# Treatment of Nontuberculous Mycobacterial Pulmonary Disease:

#### An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

#### **Online Supplement**

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Table E1. EXPERT PANEL MEMBERS

Name	Role	Society	Expertise	Location		
Charles L. Daley, MD	Lead chair	ATS	Pulmonologist	Denver, CO, USA		
Emmanuelle Cambau, PhD	Co-chair	ESCMID	Microbiologist	Paris, France		
Christoph Lange, MD, PhD	Co-chair	ERS	Pulmonologist	Borstel, Germany		
Richard J. Wallace Jr, MD	Co-chair	IDSA	Infectious diseases, microbiologist	Tyler, TX, USA		
Jonathan M. Iaccario, MD	Methodologist	ATS	Methodology	Boston, MA, USA		
Jan Brozek, MD, PhD	Methodologist	ATS	Methodology	Hamilton, Canada		
Claire Andrejak, MD	Member	ERS	Pulmonologist	Amiens, France		
Erik C. Böttger	Member	ESCMID	Microbiologist	Zurich, Switzerland		
David E. Griffith, MD	Member	ATS	Pulmonologist	Tyler, TX, USA		
Lorenzo Guglielmetti, MD, PhD	Member	ESCMID	Infectious Diseases	Paris, France		
Gwen A. Huitt, MD	Member	Ad hoc	Infectious Diseases	Denver, CO, USA		
Shandra L. Knight	Medical Librarian	Ad hoc	Systematic reviews	Denver, CO, USA		
Philip Leitman	Patient advocate	Ad hoc	Patient advocacy	Miami, FL, USA		

Theodore K. Marras, MD	Member	ATS	Pulmonologist	Toronto, Canada
Kenneth N. Olivier, MD	Member	ATS	Pulmonologist	Bethesda, MD, USA
Miguel Santin, MD	Member	ESCMID	Infectious Diseases	Barcelona, Spain
Jason E. Stout, MD	Member	IDSA	Infectious Diseases	Durham, NC, USA
Enrico Tortoli, MD	Member	Ad hoc	Microbiologist	Milan, Italy
Jakko van Ingen, MD, PhD	Member	ERS	Microbiologist	Nijmegen, the Netherlands
Dirk Wagner, MD	Member	ERS	Infectious Diseases	Freiburg, Germany
Kevin L. Winthrop, MD	Member	IDSA	Infectious Diseases	Portland, OR, USA

ATS – American Thoracic Society, ERS – European Respiratory Society, ESCMID - European Society of Clinical Microbiology and Infectious Diseases, IDSA - Infectious Diseases Society of America

#### Table E2. Search Strategy

The Medline search was adapted for execution on the Ovid Platform for Embase, Cochrane Central Register of Controlled Trials (CCTR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), and NHS Economic Evaluation Database (NHSEED). Searches for all years were limited to human studies or studies indexed with neither human nor animal; and those published in English or containing an English abstract. A final update was run through July 2018. To supplement the electronic search, reviewers contacted experts and hand searched journals, conference proceedings, reference lists, and regulatory agency Web sites for relevant articles.

#### MEDLINE 1946 to Present with Daily Update

#	Searches
1	mycobacterium infections, nontuberculous/ or mycobacterium infections, atypical/ or mycobacterium avium-intracellulare infection/
2	nontuberculous mycobacteria/ or mycobacterium avium complex/ or mycobacterium kansasii/ or mycobacterium xenopi/
3	(mycobacter\$ adj3 (atypical or kansasi\$ or malmoense or xenopi\$ or ab?cessus or massiliense or bolleti\$ or avium or intracellulare or chim?era)).tw.
4	2 or 3 [mycobacterium terms]
5	(exp Mycobacterium/ or Mycobacterium Infections/) and (MOTT or NTM or MAC or MAIC).tw.
6	(nontubercul\$ or non-tubercul\$).tw.
7	(Lady adj Windermere\$ Syndrome).tw.
8	5 or 6 or 7 [additional concepts]
9	1 or 4 or 8 [Total]
10	1/ 9 lg=en or ab=y [English or English abstract]
11	animals/ not humans/
12	10 not 11
13	(th or tu).xs.
14	12 and 13

### MEDLINE In-Process & Other Non-Indexed Citations

#	Searches
1	(mycobacter\$ adj3 (atypical or kansasi\$ or malmoense or xenop\$ or ab?cessus or massiliense or bolleti\$ or avium or intracellulare or chim?era)).tw.
2	(Mycobacter\$ and (MOTT or NTM or MAC or MAIC)).tw.
3	(nontubercul\$ or non-tubercul\$).tw.
4	1 or 2 or 3

#### Embase 1974 to Present

#	Searches
1	atypical mycobacteriosis/ or Mycobacterium avium complex lung disease/
2	atypical Mycobacterium/ or mycobacterium avium complex/ or mycobacterium kansasii/ or mycobacterium xenopi/ or mycobacterium abscessus/ or "mycobacterium abscessus subsp. bolletii"/
3	(mycobacter\$ adj3 (atypical or kansasi\$ or malmoense xenopi\$ or ab?cessus or massiliense or bolleti\$ or avium or intracellulare or chim?era)).tw.
4	2 or 3 [mycobacterium terms]
5	(exp Mycobacterium/ or mycobacteriosis/) and (MOTT or NTM or MAC or MAIC).tw.
6	(nontubercul\$ or non-tubercul\$).tw.
7	(Lady adj Windermere\$ Syndrome).tw.
8	5 or 6 or 7 [additional concepts]
9	1 or 4 or 8 [Total]
10	l/ 9 lg=en or ab=y [English or English abstract]
11	animal/ not human/
12	10 not 11
13	exp respiratory system/
14	exp thorax/

15	exp respiratory tract disease/
16	exp lung surgery/
17	exp respiratory tract agent/
18	exp respiratory function/
19	or/13-18
20	(lung\$ or pulmon\$ or respirat\$).tw.
21	19 or 20
22	12 and 21
23	random.tw. or clinical trial.mp. or exp health care quality/
24	double-blind.mp. or placebo.tw. or blind.tw.
25	(treat\$ or therap\$).ti.
26	(ad or ae or br or ca or cb or cm or co or ct or dm or dr or dt or ih or im or it or iv or pa or pc or pd or pe or pl or po or sc or si or su or th or to).fs.
27	or/23-26
28	22 and 27

### CCTR, DARE, CLHTA, CLEED

#	Searches
1	(mycobacter\$ adj3 (atypical or kansasi\$ or malmoense or xenop\$ or ab?cessus or massiliense or bolleti\$ or avium or intracellulare or chim?era)).tw.
2	(Mycobacter\$ and (MOTT or NTM or MAC or MAIC)).tw.
3	(nontubercul\$ or non-tubercul\$).tw.
4	1 or 2 or 3
5	remove duplicates from 4

MEDLINE – Medical Literature Analysis and Retrieval System Online

EMBASE – Excerpta Medica Database

CCTR – Cochrane Central Register of Controlled Trials

DARE – Database of Abstracts of Reviews of Effects

CLHTA – Health Technology Assessment

CLEED – National Health Services Economic Evaluation Database

Figure E1. PRISMA diagram of studies included and excluded for pulmonary NTM treatment guideline.

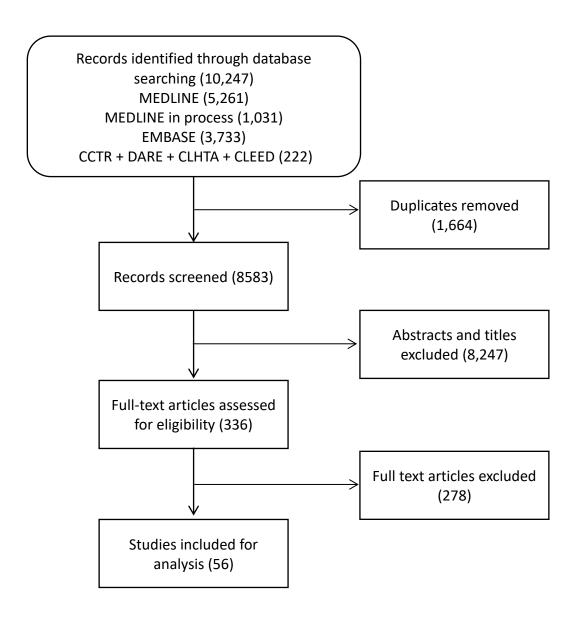


Figure E2: Inclusion and exclusion criteria for full text articles reviewed for pulmonary NTM treatment guideline.

Criteria for exclusion	
Type of publication	ANY of the following
	Review (if systematic review – exclude but keep record of any that you find)
	☐ Editorial
	Letter to editor with no original data
	Case series
	☐ Case report
	Other type of publication (i.e. not a clinical study in humans)
Population	ANY of the following
	Patients without NTM
	Patients with tuberculosis
	Patients with HIV
	Patients with cystic fibrosis
	Pediatric patients
	ANY of the following
	No pharmacological treatment (i.e. no drug used)
	NTM prevention or prophylaxis
Criteria for inclusion (	at least one criterion in each category has to be met)
Study design	Randomized trial
	Observational study with a control group (e.g. cohort, before-after, etc.)
	Retrospective review
Population	Adult patients with NTM

Intervention	ANY of the f	ollowing							
	pharmacological treatment (drug regimen) being the only treatment in ≥1 gr								
	surgical treatment in ≥1 group								
DECISION									
☐ TO BE INCLUDED	)	NOTE: ALL INCLUDED STUDIES WILL NEED TO BE FURTHER SCREENED IF THE REGIMENS USED WERE THE SAME AS THOSE SPECIFIED AS OF INTEREST FOR THESE GUIDELINES.							
FURTHER ACTION	N REQUIRED	What action:							
☐ TO BE EXCLUDED	)								

Additional comments:

# EVIDENCE TABLES (Tables E3.1-22)

Table E3.1. Question 1: Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression ("watchful waiting")?

	Quality assessment						№ of patients			Effect		
№ of studies	Study design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	any treatment	watchful waiting	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	Cure of NTM											
2	observation al studies	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	none	43/71 (60.6%)	8/23 (34.8%)	RR 2.03 (0.44 to 9.30)	358 more per 1,000 (from 195 fewer to 1,000 more)	⊕○○ ○ VERY LOW	CRITICAL
Death										l		
5	observation al studies	serious <sup>1</sup>	not serious	not serious	not serious	none	90/252 (35.7%)	85/186 (45.7%)	<b>RR 0.77</b> (0.64 to 0.92)	105 fewer per 1,000 (from 37 fewer to 165 fewer)	⊕○○ ○ VERY LOW	CRITICAL
Culture Co	onversion											
2	observation al studies	serious <sup>1</sup>	serious <sup>3</sup>	not serious	serious <sup>2</sup>	none	43/75 (57.3%)	47/93 (50.5%)	RR 1.41 (0.50 to 4.02)	207 more per 1,000 (from 253 fewer to 1,000 more)	⊕○○ ○ VERY LOW	CRITICAL
Any adver	rse effect		I	I						-		•

Quality assessment							Nº of p	atients		Effect			
№ of studies	Study design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	any treatment	watchful waiting	Relative (95% CI)	Absolute (95% CI)	Quality	Importance	
2	observation al studies	serious <sup>1</sup>	not serious	not serious	not serious	none	adverse eff	3 out of 100 fects. In neith se effects in to out presumed	⊕○○ ○ VERY LOW	IMPORTANT			
Quality of	Life - not meas	ured											
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Recurrence	ce - not measur	ed											
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Developm	Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	

- Observational studies, risk treatment group had more serious disease
   wide range in confidence interval
   Non overlapping confidence intervals between studies

Table E3.2. Question II: Should patients with NTM pulmonary disease be treated empirically or based on in-vitro drug susceptibility results?

	Quality assessment						<b>№</b> of	patients	Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	empiric treatment	susceptibility- based treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Quality o	f Life - not meas	ured			l	l						
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cure of N	ITM Disease - n	ot reported								ı		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death					l			<b>!</b>	ı		l	
1	observational studies	serious 1	not serious	serious <sup>2</sup>	not serious	none		rt no significant di Ilture-based regim			⊕○○○ VERY LOW	CRITICAL
Developr	nent of antibiotic	resistance	- not measured									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurren	Recurrence - not measured											
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture C	Conversion - not	reported	I			L		1			1	1

			Quality ass	essment			<b>№</b> of	patients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	empiric treatment	susceptibility- based treatment	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

**CI:** Confidence interval

- No randomization, no concealment
   Study used old 1997 ATS criteria

 Table E3.3. Question III: Should macrolide-susceptible MAC pulmonary disease be treated with a three-drug regimen with a macrolide or without a macrolide?

			Quality asse	essment			№ of p	atients	Effe	ect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	three drugs with a macrolide	three drugs without a macrolide	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	İTM											
2	observational studies	not serious	not serious	not serious	serious <sup>a</sup>	none	31/94 (33.0%)	34/96 (35.4%)	<b>RR 0.93</b> (0.62 to 1.37)	25 fewer per 1,000 (from 131 more to 135 fewer)	⊕○○ VERY LOW	CRITICAL
Death												<u>'</u>
1	observational studies	not serious	not serious	not serious	serious <sup>a</sup>	none	40/83 (48.2%)	26/87 (29.9%)	RR 1.61 (1.09 to 2.39)	182 more per 1,000 (from 27 more to 415 more)	⊕○○ VERY LOW	CRITICAL
Recurren	ce (relapse)											
2	observational studies	not serious	not serious	not serious	serious <sup>a</sup>	none	9/94 (9.6%)	10/96 (10.4%)	<b>RR 0.87</b> (0.37 to 2.01)	14 fewer per 1,000 (from 66 fewer to 105 more)	⊕○○○ VERY LOW	CRITICAL
Culture co	onversion											

			Quality asse	essment			<b>№</b> of p	atients	Effe	ect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	three drugs with a macrolide	three drugs without a macrolide	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
2	observational studies	not serious	serious <sup>b</sup>	not serious	serious <sup>a</sup>	none	88/97 (90.7%)	85/100 (85.0%)	<b>RR 0.98</b> (0.67 to 1.43)	17 fewer per 1,000 (from 281 fewer to 365 more)	⊕○○○ VERY LOW	CRITICAL
Any adve	rse effect					L						
1	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none	1/14 (7.1%)	4/13 (30.8%)	RR 0.23 (0.03 to 1.82)	237 fewer per 1,000 (from 252 more to 298 fewer)	⊕⊕○○ LOW	CRITICAL
Serious a	dvere effect					ı						1
1	randomised trials	not serious	not serious	not serious	serious <sup>a</sup>	none	0/14 (0.0%)	0/13 (0.0%)	not estimable		⊕⊕○○ LOW	CRITICAL
Withdraw	ral owing to adve	rse effect										
1	randomised trials	not serious	not serious	not serious	not serious	none	1/14 (7.1%)	2/13 (15.4%)	<b>RR 0.46</b> (0.05 to 4.53)	83 fewer per 1,000 (from 146 fewer to 543 more)	⊕⊕○○ LOW	CRITICAL
Quality of	l f Life - not measu	ıred										<u>I</u>

			Quality asse	essment			Nº of p	atients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	three drugs with a macrolide	three drugs without a macrolide	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Wide confidence interval

b. One study favors w/ macrolide and one favors w/o

**Table E3.4. Question IV**: In patients with newly diagnosed macrolide susceptible MAC pulmonary disease, should an azithromycin-based regimen or a clarithromycin-based regimen be used?

			Quality asse	essment			<b>№</b> of	patients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	azithromycin- based regimen	clarithromycin- based regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Death - r	not reported											
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality o	f life - not meası	ıred		l			1	1				
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture C	Conversion (follo	w up: rang	e 4 to 12 months)									
4	observational studies	serious 1	not serious	not serious	serious <sup>2</sup>	none	131/178 (73.6%)	156/190 (82.1%)	RR 0.88 (0.73 to 1.05)	fewer per 100 (from 4 more to 22 fewer)	⊕○○○ VERY LOW	CRITICAL
Recurrer	nce (relapse) - no	ot measure	ed									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Developr	nent of antibiotio	resistance	e (follow up: range	4 to 12 months	)					I		

			Quality asse	essment			Nº of	patients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	azithromycin- based regimen	clarithromycin- based regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
3	observational studies	serious 1	not serious	not serious	serious <sup>3</sup>	none	4/92 (4.3%)	9/97 (9.3%)	<b>RR 0.51</b> (0.07 to 2.79) <sup>4</sup>	5 fewer per 100 (from 9 fewer to 17 more)	⊕○○○ VERY LOW	CRITICAL
Serious a	adverse effects (	follow up: 4	4 months)									
1	observational studies	serious 1	not serious	not serious	serious <sup>5</sup>	none	0/29 (0.0%)	0/30 (0.0%)	not estimable	0 fewer per 100 (from 60 fewer to 60 more)	⊕○○○ VERY LOW	CRITICAL
Withdraw	val from study du	ue to AEs (	follow up: range 4	to 6 months)		l						
3	observational studies	serious 1	not serious	not serious	serious <sup>6</sup>	none	12/87 (13.8%)	15/104 (14.4%)	<b>RR 1.02</b> (0.45 to 2.07)	0 fewer per 100 (from 8 fewer to 15 more)	⊕○○ VERY LOW	CRITICAL
Any Adve	erse Effect (follo	up: rang	e 4 to 12 months)									

			Quality asse	essment			Nº of p	patients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	azithromycin- based regimen	clarithromycin- based regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
6	observational studies	serious 1	not serious <sup>7</sup>	not serious	serious <sup>8</sup>	none	64/215 (29.8%)	109/268 (40.7%)	RR 0.75 (0.44 to 1.28)	10 fewer per 100 (from 11 more to 23 fewer)	⊕○○○ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

- 1. Studies did not adjust for confounders in the analysis
- 2. Confidence interval does not exclude an appreciable benefit with azithromycin or no difference
- 3. Only 14 events
- 4. Based on unadjusted OR of 0.44 (0.06 to 3.41)
- 5. Only 59 patients
- 6. Only 27 events; Confidence interval does not exclude an appreciable benefit with ether intervention
- 7. There was statistical heterogeneity and CIs of some studies did not overlap; however, if one study hat was an outlier was excluded from analysis it did not change the results (RR 0.94; 95% CI: 0.68 to 1.29)
- 8. Confidence interval does not exclude an appreciable benefit with either intervention

**Table E3.5. Question V**: Should patients with macrolide susceptible MAC pulmonary disease be treated with a parenteral amikacin or streptomycin-containing regimen or without a parenteral amikacin or streptomycin-containing regimen?

			Quality ass	sessment			<b>№</b> of	patients	Ef	fect		
№ of studies	Study design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	a treatment regimen with a parenteral agent	a treatment regimen without a parenteral agent	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	ITM - not mea	sured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death												
1	randomise d trials	not serious	not serious	not serious	serious <sup>3</sup>	none	2/73 (2.7%)	2/73 (2.7%)	RR 1.00 (0.14 to 6.91)	0 fewer per 1,000 (from 24 fewer to 162 more)	⊕⊕⊕○ MODERATE	CRITICAL
Recurren	ce (relapse)						l					
1	randomise d trials	not serious	not serious	not serious	serious	none	16/52 (30.8%)	13/37 (35.1%)	<b>RR 0.88</b> (0.48 to 1.59)	<b>42 fewer per 1,000</b> (from 183 fewer to 207 more)	⊕⊕⊕○ MODERATE	CRITICAL
Culture C	Conversion	1	1	1	1	1	1	1				1

			Quality ass	essment			<b>№</b> of	patients	Ef	fect		
№ of studies	Study design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	a treatment regimen with a parenteral agent	a treatment regimen without a parenteral agent	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	randomise d trials	not serious	not serious	not serious	serious <sup>3</sup>	none	52/73 (71.2%)	37/73 (50.7%)	RR 1.41 (1.07 to 1.84)	208 more per 1,000 (from 35 more to 426 more)	⊕⊕⊕○ MODERATE	CRITICAL
Any adve	erse reaction											
1	randomise d trials	not serious	not serious	not serious	serious <sup>3</sup>	none	18/73 (24.7%)	15/73 (20.5%)	RR 1.20 (0.66 to 2.19)	<b>41 more per 1,000</b> (from 70 fewer to 245 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Serious a	adverse events	<b>,</b>										
1	randomise d trials	not serious	not serious	not serious	not serious	none	0/73 (0.0%)	0/73 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	CRITICAL
Quality o	f life - not mea	sured					l					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

			Quality ass	essment			<b>№</b> of	patients	Ef	fect		
№ of studies	Study design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	a treatment regimen with a parenteral agent	a treatment regimen without a parenteral agent	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Developr	evelopment of antibiotic resistance - not measured											
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

- No control for confounders
   Drug regimens among patients varied widely, both with/without macrolide
   Wide confidence interval

**Table E3.6. Question VI**: In patients with macrolide-susceptible MAC pulmonary disease, should a regimen with inhaled amikacin or a regimen without inhaled amikacin be used for treatment?

			Quality asso	essment			№ of p	atients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with inhaled antibiotics	a regimen without inhaled antibiotics	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	ITM											
1	observational studies	serious <sup>a</sup>	not serious	not serious	not serious	none	3/3 (100.0%)	-	-	-	⊕○○○ VERY LOW	CRITICAL
Death			,		,		,					
2	observational studies	serious <sup>a</sup>	not serious	not serious	not serious	none	2/9 (22.2%)	not pooled	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Recurren	ce (relapse)		l	L	Į.		Į.	l	Į.			l
3	randomised trials	serious	not serious	not serious	not serious	none	9/21 (42.9%)	0/0	not pooled	see comment	⊕⊕⊕○ MODERATE	CRITICAL
Culture C	Conversion											
3	randomised trials	serious <sup>b</sup>	serious <sup>c</sup>	not serious	not serious	none	16/40 (40.0%)	1/28 (3.6%)	not pooled	see comment	⊕⊕○○ LOW	CRITICAL
Any Adve	erse Effect		1	I	1	I	1	l				l

			Quality ass	essment			№ of p	atients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with inhaled antibiotics	a regimen without inhaled antibiotics	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
3	randomised trials	serious <sup>b</sup>	serious <sup>d</sup>	not serious	not serious	none	46/59 (78.0%)	40/45 (88.9%)	not pooled	see comment	⊕⊕○○ LOW	CRITICAL
Serious A	Adverse Effect	<u> </u>	·				·					
3	randomised trials	serious <sup>b</sup>	serious <sup>e</sup>	not serious	not serious	none	8/59 (13.6%)	4/45 (8.9%)	not pooled	see comment	⊕⊕○○ LOW	CRITICAL
Withdraw	val owing to adve	erse effects										
4	randomised trials	serious <sup>b</sup>	serious <sup>f</sup>	not serious	not serious	none	15/79 (19.0%)	0/45 (0.0%)	not pooled	see comment	⊕⊕○○ LOW	CRITICAL
Quality o	f Life											
1	randomised trials	not serious	not serious	serious <sup>9</sup>	not serious	none	Study used Quality of Life - Bronchiectasis - Nontuberculous Mycobacteria Module scores wi significant difference (p-0.204) between the inha antibiotic group (-7.9 [14.2], n=36) and placebo (-2.8 [13.7], n=36).				⊕⊕⊕○ MODERATE	CRITICAL
Developr	ment of Antibiotion	c Resistance	9	ı	ı	I						

			Quality ass	essment		№ of patients		Effect				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with inhaled antibiotics	a regimen without inhaled antibiotics	Relative (95% CI)	Absolute (95% CI)		Importance
1	randomised trials	not serious	not serious	serious <sup>g</sup>	not serious	none	3/44 (6.8%)	2/45 (4.4%)	not estimable		⊕⊕⊕○ MODERATE	CRITICAL

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

- a. Studies were case series without a control group
- b. Included 2 case series without a control group
- c. Conversion with inhaled antibiotics ranged from 30% to 80%
- d. Adverse effects ranged from 30% in case series to over 90% in RCT
- e. Ranged from 0% in case series to nearly 20% in RCT
- f. Ranged from 0% to 35% in inhaled group.
- g. Included both MAC and M abscessus

Table E3.7. Question VII: In patients with macrolide-susceptible MAC pulmonary disease, should a three drug regimen or a two drug regimen be used for treatment?

			Quality asse	essment			№ of p	atients		Effect		Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a three drug regimen	a two trug regimen	Relative (95% CI)	Absolute (95% CI)	Quality	
Culture C	Conversion											
1	randomised trials	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	none	24/59 (40.7%)	33/60 (55.0%)	RR 0.74 (0.50 to 1.09)	143 fewer per 1,000 (from 50 more to 275 fewer)	⊕⊕○○ LOW	CRITICAL
Serious A	Adverse Effects											1
1	randomised trials	serious <sup>1</sup>	not serious	not serious	not serious	none	0/59 (0.0%)	0/60 (0.0%)	not estimable		⊕⊕⊕○ MODERATE	CRITICAL
Withdraw	al owing to adv	erse effect										
1	randomised trials	serious 1	not serious	not serious	serious <sup>2</sup>		22/59 (37.3%)	16/60 (26.7%)	RR 1.40 (0.80 to 2.12)	107 more per 1,000 (from 53 fewer to 299 more)	-	CRITICAL
Quality of	f Life - not meas	sured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cure of N	ITM Disease - r	not measured	d							I		ı

			Quality asse	essment			№ of p	atients		Effect		Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a three drug regimen	a two trug regimen	Relative (95% CI)	Absolute (95% CI)	Quality	
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - n	Death - not reported											
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Developr	ment of antibiotion	c resistance	- not reported									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurren	nce (relapse) - n	ot measured						,				
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

- 1. not blinded, no concealment
- 2. wide confidence interval

**Table E3.8. Question VIII**: In patients with macrolide susceptible MAC pulmonary disease, should a daily or an intermittent macrolide-based regimen be used for treatment?

	Quality assessment							ients	Eff	ect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a three times per week macrolide- based regimen	daily macrolide- based regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance	
Death - r	Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Quality o	Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Cure of N	NTM Disease (fo	llow up: 12 i	months)										
1	observational studies	serious <sup>1</sup>	not serious	not serious <sup>2</sup>	not serious	none	79/118 (66.9%)	75/99 (75.8%)	RR 0.97 (0.72 to 1.14) <sup>3</sup>	2 fewer per 100 (from 11 more to 21 fewer)	⊕○○○ VERY LOW	CRITICAL	
Culture C	Conversion (follo	w up: range	6 to 12 months)										

	Quality assessment							ients	Eff	ect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a three times per week macrolide- based regimen	daily macrolide- based regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
5	observational studies	serious <sup>1</sup>	not serious	not serious <sup>4</sup>	not serious	none	328/413 (79.4%)	136/184 (73.9%)	RR 1.03 (0.93 to 1.14)	2 more per 100 (from 5 fewer to 10 more)	⊕○○○ VERY LOW	CRITICAL
Recurrence (follow up: 12 months; assessed with: microbiological recurrence of two or more positive cultures after an initial negative conversion during antibiotic therapy)												
1	observational studies	serious <sup>1</sup>	not serious	not serious <sup>2</sup>	serious <sup>5</sup>	none	3/82 (3.7%)	1/76 (1.3%)	RR 2.78 (0.30 to 26.16)	2 more per 100 (from 1 fewer to 33 more)	⊕○○○ VERY LOW	CRITICAL
Developr	nent of Antibiotic	Resistance	e (follow up: range	e 6 to 12 months	s)		l					
4	observational studies	serious <sup>1</sup>	not serious	not serious <sup>4</sup>	serious <sup>6</sup>	none	3/146 (2.1%)	10/86 (11.6%)	<b>RR 0.23</b> (0.07 to 0.74)	9 fewer per 100 (from 3 fewer to 11 fewer)	⊕○○○ VERY LOW	CRITICAL
Serious a	adverse effects -	not reported	d									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

	Quality assessment							ients	Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a three times per week macrolide- based regimen	daily macrolide- based regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Discontin	Discontinuation of the initial treatment due to adverse effects (follow up: range 6 to 12 months)											
4	observational studies	not serious <sup>1</sup>	not serious <sup>7</sup>	not serious	serious <sup>8</sup>	none	28/362 (7.7%)	45/202 (22.3%)	<b>RR 0.44</b> (0.09 to 2.16)	12 fewer per 100 (from 20 fewer to 26 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse	Effects (follow up	p: range 6 to	o 12 months)									
4	observational studies	not serious <sup>1</sup>	not serious	not serious	serious <sup>8</sup>	none	66/259 (25.5%)	72/186 (38.7%)	<b>RR 0.63</b> (0.25 to 1.55)	14 fewer per 100 (from 21 more to 29 fewer)	⊕○○○ VERY LOW	IMPORTANT

- 1. Studies did not adjust for confounders in analysis
- 2. None of the patients had cavitary disease which would make the information indirect for that population.
- 3. Based on adjusted OR of 0.891 (0.387 to 2.050)
- Some studies included only patients without cavitary disease and some included both cavitary and non-cavitary but did not report the results separately
   Only 4 events; confidence interval does not exclude an appreciable benefit from either regimen
- 6. Only 13 events
- 7. Im one study a large proportion of patients did not tolerate daily regimen; if this study was excluded from analysis the result would be 0.85 (0.48 to 1.49)
- 8. confidence interval does not exclude an appreciable harm from either regimen

**Table E3.9. Question IX**: In patients with macrolide susceptible MAC pulmonary disease, should patients be treated with less than 12 months of treatment after culture negativity or 12 or more months of treatment after culture negativity?

			Quality asses	ssment			Nº of pa	atients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<12 months of treatment after culture negativity	>/= 12 months of treatment after culture negativity	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Culture c	Culture conversion											
1	observational studies	serious <sup>1</sup>	not serious	serious <sup>2</sup>	not serious	none	6/27 (22.2%)	154/180 (85.6%)	RR 0.26 (0.13 to 0.53)	633 fewer per 1,000 (from 402 fewer to 744 fewer)	⊕○○○ VERY LOW	CRITICAL
Cure of N	ITM disease - no	ot reported										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurren	ce (relapse) - no	ot reported										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality o	f Life - not meas	ured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

			Quality asses	ssment			Nº of pa	atients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<12 months of treatment after culture negativity	>/= 12 months of treatment after culture negativity	Relative (95% CI)	Absolute (95% CI)	Quality	Importance	
Developn	nent of antibiotic	resistance	- not measured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Death - n	ot reported				1			l			l		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Adverse	verse drug effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	

- No control for confounding
   Study compares TID vs daily regimens and this is a secondary analysis of patients unable to tolerate 12 months of therapy for various reasons

**Table E3.10. Question X**: In patients with *M. kansasii* pulmonary disease, should an isoniazid-containing regimen or a macrolide-containing regimen be used for treatment?

			Quality as	sessment			Nº of p	patients	Effe	et		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a INH- containing regimen	a macrolide- contaning regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	NTM - not n	neasured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - r	not measure	ed										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Developr	ment of ant	ibiotic resistar	nce – not measure	ed								
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality o	f life - not n	neasured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture o	conversion -	not measure	ed		1							_
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse	drug effects	s - not measu	red									

			Quality as	sessment			<b>№</b> of p	atients	Effec	et			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a INH- containing regimen	a macrolide- contaning regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance	
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Recurren	Recurrence (relapse) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	

**Table E3.11. Question XI**: In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should amikacin or streptomycin be included in the treatment regimen?

			Quality ass	essment			Nº of p	atients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a treatment regimen with a parenteral agent	a treatment regimen without a parenteral agent	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	NTM											
1	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	8/10 (80.0%)	-	-	-	⊕○○○ VERY LOW	CRITICAL
Death												
2	observational studies	serious 1	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	30/121 (24.8%)	not pooled	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Recurren	nce (relapse)											
2	observational studies	serious <sup>1</sup>	not serious	not serious	< not serious	publication bias strongly suspected <sup>2</sup>	6/115 (5.2%)	not pooled	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Culture C	Conversion		<u>'</u>		-		-			<b>!</b>		

			Quality ass	essment			№ of p	atients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a treatment regimen with a parenteral agent	a treatment regimen without a parenteral agent	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
2	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	42/44 (95.5%)	not pooled	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Any adve	erse effect	l	l		l		l					
1	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	11/75 (14.7%)	-	-	-	⊕○○○ VERY LOW	CRITICAL
Serious A	Adverse Effect											
1	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	0/75 (0.0%)	-	-	-	⊕○○○ VERY LOW	CRITICAL
Withdraw	val owing to adve	erse effects										
1	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	7/75 (9.3%)	-	-	-	⊕○○○ VERY LOW	CRITICAL
Quality o	f Life - not meas	ured										

			Quality asse	essment			№ of p	atients	Effe	ct			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a treatment regimen with a parenteral agent	a treatment regimen without a parenteral agent	Relative (95% CI)	Absolute (95% CI)	Quality	Importance	
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Developr	evelopment of Antibiotic Resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

- Case series, no control group
   Based on case series data. There are likely unpublished case series not included in the analysis.

**Table E3.12. Question XII**: In patients with rifampicin susceptible *M. kansasii* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?

			Quality a	ssessment			Nº of p	atients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with a fluoroquinolone	a regimen without a fluoroquinolone	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	NTM Dise	ase - not me	asured									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Developr	nent of ar	ntibiotic resis	tance - not meas	ured				,				
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurrer	nce (relap	se) - not mea	asured					,				
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality o	f Life - no	t measured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture C	Conversio	n - not meas	ured									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - r	not measu	ired								•		

			Quality a	ssessment			Nº of p	atients	Effe	ct			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	CONCIDENTIANS	a regimen with a fluoroquinolone	a regimen without a fluoroquinolone	Relative (95% CI)	Absolute (95% CI)	Quality	Importance	
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	
Adverse	dverse drug effects - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	

CI: Confidence interval; OR: Odds ratio

Table E3.13. Question XIII: In patients with rifampicin susceptible M. kansasii pulmonary disease, should a three times per week or daily treatment regimen be used?

			Quality asse	essment			№ of p	atients	Effe	ect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a three times per week treatment regimen	a daily treatment regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	ITM											
2	observational studies	serious <sup>1</sup>	serious <sup>2</sup>	not serious	not serious	publication bias strongly suspected <sup>3</sup>	0/0	115/182 (63.2%)	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Death			<b>!</b>	l	l		l	l	l			
3	observational studies	serious <sup>3</sup>	serious <sup>2</sup>	not serious	not serious	publication bias strongly suspected <sup>3</sup>	0/18 (0.0%)	39/229 (17.0%)	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Recurren	ice (relapse)					l						
3	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>3</sup>	0/14 (0.0%)	16/178 (9.0%)	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Culture C	Conversion											
4	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>3</sup>	17/18 (94.4%)	238/257 (92.6%)	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL

			Quality asse	essment			№ of p	atients	Effe	ect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a three times per week treatment regimen	a daily treatment regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Any Adve	erse Effect											
1	observational studies	serious 1	not serious	not serious	not serious	publication bias strongly suspected <sup>3</sup>	0/18 (0.0%)	0/0	not estimable		⊕○○○ VERY LOW	CRITICAL
Serious a	adverse effects											
2	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>3</sup>	0/18 (0.0%)	0/28 (0.0%)	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Withdraw	val owing to adve	erse effects										
2	observational studies	serious <sup>1</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>3</sup>	0/18 (0.0%)	0/28 (0.0%)	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Quality o	f Life - not meas	ured		1	1			1				
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

			Quality asse	essment			Nº of p	atients	Effe	ect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a three times per week treatment regimen	a daily treatment regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance	
Developr	evelopment of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL	

- Case series, no control groups
   Wide variation between studies
- 3. Data based on case series. There are likely unpublished case series that were not included.

**Table E3.14. Question XIV**: In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should treatment be continued for less than 12 months or 12 or more months?

			Quality ass	sessment			Nº of p	atients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<12 months of treatment after culture negativity	>/= 12 months of treatment after culture negativity	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	ITM											
1	randomised trials	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	none	14/14 (100.0%)	14/14 (100.0%)	RR 1.00 (0.88 to 1.14)	0 fewer per 1,000 (from 120 fewer to 140 more)	⊕⊕○○ LOW	CRITICAL
Recurren	се											
1	randomised trials	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	none	1/14 (7.1%)	0/14 (0.0%)	<b>RR 3.00</b> (0.13 to 67.91)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	CRITICAL
Culture C	Conversion											

			Quality ass	essment			Nº of p	atients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<12 months of treatment after culture negativity	>/= 12 months of treatment after culture negativity	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	randomised trials	serious 1	not serious	not serious	serious <sup>2</sup>	none	14/14 (100.0%)	14/14 (100.0%)	RR 1.00 (0.88 to 1.14)	0 fewer per 1,000 (from 120 fewer to 140 more)	⊕⊕⊖⊖ LOW	CRITICAL
Quality of	f Life - not mea	ısured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Developn	nent of Antibio	tic Resistand	ce - not measured	j			l					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - n	not reported											•
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse I	Drug Effects - ı	not reported										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

- No blinding, unclear concealment
   Few events

**Table E3.15. Question XV**: In patients with *M. xenopi* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?

			Quality ass	sessment			Nº o	f patients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a quinolone containing regimen	regimen without a fluoroquinolone	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Death (fo	llow up: 5 year	rs)										
1	randomised trials	serious 1	not serious	not serious	serious <sup>2</sup>	none	8/17 (47.1%)	5/17 (29.4%)	<b>RR 1.60</b> (0.66 to 3.91)	18 more per 100 (from 10 fewer to 86 more)	⊕⊕⊖⊖ LOW	CRITICAL
Quality of	f life - not mea	sured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cure of N	ITM disease (f	ollow up: 5	years)									
1	randomised trials	serious 1	not serious	not serious	serious <sup>2</sup>	none	6/17 (35.3%)	6/17 (35.3%)	RR 1.00 (0.40 to 2.48)	0 fewer per 100 (from 21 fewer to 52 more)	⊕⊕⊖⊖ LOW	CRITICAL

			Quality ass	sessment			<b>N</b> º of	f patients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a quinolone containing regimen	regimen without a fluoroquinolone	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	randomised trials	serious 1	not serious	not serious	serious <sup>3</sup>	none	0/17 (0.0%)	2/17 (11.8%)	RR 0.20 (0.01 to 3.88)	9 fewer per 100 (from 12 fewer to 34 more)	⊕⊕○○ LOW	CRITICAL
Culture o	onversion - no	t reported	l	l	l							
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Developr	ment of antibiot	ic resistanc	ce - not measured									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Severe a	vere adverse effects - not reported											
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Any adve	erse effects (fol	low up: 2 y	ears)									

			Quality ass	sessment			<b>N</b> º of	f patients	Effe	ct		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a quinolone containing regimen	regimen without a fluoroquinolone	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	randomised trials	serious 1	not serious	serious <sup>4</sup>	serious <sup>5</sup>	none	38/185 (20.5%)	37/186 (19.9%)	<b>RR 1.03</b> (0.69 to 1.55)	1 more per 100 (from 6 fewer to 11 more)	⊕○○○ VERY LOW	CRITICAL

- Participants and investigators were not blinded
   Only 13 events; CI does not exclude an appreciable benefit with either intervention
   Only 2 events and 34 patients in total
   AEs were not reported separately for M. xenopi
   Only 75 events and CI does not exclude appreciable benefit with either intervention

Table E3.16. Question XVI: In patients with *M. xenopi* pulmonary disease, should a two, three or four-drug regimen be used for treatment?

			Quality asse	essment			№ of p	oatients		Effect		
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	a two drug regimen	a three drug regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Death (fo	ollow up: 5 yea	rs)	l	l	l			l				
1	randomise d trials	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	none	11/22 (50.0%)	13/20 (65.0%)	RR 0.77 (0.45 to 1.30)	150 fewer per 1,000 (from 195 more to 358 fewer)	⊕⊕○ ○ Low	CRITICAL
Cure of N	NTM											
1	randomise d trials	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	none	5/22 (22.7%)	2/20 (10.0%)	RR 2.27 (0.50 to 10.43)	127 more per 1,000 (from 50 fewer to 943 more)	⊕⊕○ ○ Low	CRITICAL
Recurrer	nce											
1	randomise d trials	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	none	2/22 (9.1%)	0/20 (0.0%)	RR 4.57 (0.23 to 89.72)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○ ○ Low	CRITICAL
Quality o	f Life - not mea	asured	1	ı	l	! 	l	·				
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

			Quality asse	essment			Nº of p	oatients		Effect				
№ of studie s	Study design	Risk of bias	Inconsistenc y	Indirectness	Imprecision	Other considerations	a two drug regimen	a three drug regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance		
Developr	evelopment of antibiotic resistance - not measured													
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL		
Culture C	Culture Conversion - not reported													
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL		

- No blinding, unclear if properly randomized/concealed
   Wide confidence interval, small number of events

Table E3.17. Question XVII: In patients with M. xenopi pulmonary disease, should amikacin or streptomycin be included in the treatment regimen?

			Quality asse	essment			Nº c	of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parenteral	no parenteral agent	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of NTM	1 disease - not	measured										
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Death - not r	measured											
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Recurrence	(relapse) - not i	neasured										
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Quality of life	e - not measure	d										
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Culture conv	version - not me	asured										
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Adverse drug	g effects - not r	neasured		l	1							1
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL

			Quality asse	essment			Nº c	of patients		Effect		
№ of studies	Study design	bias Inconsistency Indirectness Imprecision consider		Other considerations	Parenteral	no narontoral	Relative (95% CI)	Absolute (95% CI)	Quality	Importance		
Development	t of antibiotic re	esistance - no	ot measured									
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL

CI: Confidence interval

**Table E3.18. Question XVIII**: In patients with *M. xenopi* pulmonary disease, should treatment be continued for less than 12 months or 12 or more months after culture conversion?

			Quality asses	ssment			№ of p	atients	E	Effect		
№ of studie s	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<12 months of treatment after culture negativity	>/= 12 months of treatment after culture negativity	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	NTM			,								
2	observational studies	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	none	6/27 (22.2%)	13/27 (48.1%)	RR 0.54 (0.26 to 1.13)	221 fewer per 1,000 (from 63 more to 356 fewer)	⊕○○○ VERY LOW	CRITICAL
Recurrer	nce											
2	observational studies	serious 1	not serious	serious <sup>2</sup>	serious <sup>3</sup>	none	6/27 (22.2%)	10/27 (37.0%)	RR 0.58 (0.26 to 1.30)	156 fewer per 1,000 (from 111 more to 274 fewer)	⊕○○○ VERY LOW	CRITICAL
Culture of	conversion				1				·			

			Quality asses	ssment			№ of p	atients	E	Effect		
№ of studie s	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	<12 months     of     treatment     after     culture     negativity	>/= 12 months of treatment after culture negativity	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	observational studies	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	none	2/4 (50.0%)	4/7 (57.1%)	RR 0.88 (0.27 to 2.82)	69 fewer per 1,000 (from 417 fewer to 1,000 more)	⊕○○○ VERY LOW	CRITICAL
Quality o	f life - not meası	ıred										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Develop	nent of antibiotic	resistance	- not measured	Į.	Į.	L	L					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - r	not reported		Į.	Į.	l	L	L					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse	drug effects - no	t reported										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

- No control for confounding
   Not a direct comparison
   Wide confidence interval

Table E3.19. Question XIX: In patients with Mycobacterium abscessus pulmonary disease, should a macrolide-based regimen or a regimen without a macrolide be used for treatment?

			Quality asse	ssment			Nº of pa	tients	E	Effect		
№ of studie s	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a macrolide- containing regimen	a non- macrolide containing regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	ITM											
2	observational studies	serious <sup>1</sup>	Not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	48/75 (64.0%)	3/7 (42.9%)	<b>RR 2.18</b> (0.98 to 4.84)	506 more per 1,000 (from 9 fewer to 1,000 more)	⊕○○ ○ VERY LOW	CRITICAL
Death								,				
1	observational studies	serious <sup>3</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	2/65 (3.1%)	-	-	-	⊕○○ ○ VERY LOW	CRITICAL
Recurren	ce (Relapse)							,				
1	observational studies	serious <sup>3</sup>	not serious	not seririous	not serious	publication bias strongly suspected <sup>2</sup>	9/47 (19.1%)	-	-	-	⊕○○ ○ VERY LOW	CRITICAL
Culture C	Conversion											

			Quality asse	ssment			Nº of pa	tients	E	ffect		
№ of studie s	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a macrolide- containing regimen	a non- macrolide containing regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	observational studies	serious <sup>3</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	47/65 (72.3%)	-	-	-	⊕○○ ○ VERY LOW	CRITICAL
Any adve	erse effect											
1	observational studies	serious <sup>3</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	14/65 (21.5%)	-	-	-	⊕○○ ○ VERY LOW	CRITICAL
Withdrav	val owing to adve	erse effect										
1	observational studies	serious <sup>3</sup>	not serious	not serious	not serious	publication bias strongly suspected <sup>2</sup>	6/65 (9.2%)	-	-	-	ФОО О VERY LOW	CRITICAL
Develop	ment of antibiotic	resistance	- not measured									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality o	f life - not meası	ured										

			Quality asse	ssment			№ of pa	tients	E	ffect		
№ of studie s	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a macrolide- containing regimen	a non- macrolide containing regimen	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

- No control for confounding
   Data limited to case series and likely that there have been unpublished case series not captured
   No control group

Table E3.20. Question XX: How many antibiotics should be included within multidrug regimens for treatment of Mycobacterium abscessus pulmonary infection

			Quality asse	essment			Nº of p	patients	Eff	ect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	two drugs	three vs. four drugs	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	ITM disease (fol	low up: med	lian 445 days)									
1	observational studies	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious	none	13/17 (76.5%)	20/24 (83.3%)	RR 0.92 (0.67 to 1.26)	67 fewer per 1000 (from 217 more to 275 fewer)	⊕○○○ VERY LOW	CRITICAL
Recurren	ice (relapse) (fol	low up: med	lian 445 days)									
1	observational studies	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	none	3/13 (23.1%)	1/20 (5.0%)	RR 4.62 (0.54 to 39.73)	181 more per 1000 (from 23 fewer to 1000 more) <sup>2</sup>	⊕○○○ VERY LOW	CRITICAL
Any adve	erse effect (follov	v up: mediar	1 445 days)									
1	observational studies	serious 1	not serious	serious <sup>2</sup>	serious <sup>3</sup>	none	3/17 (17.6%)	15/24 (62.5%)	RR 0.28 (0.10 to 0.83)	450 fewer per 1000 (from 106 fewer to 563 fewer)	⊕○○○ VERY LOW	CRITICAL
Culture o	onversion									15.151)		

			Quality asse	essment			№ of p	atients	Effe	ect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	two drugs	three vs. four drugs	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
1	observational studies	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	none	two groups,		nificant difference rted a p-value of (		⊕○○○ VERY LOW	CRITICAL
Quality o	f Life - not meas	ured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Developr	ment of antibiotic	resistance	- not measured									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - r	ot reported						,					
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

- Observational study without blinding, randomization
   Unclear subspecies of M abscessus
   large range in confidence interval, few events

 Table E3.21. Question XXI:
 In patients with Mycobacterium abscessus pulmonary disease, should shorter or longer duration of therapy be used for treatment?

			Quality asses	ssment			Nº of p	patients	Ef	ffect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter therapy duration	longer therapy duration	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	ITM											
1	observational studies	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	none	9/13 (69.2%)	4/4 (100.0%)	RR 0.75 (0.47 to 1.20)	250 fewer per 1,000 (from 200 more to 530 fewer)	⊕○○ VERY LOW	CRITICAL
Recurren	ce (relapse) - no	ot measured	1									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture c	onversion - not r	reported	ļ	L	l			Į.	l		ļ.	
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of	f life - not measu	ıred										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Developn	nent of antibiotic	resistance	- not measured									
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

			Quality asses	ssment			<b>№</b> of p	atients	Ef	fect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter therapy duration	longer therapy duration	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Death - n	ot reported											
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse	drug effects - no	t reported										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

- No control for confounding
   Not a direct comparison, various regimens and course length
   Wide confidence interval

Table E3.22. Question XXII: Should surgery plus medical therapy or medical therapy alone be used to treat NTM pulmonary disease?

			Quality asse	ssment			<b>№</b> of p	atients	Effe	ect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	medical therapy	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Cure of N	NTM											
1	observational studies	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	none	13/23 (56.5%)	13/46 (28.3%)	not estimable		⊕○○○ VERY LOW	CRITICAL
Death												
10	observational studies	serious <sup>3</sup>	not serious	not serious	serious <sup>2</sup>	publication bias strongly suspected <sup>4</sup>	20/486 (4.1%)	13/83 (15.7%)	not estimable		⊕○○○ VERY LOW	CRITICAL
Recurrer	ice					L						
9	observational studies	serious	not serious	not serious	serious <sup>2</sup>	publication bias strongly suspected <sup>4</sup>	22/391 (5.6%)	12/102 (11.8%)	not estimable		⊕○○○ VERY LOW	CRITICAL
Culture o	conversion											
10	observational studies	serious 1,3,5	not serious	not serious	serious <sup>2</sup>	publication bias strongly suspected <sup>4</sup>	283/331 (85.5%)	18/46 (39.1%)	not estimable		⊕○○○ VERY LOW	CRITICAL
Surgical	Complication	l										

			Quality asse	ssment			Nº of p	atients	Effe	ect		_
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	medical therapy	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
9	observational studies	serious 1,3	not serious	not serious	not serious	publication bias strongly suspected <sup>4</sup>	111/563 (19.7%)	0/0	not pooled	see comment	⊕○○○ VERY LOW	CRITICAL
Quality o	f Life - not meas	ured										
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

- No control for confounding
   wide confidence interval
- 3. case series, no control group

Evidence to Decision Tables (E4.1-22)

# **Table E4.1. Question I**

Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression ("watchful waiting")?

**POPULATION:** treatment of NTM pulmonary infection

**INTERVENTION:** any treatment

**COMPARISON:** watchful waiting

MAIN OUTCOMES: Cure of NTM; Death; Culture Conversion; Any adverse effect; Quality of Life; Recurrence; Development of antibiotic resistance;

### **Assessment**

	JUDGEMENT		RESEARCH EVI	DENCE			ADDITIONAL CONSIDERATIONS
EFFECTS	How substantial are the desirable anticipated effects?	Any treatment com	npared to watchful waiting for NTM pul	monary infe	ection		
DESIRABLE EF	<ul><li>Small</li><li>Moderate</li><li>Large</li></ul>	Outcomes	Anticipated absolute effects (95% CI)	Relative effect	№ of participants (studies)	Quality of the evidence	
DES	<ul><li>∨ Varies</li><li>o Don't know</li></ul>						

	How substantial are the						
	undesirable anticipated effects?		Risk with waiting	Risk with any treatment	(95% CI)		(GRADE)
	<ul><li>Large</li><li>Moderate</li><li>Small</li><li>Trivial</li></ul>	Cure of NTM	348 per 1000	<b>706 per 1000</b> (153 to 1000)	<b>RR 2.03</b> (0.44 to 9.30)	94 (2 observational studies)	⊕○○○ VERY LOW <sup>1,2</sup>
	<ul><li>∨ Varies</li><li>o Don't know</li></ul>	Death	457 per 1000	<b>352 per 1000</b> (292 to 420)	<b>RR 0.77</b> (0.64 to 0.92)	438 (5 observational studies)	⊕○○○ VERY LOW <sup>1,3</sup>
EFFECTS		Culture Conversion	505 per 1000	<b>713 per 1000</b> (253 to 1000)	<b>RR 1.41</b> (0.50 to 4.02)	168 (2 observational studies)	⊕○○○ VERY LOW 1,2,4
UNDESIRABLE E		Any adverse effect	A total of 43 out of a treatment group had neither study was it were any adverse ef waiting group (of 67 presumably there we	d adverse effects. In specified if there fects in the watchful patients), but		167 (2 observational studies)	⊕○○○ VERY LOW <sup>1</sup>
		Quality of Life - not measured	-	-	-	-	-
		Recurrence - not measured	-	-	-	-	-
		Development of antibiotic resistance - not measured	-	-	-	-	-
<b>8</b>	What is the overall certainty of the evidence of effects?	The relative impo	rtance or values	of the main outc	omes of ir	nterest:	
EVIDENCE	• Very low	Outo	come	Relative import	ance C	ertainty of the evic	lence (GRADE)
PO	<ul><li>Low</li><li>Moderate</li><li>High</li></ul>	Cure of NTM		CRITICAL	⊕○ VER	OO Y LOW	
CERTAINTY	No included studies	Death		CRITICAL		OO Y LOW	

		T.						
		Culture Conversion		CRITICAL	⊕○○○ VERY LOW			
		Quality of Life		CRITICAL	-			
		Recurrence		CRITICAL	-			
		Development of an	tibiotic resistance	CRITICAL	-			
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • No important uncertainty or variability	this study, patient two QOL measure association betwe Hong, et al, 2014 was a direct comp with NTM reported	a, 2011 evaluated the interpretate with pulmonary NTM is significantly lower that en QOL scores and lungualso evaluated the important of the parison between patient in more health status is also independently as:	had significantly imp an historical normal co g function. hact of pulmonary NTM is with NTM disease a sues and anxiety/dep	aired health-rontrols. Multiv M on health-reind healthy su ression issues	elated quality of ariable analysic elated quality of bjects and four	of life with s showed an f life. This and patients	The is no definitive evidence. The cited studies are only on quality of life and do not compare the outcome with or without treatment. The decision for treatment is often dependent on clinical symptoms and the more severe patients in term of symptoms will probably benefit most from treatment.
	Does the balance between desirable and undesirable effects favor the intervention or the							
EFFECTS	comparison?	Any treatment co	mpared to watchful wai	ting for NTM pulmona	ry infection			
	o Favors the comparison	Outcomes	Anticipated absolute 6	effects* (95% CI)	Relative	№ of	Quality of	
BALANCE OF	<ul> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> </ul>		Risk with watchful waiting	Risk with any treatment	effect (95% CI)	participants (studies)	the evidence (GRADE)	
BAL	<ul><li>Probably favors the intervention</li><li>Favors the intervention</li><li>Varies</li></ul>	Cure of NTM	348 per 1000	<b>706 per 1000</b> (153 to 1000)	<b>RR 2.03</b> (0.44 to 9.30)		⊕○○○ VERY LOW	

	○ Don't know							
	O DOIL KNOW					studies)	1,2	
		Death	457 per 1000	<b>352 per 1000</b> (292 to 420)	<b>RR 0.77</b> (0.64 to 0.92)	438 (5 observational studies)	⊕○○○ VERY LOW	
		Culture Conversion	505 per 1000	<b>713 per 1000</b> (253 to 1000)	<b>RR 1.41</b> (0.50 to 4.02)	168 (2 observational studies)	⊕○○○ VERY LOW 1,2,4	
		Any adverse effect	A total of 43 out of 100 pa group had adverse effects specified if there were any watchful waiting group (o presumedly there were no	In neither study was it adverse effects in the f67 patients), but		167 (2 observational studies)	⊕○○○ VERY LOW	
		Quality of Life - not measured	-	-	-	-	-	
		Recurrence - not measured	-	-	-	-	-	
		Development of antibiotic resistance - not measured	-	-	-	-		
NED NED	How large are the resource requirements (costs)?	No research evider	nce was identified.					
RESOURCES REQUIRED	<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> </ul>							
RES	<ul><li> Varies</li><li> Don't know</li></ul>							

COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention  • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Reduced Probably reduced Probably no impact Probably increased Increased  Varies Don't know	No research evidence was identified.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?  O No O Probably no Probably yes Yes Varies Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement?  No Probably no Probably yes Yes  Varies Don't know	No research evidence was identified.	

				JUDGEMENT				IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

				JUDGEMENT			IMPLICATIONS
FEASIBILITY	No	Probably no	Probably yes	Yes	Varies	Don't know	

Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression ("watchful waiting")?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
RECOMMENDATION	In patients who meet the waiting, especially in the crecommendation, very low	context of positive acid-fa	st bacilli sputum smears a		

	The expert panel voted unanimously for a conditional recommendation for the intervention.
JUSTIFICATION	For those who have a positive acid-fast smear and/or cavitary disease, there may be increased rate of progression and poor treatment outcomes if treatment is delayed.
SUBGROUP CONSIDERATIONS	Some subgroups (minimal nodular/bronchiectatic disease) may be safely followed without therapy but those with cavitary disease should not be followed expectantly.  In very frail patients with very mild nodular-bronchiectatic disease, the balance between efficacy and tolerability may favor watchful waiting.
IMPLEMENTATION CONSIDERATIONS	
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Research is needed to better determine the criteria for treatment according to risk factors (age, sex, comorbidities, respiratory function score, etc) in less pathogenic organisms.

# **Table E4.2. Question II**

Should patients with NTM pulmonary disease be treated empirically or based on in vitro drug susceptibility test results?

**POPULATION:** NTM pulmonary infection

**INTERVENTION:** empiric treatment

**COMPARISON:** susceptibility-based treatment

MAIN OUTCOMES: Quality of Life; Cure of NTM Disease; Death; Development of antibiotic resistance; Recurrence; Culture Conversion;

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<u> </u>	How substantial are the desirable		The one identified study for this

	anticipated effects?  ○ Trivial		Empiric treatment compared to susceptibility-based treatment for NTM pulmonary infection						question was felt to be only indirectly related and not useful evidence upon which to base a recommendation. Additionally, it was felt that the
	<ul> <li>Small</li> <li>Moderate</li> <li>Large</li> <li>Varies</li> <li>Don't know</li> </ul>		Outcomes	Anticipated absolution (95% CI)	ute effects*	Relative effect	№ of participants	Quality of the	methods of performing susceptibility testing were outdated and not relevant to current practice.
			Risk with susceptibility- based treatment	Risk with empiric treatment	(95% CI)	(studies)	evidence (GRADE)	The utility of <i>in vitro</i> drug susceptibility testing is entirely dependent on the NTM species being treated and the drugs being tested.	
		How substantial are the undesirable anticipated effects?	Quality of Life - not measured	-	-	-	-	-	The results of standardized and validated drug susceptibility testing are useful for guiding treatment, in
	0 !	<ul><li>Large</li><li>Moderate</li><li>Small</li><li>Trivial</li></ul>	Cure of NTM Disease - not reported	-	-	-	-	-	particular for drugs where there has been a correlation between <i>in vitro</i> activity and treatment outcome, e.g. macrolides, amikacin.
	EFFECTS	<ul><li> ∨ Varies</li><li> Don't know</li></ul>	Death	Authors report no si difference between culture-based regim 75%)	empiric vs		(1 observational study)	⊕○○○ VERY LOW <sup>1,2,3</sup>	
	UNDESIRABLE		Development of antibiotic resistance - not measured	-	-	-	-	-	
			Recurrence - not measured	-	-	-	-	-	
			Culture Conversion - not reported	-	-	-	-	-	

What is the overall certainty of the evidence of effects?	The relative importance or	values of the mai	n outcomes of interest:
• Very low • Low	Outcome	Relative importance	Certainty of the evidence (GRADE)
○ Moderate ○ High ○ No included studies	Quality of Life	CRITICAL	(not measured)
No included studies	Cure of NTM Disease	CRITICAL	(not measured)
	Death	CRITICAL	⊕○○○ VERY LOW
CEKIAIN	Development of antibiotic resistance	CRITICAL	(not measured)
	Recurrence	CRITICAL	(not measured)
	Culture Conversion	CRITICAL	(not measured)
Is there important uncertainty about of variability in how much people value the main outcomes?  Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability No important uncertainty or variability	Three relevant studies were id preferences:  Mehta and Marras, 2011 evaluated quality of life. In this simpaired health-related quality than historical normal controls between QOL scores and lung.  Hong, et al, 2014 also evaluate quality of life. This was a direct and healthy subjects and foun issues and anxiety/depression also independently associated.  Czaja, et al 2015 evaluated che treatment regimens for <i>M. abs</i>	tated the impact of tudy, patients with y of life with two QCs. Multivariable analyfunction  ed the impact of put comparison between differents with NTM issues than healthy with QOL scores.	pulmonary NTM on health- pulmonary NTM had significantly DL measures significantly lower ysis showed an association  Imonary NTM on health-related een patients with NTM disease I reported more health status y controls. Lung function was

# Does the balance between desirable and undesirable effects favor the intervention or the comparison?

- Favors the comparison
- o Probably favors the comparison
- $\circ$  Does not favor either the intervention or the comparison
- o Probably favors the intervention
- o Favors the intervention
- Varies
- Don't know

# Empiric treatment compared to susceptibility-based treatment for NTM pulmonary infection

Outcomes	Anticipated absolution (95% CI)  Risk with susceptibility-based treatment	Risk with empiric	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Quality of Life - not measured	-	-	-	-	-
Cure of NTM Disease - not reported	-	-	-	-	-
Death	difference between	Authors report no significant difference between empiric vs culture-based regimens (80 vs 75%)		(1 observational study)	⊕○○○ VERY LOW <sup>1,2,3</sup>
Development of antibiotic resistance - not measured	-	-	-	-	-
Recurrence - not measured	-	-	-	-	-
Culture Conversion - not reported	-	-	-	-	-

There are other studies such as those by Jenkins, et al (Resp Med 2003) referenced in the Andrejak paper that measured outcomes of interest for two different treatment regimens for M. xenopi and looked to see whether outcomes were different based on resistance patterns on in vitro susceptibility tests (in this study they were not for the 29/40 patients who had the tests performed). In the observational study of *M. abscessus* treatment results by Jeon, et al (Am J Respir Crit Care Med 2009), the authors compared microbiologic response based on results of in vitro susceptibility testing and found a significant correlation for clarithromycin but not for the other antibiotics tested. The study by Kobashi, et al (J Infect Chemother 2006) showed similar findings for patients with M. avium complex disease with good correlation between clarithromycin susceptibility and clinical outcomes and no correlation for the other tested drugs. While these studies don't look at treatment modified based on in vitro susceptibility tests, they do provide some insight into this question.

			1
Ω	How large are the resource requirements (costs)?	No data available.	
RESOURCES REQUIRED	<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> </ul>		
SOUR	Large savings		
R.	Varies Don't know		
SS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No data available.	
COST EFFECTIVENESS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> </ul>		
COST EF	<ul><li>Probably favors the intervention</li><li>Favors the intervention</li></ul>		
	Varies     No included studies		
	What would be the impact on health equity?	No data available.	
EQUITY	<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>		
	I - Incusped	f 1	1

		Varies Don't know		
ACCEPTABILITY	sta	the intervention acceptable to key takeholders?  No Probably no Probably yes Yes  Varies Don't know	No data available.	
FEASTR11 1TV		s the intervention feasible to inplement?  No Probably no Probably yes Yes  Varies Don't know	A study by Adjemian, et al in 2014 evaluated treatment of <i>M. abscessus</i> and MAC, looking at compliance with the 2007 ATS/IDSA guidelines. This study found poor adherence with only 13% of antibiotic regimens compliant with guidelines. Of prescribed regimens for MAC, only 44% contained a macrolide, while 36% of regimens for <i>M. abscessus</i> contained a macrolide.	

		IMPLICATIONS						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

# Should patients with NTM pulmonary disease be treated empirically or based on *in vitro* drug susceptibility test results?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention or the comparison o									
RECOMMENDATION	recommendation, very low	In patients with MAC pulmonary disease, we suggest susceptibility-based treatment for macrolides and amikacin (conditional recommendation, very low confidence in estimates of effect).  In patients with <i>M. kansasii</i> pulmonary disease, we suggest susceptibility-based treatment for rifampicin (conditional								
	or against susceptibility-b	<i>i</i> pulmonary disease, the o	committee feels there is in							
	(conditional recommendal sequencing of the erm(41 recommend testing of oth recommendations in this in	tion, very low confidence i ) gene should be performer er drugs in order to guide regard.	n estimates of effect). For ed to evaluate for potentia <i>M. abscessus</i> therapy the	r macrolides, a 14-day inc al inducible macrolide resi ere is insufficient data to r	ubation and/or stance. While we nake specific					
	The panel members voted and <i>M. abscessus</i> . The pa	d unanimously for a condit nel members also voted u	ional recommendation for nanimously for no recomr	the intervention with regmendation for <i>M. xenopi</i> .	ards to MAC <i>M. kansasii</i> ,					
JUSTIFICATION		of poor outcomes in case ed <i>in vitro</i> activity with an			ence from randomized					
	Although <i>in vitro-in vivo</i> correlations have not yet been proven for all major antimycobacterial drugs and some drugs are in regimens for synergy rather than efficacy, baseline susceptibility testing is recommended according to the CLSI guidelines for NTM isolates from patients with definite disease.									
SUBGROUP CONSIDERATIONS										
IMPLEMENTATION CONSIDERATIONS		nce may be scarce, there i ut, AST may not be require cies /subspecies specific ch	ed if proper species /subs	pecies identification is don	e, as drug susceptibility					

	significant drug heterogeneity, e.g. tetracyclines and <i>M. abscessus</i> subsp. <i>abscessus</i> and <i>M. fortuitum</i> . The molecular basis for this intra-species heterogeneity is not known yet.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Quality clinical trials of fixed vs susceptibility-guided regimens for different species of NTM.

### Should macrolide-susceptible MAC pulmonary disease be treated with a three-drug regimen with a macrolide or without a macrolide?

**POPULATION:** treatment of MAC pulmonary infection

**INTERVENTION:** three drugs with a macrolide

**COMPARISON:** three drugs without a macrolide

MAIN OUTCOMES: Cure of NTM; Death; Recurrence (relapse); Culture conversion; Any adverse effect; Serious advere effect; Withdrawal owing to adverse

effect; Quality of Life;

		JUDGEMENT			RESE	ARCH EVI	DENCE			ADDITIONAL CONSIDERATIONS	
		How substantial are the desirable anticipated effects?				The committee felt that macrolide regimens are more effective based on their clinical experience and					
		<ul><li> Trivial</li><li> Small</li><li> Moderate</li></ul>	Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95%	№ of participants (studies)	Quality of the evidence	Comments	retrospective cohort studies. There were a number of concerns with the two studies included from the literature	
	E EFFECTS	<ul> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		Risk with three drugs without a macrolide	Risk with three drugs with a macrolide	CI)		(GRADE)		search. These concerns included the small sample size in the studies, underdosing of the macrolide used in the studies, and a population not representative of usual clinical practice. Additionally, the overall mortality seen in the one study that had this outcome was	
	DESIRABLE		Cure of NTM	Study population		<b>RR 0.93</b> (0.62 to	(2 V	⊕○○○ VERY		noted to be quite large for this disease, raising question to the validity of this result.	
DES	DE			354 per 1,000	<b>329 per</b> <b>1,000</b> (220 to 485)	1.37)	observational studies)	LOW <sup>a b</sup>		The committee unanimously felt that macrolides are a critical component to	
			Death	Study popul	ation	RR 1.61	170	⊕○○○		MAC treatment. Although one study appeared to have higher death rates in patients on a macrolide-containing regimen than on a regimen without, the	

	How substantial are the		299 per 1,000	<b>481 per 1,000</b> (326 to 714)	(1.09 to 2.39)	(1 observational study)	VERY LOW <sup>a b</sup>	committee felt this study was not applicable for the reasons previously stated.
	undesirable anticipated effects?	Recurrence (relapse)	Study population		<b>RR 0.87</b> (0.37 to	190 (2	⊕○○○ VERY	
	<ul><li> Large</li><li> Moderate</li><li> Small</li><li> Trivial</li></ul>		104 per 1,000	<b>91 per 1,000</b> (39 to 209)	2.01)	observational studies)	LOW <sup>a b</sup>	
	<ul><li> Varies</li><li> Don't know</li></ul>	Culture conversion	Study popu	ulation	<b>RR 0.98</b> (0.67 to	(2	⊕○○○ VERY	
CTS	Any adverse effect		850 per 1,000	<b>833 per 1,000</b> (570 to 1,000)	1.43)		LOW <sup>a b c</sup>	
BLE EFFI		adverse	erse		<b>RR 0.23</b> (0.03 to	27 (1 RCT)	⊕⊕○○ LOW <sup>a b</sup>	
UNDESIRABLE EFFECTS		effect	308 per 1,000	<b>71 per 1,000</b> (9 to 560)	1.82)			
		Serious advere	Study population		not estimable	27 (1 RCT)	⊕⊕○○ LOW <sup>b</sup>	
	Wit	effect	0 per 1,000	<b>0 per 1,000</b> (0 to 0)				
		Withdrawal owing to	Study population		<b>RR 0.46</b> (0.05 to	27 (1 RCT)	⊕⊕⊜⊝ LOW <sup>a b</sup>	
		adverse effect	154 per 1,000	<b>71 per 1,000</b> (8 to 697)	4.53)			

		Quality of Life - not measured  a. Wide confidence interval b. Unclear control for confidence c. One study favors w/ max	ounders	w/o
	What is the overall certainty of the evidence of effects?	The relative importance or va	lues of the main out	comes of interest:
	• Very low	Outcome	Relative importance	Certainty of the evidence(GRADE)
	<ul><li>○ Low</li><li>○ Moderate</li><li>○ High</li></ul>	Cure of NTM	CRITICAL	⊕○○○ VERY LOW
	∘ No included studies	Death	CRITICAL	⊕○○○ VERY LOW
CERTAINTY OF EVIDENCE		Recurrence (relapse)	CRITICAL	⊕○○○ VERY LOW
INTY OF E		Culture conversion	CRITICAL	⊕○○○ VERY LOW
CERTA		Any adverse effect	CRITICAL	⊕⊕○○ LOW
		Serious advere effect	CRITICAL	⊕⊕○○ LOW
		Withdrawal owing to adverse effect	CRITICAL	⊕⊕○○ LOW
		Quality of Life	CRITICAL	-
VALU ES	Is there important uncertainty about or variability in how	Values and preferences:		

#### much people value the main Three relevant studies were identified that provide data on patient values and preferences: outcomes? o Important uncertainty or Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality variability of life. In this study, patients with pulmonary NTM had significantly impaired health-related Possibly important uncertainty quality of life with two QOL measures significantly lower than historical normal controls. or variability Multivariable analysis showed an association between QOL scores and lung function. o Probably no important uncertainty or variability No important uncertainty or variability Hong, et al, 2014 also evaluated the impact of pulmonary NTM on health-related quality of life. This was a direct comparison between patients with NTM disease and healthy subjects and found patients with NTM reported more health status issues and anxiety/depression issues than healthy controls. Lung function was also independently associated with QOL scores. Czaja, et al 2015 evaluated change in quality of life in response to various treatment regimens for *M. abscessus* (many patients had coinfection with MAC or Pseudomonas). Mean QOL score was significantly improved after treatment at 3, 6, 12, and 24 months. Does the balance between Anticipated absolute Relative Nº of Quality **Comments** desirable and undesirable Outcomes effects\* (95% CI) effect participants of the effects favor the intervention (95% (studies) evidence or the comparison? CI) (GRADE) Risk with Risk with Favors the comparison three three Probably favors the comparison drugs drugs • Does not favor either the without a with a BALANCE OF EFFECTS intervention or the comparison macrolide macrolide Probably favors the intervention o Favors the intervention Cure of Study population RR 0.93 190 $\Theta O O O$ NTM (0.62 to (2 VERY Varies LOW<sup>a b</sup> 1.37) observational o Don't know 329 per 354 per studies) 1,000 1,000 (220 to 485) Death Study population RR 1.61 170 **@**000 **VERY** (1.09 to (1 LOW<sup>a b</sup> 2.39) observational 299 per 481 per

	1,000	<b>1,000</b> (326 to 714)		study)		
Recurrence (relapse)	Study popul	ation	<b>RR 0.87</b> (0.37 to	190 (2	⊕○○○ VERY	
	104 per 1,000	<b>91 per 1,000</b> (39 to 209)	2.01)	observational studies)	LOW <sup>a b</sup>	
Culture conversion	Study popul	ation	<b>RR 0.98</b> (0.67 to	197 (2	⊕○○○ VERY	
	850 per 1,000	<b>833 per 1,000</b> (570 to 1,000)	1.43)	observational studies)	LOW <sup>a b c</sup>	
Any adverse	Study population		<b>RR 0.23</b> (0.03 to	27 (1 RCT)	⊕⊕○○ LOW <sup>a b</sup>	
effect	308 per 1,000	<b>71 per 1,000</b> (9 to 560)	1.82)			
Serious advere	Study population		not estimable	27 (1 RCT)	⊕⊕○○ LOW <sup>b</sup>	
effect	0 per 1,000	<b>0 per 1,000</b> (0 to 0)				
Withdrawal owing to	Study popul	ation	<b>RR 0.46</b> (0.05 to	27 (1 RCT)	⊕⊕○○	
adverse effect	154 per 1,000	<b>71 per 1,000</b> (8 to 697)	4.53)			
Quality of Life - not	-	-	-	-	-	

		measured
		a. Wide confidence interval b. Unclear control for confounders c. One study favors w/ macrolide and one favors w/o
	How large are the resource requirements (costs)?	No research evidence was identified.
RESOURCES REQUIRED	<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> <li>Varies</li> <li>Don't know</li> </ul>	

	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was identified.	
COST EFFECTIVENESS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> <li>Varies</li> <li>No included studies</li> </ul>		
	What would be the impact on health equity?	No research evidence was identified.	
EQUITY	<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>		
	<ul><li>∨ Varies</li><li>∨ Don't know</li></ul>		

	Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
ACCEPTABILITY	<ul> <li>No</li> <li>Probably no</li> <li>Probably yes</li> <li>Yes</li> <li>Varies</li> <li>Don't know</li> </ul>		
FEASIBILITY	Is the intervention feasible to implement?  O No Probably no Probably yes Yes	A study by Adjemian, et al in 2014 evaluated treatment of <i>M. abscessus</i> and MAC, looking at compliance with the 2007 ATS/IDSA guidelines. This study found poor adherence with only 13% of antibiotic regimens compliant with guidelines. Of prescribed regimens for MAC, only 44% contained a macrolide, while 36% of regimens for <i>M. abscessus</i> contained a macrolide.	
	<ul><li> Varies</li><li> Don't know</li></ul>		

		IMPLICATIONS						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

# Should macrolide-susceptible MAC pulmonary disease be treated with a three-drug regimen with a macrolide or without a macrolide?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention			
RECOMMENDATION	In patients with macrolide susceptible MAC pulmonary disease, we recommend a three-drug regimen that includes a macrolide over a three-drug regimen without a macrolide (strong recommendation, very low confidence in estimates of effect). (16 Agree, 0 Conditional, 2 Abstain)  The panel members voted for a strong recommendation despite a very low confidence in estimates of effect.							
JUSTIFICATION	Historical case series data have demonstrated that macrolide containing regimens are associated with higher culture conversion rates than nonmacrolide containing regimens.  Macrolide susceptibility has been a consistent predictor of treatment success for pulmonary MAC, whereas susceptibility to other drugs has not been a predictor. This suggests that the macrolides have a key role in MAC treatment.							
SUBGROUP CONSIDERATIONS								
IMPLEMENTATION CONSIDERATIONS								
MONITORING AND EVALUATION	ECG monitoring may be relevant in patients using other drugs that can prolong the QTc interval							

## **Table E4.4. Question IV**

In patients with newly diagnosed macrolide susceptible MAC pulmonary disease, should an azithromycin-based regimen or a clarithromycin-based regimen be used?

**POPULATION:** patients with newly diagnosed pulmonary MAC

**INTERVENTION:** azithromycin-based regimen

**COMPARISON:** clarithromycin-based regimen

MAIN OUTCOMES: Death; Quality of life; Culture Conversion; Recurrence (relapse); Development of antibiotic resistance; Serious adverse effects;

Withdrawal from study due to AEs; Any Adverse Effect;

		JUDGEMENT		ı	RESEARCH EVIDEN	CE			ADDITIONAL CONSIDERATIONS
	(n	How substantial are the desirable anticipated effects?  Trivial Small Moderate Large Varies Don't know	1	pased regimen compa ed pulmonary MAC	Azithromycin has fewer drug interactions compared with clarithromycin.				
DESIRABLE EFFECTS	EFFECT		Outcomes	Anticipated absolute Risk with clarithromycin- based regimen	Risk with azithromycin-based regimen	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Azithromycin may be better tolerated than clarithromycin
	DE		Death - not reported	-	-	-	-	-	Toxicity of azithromycin may be resolved by lowering dose, while this may not be possible with clarithromycin.

		Quality of life - not measured	-	-	-	-	-	Clarithromycin may have more QT-interval prolongation.
	How substantial are the undesirable anticipated effects?  o Large o Moderate	Culture Conversion	82 per 100	<b>72 per 100</b> (60 to 86)	<b>RR 0.88</b> (0.73 to 1.05)	368 (4 observational studies)	⊕○○○ VERY LOW 1,2	In panel members observation clarithromycin may have lower ototoxicity than azithromycin. However, there was no consensus and more studies would be helpful.
	<ul><li>Small</li><li>Trivial</li><li>Varies</li></ul>	Recurrence (relapse) - not measured	-	-	-	-	-	
EFFECTS	∘ Don't know	Development of antibiotic resistance	9 per 100	<b>5 per 100</b> (1 to 26)	<b>RR 0.51</b> (0.07 to 2.79) <sup>4</sup>	189 (3 observational studies)	⊕○○○ VERY LOW 1,3	
UNDESIRABLE		Serious adverse effects	0 per 100	<b>0 per 100</b> (0 to 0)	not estimable	59 (1 observational study)	⊕○○○ VERY LOW 1,5	
		Withdrawal from study due to AEs	14 per 100	<b>15 per 100</b> (6 to 30)	<b>RR 1.02</b> (0.45 to 2.07)	191 (3 observational studies)	⊕○○○ VERY LOW 1,6	
		Any Adverse Effect	41 per 100	<b>31 per 100</b> (18 to 52)	<b>RR 0.75</b> (0.44 to 1.28)	483 (6 observational studies)	⊕○○○ VERY LOW 1,7,8	
8	What is the overall certainty of the evidence of effects?	The relative im	portance or value	s of the main outco	omes of ir	iterest:		
EVIDENCE	• Very low • Low	Ou	itcome	Relative importance	Certaint	y of the evidence	ce (GRADE)	
11	<ul><li> Low</li><li> Moderate</li><li> High</li><li> No included studies</li></ul>	Death		CRITICAL	-			
CERTAINTY OF		Quality of life		CRITICAL	-			
CEI		Culture Conversio	n	CRITICAL	⊕○○○			

		Recurrence (relapse)  Development of antibiotic resistance  Serious adverse effects  Withdrawal from study due to AEs  Any Adverse Effect	CRITICAL  CRITICAL  CRITICAL  CRITICAL	VERY LOW  -  #OOO VERY LOW  #OOO VERY LOW  #OOO VERY LOW  #OOO VERY LOW	
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • No important uncertainty or variability	We identified 1 study including 51 r 67y, MAC and M. abscessus) that n 2011,105:1718-1725).	mainly middle-age neasured QoL (Mel igher scores indicato population normals)	very Low  d to older women in Canada (mean age nta and Marras. Respiratory Medicine  te better QoL; MID~5-10 points) were	Number of pills per day is smaller with azithromycin which may increase adherence and be better accepted by patients. Based on patient observations and panel member experience clarithromycin has a metallic taste and more frequently causes nausea, which make it less preferred option.

		COPD population Mean difference lower (39 vs. 8 We found no oth	n) were lower compa in total SGRQ in NT points lower).	wer scores indicate be ared to population no M patients compared ulation of interest than nts of interest.	ormal consi I to normal	stently across a population was	all domains. s 31 points	
	Does the balance between desirable and undesirable effects favor the intervention or the comparison?		d pulmonary MAC	red to clarithromycin te effects* (95% CI)	-based reg	imen in patients	Quality of	
	<ul><li>Favors the comparison</li><li>Probably favors the comparison</li></ul>		Risk with	Risk with	effect (95% CI)	participants (studies)	the evidence	
	Does not favor either the intervention or the comparison		clarithromycin- based regimen	azithromycin- based regimen			(GRADE)	
TS	<ul> <li>Varies</li> <li>Don't know</li> </ul>	Death - not reported	-	-	-	-	-	
OF EFFECTS		Quality of life - not measured	-	-	-	-	-	
BALANCE OF		Culture Conversion follow up: range 4 to 12 months	82 per 100	<b>72 per 100</b> (60 to 86)	<b>RR 0.88</b> (0.73 to 1.05)	368 (4 observational studies)	⊕○○ VERY LOW	
		Recurrence (relapse) - not measured	-	-	-	-	-	
		Development of antibiotic resistance follow up: range 4 to 12 months	9 per 100	<b>5 per 100</b> (1 to 26)	<b>RR 0.51</b> (0.07 to 2.79) <sup>4</sup>	189 (3 observational studies)	⊕○○○ VERY LOW 1,3	

		effects follow up: 4 months  Withdrawal from 1 study due to AEs follow up: range 4 to 6 months		<b>0 per 100</b> (0 to 0) <b>15 per 100</b> (6 to 30)	not estimable  RR 1.02 (0.45 to 2.07)	59 (1 observational study)  191 (3 observational studies)	⊕○○○ VERY LOW 1,5  ⊕○○○ VERY LOW 1,6	
		Any Adverse 4 Effect follow up: range 4 to 12 months	11 per 100	<b>31 per 100</b> (18 to 52)	(0.44 to 1.28)	483 (6 observational studies)	⊕○○○ VERY LOW 1,7,8	
RESOURCES REQUIRED	How large are the resource requirements (costs)?  • Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • Don't know	No research evider	nce was identified.					In the experience of panel members there is large variability in the cost of azithromycin and clarithromycin. Cost should be considered on an individual patient level. However, panel members thought it would be unlikely that cost difference would influence general recommendation favoring azithromycin.
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention • Varies • No included studies	No research evider						
EQUI	What would be the impact on	No research evider	nce was identified.					

			1
	health equity?  Output  Reduced Probably reduced Probably no impact Probably increased Increased  Varies Don't know		
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?  No Probably no Probably yes Yes  Varies Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement?  • No • Probably no • Probably yes • Yes  • Varies • Don't know	No research evidence was identified.	Panel members could not think of any barriers to implementation, other than cost of the drug in jurisdictions where azithromycin is more expensive.

			IMPLICATIONS					
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	

		JUDGEMENT								
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know			
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know			
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know			

In patients with newly diagnosed macrolide susceptible MAC pulmonary disease, should an azithromycin-based regimen or a clarithromycin-based regimen be used?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	0	0	0	•	0
RECOMMENDATION	In patients with macrolide clarithromycin-based regi	mens. (conditional recomr	mendation, very low confid	dence in estimates of effe	
JUSTIFICATION					
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					

MONITORING AND EVALUATION	Because of potential for ototoxicity patients should be regularly asked about hearing loss or tinnitus. Some panel members perform baseline audiogram and then repeat based on symptoms or yearly.
	Because of potential for QTc prolongation some experts perform baseline EKG in patients starting macrolides, especially those receiving drug regimens that include other QTc prolonging drugs and them repeat periodically.
RESEARCH PRIORITIES	Estimate the risk of QTc prolongation, hearing loss in patients receiving azithromycin vs clarithromycin.
	Randomized trials with therapy adjusted based on monitoring drug levels to see if this prevents toxicity.

## Table E4.5. Question V

Should patients with macrolide susceptible MAC pulmonary disease be treated with a parenteral amikacin or streptomycin-containing regimen or without a parenteral amikacin or streptomycin-containing regimen?

**POPULATION:** MAC pulmonary infection

**INTERVENTION:** a treatment regimen with a parenteral agent

**COMPARISON:** a treatment regimen without a parenteral agent

MAIN OUTCOMES: Cure of NTM; Death; Recurrence (relapse); Culture Conversion; Any adverse reaction; Serious adverse events; Quality of life;

Development of antibiotic resistance;

		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
ц		How substantial are the desirable anticipated effects?		
DECIDARI	EFFECTS	<ul><li> Trivial</li><li> Small</li><li> Moderate</li><li> Large</li></ul>	Parenteral compared to no parenteral agent for MAC	

	o Small o Trivial  O Varies O Don't know  Recurrence  Culture Con  Any adverse  Serious adv.  Quality of lift measured  Developmen	Outcomes	Anticipated absolute effects* (95% CI)			Nº of participants	Quality of the evidence	
UNDESIRABLE EFFECTS			Risk with no parenteral agent	Risk with Parenteral	(95% CI)	(studies)	(GRADE)	The undesirable anticipated effects of amikacin are larger when given for 3 months.
		Cure of NTM - not measured	-	-	-	-	-	
		Death	27 per 1000	<b>27 per 1000</b> (4 to 189)	<b>RR 1.00</b> (0.14 to 6.91)	146 (1 RCT)	⊕⊕⊕⊖ MODERATE <sup>3</sup>	
		Recurrence (relapse)	351 per 1000	<b>309 per 1000</b> (169 to 559)	<b>RR 0.88</b> (0.48 to 1.59)	89 (1 RCT)	⊕⊕⊕○ MODERATE	-
		Culture Conversion	507 per 1000	<b>715 per 1000</b> (542 to 933)	<b>RR 1.41</b> (1.07 to 1.84)	146 (1 RCT)	⊕⊕⊕⊜ MODERATE <sup>3</sup>	
		Any adverse reaction	205 per 1000	<b>247 per 1000</b> (136 to 450)	<b>RR 1.20</b> (0.66 to 2.19)	146 (1 RCT)	⊕⊕⊕⊜ MODERATE <sup>3</sup>	
		Serious adverse events	0 per 1000	<b>0 per 1000</b> (0 to 0)	not estimable	146 (1 RCT)	⊕⊕⊕⊕ HIGH	
		Quality of life - not measured	-	-	-	-	-	
		Development of antibiotic resistance - not measured	-	-	-	-	-	

	What is the overall certainty of the evidence of effects?	The relative importance or values of the main outcomes of interest:				
	○ Very low	Outcome	Relative importance	Certainty of the evidence (GRADE)		
	<ul><li> Low</li><li> Moderate</li><li> High</li></ul>	Cure of NTM	CRITICAL	⊕○○○ VERY LOW		
ш	No included studies	Death	CRITICAL	⊕⊕⊕○ MODERATE		
EVIDENCE		Recurrence (relapse)	CRITICAL	⊕⊕⊕○ MODERATE		
CERTAINTY OF		Culture Conversion	CRITICAL	⊕⊕⊕⊜ MODERATE		
CERT		Any adverse reaction	CRITICAL	⊕⊕⊕○ MODERATE		
		Serious adverse events	CRITICAL	ФФФФ HIGH		
		Quality of life	CRITICAL	-		
		Development of antibiotic resistance	CRITICAL	-		
	Is there important uncertainty about or variability in how much	Values and preferences:				
	people value the main outcomes?	Three relevant studies were identifie	ed that provide data on	patient values and preferences:		
/ALUES	Possibly important uncertainty or Variability	Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls. Multivariable analysis showed an association between QOL scores and lung function				
	No important uncertainty or variability	Hong, et al, 2014 also evaluated the This was a direct comparison betwee patients with NTM reported more he healthy controls. Lung function was	en patients with NTM di alth status issues and a	sease and healthy subjects and found anxiety/depression issues than		
		Czaja, et al 2015 evaluated change	in quality of life in response	onse to various treatment regimens		

		for <i>M. abscessus</i> (many patients had coinfection with MAC or Pseudomonas). Mean QOL score was significantly improved after treatment at 3, 6, 12, and 24 months.						
	Does the balance between desirable and undesirable effects favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention	Parenteral compared to no parenteral agent for MAC						Intervention is with a parenteral agent.
		Outcomes	Anticipated absolute effects* (95% CI)		Relative effect	№ of participants	Quality of the evidence	
			Risk with no parenteral agent	Risk with Parenteral	(95% CI)	(studies)	(GRADE)	
	∨ Varies     Onn't know	Cure of NTM - not measured	-	-	-	-	-	-
FECTS		Death	27 per 1000	<b>27 per 1000</b> (4 to 189)	<b>RR 1.00</b> (0.14 to 6.91)	146 (1 RCT)	⊕⊕⊕○ MODERATE <sup>3</sup>	-
BALANCE OF EFFECTS		Recurrence (relapse)	351 per 1000	<b>309 per 1000</b> (169 to 559)	<b>RR 0.88</b> (0.48 to 1.59)	89 (1 RCT)	⊕⊕⊕○ MODERATE	
BAL		Culture Conversion	507 per 1000	<b>715 per 1000</b> (542 to 933)	<b>RR 1.41</b> (1.07 to 1.84)	146 (1 RCT)	⊕⊕⊕○ MODERATE <sup>3</sup>	_
		Any adverse reaction	205 per 1000	<b>247 per 1000</b> (136 to 450)	<b>RR 1.20</b> (0.66 to 2.19)	146 (1 RCT)	⊕⊕⊕○ MODERATE <sup>3</sup>	
		Serious adverse events	0 per 1000	<b>0 per 1000</b> (0 to 0)	not estimable	146 (1 RCT)	⊕⊕⊕⊕ HIGH	
		Quality of life - not measured	-	-	-	-	-	
		Development of antibiotic resistance - not	-	-	-	-	-	-

				T
			measured	
		How large are the resource	No research evidence was identified.	Varies with the health
1 1 1	JIKED	requirements (costs)?		system, but regardless it is likely associated with a significant cost due to need
i L	N KEUL	<ul><li> Large costs</li><li> Moderate costs</li><li> Negligible costs and savings</li></ul>		for indwelling catheter, infusion center, nursing care,
0	KESUUKCES KEQUIKED	<ul><li>Moderate savings</li><li>Large savings</li></ul>		cost of medication.
L	KESC	<ul><li> Varies</li><li> Don't know</li></ul>		
Ç	Ž,	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was identified.	
	COSI EFFECTIVENESS	<ul><li>Favors the comparison</li><li>Probably favors the comparison</li></ul>		
i C L	7 1 1	<ul><li>Does not favor either the intervention or the comparison</li></ul>		
L	202	<ul><li> Probably favors the intervention</li><li> Favors the intervention</li></ul>		
		<ul><li> Varies</li><li> No included studies</li></ul>		
		What would be the impact on health equity?	No research evidence was identified.	It depends on the health system coverage. If patients are not covered, there will be
Ì	EQUIT	<ul><li>Reduced</li><li>Probably reduced</li></ul>		a reduction in equity as they should pay for the treatment
C	J D	<ul><li> Probably no impact</li><li> Probably increased</li></ul>		to be administered (cost of the drug and administration).
		o Increased		

	<ul><li> Varies</li><li> Don't know</li></ul>		
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?  O No O Probably no O Probably yes O Yes  Varies O Don't know	No research evidence was identified. The expert panel felt that patients would prefer to avoid parenteral therapy when no clear benefit could be identified. However, in the setting of extensive or drug resistant disease, most patients would accept the intervention.	
FEASIBILITY	Is the intervention feasible to implement?  No Probably no Probably yes Yes  Varies Don't know	A study by Adjemian, et al in 2014 evaluated treatment of <i>M. abscessus</i> and MAC, looking at compliance with the 2007 ATS/IDSA guidelines. This study found poor adherence with only 13% of antibiotic regimens compliant with guidelines. Of prescribed regimens for MAC, only 44% contained a macrolide, while 36% of regimens for <i>M. abscessus</i> contained a macrolide.	In settings in which patients cannot access an infusion center, may not be able to self infuse at home.  Availability of certain medications (streptomycin, amikacin, etc) in different regions/countries

		JUDGEMENT							
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know		
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know		
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies		
VALUES	Important uncertainty or variability	Possibly important uncertainty or	Probably no important uncertainty or	No important uncertainty or variability					

		IMPLICATIONS						
		variability	variability					
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Should patients with macrolide susceptible MAC pulmonary disease be treated with a parenteral amikacin or streptomycin-containing regimen or without a parenteral amikacin or streptomycin-containing regimen?

TYPE OF RECOMMENDATION	Strong recommendation	Conditional recommendation	Conditional recommendation		Strong recommendation
	against the	against the	for either the intervention or	for the	for the

	intervention	intervention	the comparison	intervention	intervention			
	0	0	0	•	0			
RECOMMENDATION	For patients with fibro-cavitary or advanced/severe bronchiectatic or macrolide resistant MAC pulmonary disease, we suggest that parenteral streptomycin or amikacin be included in the initial treatment regimen (conditional recommendation, moderate confidence in estimates of effect).							
	The panel members voted	The panel members voted unanimously for a conditional recommendation for the intervention.						
JUSTIFICATION								
SUBGROUP CONSIDERATIONS	The addition of parenteral according to the radiologic				of the disease and			
IMPLEMENTATION CONSIDERATIONS								
MONITORING AND EVALUATION	renal function, hearing/ototoxicity, vestibular toxicity, electrolyte disturbances							
RESEARCH PRIORITIES								

## **Table E4.6. Question VI**

In patients with macrolide-susceptible MAC pulmonary disease, should a regimen with inhaled amikacin or a regimen without inhaled amikacin be used for treatment?

**POPULATION:** MAC pulmonary infection

**INTERVENTION:** a regimen with inhaled antibiotics

**COMPARISON:** a regimen without inhaled antibiotics

MAIN OUTCOMES: Cure of NTM; Death; Recurrence (relapse); Culture Conversion; Any Adverse

Effect; Serious Adverse Effect; Withdrawal owing to adverse effects; Quality

of Life; Development of Antibiotic Resistance;

	JUDGEMENT		RESEARCH EVIDENCE						ADDITIONAL CONSIDERATION
ECTS	How substantial are the desirable anticipated effects?								
DESIRABLE EFFECTS	<ul><li>Trivial</li><li>Small</li><li>Moderate</li><li>Large</li></ul>	Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95%	№ of participants (studies)	Quality of the evidence	Comments	
DESIR	<ul><li> Varies</li><li> Don't know</li></ul>		Risk with a regimen with inhaled	Risk with a regimen without	CI)		(GRADE)		
	How substantial are the undesirable anticipated effects?		antibiotics	inhaled antibiotics					
	∘ Large ∘ Moderate	Cure of NTM	Study population		not estimable	3 (1	⊕○○○ VERY LOW <sup>a</sup>		
FFECTS	○ Small ○ Trivial		3/3 (100%)			observational study)			
RABLE E	<ul><li> Varies</li><li> Don't know</li></ul>	Death	Study populatio	n	- 9 (2		⊕○○○ VERY LOW <sup>a</sup>		
UNDESIRABLE EFFECTS			2/9 (22.2%)			observational studies)			
	Recurrence (relapse)		Study populatio	n	-	21 (1 RCT and 2 observational	⊕⊕⊕○ MODERATE		
			9/21 (42.9%)			studies)			

Culture Conversion	Study populatio	n	-	68 (1 RCT and 2	HOMp c
	16/40 (40.0%)	1/28 (3.6%)		observational studies)	
Any Adverse Effect	Study populatio	n	-	104 (1 RCT and 2	⊕⊕○○ LOW <sup>b d</sup>
	46/59 (78.0%)	40/45 (88.9%)		observational studies)	
Serious Adverse	Study populatio	n	-	104 (1 RCT and 2	⊕⊕○○ LOW <sup>b e</sup>
Effect	8/59 (13.6%)	4/45 (8.9%)		observational studies)	
Withdrawal owing to	Study populatio	n	-	124 (1 RCT and 3 observational studies)	⊕⊕⊜⊝ LOW <sup>b f</sup>
adverse effects	15/79 (19.0%)	0/45 (0.0%)			
Quality of Life  Study used Quality of Life - Bronchiectasis - Nontuberculous Mycobacteria Module scores with no significant difference (p- 0.204) between the inhaled antibiotic group (-7.9 [14.2], n=36) and placebo group (-2.8 [13.7], n=36).		-	(1 RCT)	⊕⊕⊕○ MODERATE <sup>9</sup>	
Development of Antibiotic	Study populatio	n	not estimable	89 (1 RCT)	⊕⊕⊕○ MODERATE <sup>g</sup>
Resistance	3/44 (6.8%)	2/45 (4.4%)			

- a. Studies were case series without a control group
  b. Included 2 case series without a control group
  c. Conversion with inhaled antibiotics ranged from 30% to 80%
  d. Adverse effects ranged from 30% in case series to over 90% in RCT
  e. Ranged from 0% in case series to nearly 20% in RCT
  f. Ranged from 0% to 35% in inhaled group.
  g. Included both MAC and M abscessus

	What is the overall certainty of the evidence of effects?  • Very low		
CERTAINTY OF EVIDENCE	<ul> <li>Low</li> <li>Moderate</li> <li>High</li> <li>No included studies</li> </ul>		
	Is there important uncertainty about or variability in how much people value the main outcomes?	Values and preferences:  Three relevant studies were identified that provide data on patient values and preferences:	
VALUES	<ul> <li>Important uncertainty or variability</li> <li>Possibly important uncertainty or variability</li> <li>Probably no important uncertainty or variability</li> <li>No important uncertainty or variability</li> </ul>	Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls. Multivariable analysis showed an association between QOL scores and lung function.  Hong, et al, 2014 also evaluated the impact of pulmonary NTM on health-related quality of life. This was a	

		reported more was also indeported Czaja, et al 20 abscessus (ma	son between patie health status issuendently associate 15 evaluated charny patients had contreatment at 3, 6	es and anxiety/ded with QOL score age in quality of libinfection with Ma	epression is: es. fe in respon AC or Pseudo	sues than health	y controls. Lun	g function  ns for <i>M</i> .
	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Outcomes	Anticipated at	osolute effects*	Relative effect (95%	№ of participants (studies)	Quality of the evidence	Comments
	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>		Risk with a regimen with inhaled antibiotics	Risk with a regimen without inhaled antibiotics	CI)		(GRADE)	
TS	<ul><li>∨ Varies</li><li>∨ Don't know</li></ul>	Cure of NTM	Study populatio	n	not estimable		⊕○○○ VERY LOW <sup>a</sup>	
F EFFECTS			3/3 (100.0%)			observational study)		
BALANCE OF		Death	Study populatio	n	-	9 (2	⊕○○○ VERY LOW <sup>a</sup>	
BAL			2/9 (22.2%)			observational studies)		
		Recurrence (relapse)	Study populatio	n	-	21 (1 RCT and 2	⊕⊕⊕○ MODERATE	
			9/21 (42.9%)	0/0		observational studies)		
		Culture Conversion	Study populatio	n	-	68 (1 RCT and 2	DOMp c	
			16/40 (40.0%)	1/28 (3.6%)		observational studies)		

Any Adverse Effect	Study population	n	-	104 (1 RCT and 2	⊕⊕○○ LOW <sup>b d</sup>	
	46/59 (78.0%)	40/45 (88.9%)		observational studies)		
Serious Adverse	Study populatio	n	-	104 (1 RCT and 2	⊕⊕○○ LOW <sup>b e</sup>	
Effect	8/59 (13.6%)	4/45 (8.9%)		observational studies)		
Withdrawal owing to	Study population	n	-	124 (1 RCT and 3	⊕⊕⊜⊜ LOW <sup>b f</sup>	
adverse effects	15/79 (19.0%)	0/45 (0.0%)		observational studies)		
Quality of Life	Study used Quality of Life - Bronchiectasis - Nontuberculous Mycobacteria Module scores with no significant difference (p-0.204) between the inhaled antibiotic group (-7.9 [14.2], n=36) and placebo group (-2.8 [13.7], n=36).		-	(1 RCT)	⊕⊕⊕○ MODERATE <sup>9</sup>	
Development of Antibiotic	Study populatio	n	not estimable	89 (1 RCT)	⊕⊕⊕⊖ MODERATE <sup>9</sup>	
Resistance	3/44 (6.8%)	2/45 (4.4%)				

- a. Studies were case series without a control group
  b. Included 2 case series without a control group
  c. Conversion with inhaled antibiotics ranged from 30% to 80%
  d. Adverse effects ranged from 30% in case series to over 90% in RCT
  e. Ranged from 0% in case series to nearly 20% in RCT
  f. Ranged from 0% to 35% in inhaled group.
  g. Included both MAC and M abscessus

RESOURCES REQUIRED	How large are the resource requirements (costs)?  • Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • Don't know	No research evidence was identified.	The cost of parenteral amikacin (which would be used in the nebulizer) varies, but may cost the patient between \$150-400/ month depending on frequency and dosing.  Some patients are able to obtain amikacin through insurance so for them out of pocket costs are low. For patients who must pay full price, it is an expensive intervention. The cost of amikacin liposomal inhaled suspension varies but in the United States is approximately \$300 a vial. As this is an FDA approved drug, insurance is likely to cover most of the costs for most patients.

COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention  • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Output Reduced Probably reduced Probably no impact Probably increased Increased Varies Don't know	No research evidence was identified.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?  O NO O Probably no Probably yes O Yes  Varies O Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement?  Ono Probably no Probably yes Yes  Varies Don't know	A study by Adjemian, et al in 2014 evaluated treatment of <i>M. abscessus</i> and MAC, looking at compliance with the 2007 ATS/IDSA guidelines. This study found poor adherence with only 13% of antibiotic regimens compliant with guidelines. Of prescribed regimens for MAC, only 44% contained a macrolide, while 36% of regimens for <i>M. abscessus</i> contained a macrolide.	

	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

			:	JUDGEMENT			IMPLICATIONS
FEASIBILITY	No	Probably no	Probably yes	Yes	Varies	Don't know	

In patients with macrolide-susceptible MAC pulmonary disease, should a regimen with inhaled amikacin or a regimen without inhaled amikacin be used for treatment?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	commendation recommendation recommagainst the for either the fo		Strong recommendation for the intervention			
	0	•	•					
RECOMMENDATION	In patients with MAC puln liposomal inhaled suspens estimates of effect).  The panel members voted	sion as part of the initial tr	eatment regimen. (condit	ional recommendation, ve				
	recommend the use of an	MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy, we use of amikacin liposomal inhaled suspension as part of the treatment regimen. (strong recommendation, dence in estimates of effect). (5 Strong, 4 Conditional, 9 Abstain)						
	Expert panel members that	at had declared a conflict	of interest with Insmed ha	ad to abstain from voting o	on whether a strong or			

	conditional recommendation was made. Among the voting members, 5 of 9 voted for a strong recommendation for the intervention.
JUSTIFICATION	There are no good data to support the use of inhaled antibiotics as an initial treatment option. There may be a risk of developing acquired mutational amikacin resistance with either inadequate companion medications or poor and irregular antibiotic deposition in the lung with areas of low amikacin concentration.  Given the high morbidity and mortality in patients who fail treatment with an initial regimen, it is reasonable to consider inhaled therapy as part of a salvage regimen to aggressively treat MAC pulmonary disease.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Pretreatment with a bronchodilator.
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Clinical trials evaluating safety and efficacy of inhaled amikacin (liposomal or non), comparing various dosing regimens to see which are most effective.
	Clinical trials to determine the optimal companion medications to inhaled amikacin in the treatment of MAC pulmonary infection.

# **Table E4.7. Question VII**

In patients with macrolide susceptible MAC pulmonary disease, should a three-drug or a two-drug macrolide-containing regimen be used for treatment?

**POPULATION:** treatment of MAC pulmonary infection

**INTERVENTION:** a three drug regimen

**COMPARISON:** a two drug regimen

MAIN OUTCOMES: Culture Conversion; Serious Adverse Effects; Withdrawal owing to adverse effect; Quality of Life; Cure of NTM Disease; Death;

Development of antibiotic resistance; Recurrence (relapse);

	JUDGEMENT		RESEARCH EVI	ADDITIONAL CONSIDERATION			
TS	How substantial are the desirable anticipated effects?						
E EFFECTS	o Trivial ● Small	A three drug regim pulmonary infectio	en compared to a two drug re n	gimen for tı	reatment of M	AC	
DESIRABLE	○ Moderate ○ Large	Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	№ of participants	Quality of the evidence	
DE	<ul><li>∨ Varies</li><li>o Don't know</li></ul>						

	How substantial are the undesirable anticipated effects?  • Large		Risk with a	Risk with a	(95% CI)	(studies)	(GRADE)	In non-pulmonary disease, there is known to be high rates of antibiotic resistance with 2 drug therapy regimens.
	<ul><li> Edige</li><li> Moderate</li><li> Small</li><li> Trivial</li><li> Varies</li></ul>	Culture Conversion	<b>regimen</b> 550 per 1000	<b>407 per 1000</b> (275 to 600)	<b>RR 0.74</b> (0.50 to 1.09)	119 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2</sup>	
	o Don't know	Serious Adverse Effects	0 per 1000	<b>0 per 1000</b> (0 to 0)	not estimable	119 (1 RCT)	⊕⊕⊕○ MODERATE <sup>1</sup>	
UNDESIRABLE EFFECTS		Withdrawal owing to adverse effect	267 per 1000	<b>373 per</b> <b>1000</b> (213 to 565)	RR 1.40 (0.80 to 2.12)	119 (1 RCT)	_ 1,2	
DESIRABLE		Quality of Life - not measured	-	-	-	-	-	
UNI		Cure of NTM Disease - not measured	-	-	-	-	-	
		Death - not reported	-	-	-	-	-	
		Development of antibiotic resistance - not reported	-	-	-	-	-	
		Recurrence (relapse) - not measured	-	-	-	-	-	
/IDENCE	What is the overall certainty of the evidence of effects?  • Very low	The relative impor	rtance or val	ues of the ma	in outcom	es of intere	est:	
CERTAINTY OF EVIDENCE	<ul><li>Low</li><li>Moderate</li><li>High</li></ul>	Outcom	e	Relative importance		ertainty of th (GRAD		
CERTAI	∘ No included studies							

		Culture Conversion	CRITICAL	⊕⊕○○ LOW	
		Serious Adverse Effects	CRITICAL	⊕⊕⊕○ MODERATE	
		Withdrawal owing to adverse effect	CRITICAL	-	
		Quality of Life	CRITICAL	-	
		Cure of NTM Disease	CRITICAL	-	
		Death	CRITICAL	-	
		Development of antibiotic resistance	CRITICAL	-	
		Recurrence (relapse)	CRITICAL	-	
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • No important uncertainty or variability	normal controls. Multivariable an and lung function  Hong, et al, 2014 also evaluated quality of life. This was a direct chealthy subjects and found patier anxiety/depression issues than hassociated with QOL scores.	ed the impact of pul- ents with pulmonary two QOL measures alysis showed an as the impact of pulm- comparison between nts with NTM report ealthy controls. Lun- ge in quality of life y patients had coinf	Imonary NTM on health-related or NTM had significantly impaired significantly lower than historical association between QOL scores  onary NTM on health-related a patients with NTM disease and and the more health status issues and and function was also independently in response to various treatment ection with MAC or	

# Does the balance between desirable and undesirable effects favor the intervention or the comparison?

- o Favors the comparison
- o Probably favors the comparison
- Does not favor either the intervention or the comparison
- o Probably favors the intervention
- o Favors the intervention
- Varies
- o Don't know

#### 

Outcomes	Anticipated a		Relative effect	№ of participants	Quality of the evidence
	Risk with a two trug regimen	Risk with a three drug regimen	(95% CI)	(studies)	(GRADE)
Culture Conversion	550 per 1000	<b>407 per</b> <b>1000</b> (275 to 600)	<b>RR 0.74</b> (0.50 to 1.09)	119 (1 RCT)	⊕⊕○○ LOW <sup>1,2</sup>
Serious Adverse Effects	0 per 1000	<b>0 per 1000</b> (0 to 0)	not estimable	119 (1 RCT)	⊕⊕⊕○ MODERATE <sup>1</sup>
Withdrawal owing to adverse effect	267 per 1000	<b>373 per</b> <b>1000</b> (213 to 565)	<b>RR 1.40</b> (0.80 to 2.12)	119 (1 RCT)	_ 1,2
Quality of Life - not measured	-	-	-	-	-
Cure of NTM Disease - not measured	-	-	-	-	-
Death - not reported	-	-	-	-	-
Development of antibiotic resistance - not reported	-	-	-	-	-
Recurrence (relapse) - not measured	-	-	-	-	-

RESOURCES REQUIRED	How large are the resource requirements (costs)?  o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No research evidence was identified.	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Reduced Probably reduced Probably no impact Probably increased Increased  Varies Don't know	No research evidence was identified.	

	Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
ACCEPTABILITY	<ul> <li>No</li> <li>Probably no</li> <li>Probably yes</li> <li>Yes</li> <li>Varies</li> <li>Don't know</li> </ul>		
FEASIBILITY	Is the intervention feasible to implement?  O No O Probably no Probably yes Yes Varies Don't know	A study by Adjemian, et al in 2014 evaluated treatment of M abscessus and MAC, looking at compliance with the 2007 ATS/IDSA guidelines. This study found poor adherence with only 13% of antibiotic regimens compliant with guidelines. Of prescribed regimens for MAC, only 44% contained a macrolide, while 36% of regimens for M abscessus contained a macrolide.	

		JUDGEMENT							
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know		
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know		

	JUDGEMENT							IMPLICATIONS
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with macrolide susceptible MAC pulmonary disease, should a three-drug or a two-drug macrolide-containing regimen be used for treatment?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention	
	0	0	0	•	0	
RECOMMENDATION	In patients with macrolide (including a macrolide and recommendation, very low	d ethambutol) over a regir w confidence in estimates	men with two drugs (a ma of effect).	crolide and ethambutol al		
JUSTIFICATION						
SUBGROUP CONSIDERATIONS	In patients with severe, p initial 3 months of treatm			n or streptomycin (possib	le with clofazimine) in the	
IMPLEMENTATION CONSIDERATIONS						
MONITORING AND EVALUATION	Renal function, audiometry, EKG					
RESEARCH PRIORITIES						

## **Table E4.8. Question VIII**

In patients with macrolide susceptible MAC pulmonary disease, should a daily or an intermittent macrolide-based regimen be used for treatment?

**POPULATION:** patients with pulmonary MAC

**INTERVENTION:** a three times per week macrolide-based regimen

**COMPARISON:** daily macrolide-based regimen

MAIN OUTCOMES: Death; Quality of life; Cure of NTM Disease; Culture Conversion; Recurrence; Development of Antibiotic Resistance; Serious

adverse effects; Discontinuation of the initial treatment due to adverse effects; Adverse Effects;

	JUDGEMENT		RESI	EARCH EVIDENCE				ADDITIONAL CONSIDERATIONS
How substantial are the desirable anticipated effects?  o Trivial • Small								In one study 75% had to discontinue daily treatment owing to adverse events.
DESIRABLE EFFECTS	<ul><li> Moderate</li><li> Large</li><li> Varies</li><li> Don't know</li></ul>	Outcomes	Anticipated a (95% CI)  Risk with daily macrolide- based	Risk with a three times per week macrolide-	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Panel members have seen many more patients in their practice than there were in these combined studies.  In the experience of some panel
DE		Death - not reported  Quality of life - not	regimen -	based regimen	-	-	-	members the proportion of patients not tolerating daily treatment may be smaller than seen in these studies.

			measured						
			Cure of NTM Disease follow up: 12 months	76 per 100	<b>73 per 100</b> (55 to 86)	<b>RR 0.97</b> (0.72 to 1.14)	217 (1 observational study)	⊕○○○ VERY LOW <sup>1,2</sup>	This applies to nodular or bronchiectatic disease and not to cavitary.
		How substantial are the undesirable anticipated effects?  • Large • Moderate • Small	Culture Conversion follow up: range 6 to 12 months	74 per 100	<b>76 per 100</b> (69 to 84)	<b>RR 1.03</b> (0.93 to 1.14)	597 (5 observational studies)	⊕○○○ VERY LOW <sup>1,4</sup>	There is some concern about potentially increased recurrence, however, this has been based on 4 events total.
SLJ	• Trivial  • Varies  • Don't know	Recurrence assessed with: microbiological recurrence of two or more positive cultures after an initial negative conversion during antibiotic therapy follow up: 12 months	1 per 100	<b>4 per 100</b> (0 to 34)	<b>RR 2.78</b> (0.30 to 26.16)	158 (1 observational study)	⊕○○○ VERY LOW <sup>1,2,5</sup>		
INDESTRABLE FEF	-SIRABLE EFFE		Development of Antibiotic Resistance follow up: range 6 to 12 months	12 per 100	<b>3 per 100</b> (1 to 9)	<b>RR 0.23</b> (0.07 to 0.74)	232 (4 observational studies)	⊕○○○ VERY LOW <sup>1,4,6</sup>	
			Serious adverse effects - not reported	-	-	-	-	-	
			Discontinuation of the initial treatment due to adverse effects follow up: range 6 to 12 months	22 per 100	<b>10 per 100</b> (2 to 48)	<b>RR 0.44</b> (0.09 to 2.16)	564 (4 observational studies)	⊕○○○ VERY LOW <sup>1,7,8</sup>	
			Adverse Effects follow up: range 6 to 12 months	39 per 100	<b>24 per 100</b> (10 to 60)	<b>RR 0.63</b> (0.25 to 1.55)	445 (4 observational studies)	⊕○○○ VERY LOW <sup>1,8</sup>	

# CERTAINTY OF EVIDENCE

# What is the overall certainty of the evidence of effects?

- Very low
- o Low
- Moderate
- o High
- No included studies

#### The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
Death	CRITICAL	-
Quality of life	CRITICAL	-
Cure of NTM Disease	CRITICAL	⊕○○○ VERY LOW
Culture Conversion	CRITICAL	⊕○○○ VERY LOW
Recurrence	CRITICAL	⊕○○○ VERY LOW
Development of Antibiotic Resistance	CRITICAL	⊕○○○ VERY LOW
Serious adverse effects	CRITICAL	-

	Is there important uncertainty about or variability in how much people value the main outcomes?	We identified 1 study including 51 mainly middle-aged to older women in Canada (mean age 67y, MAC and M. abscessus) that measured QoL (Mehta and Marras. Respiratory Medicine 2011,105:1718-1725).	
	∘ Important uncertainty or		
	variability  o Possibly important uncertainty or	Mean SF-36 scores (scale 0-100, higher scores indicate better QoL; MID~5-10 points) were consistently much lower compared to population normal:	
VALUES	variability  o Probably no important uncertainty or variability	Physical Functioning (58 vs. 86; Δ28)	
X	No important uncertainty or variability	Role Physical (54 vs. 82; Δ28)	
		Bodily Pain (63 vs. 76; Δ13)	
		General Health Perceptions (41 vs. 77; Δ36)  Energy/Vitality (49 vs. 66; Δ17)	
		Social Functioning (63 vs. 86; Δ23)	
		3333. A. 3553. mig (33 751 33)	

		Role Emotional (75 vs. 84; Δ10)	
		Mental Health (69 vs. 76; Δ9)	
		Mean SGRQ scores (scale 0-100, lower scores indicate better QoL; MID ~4-5 points based on COPD population) were lower compared to population normal consistently across all domains. Mean difference in total SGRQ in NTM patients compared to normal population was 31 points lower (39 vs. 8 points lower).	
		We found no other study in the population of interest that would evaluate patient attitudes towards other outcomes or treatments of interest.	
CTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	No research evidence was identified.	
BALANCE OF EFFECTS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>		
	<ul><li>∨ Varies</li><li>o Don't know</li></ul>		
RESOURCES REQUIRED	How large are the resource requirements (costs)?  • Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • Don't know	No research evidence was identified.	Cost will depend on drug regimen but it will be lower with 3 times weekly compared to daily treatment because the total weekly dose of ethambutol and azithromycin will be higher. For example, for a 70 kg person, they will take 7 tablets of azithromycin a week versus 6 tablets with three times weekly dosing and 17.5 tables of ethambutol a week versus 13 given three times a week. The number of rifampin capsules will remain the same whether administered daily or

			three times a week.
ESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was identified.	
COST EFFECTIVENESS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>		
	<ul><li>∨ Varies</li><li>No included studies</li></ul>		
	What would be the impact on health equity?	No research evidence was identified.	Except for cost - no.
EQUITY	<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>		
	<ul><li>∨ Varies</li><li>o Don't know</li></ul>		

ACCEPTABILITY	Is the intervention acceptable to key stakeholders?  No Probably no Probably yes Yes  Varies Don't know	No research evidence was identified.	There may be lower or higher adherence with three times weekly regimen. Also clinicians may be less or more prone to prescribe three times weekly vs daily.
	Is the intervention feasible to implement?	No research evidence was identified.	
FEASIBILITY	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li>o Varies</li><li>o Don't know</li></ul>		

		JUDGEMENT								
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know			
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know			
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies			
VALUES	Important uncertainty or variability	Possibly important uncertainty or	Probably no important uncertainty or	No important uncertainty or variability						

				JUDGEMENT				IMPLICATIONS
		variability	variability					
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with macrolide susceptible MAC pulmonary disease, should a daily or an intermittent macrolide-based regimen be used for treatment?

TYPE OF RECOMMENDATION	Strong recommendation	Conditional recommendation	Conditional recommendation	Conditional recommendation	Strong recommendation
	r ccommendation				

	against the intervention	against the intervention	for either the intervention or the comparison	for the intervention	for the intervention			
	0	0	0	•	0			
RECOMMENDATION	Recommendation 8a: In patients with nodular/bronchiectatic macrolide susceptible MAC pulmonary disease, we suggest a three times per week macrolide-based regimen rather than a daily macrolide-based regimen. (conditional recommendation, very low confidence in estimates of effect).							
	Recommendation 8b. In patients with fibrocavitary macrolide susceptible MAC pulmonary disease we suggest a daily macrolide-based regimen rather than three times per week macrolide-based regimen. (conditional recommendation, very low confidence in estimates of effect).							
	The panel members voted unanimously for a conditional recommendation for the intervention.							
JUSTIFICATION	Recommendation to use three times weekly in non-cavitary is based on similar efficacy, fewer adverse reactions and lower costs.							
	Recommendation to use daily administration in cavitary disease is based on a single study reporting very low culture conversion rates and the experience of the committee members given high risk of treatment failure and recurrence with cavitary disease.							
SUBGROUP CONSIDERATIONS								
IMPLEMENTATION CONSIDERATIONS								
MONITORING AND EVALUATION								
RESEARCH PRIORITIES	Is there a differences in response based on MAC species?							

## **Table E4.9. Question IX**

In patients with macrolide susceptible MAC pulmonary disease, should patients be treated with less than 12 months of treatment after culture negativity or 12 or more months of treatment after culture negativity?

**POPULATION:** pulmonary MAC infection

**INTERVENTION:** <12 months of treatment after culture negativity

**COMPARISON:** >/= 12 months of treatment after culture negativity

MAIN OUTCOMES: Culture conversion; Cure of NTM disease; Recurrence (relapse); Quality of Life; Development of antibiotic resistance; Death;

Adverse drug effects;

	JUDGEMENT		RESEARCH EV	ADDITIONAL CONSIDERATIONS			
EFFECTS	How substantial are the desirable anticipated effects?  o Trivial o Small • Moderate o Large	<12 months com	pared to >12 months for MAC	Dautzenberg 1994 10 months from culture conversion?			
ABLE		Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	№ of participants	Quality of the evidence	While not a controlled study, (Wallace, et al, 1996 Am J Respir Crit Care Med) showed high rates of relapse in patients who could only tolerate a shorter antibiotic course.
DESIR	<ul><li> Varies</li><li> Don't know</li></ul>						

	How substantial are the undesirable anticipated effects?  o Large		Risk with >12 months	Risk with <12 months	(95% CI)	(studies)	(GRADE)
0	<ul><li>Moderate</li><li>Small</li><li>Trivial</li><li>Varies</li></ul>	Culture conversion	856 per 1000	<b>222 per</b> <b>1000</b> (111 to 453)	<b>RR 0.26</b> (0.13 to 0.53)	207 (1 observational study)	⊕○○○ VERY LOW
ECTS	• Don't know	Cure of NTM disease - not reported	-	-	-	-	-
UNDESIRABLE EFFECTS		Recurrence (relapse) - not reported	-	-	-	-	-
UNDESIR		Quality of Life - not measured	-	-	-	-	-
		Development of antibiotic resistance - not measured	-	-	-	-	-
		Death - not reported	-	-	-	-	-
		Adverse drug effects - not reported	-	-	-	-	-
Щ	What is the overall certainty of the evidence of effects?	The relative imp interest:	ortance	or values o	of the i	main outcon	nes of
/IDENC	Very low Low Moderate	Outcome		Relative importa	nce Cert	tainty of the evide	nce (GRADE)
CERTAINTY OF EVIDENCE	<ul><li>o High</li><li>o No included studies</li></ul>	Culture conversion		CRITICAL	⊕⊜( VER`	OO Y LOW	
CERTAI		Cure of NTM disease		CRITICAL			
		Recurrence (relapse)		CRITICAL			

		Quality of Life	CRITICAL	
		Development of antibiotic resistance	CRITICAL	
		Death	CRITICAL	
		Adverse drug effects	CRITICAL	
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability	of life. In this study, patients with related quality of life with two QOI controls. Multivariable analysis sho function  Hong, et al, 2014 also evaluated t	I the impact of pulmo pulmonary NTM had a measures significant wed an association between patients with ted more health statifunction was also industrients had coinfection to pulmonatients had coinfection was also industrients	nary NTM on health-related quality significantly impaired health-tly lower than historical normal netween QOL scores and lung ary NTM on health-related quality of NTM disease and healthy subjects us issues and anxiety/depression dependently associated with QOL response to various treatment from with MAC or Pseudomonas).

# Does the balance between desirable and undesirable effects favor the intervention or the comparison?

- o Favors the comparison
- Probably favors the comparison
- Does not favor either the intervention or the comparison
- o Probably favors the intervention
- o Favors the intervention
- Varies
- o Don't know

#### <12 months compared to >12 months for MAC

Outcomes	Anticipated a		Relative effect	№ of participants	Quality of the evidence	
	Risk with >12 months	Risk with <12 months	(95% CI)	(studies)	(GRADE)	
Culture conversion	856 per 1000	<b>222 per</b> <b>1000</b> (111 to 453)	<b>RR 0.26</b> (0.13 to 0.53)	207 (1 observational study)	⊕○○○ VERY LOW	
Cure of NTM disease - not reported	-	-	-	-	-	
Recurrence (relapse) - not reported	-	-	-	-	-	
Quality of Life - not measured	-	-	-	-	-	
Development of antibiotic resistance - not measured	-	-	-	-	-	
Death - not reported	-	-	-	-	-	
Adverse drug effects - not reported	-	-	-	-	-	

Comparison is >12 months of treatment

The specter of early disease relapse merits a conservative approach in the absence of more convincing data for shorter course therapy.

and the same of th		
	No research evidence was identified.	
requirements (costs)?		
<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> <li>Varies</li> </ul>		
∘ Don't know		
Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was identified.	
<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>		
<ul><li> Varies</li><li> No included studies</li></ul>		
What would be the impact on health equity?	No research evidence was identified.	
<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>		
<ul><li> ∨aries</li><li> Don't know</li></ul>		
Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> <li>Varies</li> <li>Don't know</li> </ul> Does the cost-effectiveness of the intervention favor the intervention or the comparison? <ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul> Varies <ul> <li>No included studies</li> </ul> What would be the impact on health equity? <ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul> Varies <ul> <li>Don't know</li> </ul> Is the intervention acceptable to key stakeholders? <ul> <li>No</li> <li>Probably yes</li> </ul> No <ul> <li>Probably yes</li> </ul>	requirements (costs)?  Large costs Moderate costs Negligible costs and savings Large savings Varies Don't know  Does the cost-effectiveness of the intervention favor the intervention favor the intervention favor the intervention or the comparison Probably favors the comparison Probably favors the intervention Probably reduced Probably neduced Probably neduced Probably increased Increased Varies Don't know  Is the intervention acceptable to key stakeholders? No research evidence was identified.  No research evidence was identified.

	<ul><li>∨ Varies</li><li>∨ Don't know</li></ul>		
	Is the intervention feasible to implement?	No research evidence was identified.	
FEASIBILITY	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li>∨ Varies</li><li>o Don't know</li></ul>		

		JUDGEMENT									
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know				
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know				
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies				
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability							
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	Varies	Don't know				

		JUDGEMENT										
			the comparison									
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know					
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know					
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know					
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know					

In patients with macrolide susceptible MAC pulmonary disease, should patients be treated with less than 12 months of treatment after culture negativity or 12 or more months of treatment after culture negativity?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	0	•	0	0	0

RECOMMENDATION	We suggest that patients with MAC pulmonary disease should receive treatment for at least 12 months after culture conversion (conditional recommendation, very low confidence in estimates of effect).  The panel members voted unanimously for a conditional recommendation for the intervention.
JUSTIFICATION	Optimal treatment length is not known. Treatment for greater than 12 months after culture negativity is a conservative approach given risks of relapse.
	The microbiologic goal is 12 months of culture negativity while on treatment
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	
MONITORING AND EVALUATION	6 month cultures - sputum culture, but no need for bronchoscopy to obtain this
RESEARCH PRIORITIES	Clinical trial with strict definitions looking at culture conversion time (patients who do not convert by 6 months)
	Treatment length, intermittent treatment for relapse/reinfection

### Table E4.10. Question X

In patients with M. kansasii pulmonary disease, should an isoniazid-containing regimen or a macrolide-containing regimen be used for treatment?

**POPULATION:** Mycobacterium kansasii

**INTERVENTION:** a INH-containing regimen

**COMPARISON:** a macrolide-containing regimen

MAIN OUTCOMES: Cure of NTM; Death; Recurrence (relapse); Development of antibiotic resistance; Quality of life; Culture conversion; Adverse drug

effects;

		JUDGEMENT		RES	EARCH EVII	DENCE			ADDITIONAL CONSIDERATIONS
		How substantial are the desirable anticipated effects?	INH compared to no INH	for <i>Mycoba</i>	cterium kansa	asii			One study from the Research Committee of the British Thoracic
		o Trivial o Small	Outcomes	Anticipated		Relative effect	№ of participants	Quality of the evidence	Society in 1994 was a prospective study of 9 months treatment with rifampin and ethambutol. They found: 9/149 deaths, 68% had
	EFFECTS	<ul><li> Moderate</li><li> Large</li></ul>		Risk with	Risk with	(95% CI)	(studies)	(GRADE)	negative sputum (32% had no sputum, 0% positive at 9 months). There was a 9.7% relapse rate -
	DESIRABLE E	<ul><li> Varies</li><li> Don't know</li></ul>	Cure of NTM - not measured	-	-	-	-	-	this study had a shorter duration of therapy and did not have INH.
DES	DES		Death - not measured	-	-	-	-	-	Removing the potential for INH toxicity is a desirable anticipated effect. The importance of INH in the treatment regimen for <i>M</i> .
			Recurrence (relapse)	-	-	-	-	-	kansasii is at best questionable, more so in an era when safer and more effective agents are available.

EFFECTS	How substantial are the undesirable anticipated effects?  o Large o Moderate	Development of antibiotic
UNDESIRABLE EF	<ul><li>Small</li><li>Trivial</li><li>Varies</li><li>Don't know</li></ul>	Culture conversion - not reported
NO		Adverse drug effects - not reported
CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects?  • Very low • Low • Moderate • High  • No included studies	No research evidence was identified.
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • No important uncertainty or variability • No known undesirable outcomes	No research evidence was identified.

BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention • Varies • Don't know	No research evidence was identified.	
RESOURCES REQUIRED	How large are the resource requirements (costs)?  o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No research evidence was identified.	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Reduced Probably reduced Probably no impact	No research evidence was identified.	

	<ul><li> Probably increased</li><li> Increased</li><li> Varies</li><li> Don't know</li></ul>		
PTABILITY	Is the intervention acceptable to key stakeholders?  O No O Probably no O Probably yes O Yes O Varies O Don't know	No research evidence was identified.	
3ILITY	Is the intervention feasible to implement?  No Probably no Probably yes Yes  Varies Don't know	No research evidence was identified.	

		JUDGEMENT									
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know				
UNDESIRABLE	Large	Moderate	Small	Trivial		Varies	Don't know				

		IMPLICATIONS						
EFFECTS								
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with *M. kansasii* pulmonary disease, should an isoniazid-containing regimen or a macrolide-containing regimen be used for treatment?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	0	0	•	0	0
RECOMMENDATION	In patients with rifampicir either isoniazid or macroli The panel members voted	ide. (conditional recomme	ndation, very low confider	nce in estimates of effect )	).
JUSTIFICATION	Isoniazid is widely used a members, there have been higher rooms.  Based on the results of tweffectively substituted for	en good outcomes when us elapse rates in regiments wo small retrospective cohe	sing this. without INH (or macrolide	s), albeit in non-comparat	tive studies.
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION					

RESEARCH PRIORITIES	

#### Table E4.11. Question XI

In patients with rifampicin-susceptible M. kansasii pulmonary disease, should amikacin or streptomycin be included in the treatment regimen?

**POPULATION:** M kansasii pulmonary infection

**INTERVENTION:** a treatment regimen with a parenteral agent

**COMPARISON:** a treatment regimen without a parenteral agent

MAIN OUTCOMES: Cure of NTM; Death; Recurrence (relapse); Culture Conversion; Any adverse effect; Serious Adverse Effect; Withdrawal owing to adverse

effects; Quality of Life; Development of Antibiotic Resistance;

	JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
ည	How substantial are the desirable anticipated effects?	Parenteral compar	ed to no parent		Except for rifampin-resistant <i>M. kansasii</i> disease, parenteral agents ae seldom needed to treat use with <i>M.</i>			
E EFFECT	<ul><li>○ Trivial</li><li>• Small</li></ul>	Outcomes	Anticipated absolute effects* (95% CI)		Relative effect	№ of participants	Quality of the	kansasii.
DESIRABLE	<ul><li>Moderate</li><li>Large</li><li>Varies</li></ul>		Risk with no parenteral	Risk with Parenteral	(95% CI)	(studies)	evidence (GRADE)	
П	o Don't know		agent					

	How substantial are the undesirable anticipated effects?	Cure of NTM	8/10 (80.0%)	-	-	10 (1 observational	⊕○○○ VERY LOW	Success rate is so high with current regimens, parenteral agents are rarely being used - risk of toxicity and adverse effects may outweigh benefit
	<ul><li>Large</li><li>Moderate</li><li>Small</li></ul>	Death	30/121	not pooled	not	study)	<del></del>	auroise circuit may cathroigh continu
	<ul><li> Trivial</li><li> Varies</li><li> Don't know</li></ul>		(24.8%)		pooled	(2 observational studies)	VERY LOW	
		Recurrence (relapse)	6/115 (5.2%)	not pooled	not pooled	115 (2 observational studies)	⊕○○○ VERY LOW 1,2	
FECTS		Culture Conversion	42/44 (95.5%)	not pooled	not pooled	44 (2 observational studies)	⊕○○○ VERY LOW 1,2	
UNDESIRABLE EFFECTS		Any adverse effect	11/75 (14.7%)	-	-	75 (1 observational study)	⊕○○ VERY LOW 1,2	
Nn		Serious Adverse Effect	0/75 (0.0%)	-	-	75 (1 observational study)	⊕○○ VERY LOW 1,2	
		Withdrawal owing to adverse effects	7/75 (9.3%)	-	-	75 (1 observational study)	⊕○○ VERY LOW 1,2	
		Quality of Life - not measured	-	-	-	-	-	
		Development of Antibiotic Resistance - not measured	-	-	-	-	-	

## What is the overall certainty of the evidence of effects?

- Very low
- o Low
- Moderate
- ∘ High
- No included studies

#### The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
Cure of NTM	CRITICAL	⊕○○○ VERY LOW
Death	CRITICAL	⊕○○○ VERY LOW
Recurrence (relapse)	CRITICAL	⊕○○○ VERY LOW
Culture Conversion	CRITICAL	⊕○○○ VERY LOW
Any adverse effect	CRITICAL	⊕○○○ VERY LOW
Serious Adverse Effect	CRITICAL	⊕○○○ VERY LOW
Withdrawal owing to adverse effects	CRITICAL	⊕○○○ VERY LOW
Quality of Life	CRITICAL	-
Development of Antibiotic Resistance	CRITICAL	-

VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability	Values and preferences:  Three relevant studies were identified that provide data on patient values and preferences:  Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls. Multivariable analysis showed an association between QOL scores and lung function  Hong, et al, 2014 also evaluated the impact of pulmonary NTM on health-related quality of life. This was a direct comparison between patients with NTM disease and healthy subjects and found patients with NTM reported more health status issues and anxiety/depression issues than healthy controls. Lung function was also independently associated with QOL scores.  Czaja, et al 2015 evaluated change in quality of life in response to various treatment regimens for <i>M. abscessus</i> (many patients had coinfection with MAC or Pseudomonas). Mean QOL score was significantly improved after treatment at 3, 6, 12, and 24 months.	

ECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison	Parenteral com Outcomes	Anticipated ab effects* (95% Risk with no	solute	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
BALANCE OF EFFECTS	<ul> <li>Probably favors the intervention</li> <li>Favors the intervention</li> <li>Varies</li> <li>Don't know</li> </ul>	Cure of NTM	agent 8/10 (80.0%)	-		10 (1 observational study)	⊕○○○ VERY LOW 1,2
		Death	30/121 (24.8%)	not pooled	not pooled	121 (2 observational studies)	⊕○○○ VERY LOW 1,2

Recurrence (relapse)	6/115 (5.2%)	not pooled	not pooled	115 (2 observational studies)	⊕○○○ VERY LOW 1,2
Culture Conversion	42/44 (95.5%)	not pooled	not pooled	44 (2 observational studies)	⊕○○○ VERY LOW 1,2
Any adverse effect	11/75 (14.7%)	-	-	75 (1 observational study)	⊕○○○ VERY LOW 1,2
Serious Adverse Effect	0/75 (0.0%)	-	-	75 (1 observational study)	⊕○○○ VERY LOW 1,2
Withdrawal owing to adverse effects	7/75 (9.3%)	-	-	75 (1 observational study)	⊕○○○ VERY LOW 1,2
Quality of Life - not measured	-	-	-	-	-
Development of Antibiotic Resistance - not measured	-	-	-	-	-

RESOURCES REQUIRED	How large are the resource requirements (costs)?  • Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • Don't know	No research evidence was identified.	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention  • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Output  Reduced Probably reduced Probably no impact Probably increased Increased Varies Don't know	No research evidence was identified.	In some settings, parenteral may only be available to select patients based on financial resources.

	Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
PTABILITY	<ul> <li>No</li> <li>Probably no</li> <li>Probably yes</li> <li>Yes</li> <li>Varies</li> <li>Don't know</li> </ul>		
	Is the intervention feasible to implement?	No research evidence was identified.	
SIBILI	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li> Varies</li><li> Don't know</li></ul>		

		JUDGEMENT									
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know				
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know				
CERTAINTY OF	Very low	Low	Moderate	High			No included studies				

		IMPLICATIONS						
EVIDENCE								
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, should amikacin or streptomycin be included in the treatment regimen?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	0	0	0	0
RECOMMENDATION	We suggest that neither a (Conditional recommenda	tion, very low confidence	in estimates of effect).(1	.0 Strong, 5 Conditional, 3	3 Abstain)
	The panel members voted effect.	l for a strong recommenda	ation against the intervent	cion despite a very low cor	nfidence in estimate of
JUSTIFICATION		drug, either isoniazid or a disease warrants intraver s. s of culture conversion and sociated with amikacin and	macrolide.  nous therapy, <i>M. kansasii</i> d treatment success obser	can be treated with a rifar ved with oral regimens fo	
	be used as mist-line thera	ру 101 <i>М. канзазн</i> .			
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION					
RESEARCH PRIORITIES					165

### **Table E4.12. Question XII**

In patients with rifampicin susceptible *M. kansasii* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?

**POPULATION:** M kansasii pulmonary infection

**INTERVENTION:** a regimen with a fluoroquinolone

**COMPARISON:** a regimen without a fluoroquinolone

MAIN OUTCOMES: Cure of NTM Disease; Development of antibiotic resistance; Recurrence

(relapse); Quality of Life; Culture Conversion; Death; Adverse drug effects;

	JUDGEMENT		RESEARC	H EVIDENCE				ADDITIONAL CONSIDERATIONS
TS	How substantial are the desirable anticipated effects?	Fluoroquinolone compared	l to no fluoroquino	lone for <i>M. kansa</i>	sii			The use of a fluoroquinolone (or a macrolide) means that INH can
E EFFECTS	<ul><li> Trivial</li><li> Small</li></ul>	Outcomes	Anticipated absol	ute effects*	Relative effect	№ of participants	Quality of the	be dropped from the regimen with the attendant risk for INH toxicity.
DESIRABLE	<ul><li> Moderate</li><li> Large</li></ul>		Risk with no Fluoroquinolone	Risk with	(95% CI)	(studies)	evidence (GRADE)	
DI	Varies     Don't know							

	How substantial are the undesirable	Cours of NTM Diseases and					
	anticipated effects?	Cure of NTM Disease - not - measured	-		-		
	∘ Large						
	Moderate	Development of antibiotic -	-		-		
	o Small	resistance - not measured					
S	o Trivial	Recurrence (relapse) - not -	-				
EFFECTS	o Varies	measured					
出	Don't know						
BLE		Quality of Life - not - measured	-		-		
SIR/							
UNDESIRABLE		Culture Conversion - not -	-		-		
5		measured					
		Death - not measured -	_		_		
		Adverse drug effects - not -	-		-		
		measured					
	What is the overall certainty of the	No wasangh ayidanga yang idankisi ad					
CERTAINTY OF EVIDENCE	evidence of effects?	No research evidence was identified.					
IDE	∘ Very low						
	∘ Low						
\ \	<ul><li>o Moderate</li><li>o High</li></ul>						
INI							
ERT/	No included studies						
Ö							
	Is there important uncertainty about	Values and preferences:					
	or variability in how much people value the main outcomes?	There are a second of the seco	عداد داداد المراسم عماية	makiamk velves	d mustau		
(0		Three relevant studies were identified	nat provide data on	patient values an	u preferences:		
VALUES	<ul><li> Important uncertainty or variability</li><li> Possibly important uncertainty or</li></ul>	Mehta and Marras, 2011 evaluated the	impact of pulmonar	y NTM on health-i	related quality		
\ A	variability	of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls.					
	Probably no important uncertainty or	Multivariable analysis showed an assoc	iation between QOL	scores and lung f	unction		
	variability  o No important uncertainty or variability	Hong, et al, 2014 also evaluated the ir	npact of pulmonary	NTM on health-rel	ated quality of		
	, , , , , , , , , , , , , , , , , , , ,	3, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	p				

Does the balance between desirable and undesirable effects favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Probab			and found patients issues than health scores.  Czaja, et al 2015 regimens for <i>M. al</i>	rect comparison betw s with NTM reported by controls. Lung fun evaluated change in bscessus (many pati was significantly impi	more health statuction was also inde quality of life in reents had coinfection	s issues a ependently esponse to on with MA	nd anxiety/de v associated v various treat C or Pseudor	epression with QOL tment monas).	
O Favors the intervention Disease - not	FECTS	and undesirable effects favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison		Anticipated absolu	te effects* (95%	Relative effect (95%	participants	the evidence	
	BALANCE OF EF	<ul><li>Favors the intervention</li><li>Varies</li></ul>	Disease - not	-	-	-	-	-	

		T.			T.
		measured			
		Quality of Life - not - measured	-	 -	
		Culture Conversion - - not measured	-	 -	
		Death - not - measured	-	 -	
		Adverse drug - effects - not measured		 -	
ED	How large are the resource requirements (costs)?	No research evidence was identified.			
RESOURCES REQUIRED	<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> </ul>				
RES	Varies Don't know				
SS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was identified.			
COST EFFECTIVENESS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>				
	Varies     No included studies				
EQUI	What would be the impact on health	No research evidence was identified.			

	equity?		
	<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>		
	<ul><li> Varies</li><li> Don't know</li></ul>		
	Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
ACCEPIABI	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li> Varies</li><li> Don't know</li></ul>		
	Is the intervention feasible to implement?	No research evidence was identified.	
SIBIL	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li> Varies</li><li> Don't know</li></ul>		

JUDGEMENT	IMPLICATIONS

				JUDGEMENT				IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

## Should a regimen with a fluoroquinolone vs. a regimen without a fluoroquinolone be used for *M. kansasii* pulmonary infection?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
RECOMMENDATION	In patients with rifampicinand either isoniazid or material effect).  In patients with rifampicin (e.g., moxifloxacin) be useffect).  The panel members voted	crolide instead of a fluoro n resistant <i>M. kansasii</i> or i ed as part of a second-lin	quinolone (conditional rec ntolerance to one of the fi e regimen (conditional rec	ommendation, very low consideration of the constant of the con	onfidence in estimates of gest a fluoroquinolone
JUSTIFICATION	Treatment success of <i>M. k</i> companion drugs is not cludrug may be isoniazid or a there is more experience companion drug, these drug treatment studies using the	ear. While ethambutol is un a macrolide. Which of the and better evidence for tr ugs should be the preferro	usually the preferred comp se drugs is superior for the eatment regimens that inc ed choice. Fluoroquinolone	panion drug, the choice of e treatment of <i>M. kansasii</i> clude isoniazid or a macro	the second companion is unclear at present. As lide as the second
SUBGROUP CONSIDERATIONS					

IMPLEMENTATION CONSIDERATIONS	
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Randomized clinical trials comparing regimens with macrolides to regimens with moxifloxacin.

#### **Table E4.13. Question XIII**

In patients with rifampicin susceptible M. kansasii pulmonary disease, should a three times per week or daily treatment regimen be used?

**POPULATION:** M kansasii pulmonary infection

**INTERVENTION:** a three times per week treatment regimen

**COMPARISON:** a daily treatment regimen

MAIN OUTCOMES: Cure of NTM; Death; Recurrence (relapse); Culture Conversion; Any Adverse Effect; Serious adverse effects; Withdrawal owing to

adverse effects; Quality of Life; Development of antibiotic resistance;

	JUDGEMENT		R	RESEARCH EVI	DENCE			ADDITIONAL CONSIDERATIONS
CTS	How substantial are the desirable anticipated effects?	M kansasii TIW compa	ared to daily fo	r M kansasii				
E EFFECTS	o Trivial ● Small	Outcomes	Anticipated effects* (95		Relative effect	№ of participants	Quality of the evidence	
DESIRABLE	<ul><li>o Moderate</li><li>o Large</li></ul>		Risk with	Risk with M	(95% CI)	(studies)	(GRADE)	
DE	<ul><li>∨ Varies</li><li>o Don't know</li></ul>							

		How substantial are the		2 / 2				
		undesirable anticipated effects?  • Large	Cure of NTM	0/0	115/182 (63.2%)	not pooled	182 (2 observational studies)	⊕○○○ VERY LOW 1,2,3
		<ul><li> Moderate</li><li> Small</li><li> Trivial</li></ul>	Death	0/18 (0.0%)	39/229 (17.0%)	not pooled	247 (3 observational studies)	⊕○○○ VERY LOW <sup>2,3</sup>
		<ul><li> Varies</li><li> Don't know</li></ul>	Recurrence (relapse)	0/14 (0.0%)	16/178 (9.0%)	not pooled	192 (3 observational studies)	⊕○○○ VERY LOW <sup>1,3</sup>
	FECTS	ECTS	Culture Conversion	17/18 (94.4%)	238/257 (92.6%)	not pooled	275 (4 observational studies)	⊕○○○ VERY LOW <sup>1,3</sup>
	UNDESIRABLE EFFECTS	Any Adverse Effect	0/18 (0.0%)	0/0	not estimable	18 (1 observational study)	⊕○○○ VERY LOW <sup>1,3</sup>	
	UNDE	UNDE	Serious adverse effects	0/18 (0.0%)	0/28 (0.0%)	not pooled	46 (2 observational studies)	⊕○○○ VERY LOW <sup>1,3</sup>
			Withdrawal owing to adverse effects	0/18 (0.0%)	0/28 (0.0%)	not pooled	46 (2 observational studies)	⊕○○○ VERY LOW <sup>1,3</sup>
			Quality of Life - not measured	-	Н	-	-	-
			Development of antibiotic resistance - not measured	-	-	-	-	-
1			-					

## What is the overall certainty of the evidence of effects?

- Very low
- o Low
- Moderate
- ∘ High
- No included studies

#### The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
Cure of NTM	CRITICAL	⊕○○○ VERY LOW
Death	CRITICAL	⊕○○○ VERY LOW
Recurrence (relapse)	CRITICAL	⊕○○○ VERY LOW
Culture Conversion	CRITICAL	⊕○○○ VERY LOW
Any Adverse Effect	CRITICAL	⊕○○○ VERY LOW
Serious adverse effects	CRITICAL	⊕○○○ VERY LOW
Withdrawal owing to adverse effects	CRITICAL	⊕○○○ VERY LOW
Quality of Life	CRITICAL	-
Development of antibiotic resistance	CRITICAL	-

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# Is there important uncertainty about or variability in how much people value the main outcomes?

- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

Values and preferences:

Three relevant studies were identified that provide data on patient values and preferences:

Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls. Multivariable analysis showed an association between QOL scores and lung function

Hong, et al, 2014 also evaluated the impact of pulmonary NTM on health-related quality of life. This was a direct comparison between patients with NTM disease and healthy subjects and found patients with NTM reported more health status issues and anxiety/depression issues than healthy controls. Lung function was also independently associated with QOL scores.

Czaja, et al 2015 evaluated change in quality of life in response to various treatment regimens for *M. abscessus* (many patients had coinfection with MAC or Pseudomonas). Mean QOL score was significantly improved after treatment at 3, 6, 12, and 24 months.

Does the balance between desirable and undesirable effects favor the intervention or the comparison?  M kansasii TIW compared to daily for M kansasii  Outcomes  Anticipated absolute effects*  (95% CI)  Risk with daily  Risk with M kansasii TIW  Probably favors the comparison  Probably favors the intervention  Probably favors the intervention  Favors the intervention  Outcomes  Anticipated absolute effects*  (95% CI)  Risk with M kansasii TIW  Cure of NTM  O/O  115/182  (63.2%)  Outcomes  Anticipated absolute effects*  (95% CI)  (95% CI)  Outcomes  Outcomes  Anticipated absolute effects*  (95% CI)  (95% CI)  Outcomes  O								
obset varional 17-19	desirable and undesirable effects favor the intervention or		Anticipated absolution (95% CI)	ite effects*	effect	participants	the evidence	
	Does not favor either the intervention or the comparison     Probably favors the intervention     Favors the intervention	Cure of NTM		kansasii TIW	not pooled	(2	⊕○○○ VERY LOW	

Death	0/18 (0.0%)	39/229 (17.0%)	not pooled	247 (3 observational studies)	⊕○○○ VERY LOW 2,3
Recurrence (relapse)	0/14 (0.0%)	16/178 (9.0%)	not pooled	192 (3 observational studies)	⊕○○○ VERY LOW 1,3
Culture Conversion	17/18 (94.4%)	238/257 (92.6%)	not pooled	275 (4 observational studies)	⊕○○○ VERY LOW 1,3
Any Adverse Effect	0/18 (0.0%)	0/0	not estimable	18 (1 observational study)	⊕○○○ VERY LOW 1,3
Serious adverse effects	0/18 (0.0%)	0/28 (0.0%)	not pooled	46 (2 observational studies)	⊕○○○ VERY LOW 1,3
Withdrawal owing to adverse effects	0/18 (0.0%)	0/28 (0.0%)	not pooled	46 (2 observational studies)	⊕○○○ VERY LOW 1,3
Quality of Life - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-

RESOURCES REQUIRED	How large are the resource requirements (costs)?  • Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • Don't know	No research evidence was identified.	
ECTIVENES	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention  • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Reduced Probably reduced Probably no impact Probably increased Increased Varies Don't know	No research evidence was identified.	

	Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
CEPTABILITY	<ul> <li>No</li> <li>Probably no</li> <li>Probably yes</li> <li>Yes</li> <li>Varies</li> <li>Don't know</li> </ul>		
	Is the intervention feasible to implement?	No research evidence was identified.	
SIBIL	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li> Varies</li><li> Don't know</li></ul>		

		JUDGEMENT									
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know				
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know				
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies				
VALUES	Important uncertainty or	Possibly important	Probably no important	No important uncertainty or							

		IMPLICATIONS						
	variability	uncertainty or variability	uncertainty or variability	variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with rifampicin susceptible *M. kansasii* pulmonary disease, should a three times per week or daily treatment regimen be used?

TYPE OF RECOMMENDATION	Strong	Conditional	Conditional	Conditional	Strong
	recommendation	recommendation	recommendation	recommendation	recommendation

	against the intervention	against the intervention	for either the intervention or the comparison	for the intervention	for the intervention				
	0	0	•	0	0				
RECOMMENDATION	In patients with nodular/bronchiectatic <i>M. kansasii</i> pulmonary disease treated with a rifampicin, ethambutol and macrolide regimen, we suggest either daily or three times weekly treatment. (conditional recommendation, very low confidence in estimates of effect).  The panel members voted unanimously for a conditional recommendation for either the intervention or comparison.								
	In patients with fibrocavitary <i>M. kansasii</i> pulmonary disease treated with a rifampicin, ethambutol and macrolide-based regimen, we suggest daily treatment as opposed to three times weekly treatment. (conditional recommendation, very low confidence in estimates of effect).								
	The panel members voted unanimously for a conditional recommendation for the comparison.								
	In all patients with <i>M. kansasii</i> pulmonary disease treated with an isoniazid, ethambutol and rifampicin regimen, we suggest treatment be given daily. (conditional recommendation, very low confidence in estimates of effect).								
	The panel members voted	I unanimously for a condit	ional recommendation for	the comparison.					
JUSTIFICATION	Cavitary disease has high	er morbidity and mortality	and warrants a more agg	ressive treatment approa	nch.				
SUBGROUP CONSIDERATIONS									

IMPLEMENTATION CONSIDERATIONS	
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	Randomized trial comparing three times weekly vs daily regimens in cavitary and nodular/bronchiectatic <i>M. kansasii</i> .  Role of higher doses of antimicrobial drugs and therapeutic drug monitoring should be explored to determine whether optimizing drug levels is beneficial
	ulug levels is beliericial

#### **Table E4.14. Question XIV**

In patients with rifampicin-susceptible M. kansasii pulmonary disease, should treatment be continued for less than 12 months or 12 or more months?

**POPULATION:** M kansasii pulmonary infection

**INTERVENTION:** <12 months of treatment after culture negativity

**COMPARISON:** >/= 12 months of treatment after culture negativity

MAIN OUTCOMES: Cure of NTM; Recurrence; Culture Conversion; Quality of Life; Development of Antibiotic Resistance; Death; Adverse Drug Effects;

v anticipated effects? that description	here are a number of studies nat describe outcomes of <i>M</i> .
C12 months compared to >12 months for M kansasii duration of	ansasii with "short" or "long" uration of treatment, but
Outcomes  Anticipated absolute  of Moderate  Large  Outcomes  Anticipated absolute  effects* (95% CI)  Relative  of participants evidence  evidence  approach  ERJ 2009	ithout direct comparison. For istance, Santin, et al., published esults on a 12 month treatment pproach (retrospective cohort - RJ 2009;33:148-52), reporting .6% relapse rate.

	How substantial are the							The undesirable anticipated effect
	undesirable anticipated effects?		Risk with		(95% CI)	(studies)	(GRADE)	might be inadequate treatment with progressive disease
	∘ Large		>12 months	<12 months				morbidity and prolonged
	<ul><li> Moderate</li><li> Small</li><li> Trivial</li></ul>	Cure of NTM	1000 per 1000	1000 per 1000 (880 to 1000)	<b>RR 1.00</b> (0.88 to 1.14)	28 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2</sup>	exposure to antibiotic toxicity
CTS	<ul><li> ∨ Varies</li><li> ⊃ Don't know</li></ul>	Recurrence	0 per 1000	<b>0 per 1000</b> (0 to 0)	<b>RR 3.00</b> (0.13 to 67.91)	28 (1 RCT)	⊕⊕○○ LOW <sup>1,2</sup>	
UNDESIRABLE EFFECTS		Culture Conversion	1000 per 1000	<b>1000 per</b> <b>1000</b> (880 to 1000)	<b>RR 1.00</b> (0.88 to 1.14)	28 (1 RCT)	⊕⊕○○ LOW <sup>1,2,3</sup>	
UNDESI		Quality of Life - not measured	-	-	-	-	-	
		Development of Antibiotic Resistance - not measured	-	-	-	-	-	
		Death - not reported	-	-	-	-	-	
		Adverse Drug Effects - not reported	-	-	-	-	-	
	What is the overall certainty of the evidence of effects?							
ENCE	• Very low	The relative importance	e or values o	of the main out	tcomes o	f interest:		
F EVID	Low     Moderate	Outcome	Re	elative importan	Certaii	nty of the evid	dence (GRADE)	
CERTAINTY OF EVIDENCE	○ High ○ No included studies	Cure of NTM	CI	RITICAL	⊕○○○ VERY L			
CER		Recurrence	CI	RITICAL	⊕○○○ VERY L			

				1	
		Culture Conversion	CRITICAL	⊕○○○ VERY LOW	
		Quality of Life	CRITICAL		
		Development of Antibiotic Resistance	CRITICAL		
		Death	CRITICAL		
		Adverse Drug Effects	CRITICAL		
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability variability	Values and preferences:  Three relevant studies were identific. Mehta and Marras, 2011 evaluated of life. In this study, patients with properties of life with two QOL measure. Multivariable analysis showed an assumed the life. This was a direct comparison be and found patients with NTM report issues than healthy controls. Lung from scores.  Czaja, et al 2015 evaluated change regimens for <i>M. abscessus</i> (many properties).	the impact of pulmor pulmonary NTM had ses significantly lower sociation between QC e impact of pulmonar etween patients with led more health statufunction was also indefined in quality of life in relations had coinfection	nary NTM on health-related quality ignificantly impaired health-related than historical normal controls. OL scores and lung function  BY NTM on health-related quality of NTM disease and healthy subjects is issues and anxiety/depression ependently associated with QOL esponse to various treatment on with MAC or Pseudomonas). Mean	

# Does the balance between desirable and undesirable effects favor the intervention or the comparison?

- o Favors the comparison
- Probably favors the comparison
- $\circ$  Does not favor either the intervention or the comparison
- Probably favors the intervention
- o Favors the intervention
- Varies
- o Don't know

#### <12 months compared to >12 months for M kansasii **Anticipated absolute** Nº of Outcomes Relative Quality of the effects\* (95% CI) effect participants evidence (95% CI) (studies) (GRADE) Risk with Risk with >12 months <12 months Cure of NTM 1000 per 1000 per **RR 1.00** 28 $\Theta\ThetaOO$ 1000 1000 (0.88 to(1 RCT) LOW 1,2 (880 to 1000) 1.14) 0 per 1000 28 0 per 1000 **RR 3.00** $\Theta\ThetaOO$ Recurrence (0 to 0)(0.13 to (1 RCT) LOW 1,2 67.91) 1000 per 1000 per **RR 1.00** 28 **Culture Conversion** $\Theta\ThetaOO$ 1000 1000 LOW 1,2,3 (0.88 to (1 RCT) (880 to 1000) 1.14) Quality of Life - not measured Development of Antibiotic Resistance - not measured Death - not reported Adverse Drug Effects - not reported

How large are the resource requirements (costs)?	No research evidence was identified.	
requirements (sects)?		
requirements (costs)?		
<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> <li>Varies</li> </ul>		
o Don't know		
Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was identified.	
<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>		
<ul><li>∨ Varies</li><li>∨ No included studies</li></ul>		
What would be the impact on health equity?	No research evidence was identified.	
<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>		
<ul><li>∨ Varies</li><li>o Don't know</li></ul>		
Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> <li>Varies</li> <li>Don't know</li> <li>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</li> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> <li>Varies</li> <li>No included studies</li> <li>What would be the impact on health equity?</li> <li>Reduced</li> <li>Probably reduced</li> <li>Probably increased</li> <li>Increased</li> <li>Varies</li> <li>Don't know</li> <li>Is the intervention acceptable to key stakeholders?</li> <li>No</li> <li>Probably yes</li> </ul>	Negligible costs and savings     Negligible costs and savings     Nederate savings     Varies     Don't know  Does the cost-effectiveness of the intervention or the comparison?     Favors the comparison     Probably favors the comparison     Probably favors the intervention or the comparison     Probably favors the intervention or the comparison     Probably favors the intervention     Favors the intervention     Varies     No included studies  What would be the impact on health equity?  Reduced     Probably reduced     Probably no impact     Probably increased     Increased     Increased     Varies     Don't know  Is the intervention acceptable to key stakeholders?  No research evidence was identified.

	o Varies o Don't know		
	Is the intervention feasible to implement?	No research evidence was identified.	
SIBILI	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li> Varies</li><li> Don't know</li></ul>		

		JUDGEMENT									
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know				
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know				
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies				
VALUES	Important uncertainty or	Possibly important	Probably no important	No important uncertainty or							

			:	JUDGEMENT				IMPLICATIONS
	variability	uncertainty or variability	uncertainty or variability	variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with rifampicin-susceptible M. kansasii pulmonary disease, should treatment be continued for less than

#### 12 months or 12 or more months?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention			
RECOMMENDATION	We suggest that patients with rifampicin susceptible <i>M. kansasii</i> pulmonary disease be treated for at least 12 months regardless of when culture conversion occurs (conditional recommendation, very low confidence in estimates of effect).  The expert panel voted unanimously for a conditional recommendation for the comparison.							
JUSTIFICATION	M. kansasii can be associa outcomes are excellent. T							
SUBGROUP CONSIDERATIONS								
IMPLEMENTATION CONSIDERATIONS								
MONITORING AND EVALUATION								
RESEARCH PRIORITIES	Clinical trials to determine optimal duration of therapy.							
	Clinical trial of shorter regimens: 9 months rifampin/ethambutol/macrolide vs. 12 months isoniazid/rifampin/ethambutol.							
	Clinical trial of 6 vs 12 mc	onths - moxifloxicin/clarith	romycin/rifampin.					

#### Table E4.15. Question XV

In patients with M. xenopi pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?

**POPULATION:** patients with newly diagnosed pulmonary M. xenopii infection

**INTERVENTION:** a quinolone containing regimen

**COMPARISON:** regimen without a fluoroquinolone

MAIN OUTCOMES: Death; Quality of life; Cure of NTM disease; Recurrence (relapse); Culture conversion; Development of antibiotic resistance; Severe

adverse effects; Any adverse effects;

	JUDGEMENT		RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
How substantial are the desirable anticipated effects?  • Trivial • Small		nining regimen compared to regimen withoused pulmonary M. xenopii infection	out a fluore	oquinolone in į	patients	An ongoing study by C. Andrejak, et al (CaMoMy study), has shown no difference between groups for 6 month sputum conversion, adverse events.	
DESIRABLE	<ul><li> Moderate</li><li> Large</li><li> Varies</li><li> Don't know</li></ul>	Outcomes	Anticipated absolute effects* (95% CI)	Relative	№ of	Quality of	

	How substantial are the undesirable anticipated effects?  • Large		Risk with regimen without a fluoroquinolone	Risk with a quinolone containing regimen	effect (95% CI)	participants (studies)	the evidence (GRADE)
	<ul><li> Moderate</li><li> Small</li><li> Trivial</li><li> Varies</li></ul>	Death follow up: 5 years	29 per 100	<b>47 per 100</b> (19 to 100)	<b>RR 1.60</b> (0.66 to 3.91)		⊕⊕○○ LOW <sup>1,2</sup>
	o Don't know	Quality of life - not measured	-	-	-	-	-
EFFECTS		Cure of NTM disease follow up: 5 years	35 per 100	<b>35 per 100</b> (14 to 88)	<b>RR 1.00</b> (0.40 to 2.48)		⊕⊕○○ LOW <sup>1,2</sup>
UNDESIRABLE EFF		Recurrence (relapse) follow up: 5 years	12 per 100	<b>2 per 100</b> (0 to 46)	<b>RR 0.20</b> (0.01 to 3.88)		⊕⊕○○ LOW <sup>1,3</sup>
UNDE		Culture conversion - not reported	-	-	-	-	-
		Development of antibiotic resistance - not measured	-	-	-	-	-
		Severe adverse effects - not reported	-	-	-	-	-
		Any adverse effects follow up: 2 years	20 per 100	<b>20 per 100</b> (14 to 31)	<b>RR 1.03</b> (0.69 to 1.55)		⊕○○ VERY LOW 1,4,5

	What is the overall certainty of the evidence of effects?	The relative importance or valu	es of the main outco	mes of interest:
	∘ Very low	Outcome	Relative importance	Certainty of the evidence (GRADE)
	<ul><li>Low</li><li>Moderate</li><li>High</li></ul>	Death	CRITICAL	⊕⊕○○ LOW
	No included studies	Quality of life	CRITICAL	-
		Cure of NTM disease	CRITICAL	⊕⊕○○ LOW
		Recurrence (relapse)	CRITICAL	⊕⊕○○ LOW
ENCE		Culture conversion	CRITICAL	-
CERTAINTY OF EVIDENCE		Development of antibiotic resistance	CRITICAL	-
VINTY O		Severe adverse effects	CRITICAL	-
CERT/		Any adverse effects	CRITICAL	⊕○○○ VERY LOW

VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • No important uncertainty or	Three relevant studies were identified that provide data on patient values and preferences: Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls. Multivariable analysis showed an association between QOL scores and lung function.  Hong, et al, 2014 also evaluated the impact of pulmonary NTM on health-related quality of life. This was a direct comparison between patients with NTM disease and healthy subjects and found patients with NTM reported more health status issues and anxiety/depression issues than healthy controls. Lung function was also independently associated with QOL scores.  Czaja, et al 2015 evaluated change in quality of life in response to various treatment regimens for <i>M. abscessus</i> (many patients had coinfection with MAC or Pseudomonas). Mean QOL score was significantly improved after treatment at 3, 6, 12, and 24 months.	

# Does the balance between desirable and undesirable effects favor the intervention or the comparison?

- Favors the comparison
- o Probably favors the comparison
- Does not favor either the intervention or the comparison
- Probably favors the intervention
- o Favors the intervention
- Varies
- o Don't know

A quinolone containing regimen compared to regimen without a fluoroquinolone in patients

with newly diagnos	sed pulmonary M. xeno	pii infection		· '	
Outcomes	Risk with regimen without a fluoroquinolone		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Death follow up: 5 years	29 per 100	<b>47 per 100</b> (19 to 100)	<b>RR 1.60</b> (0.66 to 3.91)	34 (1 RCT)	⊕⊕○○ LOW <sup>1,2</sup>
Quality of life - not measured	-	-	-	-	-
Cure of NTM disease follow up: 5 years	35 per 100	<b>35 per 100</b> (14 to 88)	<b>RR 1.00</b> (0.40 to 2.48)	34 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2</sup>
Recurrence (relapse) follow up: 5 years	12 per 100	<b>2 per 100</b> (0 to 46)	<b>RR 0.20</b> (0.01 to 3.88)	34 (1 RCT)	⊕⊕○○ LOW <sup>1,3</sup>
Culture conversion - not reported	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-
Severe adverse effects - not reported	-	-	-	-	-
Any adverse effects follow up: 2 years	20 per 100	<b>20 per 100</b> (14 to 31)	<b>RR 1.03</b> (0.69 to 1.55)	371 (1 RCT)	⊕○○○ VERY LOW 1,4,5

Intervention is fluoroquinolonecontaining regimen.

RESOURCES REQUIRED	How large are the resource requirements (costs)?  • Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings  • Varies • Don't know	No research evidence was identified.	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention  • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Reduced Probably reduced Probably no impact Probably increased Increased Varies Don't know	No research evidence was identified.	

	Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
ACCEPTABI	<ul> <li>No</li> <li>Probably no</li> <li>Probably yes</li> <li>Yes</li> <li>Varies</li> <li>Don't know</li> </ul>		
	Is the intervention feasible to implement?	No research evidence was identified.	
SIBILI	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li> Varies</li><li> Don't know</li></ul>		

		JUDGEMENT								
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know			
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know			
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies			
VALUES	Important uncertainty or variability	Possibly important uncertainty or	Probably no important uncertainty or	No important uncertainty or variability						

				JUDGEMENT				IMPLICATIONS
		variability	variability					
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with *M. xenopi* pulmonary disease, should a treatment regimen that includes a fluoroquinolone or a regimen without a fluoroquinolone be used?

TYPE OF RECOMMENDATION	Strong	Conditional	Conditional	Conditional	Strong
	recommendation	recommendation	recommendation	recommendation	recommendation

	against the intervention	against the intervention	for either the intervention or the comparison	for the intervention	for the intervention
	0	0	•	0	0
RECOMMENDATION	In patients with <i>M. xenopa</i> (conditional recommendate			regimen that includes mo	xifloxacin or a macrolide.
JUSTIFICATION	There is <i>in vitro</i> evidence inactive alone and in compactive.  There are preliminary data in treatment of <i>M. xenopi</i> Limited evidence for optin have been studied, but un	binations. From this persp a from a randomized trial infections. These data sho nal choice of optimal fluor	in favor of a non inferiority ould be confirmed with final oquinolone or macrolide -	izes a macrolide or fluoro y of fluoroquinolones in co al results of CaMoMy stud	quinolone is likely most omparison to macrolides y.
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION	ECG monitoring for potent	tial QTc interval prolongat	ion with long term of use I	macrolides and/or fluoroq	uinolones
RESEARCH PRIORITIES	Clinical trial of rifampin/et rifampin/ethambutol/mox		s. rifampin/ethambutol/azi	thromycin vs.	

#### **Table E4.16. Question XVI**

In patients with M. xenopi pulmonary disease, should a two, three or four-drug regimen be used for treatment?

**POPULATION:** treatment of M. xenopi pulmonary infection

**INTERVENTION:** a two drug regimen

**COMPARISON:** a three drug regimen

MAIN OUTCOMES: Death; Cure of NTM; Recurrence; Quality of Life; Development of antibiotic resistance; Culture Conversion;

	JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
	How substantial are the desirable anticipated effects?  • Trivial • Small	A two drug regimen	-	In vitro, clarithromycin and moxifloxacin are of equal efficacy (Ferro BE et al, Antimicrob Agents Chemother 2015) against M. xenopi. In mouse models, adding either of the two to a rifampicin-ethambutol				
o Moderat o Large  ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		Outcomes	Anticipated at (95% CI)  Risk with a three drug regimen	Risk with a two drug regimen	Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	backbone leads to 3 drug regimens of equal efficacy (Andrejak C, et al., J Antimicrob Chemother. 2013 Mar;68(3):659-65.).  There is one more informative comparative treatment trial looking at two 3 drug regimens, RE with
		Death follow up: 5 years	650 per 1000	<b>501 per</b> <b>1000</b> (293 to 845)	<b>RR 0.77</b> (0.45 to 1.30)	42 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2</sup>	macrolide or fluoroquinolone (BTS Thorax 63, 627; 2008) but that doesn't address the 2 vs 3 drug regimen. The most recent <i>M. xenopi</i> treatment data comes from case series (Andrejak et al, Thorax 64, 291; van Ingen et al EID, 2008).

UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?  • Large • Moderate • Small • Trivial  • Varies • Don't know	Cure of NTM  Recurrence  Quality of Life - not measured  Development of antibiotic resistance - not measured  Culture Conversion - not reported	100 per 1000  0 per 1000  -	227 per 1000 (50 to 1000)  O per 1000 (0 to 0)  -	RR 2.27 (0.50 to 10.43) RR 4.57 (0.23 to 89.72)	42 (1 RCT) 42 (1 RCT)	⊕⊕○○ LOW 1,2  ⊕⊕○○ LOW 1,2
	What is the overall certainty of the evidence of effects?  • Very low • Low • Moderate • High	The relative import		es of the main Relative importance		s of intere tainty of th (GRAD	e evidence
/IDENCE	∘ No included studies	Death	(	CRITICAL	⊕⊕○○ LOW		
CERTAINTY OF EVIDENCE		Cure of NTM		CRITICAL	⊕⊕○○ LOW		
CERTAI		Recurrence	(	CRITICAL	⊕⊕○○ LOW		
		Quality of Life	-	CRITICAL	-		
		Development of antibion resistance	otic (	CRITICAL	-		

		1			
		Culture Conversion	CRITICAL	-	
	Is there important uncertainty about or variability in how much people	·			
	value the main outcomes?  o Important uncertainty or variability	Three relevant studies were ident preferences:	tified that provide d	ata on patient values and	
	Possibly important uncertainty or variability     Probably no important uncertainty or variability     No important uncertainty or variability	Mehta and Marras, 2011 evaluate quality of life. In this study, patie health-related quality of life with normal controls. Multivariable an lung function	ents with pulmonary two QOL measures	NTM had significantly impaired	
VALUES		Hong, et al, 2014 also evaluated quality of life. This was a direct chealthy subjects and found patier anxiety/depression issues than hassociated with QOL scores.	omparison between nts with NTM report	patients with NTM disease and	
		Czaja, et al 2015 evaluated chan regimens for <i>M. abscessus</i> (many Mean QOL score was significantly months.	patients had coinfo	ection with MAC or Pseudomonas).	

# Does the balance between desirable and undesirable effects favor the intervention or the comparison?

- o Favors the comparison
- o Probably favors the comparison
- Does not favor either the intervention or the comparison
- o Probably favors the intervention
- Favors the intervention
- Varies
- o Don't know

# A two drug regimen compared to a three drug regimen for treatment of M. xenopi pulmonary infection

Outcomes	(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
Death follow up: 5 years	650 per 1000	<b>501 per</b> <b>1000</b> (293 to 845)	<b>RR 0.77</b> (0.45 to 1.30)	42 (1 RCT)	⊕⊕⊖⊖ LOW <sup>1,2</sup>
Cure of NTM	100 per 1000	<b>227 per</b> <b>1000</b> (50 to 1000)	<b>RR 2.27</b> (0.50 to 10.43)	42 (1 RCT)	⊕⊕○○ LOW <sup>1,2</sup>
Recurrence	0 per 1000	<b>0 per 1000</b> (0 to 0)	<b>RR 4.57</b> (0.23 to 89.72)	42 (1 RCT)	⊕⊕○○ LOW <sup>1,2</sup>
Quality of Life - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-
Culture Conversion - not reported	-	-	-	-	-

	No research evidence was identified.	
requirements (costs)?		
<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> <li>Varies</li> <li>Don't know</li> </ul>		
O DOIL KHOW		
Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was identified.	
<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>		
<ul><li>∨ Varies</li><li>∨ No included studies</li></ul>		
What would be the impact on health equity?	No research evidence was identified.	
<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>		
<ul><li>∨ Varies</li><li>o Don't know</li></ul>		
Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> <li>Varies</li> <li>Don't know</li> <li>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</li> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> <li>Varies</li> <li>No included studies</li> <li>What would be the impact on health equity?</li> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> <li>Varies</li> <li>Don't know</li> <li>Is the intervention acceptable to key stakeholders?</li> <li>No</li> <li>Probably yes</li> </ul>	requirements (costs)?  Large costs Moderate costs Negligible costs and savings Large savings Large savings Varies Don't know  Does the cost-effectiveness of the intervention favor the intervention or the comparison Favors the comparison Probably favors the comparison Probably favors the intervention Favors the intervention Probably ravors the intervention Probably reduced Probably reduced Probably no impact Probably increased Is the intervention acceptable to key stakeholders? No research evidence was identified.  No research evidence was identified.

	<ul><li>∨aries</li><li>Don't know</li></ul>		
	Is the intervention feasible to implement?	No research evidence was identified.	
SIBIL	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li>∨aries</li><li>Don't know</li></ul>		

		JUDGEMENT									
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know				
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know				
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies				
VALUES	Important uncertainty or	Possibly important	Probably no important	No important uncertainty or							

		JUDGEMENT								
	variability	uncertainty or variability	uncertainty or variability	variability						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know			
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know			
COST	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies			
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know			
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know			
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know			

#### In patients with *M. xenopi* pulmonary disease, should a two, three or four-drug regimen be used for treatment?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention			
	0	•	0	0	0			
RECOMMENDATION	In patients with <i>M xenopi</i> pulmonary disease, we recommend a daily regimen that includes at least three drugs: rifampicin, ethambutol, and either a macrolide and/or a fluoroquinolone (e.g. moxifloxacin) (conditional recommendation, very low confidence in estimates of effect). (3 Strong, 13 Conditional, 2 Abstain).							
	The panel members voted for a conditional recommendation for the comparison.							
JUSTIFICATION	In animal and in vitro mod	dels, regimens of rifampic	in, ethambutol, and either	clarithromycin or moxiflo	xacin are efficacious.			
	Given the very high morta drug regimen warranted a voted for a conditional red	strong recommendation	for a three drug treatmen					
SUBGROUP CONSIDERATIONS								
IMPLEMENTATION CONSIDERATIONS	Moxifloxacin may not be a	available in all settings and	d activity of gemifloxacin o	or gatifloxacin has not bee	n studied			
MONITORING AND EVALUATION	ECG for QTc prolongation, tendinopathy							
RESEARCH PRIORITIES	Clinical trials of rifampin/ethambutol/azithromycin vs. rifampin/ethambutol/moxifloxacin vs. rifampin/ethambutol/azithromycin/moxifloxacin.							

Clinical trials of a three times weekly regimen vs daily regimen.

#### **Table E4.17. Question XVII**

In patients with M. xenopi pulmonary disease, should amikacin or streptomycin be included in the treatment regimen?

**POPULATION:** M xenopi pulmonary infection

**INTERVENTION:** a treatment regimen with a parenteral agent

**COMPARISON:** a treatment regimen without a parenteral agent

MAIN OUTCOMES: Cure of NTM disease; Death; Recurrence (relapse); Quality of life; Culture conversion; Adverse drug effects; Development of antibiotic resistance;

	JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
	How substantial are the desirable anticipated effects?	Parenteral compared	to no parenteral	A systematic review on M. xenopi outcomes by treatment was				
	o Trivial o Small	Outcomes	Anticipated abs	solute effects*	Relative effect	№ of participants	Quality of the	published in 2009 (INT J TUBERC LUNG DIS 13(10):1210–1218). With the exception of one clinical trial, all were retrospective case
EFFECTS	○ Moderate ○ Large ○ Varies ● Don't know		Risk with no parenteral agent	Risk with Parenteral	(95% CI)	(studies)	evidence (GRADE)	series. The clinical trials did not study injectable agents. The small signal was against aminoglycosides, but the comparison was undoubtedly biased strongly by
DESIRABLE E	Don't know	Cure of NTM disease - not measured	-	-	-	-	-	disease severity.  Success rates lower in injectables,
DES		Death - not measured	-	-	-	-	-	lots of confounding by selection bias (used injectables in sicker patients).
		Recurrence (relapse) - not measured	-	-	-	-	-	Until there is better understanding of why mortality is so high with M xenopi disease, an aggressive M xenopi therapeutic regimen is warranted.

UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?  • Large • Moderate • Small • Trivial  • Varies • Don't know	Quality of life - not measured  Culture conversion - not measured  Adverse drug effects - not measured  Development of antibiotic resistance - not measured			The only data we have are on murine models of M. xenopi infection. In this study, mice treated with parenteral agent (amikacin) have a lower CFU count after 2 months of treatment
	What is the overall certainty of the evidence of effects?  • Very low	The relative importance or value		comes of interest:	(GRADE)
	<ul><li>Low</li><li>Moderate</li><li>High</li></ul>	Cure of NTM disease	CRITICAL	-	
CERTAINTY OF EVIDENCE	No included studies	Death	CRITICAL	-	
Y OF EV		Recurrence (relapse)	CRITICAL	-	
STAINT		Quality of life	CRITICAL	-	
Ü		Culture conversion	CRITICAL	-	
		Adverse drug effects	CRITICAL	-	
		Development of antibiotic resistance	CRITICAL	-	
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?	Values and preferences:  Three relevant studies were identifications.			
	o Important uncertainty or variability				

	Possibly important uncertainty or variability     Probably no important uncertainty or variability     No important uncertainty or variability	preferences:  Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls. Multivariable analysis showed an association between QOL scores and lung function  Hong, et al, 2014 also evaluated the impact of pulmonary NTM on health-related quality of life. This was a direct comparison between patients with NTM disease and healthy	
		subjects and found patients with NTM reported more health status issues and anxiety/depression issues than healthy controls. Lung function was also independently associated with QOL scores.  Czaja, et al 2015 evaluated change in quality of life in response to various treatment regimens for <i>M. abscessus</i> (many patients had coinfection with MAC or Pseudomonas). Mean QOL score was significantly improved after treatment at 3, 6, 12, and 24 months.	
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention  • Varies • Don't know	No research evidence was identified.	
RESOURCES REOUIRED		No research evidence was identified.	

	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was identified.	
COST EFFECTIVENESS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> <li>Varies</li> <li>No included studies</li> </ul>		
	What would be the impact on health equity?	No research evidence was identified.	
EQUITY	<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>		
	<ul><li>∨ Varies</li><li>o Don't know</li></ul>		
	Is the intervention acceptable to key stakeholders?	No research evidence was identified.	
ACCEPTABILITY	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
∢	<ul><li>∨ Varies</li><li>o Don't know</li></ul>		
YTT7	Is the intervention feasible to implement?	No research evidence was identified.	
FEASIBILITY	<ul><li>No</li><li>Probably no</li><li>Probably yes</li></ul>		

∘ Yes	
<ul><li> Varies</li><li> Don't know</li></ul>	

	JUDGEMENT						IMPLICATIONS	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	

		JUDGEMENT							
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know		
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know		
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know		

# In patients with *M. xenopi* pulmonary disease, should amikacin or streptomycin be included in the treatment regimen?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention			
RECOMMENDATION	In patients with fibro-cavitary or advanced/severe bronchiectatic <i>M. xenopi</i> pulmonary disease, we suggest adding parenteral amikacin to the treatment regimen and obtaining expert consultation. (conditional recommendation, very low confidence in estimates of effect).  The panel members voted unanimously for a conditional recommendation for the intervention.							
JUSTIFICATION	Barring compelling evidence to the contrary, <i>M. xenopi</i> patients should be treated aggressively given the high morbidity and mortality of the disease.  In murine models of <i>M. xenopi</i> infection, mice treated with amikacin have a lower CFU count after 2 months of treatment.							

SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	
MONITORING AND EVALUATION	renal function, audiometry (see monitoring section)
RESEARCH PRIORITIES	Randomized study comparing 3 drug regimen with and without an aminoglycoside

### **Table E4.18. Question XVIII**

In patients with M. xenopi pulmonary disease, should treatment be continued for less than 12 months or 12 or more months after culture conversion?

**POPULATION:** Mycobacterium xenopi pulmonary disease

**INTERVENTION:** <12 months of treatment after culture negativity

**COMPARISON:** >/= 12 months of treatment after culture negativity

MAIN OUTCOMES: Cure of NTM; Recurrence; Culture conversion; Quality of life; Development of antibiotic resistance; Death; Adverse drug effects;

	JUDGEMENT		RESEARCH EV	IDENCE			ADDITIONAL CONSIDERATIONS
EFFECTS	How substantial are the desirable anticipated effects?  • Trivial	<12 months compar	red to >12 months for Mycr	obacterium	xenopi		Because of the apparent very high mortality with M xenopi disease, insuring adequate therapy is important. Without
DESIRABLE EFI	<ul> <li>Small</li> <li>Moderate</li> <li>Large</li> </ul>	Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	№ of participants	Quality of the	compelling evidence, and with the potential for significant morbidity and mortality with untreated disease, a
DESI	<ul><li>∨ Varies</li><li>o Don't know</li></ul>						conservative approach is likely warranted.

	How substantial are the undesirable anticipated effects?		Risk with	Risk with	(95% CI)	(studies)	evidence (GRADE)
	<ul><li>Large</li><li>Moderate</li><li>Small</li><li>Trivial</li></ul>	Cure of NTM	<b>months</b> 481 per 1000	<b>260 per 1000</b> (125 to 544)	<b>RR 0.54</b> (0.26 to 1.13)	54 (2 observational studies)	⊕○○○ VERY LOW 1,2,3
ECTS	Don't know	Recurrence	370 per 1000	<b>215 per</b> <b>1000</b> (96 to 481)	<b>RR 0.58</b> (0.26 to 1.30)	54 (2 observational studies)	⊕○○○ VERY LOW 1,2,3
UNDESIRABLE EFFECTS		Culture conversion	571 per 1000	<b>503 per</b> <b>1000</b> (154 to 1000)	<b>RR 0.88</b> (0.27 to 2.82)	11 (1 observational study)	⊕○○ VERY LOW 1,2,3
OND		Quality of life - not measured	-	-	-	-	-
		Development of antibiotic resistance - not measured	-	-	-	-	-
		Death - not reported	-		-	-	-
		Adverse drug effects - not reported	-	-	-	-	-
/IDENCE	What is the overall certainty of the evidence of effects?  • Very low	The relative import	ance or val	ues of the m	ain outco	omes of interes	t:
CERTAINTY OF EVIDENCE	© Cow ○ Moderate ○ High	Outcome		Relative		Certainty of the (	
CERTAI	∘ No included studies	Cure of NTM		CRITICAL		OO Y LOW	

		Recurrence	CRITICAL	⊕○○○ VERY LOW	
		Culture conversion	CRITICAL	⊕○○○ VERY LOW	
		Quality of life	CRITICAL	-	
		Development of antibiotic resistance	CRITICAL	-	
		Death	CRITICAL	-	
		Adverse drug effects	CRITICAL	-	
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • No important uncertainty or variability	normal controls. Multivariable an and lung function  Hong, et al, 2014 also evaluated quality of life. This was a direct chealthy subjects and found patien	ed the impact of pullents with pulmonary two QOL measures alysis showed an as the impact of pulmo omparison between the with NTM reporte ealthy controls. Lunge in quality of life in patients had coinferns.	monary NTM on health-related NTM had significantly impaired significantly lower than historical sociation between QOL scores  onary NTM on health-related patients with NTM disease and ed more health status issues and g function was also independently  on response to various treatment ection with MAC or	

# Does the balance between desirable and undesirable effects favor the intervention or the comparison?

- o Favors the comparison
- o Probably favors the comparison
- Does not favor either the intervention or the comparison
- o Probably favors the intervention
- Favors the intervention
- Varies
- o Don't know

<12 months compare	d to >12 mon	iths for Mycol	bacterium	xenopi	
Outcomes	Anticipated effects* (95		Relative effect	№ of participants	Quality of the
	Risk with >12 months	Risk with <12 months	(95% CI)	(studies)	evidence (GRADE)
Cure of NTM	481 per 1000	<b>260 per</b> <b>1000</b> (125 to 544)	<b>RR 0.54</b> (0.26 to 1.13)	54 (2 observational studies)	⊕○○○ VERY LOW 1,2,3
Recurrence	370 per 1000	<b>215 per</b> <b>1000</b> (96 to 481)	<b>RR 0.58</b> (0.26 to 1.30)	54 (2 observational studies)	⊕○○○ VERY LOW 1,2,3
Culture conversion	571 per 1000	<b>503 per</b> <b>1000</b> (154 to 1000)	<b>RR 0.88</b> (0.27 to 2.82)	11 (1 observational study)	⊕○○○ VERY LOW 1,2,3
Quality of life - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-
Death - not reported	-	-	-	-	-
Adverse drug effects - not reported	-	-	-	-	-

			T
RESOURCES REQUIRED	How large are the resource requirements (costs)?  Large costs Moderate costs Negligible costs and savings Moderate savings Large savings Varies Don't know	No research evidence was identified.	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention  • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Reduced Probably reduced Probably no impact Probably increased Increased  Varies Don't know	No research evidence was identified.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?  O No O Probably no Probably yes Yes	No research evidence was identified.	

	<ul><li> Varies</li><li> Don't know</li></ul>		
	Is the intervention feasible to implement?	No research evidence was identified.	
FEASIBILITY	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
ŀ	<ul><li> Varies</li><li> Don't know</li></ul>		

				JUDGEMENT			IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large	Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial	Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High		No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			

				JUDGEMENT				IMPLICATIONS
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with *M. xenopi* pulmonary disease, should treatment be continued for less than 12 months or 12 or more months after culture conversion?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	0	•	0	0	0
RECOMMENDATION	In patients with <i>M. xenope</i> conversion (conditional re	ecommendation, very low	confidence in estimates of	effect).	months beyond culture
JUSTIFICATION	Because of the significant contrary, a conservative a		•	-	_
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION					
RESEARCH PRIORITIES					

### **Table E4.19. Question XIX**

In patients with M. abscessus pulmonary disease, should a macrolide-based regimen or a regimen without a macrolide be used for treatment?

**POPULATION:** Mycobacterium abscessus pulmonary infection

**INTERVENTION:** a macrolide-containing regimen

**COMPARISON:** a non-macrolide containing regimen

MAIN OUTCOMES: Cure of NTM; Death; Recurrence (Relapse); Culture Conversion; Any adverse effect; Withdrawal owing to adverse effect; Development of

antibiotic resistance; Quality of life;

	JUDGEMENT		RESEARCH	I EVIDENCE			ADDITIONAL CONSIDERATIONS
EFFECTS	How substantial are the desirable anticipated effects?  o Trivial	Macrolide compa	ared to No macrolide for Mycoba	octerium absce	ssus pulmonary infec	tion	It is important to consider identification of the M abscessus subspecies because of the difference in response to
DESIRABLE E	<ul> <li>Small</li> <li>Moderate</li> <li>Large</li> <li>Varies</li> <li>Don't know</li> </ul>	Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	№ of participants (studies)	Quality of the evidence	macrolide therapy based on the presence or absence of the inducible macrolide resistance (erm) gene.

	How substantial are the			1			
	undesirable anticipated effects?		Risk with No macrolide	Risk with Macrolide	(95% CI)		(GRADE)
	<ul><li>Large</li><li>Moderate</li><li>Small</li><li>Trivial</li></ul>	Cure of NTM	429 per 1000	934 per 1000 (420 to 1000)	<b>RR 2.18</b> (0.98 to 4.84)	82 (2 observational studies)	⊕○○○ VERY LOW
	<ul><li>∨ Varies</li><li>◆ Don't know</li></ul>	Death	no data	2/65 (3.1%)	-	65 (1 observational study)	⊕○○○ VERY LOW <sub>2,3</sub>
ECTS		Recurrence (Relapse)	no data	9/47 (19.1%)	-	47 (1 observational study)	⊕○○○ VERY LOW <sub>2,3</sub>
UNDESIRABLE EFFECTS		Culture Conversion	no data	47/65 (72.3%)	-	65 (1 observational study)	⊕○○○ VERY LOW <sub>2,3</sub>
UNDES		Any adverse effect	no data	14/65 (21.5%)	-	65 (1 observational study)	⊕○○○ VERY LOW <sub>2,3</sub>
		Withdrawal owing to adverse effect	no data	6/65 (9.2%)	-	65 (1 observational study)	⊕○○○ VERY LOW 2,3
		Development of antibiotic resistance - not measured	no data	no data	-	-	-
		Quality of life - not measured	no data	no data	-	-	-

		What is the overall certainty of the evidence of effects?	The relative importance or value	es of the main outcon	nes of interest:			
		• Very low	Outcome	Relative importance	Certainty of the evidence (GRADE)			
		<ul><li> Low</li><li> Moderate</li><li> High</li></ul>	Cure of NTM	CRITICAL	⊕○○○ VERY LOW			
į	щ	No included studies	Death	CRITICAL	⊕○○○ VERY LOW			
i	EVIDENO		Recurrence (Relapse)	CRITICAL	⊕○○○ VERY LOW			
Í	CERTAINTY OF EVIDENCE		Culture Conversion	CRITICAL	⊕○○○ VERY LOW			
i i	CERT		Any adverse effect	CRITICAL	⊕○○○ VERY LOW			
			Withdrawal owing to adverse effect	CRITICAL	⊕○○○ VERY LOW			
			Development of antibiotic resistance	CRITICAL	-			
			Quality of life	CRITICAL	-			
		Is there important uncertainty about or variability in how much	Values and preferences:					
		people value the main outcomes?	Three relevant studies were identified	ed that provide data on	patient values and preferences:			
	VALUES	<ul> <li>Important uncertainty or variability</li> <li>Possibly important uncertainty or variability</li> <li>Probably no important uncertainty or variability</li> <li>No important uncertainty or</li> </ul>	Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls. Multivariable analysis showed an association between QOL scores and lung function.					
		variability	Hong, et al, 2014 also evaluated the impact of pulmonary NTM on health-related quality of life. This was a direct comparison between patients with NTM disease and healthy subjects and found patients with NTM reported more health status issues and anxiety/depression issues than healthy controls. Lung function was also independently associated with QOL scores.					

		Czaja, et al 2015 evaluat for <i>M. abscessus</i> (many p was significantly improve	patients had coir	nfection with MA	AC or Pseud	domonas). Mean (		
	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Macrolide compared to N	o macrolide for	Mycobacterium a	abscessus į	oulmonary infection	on	Intervention is considered macrolide-containing regimens
	<ul><li>Favors the comparison</li><li>Probably favors the comparison</li></ul>	Outcomes	Anticipated ab		Relative effect	№ of participants	Quality of the	
	<ul> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>		Risk with No macrolide	Risk with Macrolide	(95% CI)	(studies)	evidence (GRADE)	
	<ul><li> Varies</li><li> Don't know</li></ul>	Cure of NTM	429 per 1000	934 per 1000 (420 to 1000)	<b>RR 2.18</b> (0.98 to 4.84)	82 (2 observational studies)	⊕○○○ VERY LOW <sup>1,2</sup>	
EFFECTS		Death	no data	2/65 (3.1%)	-	65 (1 observational study)	⊕○○○ VERY LOW <sup>2,3</sup>	
BALANCE OF I		Recurrence (Relapse)	no data	9/47 (19.1%)	-	47 (1 observational study)	⊕○○○ VERY LOW <sup>2,3</sup>	
Β		Culture Conversion	no data	47/65 (72.3%)	-	65 (1 observational study)	⊕○○○ VERY LOW <sup>2,3</sup>	
		Any adverse effect	no data	14/65 (21.5%)	-	65 (1 observational study)	⊕○○○ VERY LOW <sup>2,3</sup>	
		Withdrawal owing to adverse effect	no data	6/65 (9.2%)	-	65 (1 observational study)	⊕○○○ VERY LOW <sup>2,3</sup>	
		Development of antibiotic resistance - not measured	no data	no data	-	-	-	

		Quality of life - not no data no data measured
RED	How large are the resource requirements (costs)?	No research evidence was identified.
RESOURCES REQUIRED	<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> </ul>	
RES	○ Varies ○ Don't know	
SS	Does the cost-effectiveness of the intervention favor the interventio or the comparison?	
COST EFFECTIVENESS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>	
	<ul><li> Varies</li><li> No included studies</li></ul>	
	What would be the impact on health equity?	No research evidence was identified.
EQUITY	<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>	

	<ul><li>∨ Varies</li><li>o Don't know</li></ul>		
CEPTABILITY	Is the intervention acceptable to key stakeholders?  No Probably no Probably yes Yes  Varies Don't know	No research evidence was identified.	
FEASIBILITY	Is the intervention feasible to implement?   No Probably no Probably yes Yes  Varies Don't know	A study by Adjemian, et al in 2014 evaluated treatment of M abscessus and MAC, looking at compliance with the 2007 ATS/IDSA guidelines. This study found poor adherence with only 13% of antibiotic regimens compliant with guidelines. Of prescribed regimens for MAC, only 44% contained a macrolide, while 36% of regimens for M abscessus contained a macrolide.	

				JUDGEMENT			IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large	Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial	Varies	Don't know	

				JUDGEMENT				IMPLICATIONS
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

## In patients with *M. abscessus* pulmonary disease, should a macrolide-based regimen or a regimen without a macrolide be used for treatment?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
RECOMMENDATION	In patients with <i>M. abscess</i> macrolide-containing mult Strong, 0 Conditional, 2 A The expert panel voted for In patients with <i>M. abscess</i> suggest a macrolide-contashould not be counted as estimates of effect).  The expert panel voted un	tidrug treatment regimen.  bstain).  r a strong recommendation  ssus pulmonary disease can  aining regimen if the drug  an active drug in the mult	(strong recommendation, on for the intervention.  Sused by strains with induction is being used for its immunicidrug regimen (conditional)	, very low confidence in excible or mutational macrounomodulatory properties al recommendation, very l	stimates of effect). (16 lide resistance, we ; however, the macrolide
JUSTIFICATION	Macrolides are very active Indirect evidence supports M. abscessus can be life t	e in vitro against M. abscens	ssus. crolide-susceptible cases.		
SUBGROUP CONSIDERATIONS  IMPLEMENTATION CONSIDERATIONS	Disease caused by strains	-			,

MONITORING AND EVALUATION	Audiograms, EKG
RESEARCH PRIORITIES	Need to provide precise speciation in future trials and perform randomized trial including macrolide vs no macrolide in <i>M. abscessus</i> subspecies with macrolide resistance (inducible and acquired subgroups).

### **Table E4.20. Question XX**

In patients with M. abscessus pulmonary disease, how many antibiotics should be included within multidrug regimens?

**POPULATION:** treatment of Mycobacterium abscessus pulmonary infection

**INTERVENTION:** two drugs

**COMPARISON:** three vs. four drugs

MAIN OUTCOMES: Cure of NTM disease; Recurrence (relapse); Any adverse effect; Culture conversion; Quality of Life; Development of antibiotic resistance;

Death;

	JUDGEMENT		RESEARCH EVIDEN	ICE			ADDITIONAL CONSIDERATIONS
EFFECTS	How substantial are the desirable anticipated effects?  • Trivial	Two drugs compar	red to three vs. four drugs for <i>Mycoba</i>	cterium al	escessus pulmo	nary	It is not possible to determine the outcomes for treatment of <i>M. abscessus</i> subspecies <i>abscessus</i> as the isolates were not speciated and not randomly distributed amount
DESIRABLE	<ul><li>Small</li><li>Moderate</li><li>Large</li><li>Varies</li></ul>	Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	№ of participants	Quality of the	the patients in this observational cohort.
	∘ Don't know						

	How substantial are the						
	undesirable anticipated effects?		Risk with three	Risk with two	(95% CI)	(studies)	evidence
	Laura		vs. four drugs	drugs			(GRADE)
	<ul><li>Large</li><li>Moderate</li><li>Small</li><li>Trivial</li></ul>	Cure of NTM disease follow up: median 445 days	833 per 1000	<b>767 per 1000</b> (558 to 1000)	<b>RR 0.92</b> (0.67 to 1.26)	41 (1 observational study)	⊕○○○ VERY LOW 1,2
	<ul><li>∨ Varies</li><li>∨ Don't know</li></ul>	Recurrence (relapse) follow up: median 445 days	50 per 1000	<b>231 per 1000</b> (27 to 1000)	<b>RR 4.62</b> (0.54 to 39.73)	33 (1 observational study)	⊕○○○ VERY LOW 1,2,3
ABLE EFFECTS		Any adverse effect follow up: median 445 days	625 per 1000	<b>175 per 1000</b> (63 to 519)	<b>RR 0.28</b> (0.10 to 0.83)	41 (1 observational study)	⊕○○○ VERY LOW 1,2,3
UNDESIRABLE		Culture conversion	The study reported no difference between th but only reported a p without specifying ex-	e two groups, -value of 0.698		(1 observational study)	⊕○○○ VERY LOW 1,2,3
		Quality of Life - not measured	-	-	-	-	-
		Development of antibiotic resistance - not measured	-	-	-	-	-
		Death - not reported	-	-	-	-	-

	What is the overall certainty of the evidence of effects?  • Very low	The relative importance or values of the main outcomes of interest:						
	<ul><li>Low</li><li>Moderate</li></ul>	Outcome	Relative importance	Certainty of the evidence (GRADE)				
	<ul><li>High</li><li>No included studies</li></ul>	Cure of NTM disease	CRITICAL	⊕○○○ VERY LOW				
DENCE		Recurrence (relapse)	CRITICAL	⊕○○○ VERY LOW				
Y OF EVII		Any adverse effect	CRITICAL	⊕○○○ VERY LOW				
CERTAIN		Culture conversion	CRITICAL	⊕○○○ VERY LOW				
		Quality of Life	CRITICAL					
		Development of antibiotic resistance	CRITICAL					
		Death	CRITICAL					
	Is there important uncertainty about or variability in how much people value the main outcomes?	regimens for M abscessus (many page 1)	atients had coinfection	with MAC or Pseudomonas). Mean				
VALUES	<ul> <li>Important uncertainty or variability</li> <li>Possibly important uncertainty or variability</li> <li>Probably no important uncertainty or variability</li> <li>No important uncertainty or variability</li> </ul>							
	VALUES CERTAINTY OF EVIDENCE	The evidence of effects?  • Very low • Low • Moderate • High • No included studies   Is there important uncertainty about or variability in how much people value the main outcomes?  • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • Probably no important uncertainty or variability • No important uncertainty or	The relative importance or value  Very low Low Moderate High No included studies  Recurrence (relapse)  Any adverse effect  Culture conversion  Quality of Life  Development of antibiotic resistance  Death  Is there important uncertainty about or variability in how much people value the main outcomes?  Important uncertainty or variability Possibly important uncertainty or variability Possibly important uncertainty or variability No important uncertainty or No important uncertainty or No included studies  The relative importance or value  Cure of NTM disease  Culture conversion  Culture conversion  Czaja, et al 2015 evaluated change regimens for M abscessus (many population of the probably no important uncertainty or variability No important uncertainty or	The relative importance or values of the main outcomes or light of the properties of the main outcomes or light of the properties of the main outcomes or light of the properties of the main outcomes or light of the properties of the main outcomes or light of the properties of the main outcomes or light of the properties of the main outcomes or light of the properties of the main outcomes of the main outcomes or light of the properties of the main outcomes or light of the properties of the main outcomes or light of the properties of the main outcomes or light of the main outcomes of the main outcomes.  The relative importance or values of the main outcomes of the main outcomes.  Currence (relapse)  CRITICAL  Quality of Life  CRITICAL  Development of antibiotic resistance  CRITICAL  Death  Critical  CRITICAL  Death  Critical  CRITICAL  Death  Critical  CRITICAL  Death  Critical  Critical  Critical  Outcome  Relative importance  CRITICAL  Culture conversion  CRITICAL  Development of antibiotic resistance  CRITICAL  Death  Critical  C				

	Does the balance between						
	desirable and undesirable effects favor the intervention or the comparison?  • Favors the comparison	Two drugs compare	ed to three vs. four d	rugs for Mycoba	cterium ab	scessus pulmo	nary
	<ul><li>Probably favors the comparison</li><li>Does not favor either the</li></ul>	Outcomes	Anticipated absolut	te effects*	Relative effect	№ of participants	Quality of the
	intervention or the comparison  o Probably favors the intervention  Favors the intervention		Risk with three	Risk with two	(95% CI)	(studies)	evidence (GRADE)
EFFECTS	<ul><li>∨ Varies</li><li>∨ Don't know</li></ul>	Cure of NTM disease follow up: median 445 days	833 per 1000	<b>767 per 1000</b> (558 to 1000)	<b>RR 0.92</b> (0.67 to 1.26)	41 (1 observational study)	⊕○○○ VERY LOW 1,2
BALANCE OF E	-	Recurrence (relapse) follow up: median 445 days	50 per 1000	<b>231 per 1000</b> (27 to 1000)	<b>RR 4.62</b> (0.54 to 39.73)	33 (1 observational study)	⊕○○○ VERY LOW 1,2,3
		Any adverse effect follow up: median 445 days	625 per 1000	<b>175 per 1000</b> (63 to 519)	<b>RR 0.28</b> (0.10 to 0.83)	41 (1 observational study)	⊕○○○ VERY LOW 1,2,3
		Culture conversion	The study reported n difference between the but only reported a p without specifying ex	ne two groups, -value of 0.698		(1 observational study)	⊕○○○ VERY LOW 1,2,3
		Quality of Life - not measured	-	-	-	-	-

		Development of - antibiotic resistance - not measured	-	-	-	-	
		Death - not - reported	-	-	-	-	
e e	How large are the resource requirements (costs)?	No research data available.					
RESOURCES REQUIRED	<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> </ul>						
RES	Varies Don't know						
S	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	Comparison is considered three drugs in	this case.				
COST EFFECTIVENESS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>						
	<ul><li>Varies</li><li>No included studies</li></ul>						
	What would be the impact on health equity?	No research data available.					This is dependent on the respective health care system.
EQUITY	<ul> <li>Reduced</li> <li>Probably reduced</li> <li>Probably no impact</li> <li>Probably increased</li> <li>Increased</li> </ul>						

	<ul><li>Varies</li><li>Don't know</li></ul>		
	Is the intervention acceptable to key stakeholders?	No research data available.	
ACCE	<ul> <li>No</li> <li>Probably no</li> <li>Probably yes</li> <li>Yes</li> <li>Varies</li> <li>Don't know</li> </ul>		
	Is the intervention feasible to implement?	No research data available.	
SIE	<ul><li>No</li><li>Probably no</li><li>Probably yes</li><li>Yes</li></ul>		
	<ul><li> Varies</li><li> Don't know</li></ul>		

		JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	

				JUDGEMENT				IMPLICATIONS
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

## In patients with *M. abscessus* pulmonary disease, how many antibiotics should be included within multidrug regimens?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention	
	0	0	0	•	0	
RECOMMENDATION	In patients with <i>M. absces</i> (guided by <i>in vitro</i> suscep  The expert panel voted ur	tibility). (conditional reco	mmendation, very low cor	fidence in estimates of ef	_	
JUSTIFICATION	The severity of disease as consideration of three or f					
SUBGROUP CONSIDERATIONS	The choice of drugs may be different in patients with extensive exposure to key antimycobacterial drugs (macrolides, aminoglycosides) in whom resistance may be a serious risk.					
IMPLEMENTATION CONSIDERATIONS	Barriers/facilitators for limitation include infrastructure and financial support for intravenous therapy and for expensive oral agents.					
MONITORING AND EVALUATION						

RESEARCH PRIORITIES	There is a need for an RCT evaluating the optimal number of drugs (3 vs. 4 or more) with and without parenteral agents in
	treatment for <i>M. abscessus</i> , separated by subspecies.

### **Table E4.21. Question XXI**

In patients with M. abscessus pulmonary disease, should shorter or longer duration therapy be used for treatment?

**POPULATION:** Mycobacterium abscessus pulmonary infection

**INTERVENTION:** shorter therapy duration

**COMPARISON:** longer therapy duration

MAIN OUTCOMES: Cure of NTM; Recurrence (relapse); Culture conversion; Quality of life; Development of antibiotic resistance; Death; Adverse drug

effects;

	JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS
E EFFECTS	How substantial are the desirable anticipated effects?  o Trivial o Small	Shorter therapy durate pulmonary infection	ion compared to longer therapy dura	tion for My	cobacterium abs	scessus	
DESIRABLE	<ul><li> Moderate</li><li> Large</li><li> Varies</li><li> Don't know</li></ul>	Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	№ of participants	Quality of the evidence	

	How substantial are the undesirable anticipated effects?  • Large		Risk with longer therapy duration	Risk with shorter therapy duration	(95% CI)	(studies)	(GRADE)
	<ul><li> Moderate</li><li> Small</li><li> Trivial</li><li> Varies</li></ul>	Cure of NTM	1000 per 1000	<b>750 per 1000</b> (470 to 1000)	<b>RR 0.75</b> (0.47 to 1.20)	17 (1 observational study)	⊕○○○ VERY LOW 1,2,3
CTS	• Don't know	Recurrence (relapse) - not measured	-	-	-	-	-
ABLE EFFE		Culture conversion - not reported	-	-	-	-	-
UNDESIRABLE EFFECTS		Quality of life - not measured	-	-	-	-	-
2		Development of antibiotic resistance - not measured	-	-	-	-	-
		Death - not reported	-	-	-	-	-
		Adverse drug effects - not reported	-	-	-	-	-
	What is the overall certainty of the evidence of effects?	The relative importar	nce or values of	the main outcon	nes of int	erest:	
DENCE	• Very low	Outcome	F	Relative importance	Certair	nty of the eviden	ce (GRADE)
CERTAINTY OF EVIDENCE	<ul><li>Low</li><li>Moderate</li><li>High</li></ul>	Cure of NTM	С	RITICAL	⊕○○○ VERY LO	W	
RTAIN_	∘ No included studies	Recurrence (relapse)	С	RITICAL			
CE		Culture conversion	С	RITICAL			

		1			
		Quality of life	CRITICAL		
		Development of antibiotic resistance	CRITICAL		
		Death	CRITICAL		
		Adverse drug effects	CRITICAL		
	Is there important uncertainty about or variability in how much people value the main outcomes?	Values and preferences:  Three relevant studies were identified	d that provide data on	patient values and preferences:	
VALUES	Important uncertainty or variability     Possibly important uncertainty or variability     Probably no important uncertainty or variability     No important uncertainty or variability	Mehta and Marras, 2011 evaluated the In this study, patients with pulmonar with two QOL measures significantly showed an association between QOL Hong, et al, 2014 also evaluated the This was a direct comparison between patients with NTM reported more head controls. Lung function was also independent.	ne impact of pulmonary NTM had significantly lower than historical nacroses and lung function impact of pulmonary Non patients with NTM dialth status issues and appendently associated with quality of life in response in quality of life in response in the properties of the significant of the signif	y NTM on health-related quality of life. y impaired health-related quality of life ormal controls. Multivariable analysis on  NTM on health-related quality of life. sease and health subjects and found anxiety/depression issues than healthy with QOL scores.  onse to various treatment regimens for seudomonas). Mean QOL score was	

## Does the balance between desirable and undesirable effects favor the intervention or the comparison?

- o Favors the comparison
- o Probably favors the comparison
- Does not favor either the intervention or the comparison
- o Probably favors the intervention
- o Favors the intervention
- Varies
- o Don't know

## Shorter therapy duration compared to longer therapy duration for Mycobacterium abscessus pulmonary infection

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with longer therapy duration	Risk with shorter therapy duration			
Cure of NTM	1000 per 1000	<b>750 per 1000</b> (470 to 1000)	<b>RR 0.75</b> (0.47 to 1.20)	17 (1 observational study)	⊕○○○ VERY LOW 1,2,3
Recurrence (relapse) - not measured	-	-	-	-	-
Culture conversion - not reported	-	-	-	-	-
Quality of life - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-
Death - not reported	-	-	-	-	-
Adverse drug effects - not reported	-	-	-	-	-

RESOURCES REQUIRED	How large are the resource requirements (costs)?  • Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • Don't know	No research evidence was identified.	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?  • Favors the comparison • Probably favors the comparison • Does not favor either the intervention or the comparison • Probably favors the intervention • Favors the intervention  • Varies • No included studies	No research evidence was identified.	
EQUITY	What would be the impact on health equity?  Reduced Probably reduced Probably no impact Probably increased Increased  Varies Don't know	No research evidence was identified.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?  Output  No Output  Probably no Output  Probably yes Output  Yes	No research evidence was identified.	

	◆ Varies     ○ Don't know		
FEASIBILITY	Is the intervention feasible to implement?  O No Probably no Probably yes Yes	A study by Adjemian, et al in 2014 evaluated treatment of M abscessus and MAC, looking at compliance with the 2007 ATS/IDSA guidelines. This study found poor adherence with only 13% of antibiotic regimens compliant with guidelines. Of prescribed regimens for MAC, only 44% contained a macrolide, while 36% of regimens for M abscessus contained a macrolide.	
	<ul><li>∨aries</li><li>Don't know</li></ul>		

				JUDGEMENT			IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large	Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial	Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High		No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			

				JUDGEMENT				IMPLICATIONS
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

In patients with *M. abscessus* pulmonary disease, should shorter or longer duration therapy be used for treatment?

TYPE OF RECOMMENDATION	Strong Conditional		Conditional	Conditional	Strong
	recommendation	recommendation	recommendation	recommendation	recommendation

	against the intervention	against the intervention	for either the intervention or the comparison	for the intervention	for the intervention				
	0	0	•	0	0				
RECOMMENDATION	In the absence of data to support a shorter or longer treatment course for <i>M. abscessus</i> pulmonary disease, the expert panel decided not to make a recommendation on the length of treatment.  The expert panel voted unanimously for a conditional recommendation for either the intervention or the comparison.								
JUSTIFICATION	The one study identified was a very small study that indirectly addressed this question and was felt to be too low quality evidence upon which to base a recommendation.								
SUBGROUP CONSIDERATIONS	Nodular and cavitary disea	ase need to be considered	separately.						
IMPLEMENTATION CONSIDERATIONS									
MONITORING AND EVALUATION									
RESEARCH PRIORITIES	Urgent need for biomarkers to individualize the duration of therapy.								
	Randomized clinical trials	of fixed regimens of differ	ent durations for both nod	lular and cavitary disease					

### **Table E4.22. Question XXII**

Should surgery or medical therapy be used to treat NTM pulmonary disease?

**POPULATION:** NTM pulmonary infection

**INTERVENTION:** surgery

**COMPARISON:** medical therapy

MAIN OUTCOMES: Cure of NTM; Death; Recurrence; Culture conversion; Surgical Complication; Quality of Life;

	JUDGEMENT		RESEARCH	ADDITIONAL CONSIDERATIONS			
EFFECTS	How substantial are the desirable anticipated effects?  • Trivial	Surgery comp	pared to medical therapy for	NTM pulmon	ary infection		Data obtained from case series and outcomes with medical therapy not comparable with surgery
ESIRABLE	<ul> <li>Small</li> <li>Moderate</li> <li>Large</li> <li>Varies</li> <li>Don't know</li> </ul>	Outcomes	Anticipated absolute effects* (95% CI)	Relative effect	№ of participants	Quality of the	outcomes.

	How substantial are the undesirable anticipated effects?		Risk with medical therapy	Risk with surgery	(95% CI)	(studies)	evidence (GRADE)
	<ul><li> Large</li><li> Moderate</li><li> Small</li><li> Trivial</li></ul>	Cure of NTM	13/46 (28.2%)	13/23 (56.5%)	not estimable	69 (1 observational study)	⊕○○○ VERY LOW
FFFECTS	<ul><li>∨ Varies</li><li>∘ Don't know</li></ul>	Death	13/83 (15.7%)	20/486 (4.1%)	not estimable	569 (10 observational studies)	⊕○○○ VERY LOW <sub>2,3,4</sub>
UNDESTRABLE FE		Recurrence	12/102 (11.8%)	22/391 (5.6%)	not estimable	493 (9 observational studies)	⊕○○○ VERY LOW 1,2,3,4
HOND		Culture conversion	18/46 (39.1%)	283/331 (85.5%)	not estimable	377 (10 observational studies)	⊕○○○ VERY LOW 1,2,3,4,5
		Surgical Complication	not pooled	111/563 (19.7%)	not pooled	563 (9 observational studies)	⊕○○○ VERY LOW 1,3,4
		Quality of Life - not measured	-	-	-	-	-

	What is the overall certainty of the evidence of effects?	The relative importa	nce or values of the	main outcomes of interest:			
	• Very low • Low • Moderate	Outcome	Relative importance	Certainty of the evidence (GRADE)			
ICE	<ul><li>High</li><li>No included studies</li></ul>	Cure of NTM	CRITICAL	⊕○○○ VERY LOW			
F EVIDENCE		Death	CRITICAL	⊕○○○ VERY LOW			
CERTAINTY OF		Recurrence	CRITICAL	⊕○○○ VERY LOW			
CER'		Culture conversion	CRITICAL	⊕○○○ VERY LOW			
		Surgical Complication	CRITICAL	⊕○○○ VERY LOW			
		Quality of Life	CRITICAL	-			
	Is there important uncertainty about or variability in how much people value the main outcomes?	Values and preferences:  Three relevant studies were identified that provide data on patient values and preferences:					
VALUES	<ul> <li>Important uncertainty or variability</li> <li>Possibly important uncertainty or variability</li> <li>Probably no important uncertainty or variability</li> </ul>	Mehta and Marras, 2011 evaluated the impact of pulmonary NTM on health-related quality of life. In this study, patients with pulmonary NTM had significantly impaired health-related quality of life with two QOL measures significantly lower than historical normal controls. Multivariable analysis showed an association between QOL scores and lung function					
	No important uncertainty or variability	quality of life. This was health subjects and for	s a direct comparison be and patients with NTM i	of pulmonary NTM on health-related etween patients with NTM disease and reported more health status issues and ols. Lung function was also			

		Czaja, et al 201 treatment regir Pseudomonas).	rdependently associated with QOL scores.  zaja, et al 2015 evaluated change in quality of life in response to various reatment regimens for M abscessus (many patients had coinfection with MAC or seudomonas). Mean QOL score was significantly improved after treatment at 3, 6, 2, and 24 months.							
	Does the balance between desirable and undesirable									
	effects favor the intervention or the comparison?	Surgery compared to medical therapy for NTM pulmonary infection								
	<ul><li>Favors the comparison</li><li>Probably favors the comparison</li></ul>	Outcomes	Anticipated a		Relative effect	№ of participants	Quality of the			
	<ul> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>		Risk with medical therapy	Risk with surgery	(95% CI)	(studies)	evidence (GRADE)			
EFFECTS	<ul><li>∨ Varies</li><li>o Don't know</li></ul>	Cure of NTM	13/46 (28.2%)	13/23 (56.5%)	not estimable	69 (1 observational study)	⊕○○○ VERY LOW <sup>1,2</sup>			
BALANCE OF EFFECTS		Death	13/83 (15.7%)	20/486 (4.1%)	not estimable	569 (10 observational studies)	⊕○○○ VERY LOW <sup>2,3,4</sup>			
		Recurrence	12/102 (11.8%)	22/391 (5.6%)	not estimable	493 (9 observational studies)	⊕○○○ VERY LOW¹,2,3,4			
		Culture conversion	18/46 (39.1%)	283/331 (85.5%)	not estimable	377 (10 observational studies)	⊕○○○ VERY LOW <sup>1,2,3,4,5</sup>			
		Surgical	not pooled	111/563	not	563 (9 observational	⊕○○○ VERY			

		T				
		Complication	(19.7%)	pooled	studies)	LOW <sup>1,3,4</sup>
		Quality of Life not measured	-	-	-	-
Ð	How large are the resource requirements (costs)?	No research evidence was iden	tified.			
RESOURCES REQUIRED	<ul> <li>Large costs</li> <li>Moderate costs</li> <li>Negligible costs and savings</li> <li>Moderate savings</li> <li>Large savings</li> </ul>					
RES	<ul><li>∨ Varies</li><li>o Don't know</li></ul>					
ESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	No research evidence was iden	tified.			
COST EFFECTIVENESS	<ul> <li>Favors the comparison</li> <li>Probably favors the comparison</li> <li>Does not favor either the intervention or the comparison</li> <li>Probably favors the intervention</li> <li>Favors the intervention</li> </ul>					
	<ul><li> Varies</li><li> No included studies</li></ul>					
EQUITY	What would be the impact on health equity?	No research evidence was iden	tified.			

	• Pr • Pr • Pr • In	educed robably reduced robably no impact robably increased ncreased aries on't know		
ACCEPTABILITY	o No Pr Pr Ye Va	key stakeholders?  lo robably no robably yes	No research evidence was identified.	
FEASIBILITY	imp  o No o Pr  o Pr  o Ye  o Va	plement?  Io  robably no  robably yes	No research evidence was identified.	

		JUDGEMENT							
DESIRABLE	Trivial	Small	Moderate	Large		Varies	Don't know		

			-	IUDGEMENT				IMPLICATIONS
EFFECTS								
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	

	JUDGEMENT					IMPLICATIONS		
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

### Should surgery plus medical therapy or medical therapy alone be used to treat NTM pulmonary disease?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	0	0	0	•	0

RECOMMENDATION	In selected patients with NTM pulmonary disease, we suggest surgical resection as an adjuvant to medical therapy after expert consultation (conditional recommendation, very low confidence in estimates of effect).  The expert panel voted unanimously for a conditional recommendation for the intervention.
JUSTIFICATION	Consider whether surgical resection can improve treatment outcomes or potential to be curative. Prognosis can be improved in select cases: hemoptysis, localized cavitary disease, macrolide resistance.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	
MONITORING AND EVALUATION	
RESEARCH PRIORITIES	