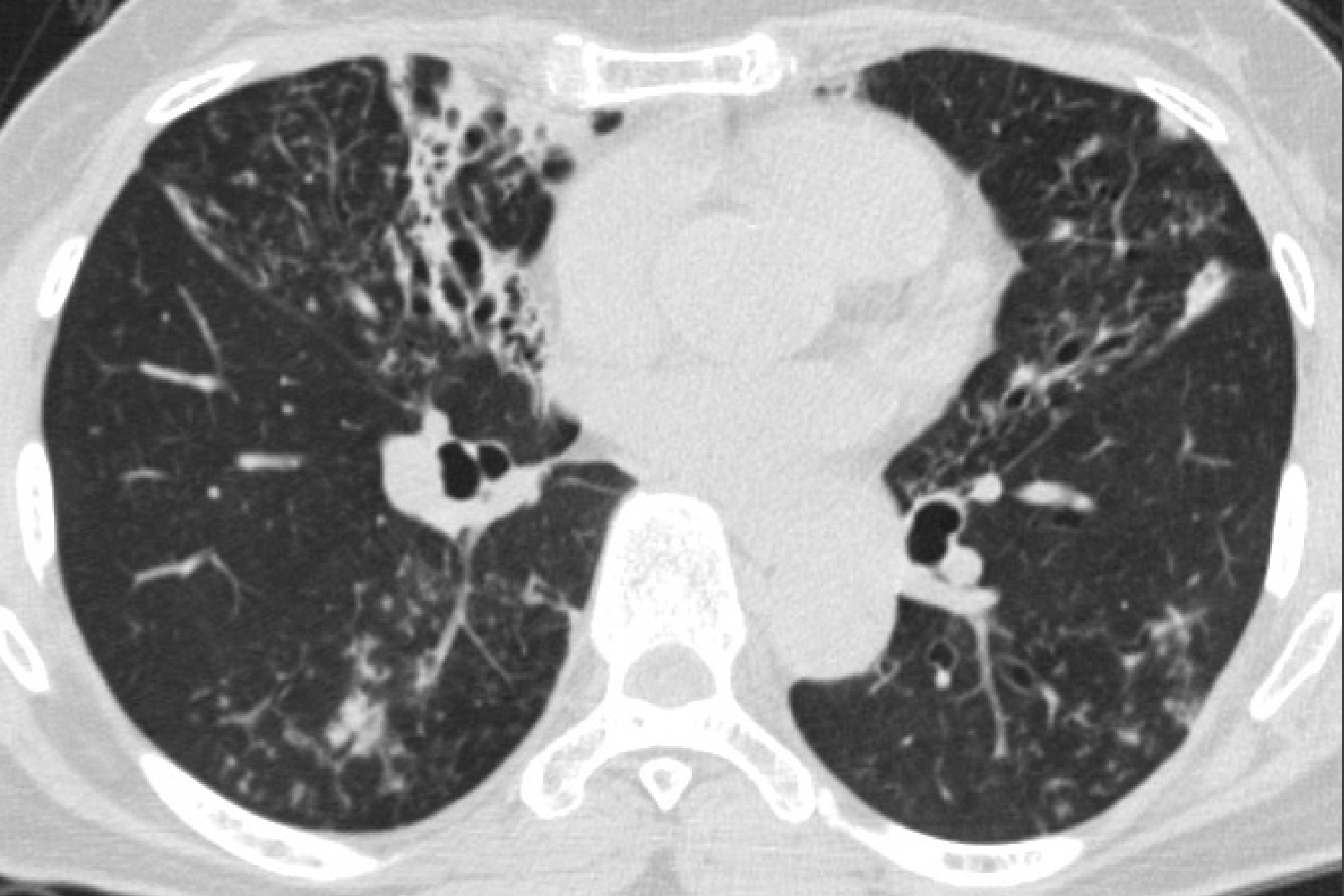
Forma fibrocavitaria

- *Hombres >50 años*
- *Predominio en lóbulos superiores*
- *Patología broncopulmonar previa*

Forma fibrocavitaria por *M. xenopi*







Haworth CS et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 2017;72:iii1-ii-64

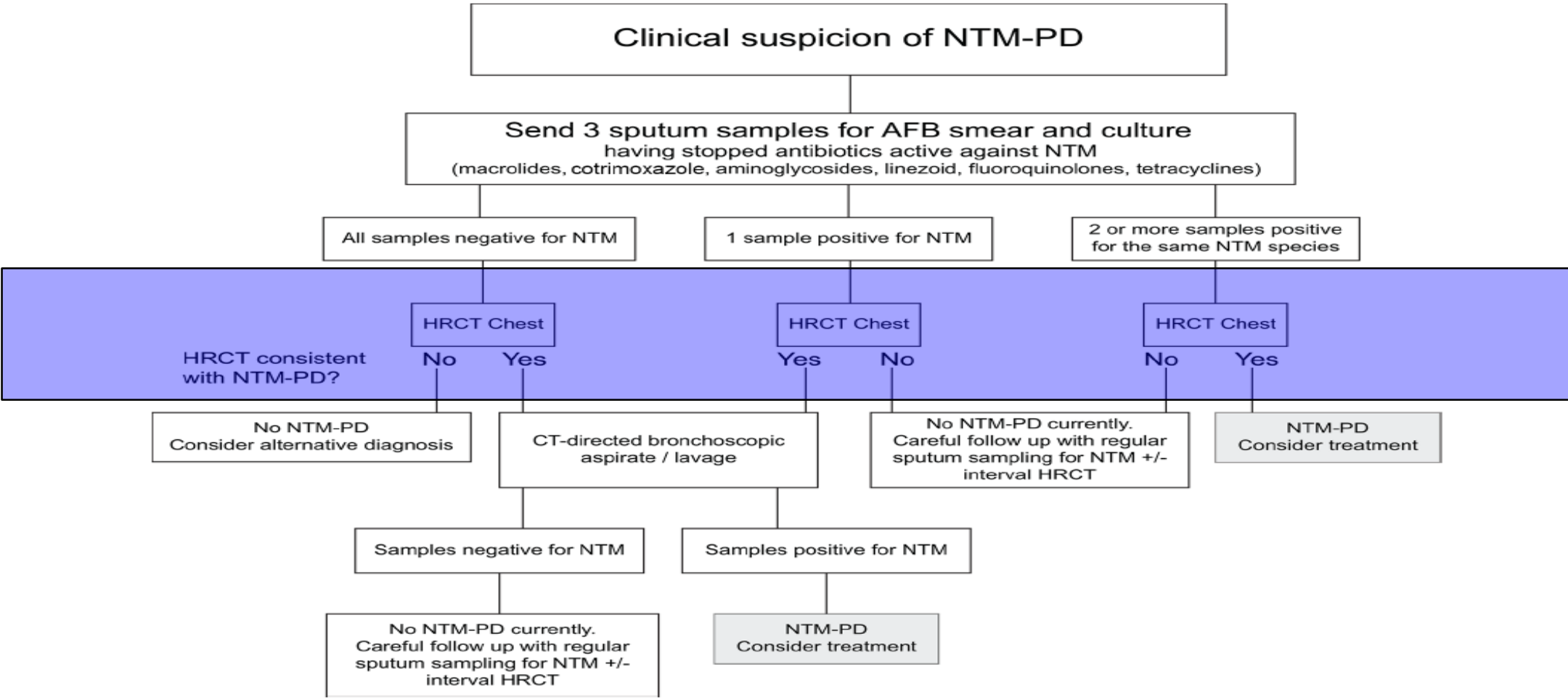
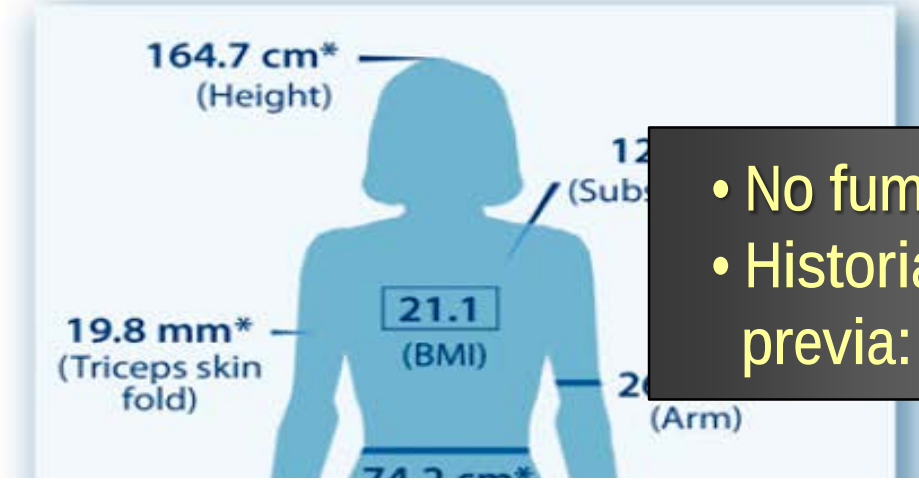
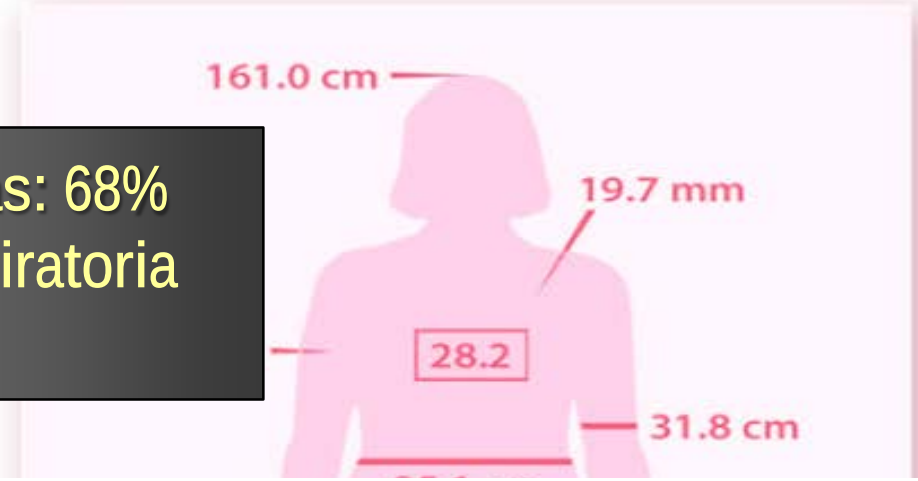


Figure 1 A suggested algorithm for the investigation of individuals with clinical suspicion of NTM-PD. AFB, acid-fast bacilli; HRCT, high-resolution CT; NTM-PD, non-tuberculous mycobacterial pulmonary disease.

Kim RD, et al. Pulmonary nontuberculous mycobacterial disease. Prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med 2008;178:1066-74.



- No fumadoras: 68%
- Historia respiratoria previa: 30%



	No. (%)	% población general	
Scoliosis	32 (51)	1.9	<0.001
Pectus excavatum	7 (11)	1	<0.001
Mitral valve prolapse	5/56 (9)	2.4	0.004
CFTR mutation, n (%)	23 (36.5)		

Olivier KN, et al. Lady Windermere dissected: more form than fastidious. AnnalsATS 2016;13:1674.

Fibrosis quística

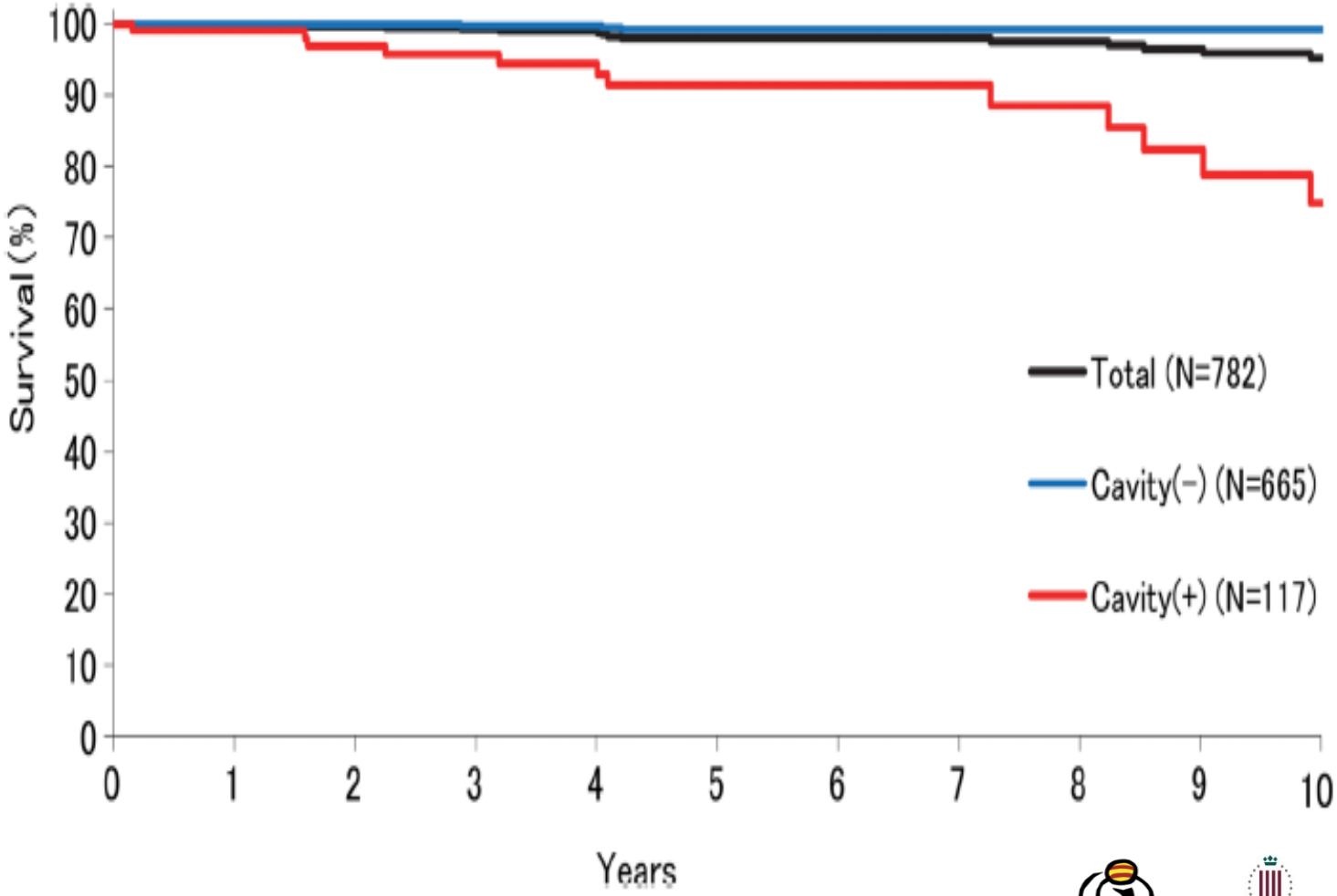
Marfan/ aranodactilia

Discinesia ciliar primaria

Hiper_IgE (síndrome de Job)

Gochi M, et al. Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/bronchiectatic Mycobacterium avium complex lung disease. BMJ Open 2015;5:e008058.

Figure 2 Kaplan-Meier survival curves of *Mycobacterium avium* complex lung disease (MAC-LD) progression mortality of patients with nodular/bronchiectatic MAC-LD with or without cavity. Five-year and 10-year MAC-LD progression mortality rates were 2% and 4.8%, respectively. Five-year and 10-year MAC-LD progression mortality rates in the patients with cavity were 8.5% and 25.1%, versus 0.8% for each period in those without cavity, respectively ($p<0.001$).



Indicaciones de tratamiento inmediato de la infección respiratoria por MNT en pacientes con criterios de enfermedad (ATS/IDSA 2007)

- Forma cavitaria o nodular bronquiectásica con cavitación
- Forma nodular bronquiectásica o no clasificable en pacientes con:
  - Inmumodepresión (neoplasia activa, trasplante, VIH avanzado, primaria)
  - Anti-TNF y posiblemente otros inmunosupresores
  - Artritis reumatoide
  - Fribrosis quística y *M. abscessus*
  - Enfermedad instersticial idiopática
  - Desnutrición, hipoalbuminemia, BMI <18,5
  - Empeoramiento de síntomas o progresión radiológica

Griffith RJ et al. AJRCCM 2007;175:367. Lee G et al. Ann Am Thoraci Soc 2013;10:299. Gochi M et al. BMJ Open 2015;5:e008058. Henkle E. Clin Chest Med 2015;36:91. Liao TL et al. Scien Rpt 2016;6:29443. Stolnik K et al. Curr Treat Options Infect Dis 2016;8:259. Kim SJ et al. BMC Pulm Med 2017;17:5.

Haworth CS et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 2017;72:iii1-ii64

Table 3 Suggested antibiotic regimens for adults with *M. avium* complex-pulmonary disease

M. avium complex-pulmonary disease	Antibiotic regimen
Non-severe MAC-pulmonary disease (ie, AFB smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	Rifampicin 600 mg 3× per week and Ethambutol 25 mg/kg 3× per week and Azithromycin 500 mg 3× per week or clarithromycin 1 g in two divided doses 3× per week Antibiotic treatment should continue for a minimum of 12 months after culture conversion.
Severe MAC-pulmonary disease (ie, AFB smear-positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness)	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily and consider intravenous amikacin for up to 3 months or nebulised amikacin Antibiotic treatment should continue for a minimum of 12 months after culture conversion.
Clarithromycin-resistant MAC-pulmonary disease	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Isoniazid 300 mg (+pyridoxine 10 mg) daily or moxifloxacin 400 mg daily and consider intravenous amikacin for up to 3 months or nebulised amikacin Antibiotic treatment should continue for a minimum of 12 months after culture conversion.

Alternativas

- Rifabutina
- Clofazimina
- Bedaquilina
- Delamanid
- Linezolid, tedizolid

Asociada con Cmáx baja (<0,2 mg/l) en 47% de pacientes y mala respuesta microbiológica (Jeong BH. Antimicrob Agents Chemother 2016;60:6076)

Haworth CS et al. *British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 2017;72:iii1-ii-64*

Table 8 Suggested antibiotic regimens for adults with *Mycobacterium abscessus*-pulmonary disease

M. abscessus	Antibiotic regimen
Clarithromycin sensitive isolates or inducible macrolide-resistant isolates	**Initial phase: ≥1 month†** intravenous amikacin 15 mg/kg daily or 3× per week‡ and intravenous tigecycline 50 mg twice daily and where tolerated intravenous imipenem 1 g twice daily and where tolerated oral clarithromycin 500 mg twice daily or oral azithromycin 250–500 mg daily **Continuation phase:** nebulised amikacin‡ and oral clarithromycin 500 mg twice daily or azithromycin 250–500 mg daily and 1–3 of the following antibiotics guided by drug susceptibility results and patient tolerance: oral clofazimine 50–100 mg daily§ oral linezolid 600 mg daily or twice daily oral minocycline 100 mg twice daily oral moxifloxacin 400 mg daily oral co-trimoxazole 960 mg twice daily

†Due to the poorer response rates in patients with inducible or constitutive macrolide-resistant isolates and the greater efficacy of antibiotics administered through the intravenous route, extending the duration of intravenous antibiotic therapy to 3–6 months in those that can tolerate it may be the most appropriate treatment strategy in this subgroup of patients.

‡Substitute intravenous/nebulised amikacin with an alternative antibiotic if the *M. abscessus* is resistant to amikacin (ie, minimum inhibitory concentration >64 mg/L or known to have a 16S rRNA gene mutation conferring constitutive amikacin resistance).

§Start clofazimine during the initial phase of treatment if tolerated as steady-state serum concentrations may not be reached until ≥30 days of treatment.

- *Clofazimina es sinérgica con claritromicina o amikacina y previene in vitro la selección de resistencia a ambos (Ferro BE, AAC 2016;60:1097)*

Alternativas:

- Bedaquilina
- (avibactam+carbapenem)

Tratamiento de la infección respiratoria por MNT: no todo está resuelto

Especie	Éxito terapéutico	Recaídas	Toxicidad
• *M. avium* complex	66%	8%-57% (45%-75% re-infecciones)	30%-90%
– Forma cavitaria	42%		
– Forma NB	70-85%		
– No macrólido	28%		
• *M. abscessus*	25%-45%	12%-23%	25%-50%
• *M. massiliense*	80%-95%		
• *M. kansasii*	>95%	<5%	
• *M xenopi*	40-70%	5-25%	
• *M. malmoense*	≈54%	≈10%	

Wallace RJ et al. J Infect Dis 2002;186:266. Griffith De et al. AJRCCM 2006;174:298. Xu HB et al. Eur J Clin Microbiol Infect Dis 2014;33:247. Wallace RJ et al. Chest 2014;146:276Jeon BH et al. AJRCCMed 2015;191:96. Koh WJ et al. AJRCCM 2011;183:405. Lyu J H et al. Respir Med 2014;108:1706. Koh WJ et al CID 2017;64:309. Park J et al. CID 2017;64:301. Diel R. et al. Chest 2017;152:120- Diel R et al. Chest 2018;153:888.

Otras formas clínicas de infección por micobacterias no tuberculosas

Entidad clínica	Tratamiento atb	Duración, consideraciones
• MAC diseminada en inmunodeprimidos (fiebre, hepatoesplenomeglia, diarrea, adenopatía retroperitoneal, anemia, bacteriemia)	• Diario, azitro 500 mg/d, rifabutina en vez de rifampicina	• VIH: hasta >100 CD4 x 6 m (vivos 60% con ART a 454 d) • **no VIH: ≥1 año, considerar** profilaxis secundaria si inmunosupresión severa
• Endocarditis sobre válvula protésica, implante o dispositivo cardíaco por *M. chimaera*	• Macrólido+eta+rifabutina+ amikacina±moxi	• Duración no definida **(≥1 año); fracaso** terapéutico hasta 80% • Retirada prótesis
• Crecimiento rápido	• Como *M. abscessus* pulmonar	• Retirada de catéteres y material protésico • Cirugía (desbridamiento) • **Catéter venoso: ≈4 s** • Otras: 4-6 meses

Karakousis PC et al. Lancet Infect Dis 2004;4:557
Kaspeerbauer SH et al. Clin Chest Med 2015;36:67
Collins LF et al. Open Forum Infect Dis 2017;4 (3)
Bronw-Elliott B et al. Microbiol Spectr 2017 Jan;5(1)

Conclusiones

- La incidencia de infecciones causadas por MNT es creciente, tal vez debido a una mayor frecuencia en la población de comorbilidades predisponentes, conductas y procedimientos médicos de riesgo y de una mayor presencia de estas especies en las fuentes de agua potable
- La forma clínica más frecuente es la pulmonar y su tratamiento es complejo, prolongado, penoso (efectos adversos) y de eficacia (salvo para *M. kansasii*) moderada. La decisión de tratar ha de basarse en la constatación razonable de la existencia de enfermedad
- Cuando se asocian a biomateriales, estos deben retirarse y en las infecciones supurativas de piel y partes blandas y osteoarticulares la exéresis quirúrgica o el desbridamiento ha de considerarse siempre

Haworth CS et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 2017;72:iii1-ii-64

	No grave	Grave
M. kansasii	Rifampicina+etambultol+isoniazida o azitro o claritromicina	
M. malmoense	Rifampicina+etambultol+ azitro o claritromicina	Amikacina iv o nebulizada x 3 meses
M. xenopi	Rifampicina+etambultol+ azitro o claritromicina+ moxifloxacino	

Duración: 12 meses tras la negatividad del cutivo de esputo

Formas radiológicas pumonares de acuerdo con la especie

Especie	Frecuencia	
	Cavitación	Nódulos-bronquiectasias
M. avium complex	16%-77%	53%-76%
M. kansasii	53%-95%	27%
M. xenopi	44%	34%
M. malmoense	83%	-
M. szulgai	46%	20%
M. celatum	42%	-
M. simiae	3%	-
M. abscessus	14%-35%	81%

Hollings NP et al. Eur Radiol 2002;12:2211. Christiansen DC et al. Diag Microbiol Infect Dis 2004;49:19. Chung MJ et al. J Korean Med Sci 2005;20:777. van Ingen J et al. CID 2008;46:1200. Shitrit D et al. Respir Med 2008;102:1598. Marras TK et al. Lung 2010;188:289. Hayashi M et al. Am J Respir Crit Care Med 2012;185:575. Gommans EPAT et al.Respir Med 2015;109:137

Riesgo alto

M. kansasii
M. malmoense
M. szulgai

Riesgo medio

M. avium complex
M. abscessus
M. xenopi
M. celatum

Riesgo bajo o muy bajo

M. chelonae
M. fortuitum
M. simiae

M. gordonae
M. terrae
M. lentiflavum
Otros

Riesgo de significación clínica en aislados de muestras respiratorias

≤5% **6%-25%** **26%-50%** **>50%**