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	..l/ 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.

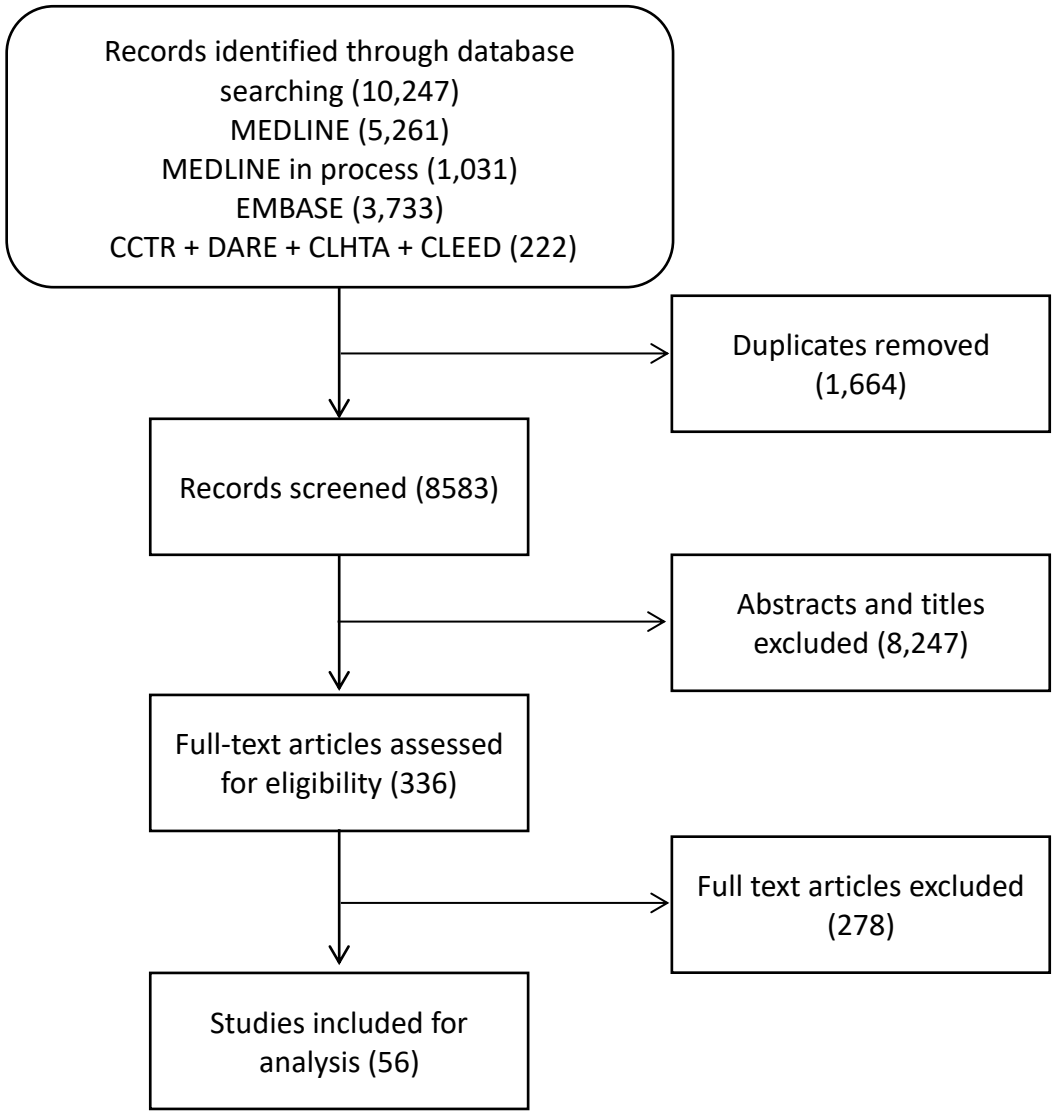

Figure E2: Inclusion and exclusion criteria for full text articles reviewed for pulmonary NTM treatment guideline.

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 following ☐ **pharmacological treatment** (drug regimen) being the only treatment in ≥1 group ☐ **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 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		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**any treatment**	**watchful waiting**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cure of NTM												
2	observational studies	serious [1]	not serious	not serious	serious [2]	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												
5	observational studies	serious [1]	not serious	not serious	not serious	none	90/252 (35.7%)	85/186 (45.7%)	**RR 0.77** (0.64 to 0.92)	**105 fewer per 1,000** (from 37 fewer to 165 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Culture Conversion												
2	observational studies	serious [1]	serious [3]	not serious	serious [2]	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 adverse effect												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**any treatment**	**watchful waiting**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	observational studies	serious [1]	not serious	not serious	not serious	none	A total of 43 out of 100 patients in the treatment group had adverse effects. In neither study was it specified if there were any adverse effects in the watchful waiting group (of 67 patients), but presumedly there were none.				⨁◯◯◯ VERY LOW	IMPORTANT
Quality of Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurrence - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Observational studies, risk treatment group had more serious disease
2. wide range in confidence interval
3. 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							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**empiric treatment**	**susceptibility-based treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cure of NTM Disease - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death												
1	observational studies	serious [1]	not serious	serious [2]	not serious	none	Authors report no significant difference between empiric vs culture-based regimens (80 vs 75%)				⨁◯◯◯ VERY LOW	CRITICAL
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurrence - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture Conversion - not reported												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	empiric treatment	susceptibility-based treatment	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval

1. No randomization, no concealment
2. 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Cure of NTM												
2	observational studies	not serious	not serious	not serious	serious [a]	none	31/94 (33.0%)	34/96 (35.4%)	**RR 0.93** (0.62 to 1.37)	**25 fewer per 1,000** (from 131 more to 135 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Death												
1	observational studies	not serious	not serious	not serious	serious [a]	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
Recurrence (relapse)												
2	observational studies	not serious	not serious	not serious	serious [a]	none	9/94 (9.6%)	10/96 (10.4%)	**RR 0.87** (0.37 to 2.01)	**14 fewer per 1,000** (from 66 fewer to 105 more)	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
2	observational studies	not serious	serious [b]	not serious	serious [a]	none	88/97 (90.7%)	85/100 (85.0%)	**RR 0.98** (0.67 to 1.43)	**17 fewer per 1,000** (from 281 fewer to 365 more)	⊕◯◯◯ VERY LOW	CRITICAL
Any adverse effect												
1	randomised trials	not serious	not serious	not serious	serious [a]	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 advere effect												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	0/14 (0.0%)	0/13 (0.0%)	not estimable		⊕⊕◯◯ LOW	CRITICAL
Withdrawal owing to adverse effect												
1	randomised trials	not serious	not serious	not serious	not serious	none	1/14 (7.1%)	2/13 (15.4%)	**RR 0.46** (0.05 to 4.53)	**83 fewer per 1,000** (from 146 fewer to 543 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of Life - not measured												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

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 assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**azithromycin-based regimen**	**clarithromycin-based regimen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture Conversion (follow up: range 4 to 12 months)												
4	observational studies	serious [1]	not serious	not serious	serious [2]	none	131/178 (73.6%)	156/190 (82.1%)	**RR 0.88** (0.73 to 1.05)	**10 fewer per 100** (from 4 more to 22 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Recurrence (relapse) - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance (follow up: range 4 to 12 months)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**azithromycin-based regimen**	**clarithromycin-based regimen**	**Relative (95% CI)**	**Absolute (95% CI)**		
3	observational studies	serious [1]	not serious	not serious	serious [3]	none	4/92 (4.3%)	9/97 (9.3%)	**RR 0.51** (0.07 to 2.79) [4]	**5 fewer per 100** (from 9 fewer to 17 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects (follow up: 4 months)												
1	observational studies	serious [1]	not serious	not serious	serious [5]	none	0/29 (0.0%)	0/30 (0.0%)	not estimable	**0 fewer per 100** (from 60 fewer to 60 more)	⊕◯◯◯ VERY LOW	CRITICAL
Withdrawal from study due to AEs (follow up: range 4 to 6 months)												
3	observational studies	serious [1]	not serious	not serious	serious [6]	none	12/87 (13.8%)	15/104 (14.4%)	**RR 1.02** (0.45 to 2.07)	**0 fewer per 100** (from 8 fewer to 15 more)	⊕◯◯◯ VERY LOW	CRITICAL
Any Adverse Effect (follow up: range 4 to 12 months)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**azithromycin-based regimen**	**clarithromycin-based regimen**	**Relative (95% CI)**	**Absolute (95% CI)**		
6	observational studies	serious [1]	not serious [7]	not serious	serious [8]	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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Cure of NTM - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death												
1	randomised trials	not serious	not serious	not serious	serious [3]	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
Recurrence (relapse)												
1	randomised trials	not serious	not serious	not serious	serious	none	16/52 (30.8%)	13/37 (35.1%)	**RR 0.88** (0.48 to 1.59)	**42 fewer per 1,000** (from 183 fewer to 207 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Culture Conversion												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
1	randomised trials	not serious	not serious	not serious	serious [3]	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 adverse reaction												
1	randomised trials	not serious	not serious	not serious	serious [3]	none	18/73 (24.7%)	15/73 (20.5%)	**RR 1.20** (0.66 to 2.19)	**41 more per 1,000** (from 70 fewer to 245 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/73 (0.0%)	0/73 (0.0%)	not estimable		⨁⨁⨁⨁ HIGH	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No control for confounders
2. Drug regimens among patients varied widely, both with/without macrolide
3. 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Cure of NTM												
1	observational studies	serious [a]	not serious	not serious	not serious	none	3/3 (100.0%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Death												
2	observational studies	serious [a]	not serious	not serious	not serious	none	2/9 (22.2%)	not pooled	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Recurrence (relapse)												
3	randomised trials	serious	not serious	not serious	not serious	none	9/21 (42.9%)	0/0	not pooled	see comment	⊕⊕⊕◯ MODERATE	CRITICAL
Culture Conversion												
3	randomised trials	serious [b]	serious [c]	not serious	not serious	none	16/40 (40.0%)	1/28 (3.6%)	not pooled	see comment	⊕⊕◯◯ LOW	CRITICAL
Any Adverse Effect												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
3	randomised trials	serious [b]	serious [d]	not serious	not serious	none	46/59 (78.0%)	40/45 (88.9%)	not pooled	see comment	⊕⊕◯◯ LOW	CRITICAL
Serious Adverse Effect												
3	randomised trials	serious [b]	serious [e]	not serious	not serious	none	8/59 (13.6%)	4/45 (8.9%)	not pooled	see comment	⊕⊕◯◯ LOW	CRITICAL
Withdrawal owing to adverse effects												
4	randomised trials	serious [b]	serious [f]	not serious	not serious	none	15/79 (19.0%)	0/45 (0.0%)	not pooled	see comment	⊕⊕◯◯ LOW	CRITICAL
Quality of Life												
1	randomised trials	not serious	not serious	serious [g]	not serious	none	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).				⊕⊕⊕◯ MODERATE	CRITICAL
Development of Antibiotic Resistance												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
1	randomised trials	not serious	not serious	serious [g]	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 assessment							№ of patients		Effect		Quality	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)**		
Culture Conversion												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	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 Adverse Effects												
1	randomised trials	serious [1]	not serious	not serious	not serious	none	0/59 (0.0%)	0/60 (0.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
Withdrawal owing to adverse effect												
1	randomised trials	serious [1]	not serious	not serious	serious [2]		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 Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cure of NTM Disease - not measured												

Quality assessment							№ of patients		Effect		Quality	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)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurrence (relapse) - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

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							№ of patients		Effect		Quality	Importance
№ 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)**		
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cure of NTM Disease (follow up: 12 months)												
1	observational studies	serious [1]	not serious	not serious [2]	not serious	none	79/118 (66.9%)	75/99 (75.8%)	**RR 0.97** (0.72 to 1.14) [3]	**2 fewer per 100** (from 11 more to 21 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Culture Conversion (follow up: range 6 to 12 months)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
5	observational studies	serious [1]	not serious	not serious [4]	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 [1]	not serious	not serious [2]	serious [5]	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
Development of Antibiotic Resistance (follow up: range 6 to 12 months)												
4	observational studies	serious [1]	not serious	not serious [4]	serious [6]	none	3/146 (2.1%)	10/86 (11.6%)	**RR 0.23** (0.07 to 0.74)	**9 fewer per 100** (from 3 fewer to 11 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
Discontinuation of the initial treatment due to adverse effects (follow up: range 6 to 12 months)												
4	observational studies	not serious [1]	not serious [7]	not serious	serious [8]	none	28/362 (7.7%)	45/202 (22.3%)	**RR 0.44** (0.09 to 2.16)	**12 fewer per 100** (from 20 fewer to 26 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse Effects (follow up: range 6 to 12 months)												
4	observational studies	not serious [1]	not serious	not serious	serious [8]	none	66/259 (25.5%)	72/186 (38.7%)	**RR 0.63** (0.25 to 1.55)	**14 fewer per 100** (from 21 more to 29 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

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)
4. Some studies included only patients without cavitary disease and some included both cavitary and non-cavitary but did not report the results separately
5. 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Culture conversion												
1	observational studies	serious [1]	not serious	serious [2]	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 NTM disease - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurrence (relapse) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse drug effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No control for confounding
2. 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)		
Cure of NTM - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance – not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture conversion - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse drug effects - not measured												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurrence (relapse) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Cure of NTM												
1	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [2]	8/10 (80.0%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Death												
2	observational studies	serious [1]	not serious	not serious	not serious [2]	publication bias strongly suspected [2]	30/121 (24.8%)	not pooled	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Recurrence (relapse)												
2	observational studies	serious [1]	not serious	not serious	< not serious	publication bias strongly suspected [2]	6/115 (5.2%)	not pooled	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Culture Conversion												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
2	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [2]	42/44 (95.5%)	not pooled	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Any adverse effect												
1	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [2]	11/75 (14.7%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Serious Adverse Effect												
1	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [2]	0/75 (0.0%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Withdrawal owing to adverse effects												
1	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [2]	7/75 (9.3%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Quality of Life - not measured												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of Antibiotic Resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

1. Case series, no control group
2. 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Cure of NTM Disease - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurrence (relapse) - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture Conversion - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - not measured												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Cure of NTM												
2	observational studies	serious [1]	serious [2]	not serious	not serious	publication bias strongly suspected [3]	0/0	115/182 (63.2%)	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Death												
3	observational studies	serious [3]	serious [2]	not serious	not serious	publication bias strongly suspected [3]	0/18 (0.0%)	39/229 (17.0%)	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Recurrence (relapse)												
3	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [3]	0/14 (0.0%)	16/178 (9.0%)	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Culture Conversion												
4	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [3]	17/18 (94.4%)	238/257 (92.6%)	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
Any Adverse Effect												
1	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [3]	0/18 (0.0%)	0/0	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects												
2	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [3]	0/18 (0.0%)	0/28 (0.0%)	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Withdrawal owing to adverse effects												
2	observational studies	serious [1]	not serious	not serious	not serious	publication bias strongly suspected [3]	0/18 (0.0%)	0/28 (0.0%)	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Quality of Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Case series, no control groups
2. 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Cure of NTM												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	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
Recurrence												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	none	1/14 (7.1%)	0/14 (0.0%)	**RR 3.00** (0.13 to 67.91)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL
Culture Conversion												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
1	randomised trials	serious [1]	not serious	not serious	serious [2]	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 Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of Antibiotic Resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse Drug Effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No blinding, unclear concealment
2. 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
Death (follow up: 5 years)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	none	8/17 (47.1%)	5/17 (29.4%)	**RR 1.60** (0.66 to 3.91)	**18 more per 100** (from 10 fewer to 86 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cure of NTM disease (follow up: 5 years)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	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
Recurrence (relapse) (follow up: 5 years)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
1	randomised trials	serious [1]	not serious	not serious	serious [3]	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 conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Severe adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Any adverse effects (follow up: 2 years)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)**		
1	randomised trials	serious [1]	not serious	serious [4]	serious [5]	none	38/185 (20.5%)	37/186 (19.9%)	**RR 1.03** (0.69 to 1.55)	**1 more per 100** (from 6 fewer to 11 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Participants and investigators were not blinded
2. Only 13 events; CI does not exclude an appreciable benefit with either intervention
3. Only 2 events and 34 patients in total
4. AEs were not reported separately for M. xenopi
5. 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 assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a two drug regimen**	**a three drug regimen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death (follow up: 5 years)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	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 NTM												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	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
Recurrence												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	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 of Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a two drug regimen	a three drug regimen	Relative (95% CI)	Absolute (95% CI)		
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture Conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No blinding, unclear if properly randomized/concealed
2. 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 assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parenteral	no parenteral agent	Relative (95% CI)	Absolute (95% CI)		
Cure of NTM disease - not measured												
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Death - not measured												
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Recurrence (relapse) - not measured												
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Culture conversion - not measured												
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL
Adverse drug effects - not measured												
-	-	-	-	-	-	-	-	-	-	see comment	-	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Parenteral**	**no parenteral agent**	**Relative (95% CI)**	**Absolute (95% CI)**		
Development of antibiotic resistance - not 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 assessment							№ of patients		Effect		Quality	Importance
№ 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)		
Cure of NTM												
2	observational studies	serious [1]	not serious	serious [2]	serious [3]	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
Recurrence												
2	observational studies	serious [1]	not serious	serious [2]	serious [3]	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 conversion												

Quality assessment							№ of patients		Effect		Quality	Importance
№ 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)		
1	observational studies	serious [1]	not serious	serious [2]	serious [3]	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 of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse drug effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No control for confounding
2. Not a direct comparison
3. 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 assessment							№ of patients		Effect		Quality	Importance
№ of studies	**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)**		
Cure of NTM												
2	observational studies	serious [1]	Not serious	not serious	not serious	publication bias strongly suspected [2]	48/75 (64.0%)	3/7 (42.9%)	**RR 2.18** (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 [3]	not serious	not serious	not serious	publication bias strongly suspected [2]	2/65 (3.1%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Recurrence (Relapse)												
1	observational studies	serious [3]	not serious	not seririous	not serious	publication bias strongly suspected [2]	9/47 (19.1%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Culture Conversion												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	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)		
1	observational studies	serious [3]	not serious	not serious	not serious	publication bias strongly suspected [2]	47/65 (72.3%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Any adverse effect												
1	observational studies	serious [3]	not serious	not serious	not serious	publication bias strongly suspected [2]	14/65 (21.5%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal owing to adverse effect												
1	observational studies	serious [3]	not serious	not serious	not serious	publication bias strongly suspected [2]	6/65 (9.2%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	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)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No control for confounding
2. Data limited to case series and likely that there have been unpublished case series not captured
3. 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 assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**two drugs**	**three vs. four drugs**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cure of NTM disease (follow up: median 445 days)												
1	observational studies	serious [1]	not serious	serious [2]	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
Recurrence (relapse) (follow up: median 445 days)												
1	observational studies	serious [1]	not serious	serious [2]	serious [3]	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) [2]	⊕◯◯◯ VERY LOW	CRITICAL
Any adverse effect (follow up: median 445 days)												
1	observational studies	serious [1]	not serious	serious [2]	serious [3]	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 conversion												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**two drugs**	**three vs. four drugs**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [1]	not serious	serious [2]	serious [3]	none	The study reported no significant difference between the two groups, but only reported a p-value of 0.698 without specifying exact numbers.				⨁◯◯◯ VERY LOW	CRITICAL
Quality of Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Observational study without blinding, randomization
2. Unclear subspecies of M abscessus
3. 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 assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**shorter therapy duration**	**longer therapy duration**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cure of NTM												
1	observational studies	serious [1]	not serious	serious [2]	serious [3]	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
Recurrence (relapse) - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Development of antibiotic resistance - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter therapy duration	longer therapy duration	Relative (95% CI)	Absolute (95% CI)		
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse drug effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No control for confounding
2. Not a direct comparison, various regimens and course length
3. 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 assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**medical therapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cure of NTM												
1	observational studies	serious [1]	not serious	not serious	serious [2]	none	13/23 (56.5%)	13/46 (28.3%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Death												
10	observational studies	serious [3]	not serious	not serious	serious [2]	publication bias strongly suspected [4]	20/486 (4.1%)	13/83 (15.7%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Recurrence												
9	observational studies	serious [1,3]	not serious	not serious	serious [2]	publication bias strongly suspected [4]	22/391 (5.6%)	12/102 (11.8%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion												
10	observational studies	serious [1,3,5]	not serious	not serious	serious [2]	publication bias strongly suspected [4]	283/331 (85.5%)	18/46 (39.1%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Surgical Complication												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**surgery**	**medical therapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
9	observational studies	serious [1,3]	not serious	not serious	not serious	publication bias strongly suspected [4]	111/563 (19.7%)	0/0	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL
Quality of Life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. No control for confounding
2. 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 EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Any treatment compared to watchful waiting for NTM pulmonary infection**	

Outcomes	Anticipated absolute effects (95% CI)	Relative effect	№ of participants (studies)	Quality of the evidence

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

	Risk with watchful waiting	Risk with any treatment	(95% CI)		(GRADE)
Cure of NTM	348 per 1000	**706 per 1000** (153 to 1000)	**RR 2.03** (0.44 to 9.30)	94 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2]
Death	457 per 1000	**352 per 1000** (292 to 420)	**RR 0.77** (0.64 to 0.92)	438 (5 observational studies)	⊕◯◯◯ VERY LOW [1,3]
Culture Conversion	505 per 1000	**713 per 1000** (253 to 1000)	**RR 1.41** (0.50 to 4.02)	168 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2,4]
Any adverse effect	A total of 43 out of 100 patients in the treatment group had adverse effects. In neither study was it specified if there were any adverse effects in the watchful waiting group (of 67 patients), but presumably there were none.			167 (2 observational studies)	⊕◯◯◯ VERY LOW [1]
Quality of Life - not measured	-	-	-	-	-
Recurrence - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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

		Culture Conversion	CRITICAL	⊕◯◯◯ VERY LOW
		Quality of Life	CRITICAL	-
		Recurrence	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	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.		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.
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	**Any treatment compared to watchful waiting for NTM pulmonary infection**		

Outcomes	**Anticipated absolute effects* (95% CI)**		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with watchful waiting	**Risk with any treatment**			
Cure of NTM	348 per 1000	**706 per 1000** (153 to 1000)	**RR 2.03** (0.44 to 9.30)	94 (2 observational	⊕◯◯◯ VERY LOW

	○ Don't know						
						studies)	[1,2]
		Death	457 per 1000	**352 per 1000** (292 to 420)	**RR 0.77** (0.64 to 0.92)	438 (5 observational studies)	⊕◯◯◯ VERY LOW [1,3]
		Culture Conversion	505 per 1000	**713 per 1000** (253 to 1000)	**RR 1.41** (0.50 to 4.02)	168 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2,4]
		Any adverse effect	A total of 43 out of 100 patients in the treatment group had adverse effects. In neither study was it specified if there were any adverse effects in the watchful waiting group (of 67 patients), but presumedly there were none.			167 (2 observational studies)	⊕◯◯◯ VERY LOW [1]
		Quality of Life - not measured	-	-	-	-	-
		Recurrence - 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?** ○ 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?** ○ 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.	

Summary of judgments

	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	

Conclusions

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 diagnostic criteria for NTM pulmonary disease, we suggest initiation of treatment rather than watchful waiting, especially in the context of positive acid-fast bacilli sputum smears and/or cavitary lung disease (conditional recommendation, very low confidence in estimates of effect).				

	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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
EF LE AD	**How substantial are the desirable**		The one identified study for this

anticipated effects?

○ Trivial
○ Small
○ Moderate
○ Large

○ Varies
● Don't know

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

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

question was felt to be only indirectly related and not useful evidence upon which to base a recommendation. Additionally, it was felt that the methods of performing susceptibility testing were outdated and not relevant to current practice.

The utility of *in vitro* drug susceptibility testing is entirely dependent on the NTM species being treated and the drugs being tested.

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
○ Trivial

○ Varies
● Don't know

The results of standardized and validated drug susceptibility testing are useful for guiding treatment, in particular for drugs where there has been a correlation between *in vitro* activity and treatment outcome, e.g. macrolides, amikacin.

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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)
Quality of Life	CRITICAL	(not measured)
Cure of NTM Disease	CRITICAL	(not measured)
Death	CRITICAL	⊕◯◯◯ VERY LOW
Development of antibiotic resistance	CRITICAL	(not measured)
Recurrence	CRITICAL	(not measured)
Culture Conversion	CRITICAL	(not measured)

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 *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.

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with susceptibility-based treatment	**Risk with empiric treatment**			
Quality of Life - not measured	-	-	-	-	-
Cure of NTM Disease - not reported	-	-	-	-	-
Death	Authors report no significant difference between empiric vs culture-based regimens (80 vs 75%)			(1 observational study)	⊕◯◯◯ VERY LOW [1,2,3]
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.

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 data available.	
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 data available.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased	No data available.	

	○ Varies ○ Don't know		
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No data available.	
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.	

Summary of judgments

	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	

Conclusions

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 ○	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 MAC pulmonary disease, we suggest susceptibility-based treatment for macrolides and amikacin (conditional recommendation, very low confidence in estimates of effect). In patients with *M. kansasii* pulmonary disease, we suggest susceptibility-based treatment for rifampicin (conditional recommendation, very low confidence in estimates of effect). In patients with *M. xenopi* pulmonary disease, the committee feels there is insufficient evidence to make a recommendation for or against susceptibility-based treatment. In patients with *M. abscessus* pulmonary disease we suggest susceptibility-based treatment for macrolides and amikacin (conditional recommendation, very low confidence in estimates of effect). For macrolides, a 14-day incubation and/or sequencing of the *erm*(41) gene should be performed to evaluate for potential inducible macrolide resistance. While we recommend testing of other drugs in order to guide *M. abscessus* therapy there is insufficient data to make specific recommendations in this regard. The panel members voted unanimously for a conditional recommendation for the intervention with regards to MAC *M. kansasii*, and *M. abscessus*. The panel members also voted unanimously for no recommendation for *M. xenopi*.				
JUSTIFICATION	There is indirect evidence of poor outcomes in cases of macrolide or amikacin resistance. There is evidence from randomized clinical trials that correlated *in vitro* activity with amikacin and treatment outcomes. Although *in vitro-in vivo* 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	While the available evidence may be scarce, there is a need for proper drug susceptibility testing in guiding therapy. If acquired resistance can be ruled out, AST may not be required if proper species /subspecies identification is done, as drug susceptibility to a large extent is a species /subspecies specific character. However, for certain species/drug combinations there is also				

	significant drug heterogeneity, e.g. tetracyclines and *M. abscessus* subsp. *abscessus* and *M. fortuitum*. 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.

Table E4.3. Question III

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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See table below	The committee felt that macrolide regimens are more effective based on their clinical experience and retrospective cohort studies. There were a number of concerns with the two studies included from the literature search. These concerns included the small sample size in the studies, under-dosing 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 noted to be quite large for this disease, raising question to the validity of this result. The committee unanimously felt that macrolides are a critical component to MAC treatment. Although one study appeared to have higher death rates in patients on a macrolide-containing regimen than on a regimen without, the

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with three drugs without a macrolide	Risk with three drugs with a macrolide				
Cure of NTM	Study population		**RR 0.93** (0.62 to 1.37)	190 (2 observational studies)	⊕◯◯◯ VERY LOW[a b]	
	354 per 1,000	**329 per 1,000** (220 to 485)				
Death	Study population		**RR 1.61**	170	⊕◯◯◯	

			299 per 1,000	**481 per 1,000** (326 to 714)	(1.09 to 2.39)	(1 observational study)	VERY LOW[a b]	committee felt this study was not applicable for the reasons previously stated.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Recurrence (relapse)	Study population		**RR 0.87** (0.37 to 2.01)	190 (2 observational studies)	⊕◯◯◯ VERY LOW[a b]	
			104 per 1,000	**91 per 1,000** (39 to 209)				
		Culture conversion	Study population		**RR 0.98** (0.67 to 1.43)	197 (2 observational studies)	⊕◯◯◯ VERY LOW[a b c]	
			850 per 1,000	**833 per 1,000** (570 to 1,000)				
		Any adverse effect	Study population		**RR 0.23** (0.03 to 1.82)	27 (1 RCT)	⊕⊕◯◯ LOW[a b]	
			308 per 1,000	**71 per 1,000** (9 to 560)				
		Serious advere effect	Study population		not estimable	27 (1 RCT)	⊕⊕◯◯ LOW[b]	
			0 per 1,000	**0 per 1,000** (0 to 0)				
		Withdrawal owing to adverse effect	Study population		**RR 0.46** (0.05 to 4.53)	27 (1 RCT)	⊕⊕◯◯ LOW[a b]	
			154 per 1,000	**71 per 1,000** (8 to 697)				

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

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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	⊕⊕◯◯ LOW
Serious advere effect	CRITICAL	⊕⊕◯◯ LOW
Withdrawal owing to adverse effect	CRITICAL	⊕⊕◯◯ LOW
Quality of Life	CRITICAL	-

VALUES

Is there important uncertainty about or variability in how

Values and preferences:

	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	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.	
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		

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with three drugs without a macrolide	Risk with three drugs with a macrolide				
Cure of NTM	Study population		**RR 0.93** (0.62 to 1.37)	190 (2 observational studies)	⊕◯◯◯ VERY LOW[a b]	
	354 per 1,000	**329 per 1,000** (220 to 485)				
Death	Study population		**RR 1.61** (1.09 to 2.39)	170 (1 observational	⊕◯◯◯ VERY LOW[a b]	
	299 per	**481 per**				

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

Summary of judgments

	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	

Conclusions

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				

RESEARCH PRIORITIES	

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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Azithromycin-based regimen compared to clarithromycin-based regimen in patients with newly diagnosed pulmonary MAC**	Azithromycin has fewer drug interactions compared with clarithromycin. Azithromycin may be better tolerated than clarithromycin Toxicity of azithromycin may be resolved by lowering dose, while this may not be possible with clarithromycin.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with clarithromycin-based regimen	Risk with azithromycin-based regimen			
Death - not reported	-	-	-	-	-

		Quality of life - not measured	-	-	-	-	-	Clarithromycin may have more QT-interval prolongation.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Culture Conversion	82 per 100	**72 per 100** (60 to 86)	**RR 0.88** (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.
		Recurrence (relapse) - not measured	-	-	-	-	-	
		Development of antibiotic resistance	9 per 100	**5 per 100** (1 to 26)	**RR 0.51** (0.07 to 2.79) [4]	189 (3 observational studies)	⊕◯◯◯ VERY LOW [1,3]	
		Serious adverse effects	0 per 100	**0 per 100** (0 to 0)	not estimable	59 (1 observational study)	⊕◯◯◯ VERY LOW [1,5]	
		Withdrawal from study due to AEs	14 per 100	**15 per 100** (6 to 30)	**RR 1.02** (0.45 to 2.07)	191 (3 observational studies)	⊕◯◯◯ VERY LOW [1,6]	
		Any Adverse Effect	41 per 100	**31 per 100** (18 to 52)	**RR 0.75** (0.44 to 1.28)	483 (6 observational studies)	⊕◯◯◯ VERY LOW [1,7,8]	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ 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)
Death	CRITICAL	-
Quality of life	CRITICAL	-
Culture Conversion	CRITICAL	⊕◯◯◯

		Recurrence (relapse)	CRITICAL	-
		Development of antibiotic resistance	CRITICAL	⊕◯◯◯ VERY LOW
		Serious adverse effects	CRITICAL	⊕◯◯◯ VERY LOW
		Withdrawal from study due to AEs	CRITICAL	⊕◯◯◯ VERY LOW
		Any Adverse Effect	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 variability	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). Mean SF-36 scores (scale 0-100, higher scores indicate better QoL; MID~5-10 points) were consistently much lower compared to population normal: Physical Functioning (58 vs. 86; Δ28) 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) Role Emotional (75 vs. 84; Δ10) Mental Health (69 vs. 76; Δ9)		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.

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.

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

Azithromycin-based regimen compared to clarithromycin-based regimen in patients with newly diagnosed pulmonary MAC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with clarithromycin-based regimen	**Risk with azithromycin-based regimen**			
Death - not reported	-	-	-	-	-
Quality of life - not measured	-	-	-	-	-
Culture Conversion follow up: range 4 to 12 months	82 per 100	**72 per 100** (60 to 86)	**RR 0.88** (0.73 to 1.05)	368 (4 observational studies)	⊕◯◯◯ VERY LOW [1,2]
Recurrence (relapse) - not measured	-	-	-	-	-
Development of antibiotic resistance follow up: range 4 to 12 months	9 per 100	**5 per 100** (1 to 26)	**RR 0.51** (0.07 to 2.79) [4]	189 (3 observational studies)	⊕◯◯◯ VERY LOW [1,3]

		Serious adverse effects follow up: 4 months	0 per 100	**0 per 100** (0 to 0)	not estimable	59 (1 observational study)	⊕◯◯◯ VERY LOW [1,5]	
		Withdrawal from study due to AEs follow up: range 4 to 6 months	14 per 100	**15 per 100** (6 to 30)	**RR 1.02** (0.45 to 2.07)	191 (3 observational studies)	⊕◯◯◯ VERY LOW [1,6]	
		Any Adverse Effect follow up: range 4 to 12 months	41 per 100	**31 per 100** (18 to 52)	**RR 0.75** (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 evidence 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 evidence was identified.						
EQUITY	**What would be the impact on**	No research evidence was identified.						

	health equity? ○ 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.

Summary of judgments

	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							IMPLICATIONS
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	

Conclusions

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 ○
RECOMMENDATION	In patients with macrolide-susceptible MAC pulmonary disease we suggest azithromycin-based treatment regimens rather than clarithromycin-based regimens. (conditional recommendation, very low confidence in estimates of effect). The panel members voted unanimously for a conditional recommendation for the intervention.				
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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large	**Parenteral compared to no parenteral agent for MAC**	

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
● Moderate
○ Small
○ Trivial

○ Varies
○ Don't know

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with no parenteral agent	**Risk with Parenteral**			
Cure of NTM - not measured	-	-	-	-	-
Death	27 per 1000	**27 per 1000** (4 to 189)	**RR 1.00** (0.14 to 6.91)	146 (1 RCT)	⊕⊕⊕◯ MODERATE [3]
Recurrence (relapse)	351 per 1000	**309 per 1000** (169 to 559)	**RR 0.88** (0.48 to 1.59)	89 (1 RCT)	⊕⊕⊕◯ MODERATE
Culture Conversion	507 per 1000	**715 per 1000** (542 to 933)	**RR 1.41** (1.07 to 1.84)	146 (1 RCT)	⊕⊕⊕◯ MODERATE [3]
Any adverse reaction	205 per 1000	**247 per 1000** (136 to 450)	**RR 1.20** (0.66 to 2.19)	146 (1 RCT)	⊕⊕⊕◯ MODERATE [3]
Serious adverse events	0 per 1000	**0 per 1000** (0 to 0)	not estimable	146 (1 RCT)	⊕⊕⊕⊕ HIGH
Quality of life - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-

The undesirable anticipated effects of amikacin are larger when given for 3 months.

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

○ Very low
○ 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	⊕⊕⊕◯ MODERATE
Recurrence (relapse)	CRITICAL	⊕⊕⊕◯ MODERATE
Culture Conversion	CRITICAL	⊕⊕⊕◯ MODERATE
Any adverse reaction	CRITICAL	⊕⊕⊕◯ MODERATE
Serious adverse events	CRITICAL	⊕⊕⊕⊕ HIGH
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 *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.	
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	**Parenteral compared to no parenteral agent for MAC**	Intervention is with a parenteral agent.

Outcomes	**Anticipated absolute effects*** **(95% CI)**		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with no parenteral agent	**Risk with Parenteral**			
Cure of NTM - not measured	-	-	-	-	-
Death	27 per 1000	**27 per 1000** (4 to 189)	**RR 1.00** (0.14 to 6.91)	146 (1 RCT)	⊕⊕⊕◯ MODERATE [3]
Recurrence (relapse)	351 per 1000	**309 per 1000** (169 to 559)	**RR 0.88** (0.48 to 1.59)	89 (1 RCT)	⊕⊕⊕◯ MODERATE
Culture Conversion	507 per 1000	**715 per 1000** (542 to 933)	**RR 1.41** (1.07 to 1.84)	146 (1 RCT)	⊕⊕⊕◯ MODERATE [3]
Any adverse reaction	205 per 1000	**247 per 1000** (136 to 450)	**RR 1.20** (0.66 to 2.19)	146 (1 RCT)	⊕⊕⊕◯ MODERATE [3]
Serious adverse events	0 per 1000	**0 per 1000** (0 to 0)	not estimable	146 (1 RCT)	⊕⊕⊕⊕ HIGH
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.	Varies with the health system, but regardless it is likely associated with a significant cost due to need for indwelling catheter, infusion center, nursing care, cost of medication.
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	No research evidence was identified.	It depends on the health system coverage. If patients are not covered, there will be a reduction in equity as they should pay for the treatment to be administered (cost of the drug and administration).

	● 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. 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 *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.	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

Summary of judgments

	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**	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	

Conclusions

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 against the	Conditional recommendation against the	Conditional recommendation for either the intervention or	Conditional recommendation for the	Strong recommendation for the

	intervention ○	intervention ○	the comparison ○	intervention ●	intervention ○
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 unanimously for a conditional recommendation for the intervention.				
JUSTIFICATION					
SUBGROUP CONSIDERATIONS	The addition of parenteral agents (i.e; aminoglycosides) should be discussed according to the severity of the disease and according to the radiological features (cavitary or nodular bronchiectatic disease).				
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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know		
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with a regimen with inhaled antibiotics	Risk with a regimen without inhaled antibiotics				
Cure of NTM	Study population		not estimable	3 (1 observational study)	⊕◯◯◯ VERY LOW[a]	
	3/3 (100%)	--				
Death	Study population		-	9 (2 observational studies)	⊕◯◯◯ VERY LOW[a]	
	2/9 (22.2%)	--				
Recurrence (relapse)	Study population		-	21 (1 RCT and 2 observational studies)	⊕⊕⊕◯ MODERATE	
	9/21 (42.9%)	--				

Culture Conversion	Study population		-	68 (1 RCT and 2 observational studies)	⊕⊕◯◯ LOW[b c]	
	16/40 (40.0%)	1/28 (3.6%)				
Any Adverse Effect	Study population		-	104 (1 RCT and 2 observational studies)	⊕⊕◯◯ LOW[b d]	
	46/59 (78.0%)	40/45 (88.9%)				
Serious Adverse Effect	Study population		-	104 (1 RCT and 2 observational studies)	⊕⊕◯◯ LOW[b e]	
	8/59 (13.6%)	4/45 (8.9%)				
Withdrawal owing to adverse effects	Study population		-	124 (1 RCT and 3 observational studies)	⊕⊕◯◯ LOW[b f]	
	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[g]	
Development of Antibiotic Resistance	Study population		not estimable	89 (1 RCT)	⊕⊕⊕◯ MODERATE[g]	
	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

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
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 *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.

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with a regimen with inhaled antibiotics	Risk with a regimen without inhaled antibiotics				
Cure of NTM	Study population		not estimable	3 (1 observational study)	⊕◯◯◯ VERY LOW[a]	
	3/3 (100.0%)	--				
Death	Study population		-	9 (2 observational studies)	⊕◯◯◯ VERY LOW[a]	
	2/9 (22.2%)	--				
Recurrence (relapse)	Study population		-	21 (1 RCT and 2 observational studies)	⊕⊕⊕◯ MODERATE	
	9/21 (42.9%)	0/0				
Culture Conversion	Study population		-	68 (1 RCT and 2 observational studies)	⊕⊕◯◯ LOW[b c]	
	16/40 (40.0%)	1/28 (3.6%)				

Any Adverse Effect	Study population		-	104 (1 RCT and 2 observational studies)	⊕⊕◯◯ LOW[b d]	
	46/59 (78.0%)	40/45 (88.9%)				
Serious Adverse Effect	Study population		-	104 (1 RCT and 2 observational studies)	⊕⊕◯◯ LOW[b e]	
	8/59 (13.6%)	4/45 (8.9%)				
Withdrawal owing to adverse effects	Study population		-	124 (1 RCT and 3 observational studies)	⊕⊕◯◯ LOW[b f]	
	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[g]	
Development of Antibiotic Resistance	Study population		not estimable	89 (1 RCT)	⊕⊕⊕◯ MODERATE[g]	
	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?** ○ 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?** ○ 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.	

Summary of judgments

	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	

Conclusions

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	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	●
RECOMMENDATION	In patients with MAC pulmonary disease, we suggest neither the use of commercially available parenteral amikacin nor amikacin liposomal inhaled suspension as part of the initial treatment regimen. (conditional recommendation, very low confidence in estimates of effect). The panel members voted for a conditional recommendation for the intervention. In patients with MAC pulmonary disease who have failed therapy after at least six months of guideline-based therapy, we recommend the use of amikacin liposomal inhaled suspension as part of the treatment regimen. (strong recommendation, moderate confidence in estimates of effect). (5 Strong, 4 Conditional, 9 Abstain) Expert panel members that had declared a conflict of interest with Insmed had to abstain from voting 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);

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**A three drug regimen compared to a two drug regimen for treatment of MAC pulmonary infection**	

Outcomes	**Anticipated absolute effects* (95% CI)**	Relative effect	№ of participants	Quality of the evidence

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know

	Risk with a two trug regimen	Risk with a three drug regimen	(95% CI)	(studies)	(GRADE)
Culture Conversion	550 per 1000	**407 per 1000** (275 to 600)	**RR 0.74** (0.50 to 1.09)	119 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Serious Adverse Effects	0 per 1000	**0 per 1000** (0 to 0)	not estimable	119 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
Withdrawal owing to adverse effect	267 per 1000	**373 per 1000** (213 to 565)	**RR 1.40** (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	-	-	-	-	-

In non-pulmonary disease, there is known to be high rates of antibiotic resistance with 2 drug therapy regimens.

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

○ Very low
● 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)

		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	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.		

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

A three drug regimen compared to a two trug regimen for treatment of MAC pulmonary infection

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with a two trug regimen	**Risk with a three drug regimen**			
Culture Conversion	550 per 1000	**407 per 1000** (275 to 600)	**RR 0.74** (0.50 to 1.09)	119 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Serious Adverse Effects	0 per 1000	**0 per 1000** (0 to 0)	not estimable	119 (1 RCT)	⊕⊕⊕◯ MODERATE [1]
Withdrawal owing to adverse effect	267 per 1000	**373 per 1000** (213 to 565)	**RR 1.40** (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)?** ○ 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?** ○ 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.	

Summary of judgments

	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	

Conclusions

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 ○
RECOMMENDATION	In patients with macrolide susceptible MAC pulmonary disease, we suggest a treatment regimen with at least three drugs (including a macrolide and ethambutol) over a regimen with two drugs (a macrolide and ethambutol alone). (conditional recommendation, very low confidence in estimates of effect). The panel members voted unanimously for a conditional recommendation for the intervention.				
JUSTIFICATION					
SUBGROUP CONSIDERATIONS	In patients with severe, particularly fibrocavitary disease, addition of amikacin or streptomycin (possible with clofazimine) in the initial 3 months of treatment is worth serious consideration.				
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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**A three times per week macrolide-based regimen compared to daily macrolide-based regimen in patients with pulmonary MAC**	In one study 75% had to discontinue daily treatment owing to adverse events. Panel members have seen many more patients in their practice than there were in these combined studies. In the experience of some panel members the proportion of patients not tolerating daily treatment may be smaller than seen in these studies.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with daily macrolide-based regimen	**Risk with a three times per week macrolide-based regimen**			
Death - not reported	-	-	-	-	-
Quality of life - not	-	-	-	-	-

		measured					
		Cure of NTM Disease follow up: 12 months	76 per 100	**73 per 100** (55 to 86)	**RR 0.97** (0.72 to 1.14)	217 (1 observational study)	⊕◯◯◯ VERY LOW [1,2]	This applies to nodular or bronchiectatic disease and not to cavitary.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Culture Conversion follow up: range 6 to 12 months	74 per 100	**76 per 100** (69 to 84)	**RR 1.03** (0.93 to 1.14)	597 (5 observational studies)	⊕◯◯◯ VERY LOW [1,4]	There is some concern about potentially increased recurrence, however, this has been based on 4 events total.
		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	**4 per 100** (0 to 34)	**RR 2.78** (0.30 to 26.16)	158 (1 observational study)	⊕◯◯◯ VERY LOW [1,2,5]	
		Development of Antibiotic Resistance follow up: range 6 to 12 months	12 per 100	**3 per 100** (1 to 9)	**RR 0.23** (0.07 to 0.74)	232 (4 observational studies)	⊕◯◯◯ VERY LOW [1,4,6]	
		Serious adverse effects - not reported	-	-	-	-	-	
		Discontinuation of the initial treatment due to adverse effects follow up: range 6 to 12 months	22 per 100	**10 per 100** (2 to 48)	**RR 0.44** (0.09 to 2.16)	564 (4 observational studies)	⊕◯◯◯ VERY LOW [1,7,8]	
		Adverse Effects follow up: range 6 to 12 months	39 per 100	**24 per 100** (10 to 60)	**RR 0.63** (0.25 to 1.55)	445 (4 observational studies)	⊕◯◯◯ VERY LOW [1,8]	

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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)
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	-

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 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). Mean SF-36 scores (scale 0-100, higher scores indicate better QoL; MID~5-10 points) were consistently much lower compared to population normal: Physical Functioning (58 vs. 86; Δ28) 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)	

		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.	
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)?** ○ 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.
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.	Except for cost - no.

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.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgments

	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	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	

Conclusions

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

	against the intervention ○	against the intervention ○	for either the intervention or the comparison ○	for the intervention ●	for the intervention ○
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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**<12 months compared to >12 months for MAC** Outcomes | **Anticipated absolute effects* (95% CI)** | Relative effect | № of participants | Quality of the evidence	Dautzenberg 1994 10 months from culture conversion? 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.

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
○ Trivial

○ Varies
● Don't know

	Risk with >12 months	Risk with <12 months	(95% CI)	(studies)	(GRADE)
Culture conversion	856 per 1000	**222 per 1000** (111 to 453)	**RR 0.26** (0.13 to 0.53)	207 (1 observational study)	⊕◯◯◯ VERY LOW [1,2]
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	-	-	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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)
Culture conversion	CRITICAL	⊕◯◯◯ VERY LOW
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	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.	

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

<12 months compared to >12 months for MAC

Outcomes	**Anticipated absolute effects* (95% CI)**		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with >12 months	**Risk with <12 months**			
Culture conversion	856 per 1000	**222 per 1000** (111 to 453)	**RR 0.26** (0.13 to 0.53)	207 (1 observational study)	⨁◯◯◯ VERY LOW [1,2]
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.

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?** ○ No ○ Probably no ● Probably yes ○ Yes	No research evidence was identified.	

	○ Varies ○ Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgments

	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	Probably favors the intervention	Favors the intervention	Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
			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	

Conclusions

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
	○	●	○	○	○

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

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>DESIRABLE EFFECTS</td>
<td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
○ Large

○ Varies
● Don't know</td>
<td>
INH compared to no INH for Mycobacterium kansasii
<table>
<tr><th rowspan="2">Outcomes</th><th colspan="2">Anticipated absolute effects* (95% CI)</th><th rowspan="2">Relative effect (95% CI)</th><th rowspan="2">№ of participants (studies)</th><th rowspan="2">Quality of the evidence (GRADE)</th></tr>
<tr><th>Risk with no INH</th><th>Risk with INH</th></tr>
<tr><td>Cure of NTM - not measured</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Death - not measured</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Recurrence (relapse)</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
</td>
<td>One study from the Research Committee of the British Thoracic Society in 1994 was a prospective study of 9 months treatment with rifampin and ethambutol. They found: 9/149 deaths, 68% had negative sputum (32% had no sputum, 0% positive at 9 months). There was a 9.7% relapse rate - this study had a shorter duration of therapy and did not have INH.

Removing the potential for INH toxicity is a desirable anticipated effect. The importance of INH in the treatment regimen for M. kansasii is at best questionable, more so in an era when safer and more effective agents are available.</td>
</tr>
</table>

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Development of antibiotic resistance - not measured	-	-	-	-	-
		Quality of life - not measured	-	-	-	-	-
		Culture conversion - not reported	-	-	-	-	-
		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)?** ○ 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	No research evidence was identified.	

	○ 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.	

Summary of judgments

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

	JUDGEMENT							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	

Conclusions

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 ○
RECOMMENDATION	In patients with rifampicin susceptible *M. kansasii* pulmonary disease, we suggest a regimen of rifampicin, ethambutol, and either isoniazid or macrolide. (conditional recommendation, very low confidence in estimates of effect). The panel members voted unanimously for a conditional recommendation for either the intervention or comparison.				
JUSTIFICATION	Isoniazid is widely used at present for treatment of *M. kansasii* and in clinical studies and the experience of the committee members, there have been good outcomes when using this. There have been higher relapse rates in regiments without INH (or macrolides), albeit in non-comparative studies. Based on the results of two small retrospective cohort studies and the experience of the committee, a macrolide may be effectively substituted for INH.				
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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Parenteral compared to no parenteral agent for M kansasii**	Except for rifampin-resistant *M. kansasii* disease, parenteral agents ae seldom needed to treat use with *M. kansasii*.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no parenteral agent	Risk with Parenteral			

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Cure of NTM	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	-	-	-	-	-

Success rate is so high with current regimens, parenteral agents are rarely being used - risk of toxicity and adverse effects may outweigh benefit

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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 *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.	

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

Parenteral compared to no parenteral agent for M kansasii

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no parenteral agent	**Risk with Parenteral**			
Cure of NTM	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?** ○ 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.

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.	

Summary of judgments

	JUDGEMENT							IMPLICATIONS
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	

	JUDGEMENT							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	

Conclusions

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 ○
RECOMMENDATION	We suggest that neither amikacin nor streptomycin be used routinely for treating patients with *M. kansasii* pulmonary disease (Conditional recommendation, very low confidence in estimates of effect). (10 Strong, 5 Conditional, 3 Abstain) The panel members voted for a strong recommendation against the intervention despite a very low confidence in estimate of effect.				
JUSTIFICATION	Treatment outcomes in *M. kansasii* pulmonary disease are very good when using a rifamycin-based regimen with ethambutol and a second companion drug, either isoniazid or a macrolide. Unless the severity of the disease warrants intravenous therapy, *M. kansasii* can be treated with a rifamycin-based combination of 3 orally available drugs. Given generally high rates of culture conversion and treatment success observed with oral regimens for *M. kansasii* and the high risk of adverse effects associated with amikacin and streptomycin, the committee felt strongly that parenteral agents should not be used as first-line therapy for *M. kansasii.*				
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION					
RESEARCH PRIORITIES					

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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Fluoroquinolone compared to no fluoroquinolone for *M. kansasii***	The use of a fluoroquinolone (or a macrolide) means that INH can be dropped from the regimen with the attendant risk for INH toxicity.

Outcomes	**Anticipated absolute effects* (95% CI)**		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no Fluoroquinolone	**Risk with Fluorquinolone**			

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Cure of NTM Disease - not measured	-	-	-	-	-
		Development of antibiotic resistance - not measured	-	-	-	-	-
		Recurrence (relapse) - not measured	-	-	-	-	-
		Quality of Life - not measured	-	-	-	-	-
		Culture Conversion - not measured	-	-	-	-	-
		Death - not measured	-	-	-	-	-
		Adverse drug effects - not measured	-	-	-	-	-
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	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.	
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	**Fluorquinolone compared to no Fluoroquinolone for M kansasii** | Outcomes	**Anticipated absolute effects* (95% CI)**		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no Fluoroquinolone	**Risk with Fluorquinolone**			
Cure of NTM Disease - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-
Recurrence (relapse) - not	-	-	-	-	-		

		measured					
		Quality of Life - not measured	-	-	-	-	-
		Culture Conversion - not measured	-	-	-	-	-
		Death - not measured	-	-	-	-	-
		Adverse drug effects - 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**	No research evidence was identified.					

	equity? ○ 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.	

Summary of judgments

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	

Conclusions

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 rifampicin susceptible *M. kansasii* pulmonary disease, we suggest using a regimen of rifampicin, ethambutol, and either isoniazid or macrolide instead of a fluoroquinolone (conditional recommendation, very low confidence in estimates of effect). In patients with rifampicin resistant *M. kansasii* or intolerance to one of the first line antibiotics we suggest a fluoroquinolone (e.g., moxifloxacin) be used as part of a second-line regimen (conditional recommendation, very low confidence in estimates of effect). The panel members voted unanimously for a conditional recommendation against the intervention.				
JUSTIFICATION	Treatment success of *M. kansasii* pulmonary disease with a rifamycin-based drug regimen is excellent. The optimal choice of companion drugs is not clear. While ethambutol is usually the preferred companion drug, the choice of the second companion drug may be isoniazid or a macrolide. Which of these drugs is superior for the treatment of *M. kansasii* is unclear at present. As there is more experience and better evidence for treatment regimens that include isoniazid or a macrolide as the second companion drug, these drugs should be the preferred choice. Fluoroquinolones have excellent in vitro activity but there are no treatment studies using these for the treatment of *M. kansasii*.				
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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**M kansasii TIW compared to daily for M kansasii**	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with daily	Risk with M kansasii TIW			

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
○ Trivial

○ Varies
● Don't know

Cure of NTM	0/0	115/182 (63.2%)	not pooled	182 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2,3]
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	-	-	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

- ● Very low
- ○ 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	-

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 *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.	

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

M kansasii TIW compared to daily for M kansasii

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with daily	**Risk with M kansasii TIW**			
Cure of NTM	0/0	115/182 (63.2%)	not pooled	182 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2,3]

		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.	
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?** ○ 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.	

Summary of judgments

	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	**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	

Conclusions

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 recommendation	Conditional recommendation	Conditional recommendation	Conditional recommendation	Strong recommendation

	against the intervention ○	against the intervention ○	for either the intervention or the comparison ●	for the intervention ○	for the intervention ○
RECOMMENDATION	In patients with nodular/bronchiectatic *M. kansasii* 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 *M. kansasii* 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 *M. kansasii* 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 unanimously for a conditional recommendation for the comparison.				
JUSTIFICATION	Cavitary disease has higher morbidity and mortality and warrants a more aggressive treatment approach.				
SUBGROUP CONSIDERATIONS					

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

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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**<12 months compared to >12 months for M kansasii**	There are a number of studies that describe outcomes of *M. kansasii* with "short" or "long" duration of treatment, but without direct comparison. For instance, Santin, et al., published results on a 12 month treatment approach (retrospective cohort - ERJ 2009;33:148-52), reporting 6.6% relapse rate.

Outcomes	**Anticipated absolute effects* (95% CI)**	Relative effect	Nº of participants	Quality of the evidence

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

	Risk with >12 months	Risk with <12 months	(95% CI)	(studies)	(GRADE)
Cure of NTM	1000 per 1000	**1000 per 1000** (880 to 1000)	**RR 1.00** (0.88 to 1.14)	28 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Recurrence	0 per 1000	**0 per 1000** (0 to 0)	**RR 3.00** (0.13 to 67.91)	28 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Culture Conversion	1000 per 1000	**1000 per 1000** (880 to 1000)	**RR 1.00** (0.88 to 1.14)	28 (1 RCT)	⊕⊕◯◯ LOW [1,2,3]
Quality of Life - not measured	-	-	-	-	-
Development of Antibiotic Resistance - not measured	-	-	-	-	-
Death - not reported	-	-	-	-	-
Adverse Drug Effects - not reported	-	-	-	-	-

The undesirable anticipated effect might be inadequate treatment with progressive disease morbidity and prolonged exposure to antibiotic toxicity

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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
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	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.		

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

<12 months compared to >12 months for M kansasii

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with >12 months	Risk with <12 months			
Cure of NTM	1000 per 1000	**1000 per 1000** (880 to 1000)	**RR 1.00** (0.88 to 1.14)	28 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Recurrence	0 per 1000	**0 per 1000** (0 to 0)	**RR 3.00** (0.13 to 67.91)	28 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Culture Conversion	1000 per 1000	**1000 per 1000** (880 to 1000)	**RR 1.00** (0.88 to 1.14)	28 (1 RCT)	⊕⊕◯◯ LOW [1,2,3]
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?** ○ No ○ Probably no ● Probably yes ○ Yes	No research evidence was identified.	

	○ Varies ○ Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgments

	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	**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	

Conclusions

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 *M. kansasii* 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 associated with significant lung destruction if undertreated. However, if treated appropriately, treatment outcomes are excellent. Therefore, a conservative treatment approach is warranted, favoring a longer treatment course.				
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 months - moxifloxicin/clarithromycin/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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**A quinolone containing regimen compared to regimen without a fluoroquinolone in patients with newly diagnosed pulmonary M. xenopii infection** Outcomes | **Anticipated absolute effects* (95% CI)** | Relative | Nº of | Quality of	An ongoing study by C. Andrejak, et al (CaMoMy study), has shown no difference between groups for 6 month sputum conversion, adverse events.

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know

	Risk with regimen without a fluoroquinolone	**Risk with a quinolone containing regimen**	effect (95% CI)	participants (studies)	the evidence (GRADE)
Death follow up: 5 years	29 per 100	**47 per 100** (19 to 100)	**RR 1.60** (0.66 to 3.91)	34 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Quality of life - not measured	-	-	-	-	-
Cure of NTM disease follow up: 5 years	35 per 100	**35 per 100** (14 to 88)	**RR 1.00** (0.40 to 2.48)	34 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Recurrence (relapse) follow up: 5 years	12 per 100	**2 per 100** (0 to 46)	**RR 0.20** (0.01 to 3.88)	34 (1 RCT)	⊕⊕◯◯ LOW [1,3]
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	**20 per 100** (14 to 31)	**RR 1.03** (0.69 to 1.55)	371 (1 RCT)	⊕◯◯◯ VERY LOW [1,4,5]

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

○ Very low
● 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)
Death	CRITICAL	⊕⊕◯◯ LOW
Quality of life	CRITICAL	-
Cure of NTM disease	CRITICAL	⊕⊕◯◯ LOW
Recurrence (relapse)	CRITICAL	⊕⊕◯◯ LOW
Culture conversion	CRITICAL	-
Development of antibiotic resistance	CRITICAL	-
Severe adverse effects	CRITICAL	-
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 variability	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.	

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

A quinolone containing regimen compared to regimen without a fluoroquinolone in patients with newly diagnosed pulmonary M. xenopii infection

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with regimen without a fluoroquinolone	**Risk with a quinolone containing regimen**			
Death follow up: 5 years	29 per 100	**47 per 100** (19 to 100)	**RR 1.60** (0.66 to 3.91)	34 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Quality of life - not measured	-	-	-	-	-
Cure of NTM disease follow up: 5 years	35 per 100	**35 per 100** (14 to 88)	**RR 1.00** (0.40 to 2.48)	34 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Recurrence (relapse) follow up: 5 years	12 per 100	**2 per 100** (0 to 46)	**RR 0.20** (0.01 to 3.88)	34 (1 RCT)	⊕⊕◯◯ LOW [1,3]
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	**20 per 100** (14 to 31)	**RR 1.03** (0.69 to 1.55)	371 (1 RCT)	⊕◯◯◯ VERY LOW [1,4,5]

Intervention is fluoroquinolone-containing 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.	

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.	

Summary of judgments

	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**	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	

Conclusions

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 recommendation	Conditional recommendation	Conditional recommendation	Conditional recommendation	Strong recommendation

	against the intervention ○	against the intervention ○	for either the intervention or the comparison ●	for the intervention ○	for the intervention ○
RECOMMENDATION	In patients with *M. xenopi* pulmonary disease, we suggest using a treatment regimen that includes moxifloxacin or a macrolide. (conditional recommendation, low confidence in estimates of effect).				
JUSTIFICATION	There is *in vitro* evidence that macrolides and fluoroquinolones are active against *M. xenopi*, while rifampin and ethambutol are inactive alone and in combinations. From this perspective, a regimen that utilizes a macrolide or fluoroquinolone is likely most active. There are preliminary data from a randomized trial in favor of a non inferiority of fluoroquinolones in comparison to macrolides in treatment of *M. xenopi* infections. These data should be confirmed with final results of CaMoMy study. Limited evidence for optimal choice of optimal fluoroquinolone or macrolide - ciprofloxacin, moxifloxacin, and clarithromycin have been studied, but unclear if effects represent entire class of drugs.				
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION	ECG monitoring for potential QTc interval prolongation with long term of use macrolides and/or fluoroquinolones				
RESEARCH PRIORITIES	Clinical trial of rifampin/ethambutol/moxifloxacin vs. rifampin/ethambutol/azithromycin vs. rifampin/ethambutol/moxifloxacin/azithromycin.				

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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**A two drug regimen compared to a three drug regimen for treatment of M. xenopi pulmonary infection**	*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 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 macrolide or fluoroquinolone (BTS Thorax 63, 627; 2008) but that doesn't address the 2 vs 3 drug regimen. The most recent *M. xenopi* treatment data comes from case series (Andrejak et al, Thorax 64, 291; van Ingen et al EID, 2008).

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with a three drug regimen	Risk with a two drug regimen			
Death follow up: 5 years	650 per 1000	**501 per 1000** (293 to 845)	**RR 0.77** (0.45 to 1.30)	42 (1 RCT)	⊕⊕◯◯ LOW [1,2]

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know

Cure of NTM	100 per 1000	**227 per 1000** (50 to 1000)	**RR 2.27** (0.50 to 10.43)	42 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Recurrence	0 per 1000	**0 per 1000** (0 to 0)	**RR 4.57** (0.23 to 89.72)	42 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Quality of Life - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-
Culture Conversion - not reported	-	-	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

○ Very low
● 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)
Death	CRITICAL	⊕⊕◯◯ LOW
Cure of NTM	CRITICAL	⊕⊕◯◯ LOW
Recurrence	CRITICAL	⊕⊕◯◯ LOW
Quality of Life	CRITICAL	-
Development of antibiotic resistance	CRITICAL	-

		<table><tr><td>Culture Conversion</td><td>CRITICAL</td><td>-</td></tr></table>	
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 *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.	

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with a three drug regimen	**Risk with a two drug regimen**			
Death follow up: 5 years	650 per 1000	**501 per 1000** (293 to 845)	**RR 0.77** (0.45 to 1.30)	42 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Cure of NTM	100 per 1000	**227 per 1000** (50 to 1000)	**RR 2.27** (0.50 to 10.43)	42 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Recurrence	0 per 1000	**0 per 1000** (0 to 0)	**RR 4.57** (0.23 to 89.72)	42 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Quality of Life - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-
Culture Conversion - 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?** ○ No ○ Probably no ● Probably yes ○ Yes	No research evidence was identified.	

	○ Varies ○ Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgments

	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	**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	

Conclusions

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 ○
RECOMMENDATION	In patients with *M xenopi* 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* models, regimens of rifampicin, ethambutol, and either clarithromycin or moxifloxacin are efficacious. Given the very high mortality with *M. xenopi*, some members of expert panel felt the large risk of treatment failure with a two drug regimen warranted a strong recommendation for a three drug treatment regimen. However, the majority of the members voted for a conditional recommendation for three or more drugs.				
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS	Moxifloxacin may not be available in all settings and activity of gemifloxacin or gatifloxacin has not been 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;

Assessment

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with no parenteral agent	Risk with Parenteral			
Cure of NTM disease - not measured	-	-	-	-	-
Death - not measured	-	-	-	-	-
Recurrence (relapse) - not measured	-	-	-	-	-

		Quality of life - 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
		Culture conversion - not measured	-	-	-	-	-	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Adverse drug effects - not measured	-	-	-	-	-	
		Development of antibiotic resistance - not measured	-	-	-	-	-	

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ 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 disease	CRITICAL	-
Death	CRITICAL	-
Recurrence (relapse)	CRITICAL	-
Quality of life	CRITICAL	-
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?** ○ Important uncertainty or variability	Values and preferences: Three relevant studies were identified that provide data on patient values and

	● 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 *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.	
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)?** ○ 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?** ○ 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	No research evidence was identified.	

	○ Yes ● Varies ○ Don't know		

Summary of judgments

	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							IMPLICATIONS
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	

Conclusions

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 *M. xenopi* 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, *M. xenopi* patients should be treated aggressively given the high morbidity and mortality of the disease. In murine models of *M. xenopi* 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;

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>DESIRABLE EFFECTS</td>
<td>How substantial are the desirable anticipated effects?

● Trivial
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know</td>
<td>
<12 months compared to >12 months for Mycobacterium xenopi
<table>
<tr><th>Outcomes</th><th>Anticipated absolute effects* (95% CI)</th><th>Relative effect</th><th>№ of participants</th><th>Quality of the</th></tr>
</table>
</td>
<td>Because of the apparent very high mortality with M xenopi disease, insuring adequate therapy is important. Without compelling evidence, and with the potential for significant morbidity and mortality with untreated disease, a conservative approach is likely warranted.</td>
</tr>
</table>

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
○ Trivial

○ Varies
● Don't know

	Risk with >12 months	Risk with <12 months	(95% CI)	(studies)	evidence (GRADE)
Cure of NTM	481 per 1000	**260 per 1000** (125 to 544)	**RR 0.54** (0.26 to 1.13)	54 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2,3]
Recurrence	370 per 1000	**215 per 1000** (96 to 481)	**RR 0.58** (0.26 to 1.30)	54 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2,3]
Culture conversion	571 per 1000	**503 per 1000** (154 to 1000)	**RR 0.88** (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	-	-	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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

		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	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.		

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

<12 months compared to >12 months for Mycobacterium xenopi

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with >12 months	**Risk with <12 months**			
Cure of NTM	481 per 1000	**260 per 1000** (125 to 544)	**RR 0.54** (0.26 to 1.13)	54 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2,3]
Recurrence	370 per 1000	**215 per 1000** (96 to 481)	**RR 0.58** (0.26 to 1.30)	54 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2,3]
Culture conversion	571 per 1000	**503 per 1000** (154 to 1000)	**RR 0.88** (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	-	-	-	-	-

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?** ○ No ○ Probably no ● Probably yes ○ Yes	No research evidence was identified.	

	○ Varies ○ Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgments

	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	

Conclusions

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 ○
RECOMMENDATION	In patients with *M. xenopi* pulmonary disease, we suggest that treatment be continued for at least 12 months beyond culture conversion (conditional recommendation, very low confidence in estimates of effect). The panel members voted unanimously for a conditional recommendation for the comparison.				
JUSTIFICATION	Because of the significant morbidity and mortality of untreated *M. xenopi* disease and without compelling evidence to the contrary, a conservative approach should be undertaken with treatment of at least 12 months beyond culture conversion.				
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;

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Macrolide compared to No macrolide for Mycobacterium abscessus pulmonary infection** Outcomes | **Anticipated absolute effects* (95% CI)** | Relative effect | № of participants (studies) | Quality of the evidence	It is important to consider identification of the M abscessus subspecies because of the difference in response to macrolide therapy based on the presence or absence of the inducible macrolide resistance (erm) gene.

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
○ Trivial

○ Varies
● Don't know

	Risk with No macrolide	**Risk with Macrolide**	(95% CI)		(GRADE)
Cure of NTM	429 per 1000	934 per 1000 (420 to 1000)	**RR 2.18** (0.98 to 4.84)	82 (2 observational studies)	⊕◯◯◯ VERY LOW [1,2]
Death	no data	2/65 (3.1%)	-	65 (1 observational study)	⊕◯◯◯ VERY LOW [2,3]
Recurrence (Relapse)	no data	9/47 (19.1%)	-	47 (1 observational study)	⊕◯◯◯ VERY LOW [2,3]
Culture Conversion	no data	47/65 (72.3%)	-	65 (1 observational study)	⊕◯◯◯ VERY LOW [2,3]
Any adverse effect	no data	14/65 (21.5%)	-	65 (1 observational study)	⊕◯◯◯ VERY LOW [2,3]
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	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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
Withdrawal owing to adverse effect	CRITICAL	⊕◯◯◯ VERY LOW
Development of antibiotic resistance	CRITICAL	-
Quality of life	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 *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.	
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	**Macrolide compared to No macrolide for Mycobacterium abscessus pulmonary infection**	Intervention is considered macrolide-containing regimens

Outcomes	**Anticipated absolute effects* (95% CI)**		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with No macrolide	**Risk with Macrolide**			
Cure of NTM	429 per 1000	934 per 1000 (420 to 1000)	**RR 2.18** (0.98 to 4.84)	82 (2 observational studies)	⊕◯◯◯ VERY LOW[1,2]
Death	no data	2/65 (3.1%)	-	65 (1 observational study)	⊕◯◯◯ VERY LOW[2,3]
Recurrence (Relapse)	no data	9/47 (19.1%)	-	47 (1 observational study)	⊕◯◯◯ VERY LOW[2,3]
Culture Conversion	no data	47/65 (72.3%)	-	65 (1 observational study)	⊕◯◯◯ VERY LOW[2,3]
Any adverse effect	no data	14/65 (21.5%)	-	65 (1 observational study)	⊕◯◯◯ VERY LOW[2,3]
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	-	-	-	
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	No research evidence was identified.						

	○ 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	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.	

Summary of judgments

	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	

Conclusions

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 *M. abscessus* pulmonary disease caused by strains without inducible or mutational resistance, we recommend a macrolide-containing multidrug treatment regimen. (strong recommendation, very low confidence in estimates of effect). (16 Strong, 0 Conditional, 2 Abstain). The expert panel voted for a strong recommendation for the intervention. In patients with *M. abscessus* pulmonary disease caused by strains with inducible or mutational macrolide resistance, we suggest a macrolide-containing regimen if the drug is being used for its immunomodulatory properties; however, the macrolide should not be counted as an active drug in the multidrug regimen (conditional recommendation, very low confidence in estimates of effect). The expert panel voted unanimously for a conditional recommendation for the intervention.				
JUSTIFICATION	Macrolides are very active *in vitro* against *M. abscessus*. Indirect evidence supports use of macrolides in macrolide-susceptible cases. *M. abscessus* can be life threatening and the use of macrolides is potentially of great benefit.				
SUBGROUP CONSIDERATIONS	Disease caused by strains with and without inducible macrolide resistance should be treated differently.				
IMPLEMENTATION CONSIDERATIONS					

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 *M. abscessus* 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;

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>DESIRABLE EFFECTS</td>
<td>How substantial are the desirable anticipated effects?

● Trivial
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know</td>
<td>Two drugs compared to three vs. four drugs for Mycobacterium abscessus pulmonary infection

<table>
<tr><th>Outcomes</th><th>Anticipated absolute effects* (95% CI)</th><th>Relative effect</th><th>№ of participants</th><th>Quality of the</th></tr>
</table>
</td>
<td>It is not possible to determine the outcomes for treatment of M. abscessus subspecies abscessus as the isolates were not speciated and not randomly distributed amount the patients in this observational cohort.</td>
</tr>
</table>

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
● Moderate
○ Small
○ Trivial

○ Varies
○ Don't know

	Risk with three vs. four drugs	**Risk with two drugs**	(95% CI)	(studies)	evidence (GRADE)
Cure of NTM disease follow up: median 445 days	833 per 1000	**767 per 1000** (558 to 1000)	**RR 0.92** (0.67 to 1.26)	41 (1 observational study)	⊕◯◯◯ VERY LOW [1,2]
Recurrence (relapse) follow up: median 445 days	50 per 1000	**231 per 1000** (27 to 1000)	**RR 4.62** (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	**175 per 1000** (63 to 519)	**RR 0.28** (0.10 to 0.83)	41 (1 observational study)	⊕◯◯◯ VERY LOW [1,2,3]
Culture conversion	The study reported no significant difference between the two groups, but only reported a p-value of 0.698 without specifying exact numbers.			(1 observational study)	⊕◯◯◯ VERY LOW [1,2,3]
Quality of Life - not measured	-	-	-	-	-
Development of antibiotic resistance - not measured	-	-	-	-	-
Death - not reported	-	-	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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 disease	CRITICAL	⊕◯◯◯ VERY LOW
Recurrence (relapse)	CRITICAL	⊕◯◯◯ VERY LOW
Any adverse effect	CRITICAL	⊕◯◯◯ VERY LOW
Culture conversion	CRITICAL	⊕◯◯◯ VERY LOW
Quality of Life	CRITICAL	
Development of antibiotic resistance	CRITICAL	
Death	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

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.

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

Two drugs compared to three vs. four drugs for Mycobacterium abscessus pulmonary infection

Outcomes	**Anticipated absolute effects*** **(95% CI)**		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with three vs. four drugs	**Risk with two drugs**			
Cure of NTM disease follow up: median 445 days	833 per 1000	**767 per 1000** (558 to 1000)	**RR 0.92** (0.67 to 1.26)	41 (1 observational study)	⊕◯◯◯ VERY LOW [1,2]
Recurrence (relapse) follow up: median 445 days	50 per 1000	**231 per 1000** (27 to 1000)	**RR 4.62** (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	**175 per 1000** (63 to 519)	**RR 0.28** (0.10 to 0.83)	41 (1 observational study)	⊕◯◯◯ VERY LOW [1,2,3]
Culture conversion	The study reported no significant difference between the two groups, but only reported a p-value of 0.698 without specifying exact numbers.			(1 observational study)	⊕◯◯◯ VERY LOW [1,2,3]
Quality of Life - not measured	-	-	-	-	-

		Development of antibiotic resistance - not measured - - - - -	
		Death - 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 data available.	
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	Comparison is considered three drugs in this case.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	No research data available.	This is dependent on the respective health care system.

	● Varies ○ Don't know		
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research data available.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research data available.	

Summary of judgments

	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	

Conclusions

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 ○
RECOMMENDATION	In patients with *M. abscessus* pulmonary disease, we suggest a multidrug regimen that includes at least three active drugs (guided by *in vitro* susceptibility). (conditional recommendation, very low confidence in estimates of effect). The expert panel voted unanimously for a conditional recommendation for the comparison.				
JUSTIFICATION	The severity of disease associated with *M. abscessus,* poor treatment outcomes, and high recurrence rates, warrants consideration of three or four drugs even if associated with a higher risk of adverse effects and higher cost.				
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 *M. abscessus*, 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;

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
○ Large

○ Varies
● Don't know</td><td>Shorter therapy duration compared to longer therapy duration for Mycobacterium abscessus pulmonary infection
<table><tr><th>Outcomes</th><th>Anticipated absolute effects* (95% CI)</th><th>Relative effect</th><th>№ of participants</th><th>Quality of the evidence</th></tr></table></td><td></td></tr>
</table>

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ Small
○ Trivial

○ Varies
● Don't know

	Risk with longer therapy duration	Risk with shorter therapy duration	(95% CI)	(studies)	(GRADE)
Cure of NTM	1000 per 1000	**750 per 1000** (470 to 1000)	**RR 0.75** (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	-	-	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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
Recurrence (relapse)	CRITICAL	
Culture conversion	CRITICAL	

		<table><tr><td>Quality of life</td><td>CRITICAL</td><td></td></tr><tr><td>Development of antibiotic resistance</td><td>CRITICAL</td><td></td></tr><tr><td>Death</td><td>CRITICAL</td><td></td></tr><tr><td>Adverse drug effects</td><td>CRITICAL</td><td></td></tr></table>	
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 health 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.	

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with longer therapy duration	**Risk with shorter therapy duration**			
Cure of NTM	1000 per 1000	**750 per 1000** (470 to 1000)	**RR 0.75** (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?** ○ No ○ Probably no ○ Probably yes ○ Yes	No research evidence was identified.	

	● Varies ○ Don't know		
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.	

Summary of judgments

	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	

Conclusions

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

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

	against the intervention ○	against the intervention ○	for either the intervention or the comparison ●	for the intervention ○	for the intervention ○
RECOMMENDATION	In the absence of data to support a shorter or longer treatment course for *M. abscessus* 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 disease 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 different durations for both nodular 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;

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know</td><td>Surgery compared to medical therapy for NTM pulmonary infection
<table><tr><th>Outcomes</th><th>Anticipated absolute effects* (95% CI)</th><th>Relative effect</th><th>№ of participants</th><th>Quality of the</th></tr></table></td><td>Data obtained from case series and outcomes with medical therapy not comparable with surgery outcomes.</td></tr>
</table>

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

	Risk with medical therapy	**Risk with surgery**	(95% CI)	(studies)	evidence (GRADE)
Cure of NTM	13/46 (28.2%)	**13/23 (56.5%)**	not estimable	69 (1 observational study)	⊕◯◯◯ VERY LOW [1,2]
Death	13/83 (15.7%)	**20/486 (4.1%)**	not estimable	569 (10 observational studies)	⊕◯◯◯ VERY LOW [2,3,4]
Recurrence	12/102 (11.8%)	**22/391 (5.6%)**	not estimable	493 (9 observational studies)	⊕◯◯◯ VERY LOW [1,2,3,4]
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	-	-	-	-	-

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

● Very low
○ 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	CRITICAL	⊕◯◯◯ VERY LOW
Culture conversion	CRITICAL	⊕◯◯◯ VERY LOW
Surgical Complication	CRITICAL	⊕◯◯◯ VERY LOW
Quality of Life	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 health 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.	
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	**Surgery compared to medical therapy for NTM pulmonary infection**	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk with medical therapy	**Risk with surgery**			
Cure of NTM	13/46 (28.2%)	**13/23 (56.5%)**	not estimable	69 (1 observational study)	⊕◯◯◯ VERY LOW[1,2]
Death	13/83 (15.7%)	**20/486 (4.1%)**	not estimable	569 (10 observational studies)	⊕◯◯◯ VERY LOW[2,3,4]
Recurrence	12/102 (11.8%)	**22/391 (5.6%)**	not estimable	493 (9 observational studies)	⊕◯◯◯ VERY LOW[1,2,3,4]
Culture conversion	18/46 (39.1%)	**283/331 (85.5%)**	not estimable	377 (10 observational studies)	⊕◯◯◯ VERY LOW[1,2,3,4,5]
Surgical	not pooled	**111/563**	not	563 (9 observational	⊕◯◯◯ VERY

		Complication	**(19.7%)**	pooled	studies)	LOW[1,3,4]
		Quality of Life - 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?**	No research evidence was identified.				

	○ 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.	

Summary of judgments

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

	JUDGEMENT							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	

Conclusions

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
	○	○	○	●	○

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	