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1 **Title: *Mycobacterium simiae*: clinical, radiological and microbiological characteristics in**  
2 **97 patients**

3 **Running title: *Mycobacterium simiae* pulmonary infection in Reunion Island.**

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31

32 **Abstract**

33 *Mycobacterium simiae* is a rare species of slow-growing nontuberculous mycobacteria  
34 (NTM).

35 From 2002 to 2017, we conducted a retrospective study that included all patients with NTM-  
36 positive respiratory samples detected in two university hospitals of the French overseas  
37 department of Reunion Island. We recorded the prevalence of *M. simiae* in this cohort, as well  
38 as the clinical, radiological, and microbiological features of patients with at least one sample  
39 positive for *M. simiae*.

40 In our cohort, 97 patients (15.1%) were positive for *M. simiae*. Twenty-one patients (21.6%)  
41 met the American Thoracic Society (ATS) criteria for infection. *M. simiae* infection was  
42 associated with bronchiectasis, micronodular lesions and weight loss. Antibiotic susceptibility  
43 testing was performed in 60 patients and the isolates were found to have low susceptibility to  
44 antibiotics, except for amikacin, fluoroquinolones, and clarithromycin. Treatment failed in 4  
45 of the 8 patients treated for *M. simiae* infection.

46 Here, we describe a specific cluster corresponding to a large cohort of patients with *M.*  
47 *simiae*, a rare nontuberculous mycobacteria associated with low pathogenicity and a poor  
48 susceptibility to antibiotics.

49

50 **INTRODUCTION**

51 Nontuberculous mycobacteria (NTM) constitute a large group of more than 150 pathogens  
52 (1). *Mycobacterium simiae* is a rare species of NTM that was first detected in monkeys in  
53 1965 (2). A few geographic clusters have since been identified—namely, in Arizona, Cuba,  
54 and Israel (3, 4)—suggesting environmental contamination. *M. simiae* was detected in local  
55 tap water in some clusters, and a pseudo-outbreak caused by water contamination was  
56 reported by Hana *et al.* (5).

57 When considering small series of patients with clinical *M. simiae* isolates, pathogenicity  
58 appears to be low (4, 6, 7). Some authors have reported very rare cases of pulmonary  
59 infections (8-11) and lymphadenitis (12). Most of these infections occurred in  
60 immunocompromised patients with acquired immunodeficiency syndrome (AIDS) (10, 13,14)  
61 or with predisposing conditions: children (12), the elderly, patients with diabetes mellitus  
62 (11).

63 *M. simiae* is common in the French overseas department of Reunion Island. We conducted a  
64 retrospective study to determine the prevalence of *M. simiae* on the island, and we recorded  
65 the clinical, radiological, and microbiological features of all patients positive for *M. simiae*.

66 **METHODS**

67 We conducted a retrospective study including all patients whose respiratory samples tested  
68 positive for NTM between January 2002 and July 2017 in the microbiological laboratories of  
69 the two university hospitals of Reunion Island (St Denis and St Pierre). Among patients with  
70 NTM isolates, only those with one or more isolate(s) positive for *M. simiae* were included in  
71 the study.

72 All patient data (clinical information, biological and radiological exams) were recorded in the  
73 informatics databases of the two centers from 2002 to 2017. The results of exams conducted  
74 out of hospital were also included in the data collection when found in the archived files or  
75 reported in clinical observation. We retrospectively reported the following:

- 76 - Clinical findings: demographic data, predisposing conditions, clinical symptoms of  
77 NTM infection as per the American Thoracic Society (ATS) criteria (1).
- 78 - Radiological findings: radiological signs of NTM infection meeting the ATS criteria  
79 (1). Radiologist interpretations of CT scans were included in patient files and  
80 retrospectively reviewed by two pulmonologists.
- 81 - Microbiological findings: number, type, and result of respiratory sample, drug  
82 susceptibility.
- 83 - For treated patients: treatment regimen, duration of treatment, outcome.

84 Patient isolates were submitted to the local laboratory or referred to the National Reference  
85 Center for Mycobacteria in Paris for identification and drug susceptibility testing of  
86 Mycobacterium isolates. Drug susceptibility testing was performed with the agar dilution  
87 method, using 7H9 broth and the SLOMYCO© sensitive panel.

#### 88 **Statistical analysis**

89 Results were expressed as total number (percentage) for categorical variables and as median  
90 (25<sup>th</sup>-75<sup>th</sup> percentiles) for continuous variables. Continuous variables were compared using the  
91 Mann-Whitney U test. Categorical variables were compared using the Chi-square test or the  
92 Fisher's exact test, as appropriate. After bivariate analysis, risk factors for *M. simiae* infection  
93 as defined by the ATS were entered into a multivariate logistic regression analysis using  
94 backward selection with  $P < 0.15$ . Collinearity between independent factors was investigated.  
95 When identified, the most clinically relevant factor was chosen for use in the multivariate

96 model. A  $P$  value  $< 0.05$  was considered significant. Analyses were performed using SAS  
97 statistical software (8.2, Cary, NC, USA).

98 This study was approved by the *Comité d'Evaluation des Protocoles de Recherche*  
99 *Observationnelle* of the *Société de Pneumologie de Langue Française*. Data collection was  
100 declared to the *Commission Nationale de l'Informatique et des Libertés*.

## 101 RESULTS

102 Over the study period, 202 samples in 97 patients tested positive for *M. simiae*. This  
103 represented a prevalence of 15.1% in our cohort of patients with respiratory samples positive  
104 for NTM. One of these 97 patients also had a lymph node positive for *M. simiae*. No other  
105 patients had an extrapulmonary sample positive for *M. simiae*. Other mycobacteria were  
106 found in 22 patients (22.7%), including *M. intracellulare* in 6 patients, *M. fortuitum* in 4  
107 patients, *M. abscessus* in 4 patients, *M. goodii* in 4 patients, undefined mycobacterial  
108 species in 4 patients, *M. tuberculosis* in 2 patients, and *M. xenopi* in 1 patient.

109 The *M. simiae* isolates were cultured from sputum (57.8%), gastric aspirates (14.4%), and  
110 fiber optic samples (obtained through bronchoalveolar lavage or bronchial aspiration) (45.3%)  
111 (Table 1). Positive fiber optic samples were significantly more common in patients who met  
112 the ATS criteria for infection than in those who did not: 71.4% versus 38.2% ( $P = 0.008$ ).  
113 There were 6 (2-13) respiratory samples in patients who met the ATS criteria for *M. simiae*  
114 infection versus 4.5 (2-13) in patients who did not ( $P = 0.06$ ). The number of positive  
115 respiratory samples was significantly higher in patients who met the ATS criteria for infection  
116 than in those who did not: 2 (2-4) versus 1 (1-2) ( $P = 0.0002$ ).

117 Drug susceptibility testing was performed in 60 patients using a single isolate per patient.  
118 Most *M. simiae* strains were found to be susceptible to amikacin, moxifloxacin, ciprofloxacin,

119 and clarithromycin in, respectively, 96%, 92%, 87%, and 100% of tested patients. They were  
120 found to be resistant to rifampicin, ethambutol, and isoniazid in, respectively, 85%, 89%, and  
121 92% of tested patients.

122 Patient characteristics are presented in Table 2. Of the 97 patients who tested positive for *M.*  
123 *simiae*, 21 (21.6%) met the ATS criteria for NTM infection with *M. simiae*.

124 Cough and/or sputum (68%), fever and/or sweat (17.5%), and weight loss (48.4%) were the  
125 most commonly reported symptoms. Weight loss and fever and/or sweat were significantly  
126 more common in patients who met the ATS criteria for NTM infection (Tables 3 and 4).

127 The most common radiological findings were micronodular or “tree-in-bud” lesions (50.5%  
128 of patients) and cavitary lesions (25.8% of patients). Micronodules were significantly more  
129 common in patients who met the ATS criteria (Tables 3 and 4).

130 Microbiological ATS criteria were met in 64.9% of patients (Table 3).

131 Twelve patients started drug therapy, including 8 who were treated for *M. simiae* infection  
132 (8.2%). Two patients were treated for pulmonary tuberculosis; two others were treated for *M.*  
133 *intracellulare* and *M. xenopi* infections, respectively. The clinical, radiological, and  
134 microbiological characteristics of the patients treated for *M. simiae* infections are reported in  
135 Table 5, along with their treatment regimen and clinical outcome. The CT scan of patient 8 is  
136 shown in Figure 1. Among 21 patients with ATS criteria for infection, 7 out of 8 treated  
137 patients had at least one positive smear as 7 out of 13 untreated patients had positive smears.  
138 The only treated patient with negative smears (patient 2) had a good outcome.

139

## 140 **DISCUSSION**



141 To our knowledge, this is the largest cohort of patients with clinical isolates of *M. simiae*  
142 reported in the literature to date (4, 6, 7, 17). Reunion Island is a French overseas department  
143 located in the Indian Ocean, with a population estimated in 2016 at more than 850,000  
144 (*Institut National de la Statistique et des Etudes Economiques*). Medical care in Reunion  
145 Island is similar to that offered in metropolitan France. Incidence of tuberculosis in Reunion  
146 Island is similar to metropolitan France, around 8/100000 per habitant per year. Except for a  
147 few private laboratories that send respiratory samples to metropolitan France for NTM  
148 identification, most mycobacterial samples are referred to one of the two university  
149 laboratories of the island (St Pierre and St Denis). Moreover, even if patients are initially  
150 tested in private laboratories, the majority of those found to be infected with mycobacteria are  
151 referred to one of Reunion's two university hospital centers. Although our study was not  
152 exhaustive, we estimated a high incidence of NTM in Reunion Island: approximately 5 per  
153 100,000 habitants per year, or about 5 times the incidence observed in metropolitan France.  
154 As cystic fibrosis prevalence in Reunion Island is similar to metropolitan France, NTM  
155 prevalence in cystic fibrosis patients is 3 times higher in Reunion Island than it is in  
156 metropolitan France (15). *M. simiae* was common in our cohort, accounting for 15.1% of all  
157 patients with NTM isolates—a rate that is 15 times higher than that observed in metropolitan  
158 France (16). We hypothesize that the tropical climate and hence highwater temperatures,  
159 explains the high incidence of NTM, and especially of *M. simiae*, in Reunion Island (18).  
160 NTM species have indeed been found to be common in other tropical regions, for instance by  
161 Adjemian et al. (19) in Hawaii. High vapor pressure and household proximity to water have  
162 also been reported to be associated with NTM infection in cystic fibrosis patients (20-22).  
163 Another explanatory factor for the high incidence of NTM may be the contamination of water  
164 supplies with *M. simiae*, a finding that was previously reported in a study conducted in Texas  
165 (5).

166 Underlying diseases were common in our patients with *M. simiae*. The main general  
167 predisposing factor was immunodepression, with HIV infection affecting 4.1 % of patients  
168 positive for *M. simiae* and 25% of patients treated for *M. simiae* infection. Other general  
169 predisposing factors were diabetes mellitus and alcohol abuse. Unfortunately, tobacco status  
170 or occupational exposure were not clearly reported in our data sources. Wood smoke exposure  
171 was common until the early 1980s in Reunion island due to cooking habits, but it is rarely  
172 notified or quantified in medical reports. Non-CF bronchiectasis was the most prevalent local  
173 predisposing factor, as it affected 49.5% of our cohort patients and 71.4% of those who met  
174 the ATS criteria for infection. Bronchiectasis was significantly higher in patients who met the  
175 ATS criteria for *M. simiae* infection in multivariate analysis. Our conclusions are nevertheless  
176 limited, as bronchiectasis diagnosis and NTM isolation were often performed simultaneously,  
177 making it difficult to determine whether bronchiectasis was a predisposing factor or a  
178 consequence of *M. simiae* infection. Pre-existing bronchiectasis was documented in only 2 of  
179 the 6 patients treated for *M. simiae* infection.

180 Our study confirms the low pathogenicity of *M. simiae* in humans: 21,6% of our cohort  
181 patients met the ATS criteria for infection, and only 8.2% (8 patients) received treatment. In  
182 the Texas study, only 6 (10%) of the 62 patients with *M. simiae* isolates had definite  
183 infections (4). Similarly, Rynkiewicz et al. (23) found in their study that only 2 out of 23  
184 patients with *M. simiae* isolates (9%) had a true *M. simiae* infection. In a study conducted in  
185 the Netherlands, Van Ingen et al. (7) found 28 patients with clinical isolates of *M. simiae*,  
186 among whom only 8 (21%) met the ATS criteria for infection and only 6 received treatment  
187 (7). While the appropriateness of gastric aspiration for the diagnosis of *M. simiae* pulmonary  
188 infection may be debated, it did not impact the proportion of infected patients in our cohort.

189 As reported elsewhere (7, 17), clinical signs of infection in our cohort patients were mostly  
190 respiratory symptoms like productive cough. Our study confirms the findings of Van Ingen et  
191 al (7), whereby patients who lost weight were significantly more likely to meet the ATS  
192 diagnostic criteria.

193 Micronodular lesions were the most common radiological findings and were associated with  
194 ATS criteria for *M. simiae* in multivariate analysis. Cavitory lesions were present in 25.8% of  
195 our cohort patients, as compared with studies that reported cavitory lesions in 3% to 15% of  
196 patients (11,17). Unlike in the study by Van Ingen et al. (7), cavitory lesions were not  
197 associated with ATS criteria for infection in our cohort. We found cavitory lesions in 5 of the  
198 8 treated patients, suggesting more cavitory lesions with *M. simiae* disease than with  
199 *Mycobacterium avium complex* (MAC) species.

200 *In vitro* drug susceptibility testing showed a natural multidrug resistance profile. As in the  
201 study by Van Ingen et al. (7), we found most strains to be resistant to rifampicin, ethambutol,  
202 and isoniazid. However, unlike Van Ingen et al. (7), we found susceptibility to amikacin,  
203 fluoroquinolones, and clarithromycin to be significant. While previous studies have shown *M.*  
204 *simiae* strains to be susceptible to clofazimine and cycloserine (7, 24), susceptibility to these  
205 antibiotic agents was not tested in our study.

206 The treatment regimens administered to our patients included macrolides, rifampicin,  
207 ethambutol, moxifloxacin, clofazimine, and amikacin. Treatment decision was more frequent  
208 in infected patients with positive smears. Response to treatment was poor, as 3 out of 7  
209 patients who completed the treatment regimen failed or relapsed. These results, however, are  
210 better than those reported in the literature: Van Ingen et al. (7) found in their study that  
211 treatment was successful in only 1 of 3 patients; in the Texas study by Al Badely, 14 out of 18  
212 patients with AIDS died within 6 months, with no response to antibiotics (25).

213 This study has several limitations. The retrospective nature of the analysis is clearly a  
214 weakness. Despite being the largest study to date, the low numbers of evaluated patients and  
215 events may have resulted in a lack of power. The small number of respiratory samples in  
216 patients who did not meet the ATS criteria for infection is another limitation of our study, as it  
217 suggests that some patients were misclassified due to missing microbiological data.

218 The data reported here reflect common medical practice, which may also be viewed as a  
219 limitation. The conclusions of this double-centre study cannot be extrapolated to institutions  
220 outside Reunion Island, especially as regards the choice of antibiotics. While single-centre  
221 studies are useful to reveal local ecological patterns, larger studies can help to uncover  
222 regional and global trends that are not apparent in smaller studies.

## 223 **CONCLUSION**

224 In Reunion Island, *M. simiae* isolates are common, yet are associated with low pathogenicity.  
225 *In vitro* susceptibility to antibiotics is low and clinical response to treatment is poor. Further  
226 studies are needed to explore the impact of the environment on NTM isolates in this specific  
227 region.

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229

230 **REFERENCES**

- 231 1. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM,  
232 Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace  
233 RJ Jr, Winthrop K. 2007. An official ATS/IDSA statement: diagnosis, treatment, and  
234 prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*  
235 175(4):367–416.
- 236 2. Karassova V, Weissfeiler J, Krasznay E. 1965. Occurrence of atypical mycobacteria in  
237 *Macacus rhesus*. *Acta Microbiol Acad Sci Hung* 12:275–282.
- 238 3. Lavy A, Yoshpe-Purer Y. 1992. Isolation of *Mycobacterium simiae* from clinical  
239 specimens in Israel. *Tubercle* 63:279–285.
- 240 4. Valero G, Peters J, Jorgensen JH, Graybill JR. 1995. Clinical isolates of *Mycobacterium*  
241 *simiae* in San Antonio, Texas. An 11-yr review. *Am J Respir Crit Care Med* 152(5):1555–  
242 1557.
- 243 5. Hana M, Sahly EL, Septimus E, Hanna S, Septimus J, Wallace RJ Jr, Williams-Bouyer XP,  
244 Musser JM, Graviss EA. 2002. *Mycobacterium simiae* pseudo-outbreak resulting from a  
245 contaminated hospital water supply in Houston, Texas. *Clin Infect Dis* 35:802–807.
- 246 6. Bell R. C, Higuchi JH, Donovan WN, Krasnow I, Johanson WG Jr. 1983. *Mycobacterium*  
247 *simiae*. Clinical features and follow-up of twenty-four patients. *Am Rev Respir Dis*  
248 127(1):35–38.
- 249 7. Van Ingen J, Boeree MJ, Dekhuijzen PN, van Soolingen D. 2008. *Eur Respir J* 31(1):106-9.
- 250 8. Barrera L, Palmero D, Paul R, Lopez B. 2010. Disease due to *Mycobacterium simiae* and  
251 “*Mycobacterium sherrisii*” in Argentina. *Medicina* 70(4):343–346.

- 252 9. Phillips DR, Krishnan H, Watson J. 2008. First UK report of successful treatment of  
253 *Mycobacterium simiae* and immune reconstitution inflammatory syndrome in an HIV-  
254 seropositive patient. Sexually Transmitted Infections 84(4): 271–272.
- 255 10. Braun-Saro B, Esteban J, Jiménez S, Castrillo JM, Fernández-Guerrero ML. 2002.  
256 *Mycobacterium simiae* infection in an immunocompromised patient without acquired  
257 immunodeficiency syndrome. Clin Infect Dis 34(5):e26–e27.
- 258 11. Shitrit D, Peled N, Bishara J, Priess R, Pitlik S, Samra Z, Kramer MR. 2008. Clinical and  
259 radiological features of *Mycobacterium kansasii* infection and *Mycobacterium simiae*  
260 infection. Respiratory Med 102(11):1598–1603.
- 261 12. Patel NC, Minifee PK, Dishop MK, Munoz FM. 2007. *Mycobacterium simiae* cervical  
262 lymphadenitis. Pediatr Infect Dis J 26(4):362–363.
- 263 13. Legrand E, Devallois A, Horgen L, Rastogi N. 2000. A molecular epidemiological study  
264 of *Mycobacterium simiae* isolated from AIDS patients in Guadeloupe. J Clin Microbiol  
265 38:3080–3084.
- 266 14. Sampaio JL, Pereira RM, Souza JR, Leite JP. 2001. *Mycobacterium simiae* infection in a  
267 patient with acquired immunodeficiency syndrome. Braz J Infect Dis 5:352–355.
- 268 15. Ho D, Payet A, Rittie JL, Tasset C, Picot S, Belmonte O, Coolen-Allou N. Non  
269 tuberculous mycobacteria in cystic fibrosis patients in Reunion island, abstr AD-04. Abstr of  
270 the 22nd Congrès de Pneumologie de Langue Française, Lyon, France, 2018. Société de  
271 Pneumologie de Langue Française, Paris, France.
- 272

- 273 16. Dailloux M, Abalain ML, Laurain C, Lebrun L, Loos-Ayav C, Lozniewski A, Maugein J;  
274 French Mycobacteria Study Group. 2006. Respiratory infections associated with  
275 nontuberculous mycobacteria in non-HIV patients. *Eur Respir J* 28(6):1211-5.
- 276 17. Baghizadeh A, Mehrian P, Farnia P. 2017. Computed Tomography Findings of  
277 Pulmonary *Mycobacterium simiae* Infection. *Can Respir J* 2017: 6913564.
- 278 18. Kirschner RA, Parker BC, Falkinham JO. 1992. Epidemiology of infection by non  
279 tuberculous mycobacteria. *Mycobacterium avium*, *Mycobacterium intracellulare*, and  
280 *Mycobacterium scrofulaceum* in acid, brown-water swamps of the southeastern United States  
281 and their association with environmental variables. *Am Rev Respir Dis* 145:271-5.
- 282 19. Adjemian J, Frankland TB, Daida YG, Honda JR, Olivier KN, Zelazny A, Honda S,  
283 Prevots DR. 2017. Epidemiology of Nontuberculous Mycobacterial Lung Disease and  
284 Tuberculosis, Hawaii, USA. *Emerg Infect Dis* 23(3):439-447.
- 285 20. Adjemian J, Olivier KN, Prevots DR. 2014. Nontuberculous mycobacteria among patients  
286 with cystic fibrosis in the United States: screening practices and environmental risk. *Am J*  
287 *Respir Crit Care Med* 190(5):581-6.
- 288 21. Prevots DR, Adjemian J, Fernandez AG, Knowles MR, Olivier KN. 2014. Environmental  
289 risks for nontuberculous mycobacteria. Individual exposures and climatic factors in the cystic  
290 fibrosis population. *Ann Am Thorac Soc* 11(7):1032-8.
- 291 22. Bouso JM, Burns JJ, Amin R, Livingston FR, Elidemir O. 2017. Household proximity to  
292 water and nontuberculous mycobacteria in children with cystic fibrosis. *Pediatr Pulmonol*  
293 52(3):324-330.

- 294 23. Rynkiewicz DL, Cage GD, Butler WR, Ampel NM. 1998. Clinical and microbiological  
295 assessment of *Mycobacterium simiae* isolates from a single laboratory in southern Arizona.  
296 Clin Infect Dis 26:625–630.
- 297 24. Van Ingen J, Totten SE, Heifets LB, Boeree MJ, Daley CL. 2012. Drug susceptibility  
298 testing and pharmacokinetics question current treatment regimens in *Mycobacterium simiae*  
299 complex disease. Int J Antimicrob Agents 39(2):173-6.
- 300 25. Al-Abdely HM, Revankar SG, Graybill JR. 2000. Disseminated *Mycobacterium simiae*  
301 infection in patients with AIDS. J Infect 41(2):143-7.
- 302



303

304 **TABLES**305 Table 1: Microbiological data in patients with respiratory samples positive for *M. Simiae*.

	Total (n= 97)	ATS diagnostic criteria for infection		<i>P</i> -value
		Not met (n=76)	Met (n=21)	
Respiratory samples tested for NTM (per patient):	5 (2-8)	4.5 (2-7)	6 (2-13)	0.06
- Total	1 (1-2)	1 (1-2)	2 (2-4)	0.0002
- Positive for <i>M. simiae</i>				
Type of positive respiratory sample:				
- Sputum	56 (57.8)	44 (57.9)	13 (61.9)	0.22
- Gastric	14 (14.4)	10 (13.1)	4 (19.0)	0.62
- Fiber optic samples	44 (45.3)	29 (38.2)	15 (71.4)	0.008

306

307 NTM: Nontuberculous Mycobacteria; ATS: American Thoracic Society.

308 Results are expressed as median (25<sup>th</sup> – 75<sup>th</sup> percentiles) or number (percentage).

309

310 Table 2: Characteristics of patients with clinical sample positive for *M. simiae*.

	Total (n= 97)	ATS diagnostic criteria for infection		P-value
		Not met (n=76)	Met (n=21)	
Age (years)	61 (50-74)	65 (50-74.3)	57 (51-66)	0.3
Male gender	51 (52.7)	42 (55.3)	9 (39.1)	0.32
Body mass index (kg/m <sup>2</sup> )	19 (16.5-22.1)	19.5 (17-23)	18.8 (16.5-20.9)	0.42
Respiratory diseases:				
- Non-CF bronchiectasis	48 (49.5)	33 (43.4)	15 (71.4)	0.04
- CF	6 (6.2)	5 (6.6)	1 (4.8)	0.73
- COPD	24 (24.7)	20 (26.3)	4 (19)	0.42
- Previous TB	15 (15.5)	11 (14.5)	4 (19.0)	0.67
- Lung neoplasia	9 (9.3)	9 (11.8)	0 (0)	0.09
- Interstitial pneumonia	5 (5.1)	5 (6.6)	0 (0)	0.5
Other diseases:				
- Other neoplasia	5 (5.1)	4 (5.3)	1 (4.8)	0.85
- HIV infection	4 (4.1)	2 (2.6)	2 (9.5)	0.44
- Other immunodeficiency				
- Diabetes mellitus	5 (5.1)	5 (6.6)	0 (0)	0.32
- Renal insufficiency	11 (11.3)	10 (13.1)	1 (4.8)	0.27
- Gastroesophageal reflux*	6 (6.2)	4 (5.3)	2 (9.5)	0.48
- Alcohol abuse	8 (8.2)	6 (7.9)	2 (9.5)	0.85
	16 (16.5)	14 (18.4)	2 (9.5)	0.3
Lung function:				
- FEV1 (L)	1.60 (1.11-2.30)	1.55 (1.05-2.42)	1.82 (1.50-2.20)	0.54
- FEV1 (%)	72 (53-90)	70 (52-90)	62 (64-81)	0.64
- FVC (L)	2.42 (1.72-3.25)	2.33 (1.71-3.63)	2.55 (1.93-2.70)	0.93
- FVC (%)	81 (62-92)	76 (52-92)	84.5 (73-90)	0.33
Long-term treatment:				
- Inhaled corticosteroid	25 (25.8)	19 (25)	6 (28.6)	0.84
- Systemic corticosteroid**	11 (11.3)	10 (13.1)	1 (4.8)	0.3
- Long-term macrolide	19 (19.6)	14 (18.4)	5 (23.8)	0.6

311

312 CF: Cystic Fibrosis; COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced  
313 Expiratory Volume in one second; FVC: Forced Vital Capacity.

314 Results are expressed as median (25<sup>th</sup> – 75<sup>th</sup> percentiles) or number (percentage).

315 \* Gastroesophageal reflux was diagnosed based on evocative symptoms and/or anti-acid  
316 treatment.

317 \*\*Systemic corticosteroid use was defined as more than 10 mg/day of prednisone or  
318 equivalent for more than 2 weeks.

319

320

321 Table 3: Clinical, radiological, and microbiological criteria for *M. simiae* infection as defined  
322 by the ATS statement.

	Total (n= 97)	ATS diagnostic criteria for infection		<i>P</i> -value
		Not met (n=76)	Met (n=21)	
Clinical ATS criteria:	84 (86.6)	63 (82.3)	21 (100)	0.06
- Fever/sweating	17 (17.5)	10 (13.1)	7 (33.3)	0.04
- Cough/sputum	66 (68.0)	49 (64.5)	17 (80.9)	0.2
- Weight loss*	47 (48.4)	32 (42.1)	15 (71.4)	0.02
- Hemoptysis	3 (3.1)	2 (2.6)	1 (4.8)	0.53
Radiological ATS criteria :	74 (76.3)	55 (72.4)	21 (100)	0.04
- Nodules < 1cm	49 (50.5)	35 (46)	14 (66.7)	0.08
- Nodules > 1cm	9 (9.3)	8 (10.5)	1 (4.8)	0.42
- Consolidation	30 (30.9)	24 (31.6)	6 (28.6)	0.76
- Cavitory lesions	25 (25.8)	17 (22.4)	8 (38.1)	0.14
Microbiological ATS criteria	63 (64.9)	44 (57.9)	21 (100)	0.006

323

324 ATS: American Thoracic Society.

325 \*Weight loss was defined as a weight reduction of more than 5 kilograms or 5% of the normal  
326 body weight in the previous 6 months

327 Results are expressed as median (25<sup>th</sup> – 75<sup>th</sup> percentiles) or numbers (percentage).

328

329 Table 4 - Multivariate analysis of risk factors meeting ATS criteria for *M. simiae* infection.

Variables	Adjusted Odds Ratio (CI 95%)	<i>P</i> -value
Non-CF bronchiectasis	4.11 (0.98-17.24)	0.05
Weight loss	8.13 (2.04-32.26)	0.003
Nodules < 1cm	-4.29 (1.01-18.18)	0.05
Lung neoplasia		0.97
Fever/sweating		0.12
Cavitary lesions		0.36

330

331 The Hosmer-Lemeshow goodness-of-fit test *P*-value was 0.979. The Nagelkerke and  
332 Cox/Snell R squares were 0.388 and 0.254, respectively.

333 CI: Confidence Intervals; CF: Cystic Fibrosis.

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- 338 Table 5: separate document (main document “manuscript 2”)  
339 Figure 1: deleted

Table 5: Description of *M. simiae* infected patients who required antibiotic treatment

	1	2	3	4	5	6	7	8
Age	61	49	44	52	67	49	65	69
Gender	F	M	M	F	M	F	F	F
Underlying conditions	Bronchiectasis GORD	HIV CD4 = 79	HIV CD4 = 9	Bronchiectasis GORD	Bronchiectasis Renal insufficiency	Bronchiectasis	Bronchiectasis	Bronchiectasis COPD GORD
Clinical findings	Hemoptysis Cough/Sputum Weight loss	Cough	Weight loss	Cough/Sputum	Cough/Sputum	Cough/Sputum Weight loss Sweat	Cough/Sputum	Cough/Sputum Weight loss Fever
Radiological findings	Micronodular	Cavitary with aspergilloma	Micronodular Adenopathy	Cavitary Nodular	Cavitary Micronodular	Micronodular	Micronodular Cavitary	Micronodular Cavitary
Microbiological findings	11/13 : 2 sputum 4 GA 7 BA/BAL	2/24 : 1 sputum 1 BA	2/5 : 1 BA 1 lymph node	6/16 4 sputum 2 GA	4/19 : 3 GA 1 BA	7/19 : 7 sputum	2/2 : 2 sputum	3/4: 2 BA 1 BAL
Treatment regimen	Amikacin Ethambutol Clarithromycin Moxifloxacin	Ethambutol Azithromycin/ Clarithromycin Ansatipline	Ethambutol Clarithromycin	Azithromycin Ethambutol Moxifloxacin Clofazimine  + surgical resection	Clarithromycin Moxifloxacin Ethambutol Clofazimine	Clarithromycin Moxifloxacin Clofazimine Amikacin (1 month) Then: Azithromycin Moxifloxacin Clofazimine Imipenem/Cefoxitin	Amikacin Moxifloxacin Rifabutin Azithromycin	Clarithromycin Moxifloxacin Ethambutol Clofazimine Amikacin
Duration	1 month (hepatitis)	4 months	In progress	15 months	18 months	12+5 months	12 months	8 months
Outcome	Treatment failure Death (4 yrs later)	No relapse Alive (10 yrs later)	Alive (5 months later)	<i>Simiae</i> : no relapse Secondary infection with <i>M. intracellulare</i> Alive (3 yrs later)	No relapse Alive (2 yrs later)	<i>M. simiae</i> : no relapse Secondary infection with <i>M. abscessus</i> Alive (3 yrs later)	Relapse 1 year after Alive (6 yrs later)	Treatment failure Alive (1 yr after)

BAL : BronchoAlveolar Lavage, BA : Bronchial Aspiration, GA : gastric aspiration, GORD : Gastro Esophageal Reflux Disease, COPD : Chronic Obstructive Pulmonary Disease, HIV : Human Immunodeficiency Virus.

