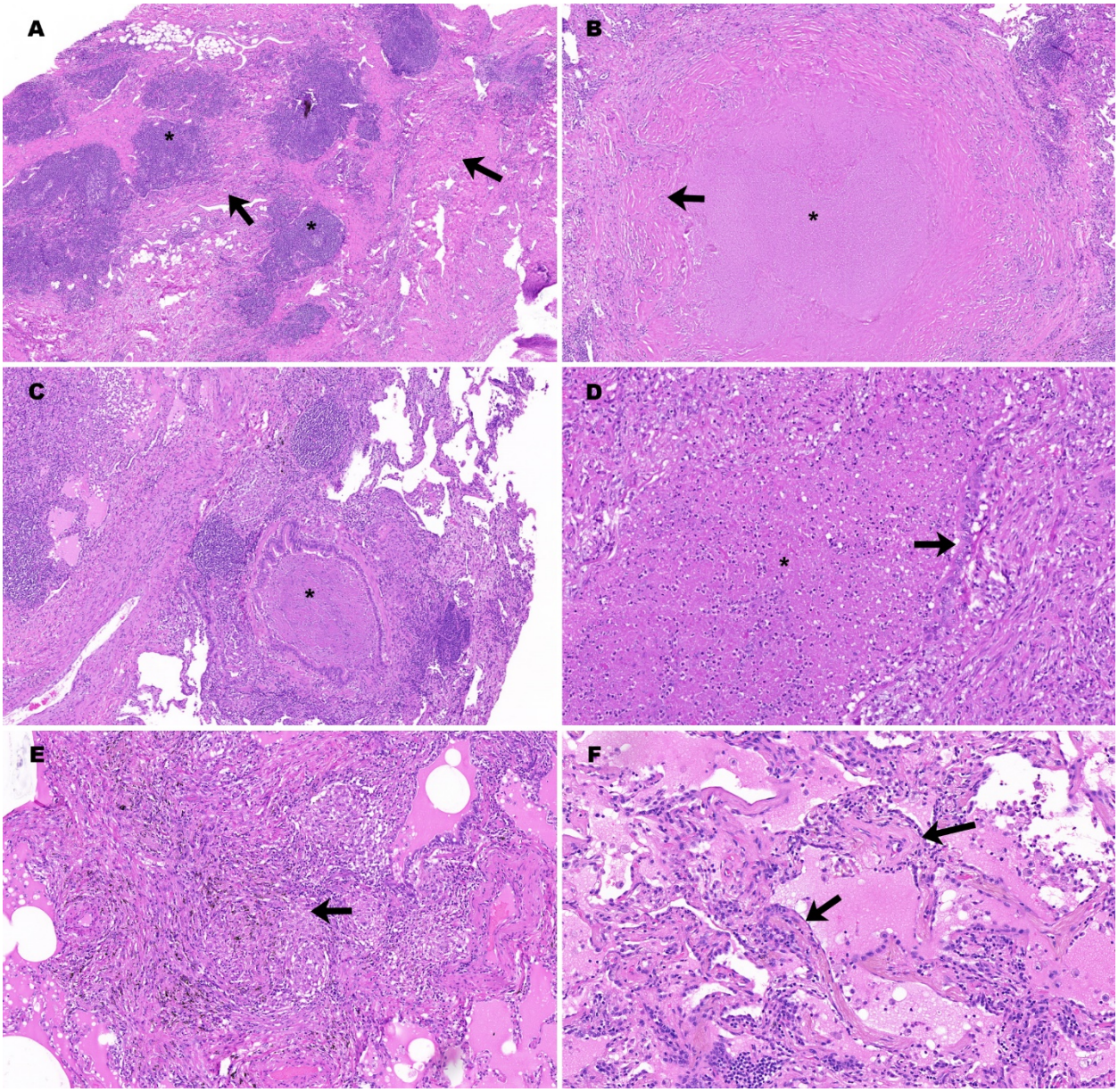

Figure S1. Histopathological features of chronic NTM infection in human lung. (A) Extensive pulmonary and pleural fibrosis (arrows) with adhesion and numerous secondary lymphoid follicles (*). (B) Chronic fibrosis (arrow) and pauci-inflammatory response surrounding caseous necrosis (*). (C) Caseous debris filling an intact bronchiolar airway, indicative of bronchogenic spread (*). (D) Caseous debris and neutrophils fill an airway (*) with effaced epithelium and fibrosis (arrow). (E) Chronic fibrosis among solid macrophage dominated granulomas (arrows). (F) Chronic interstitial fibrosis with lymphocytic inflammation in alveolar tissue (arrow).

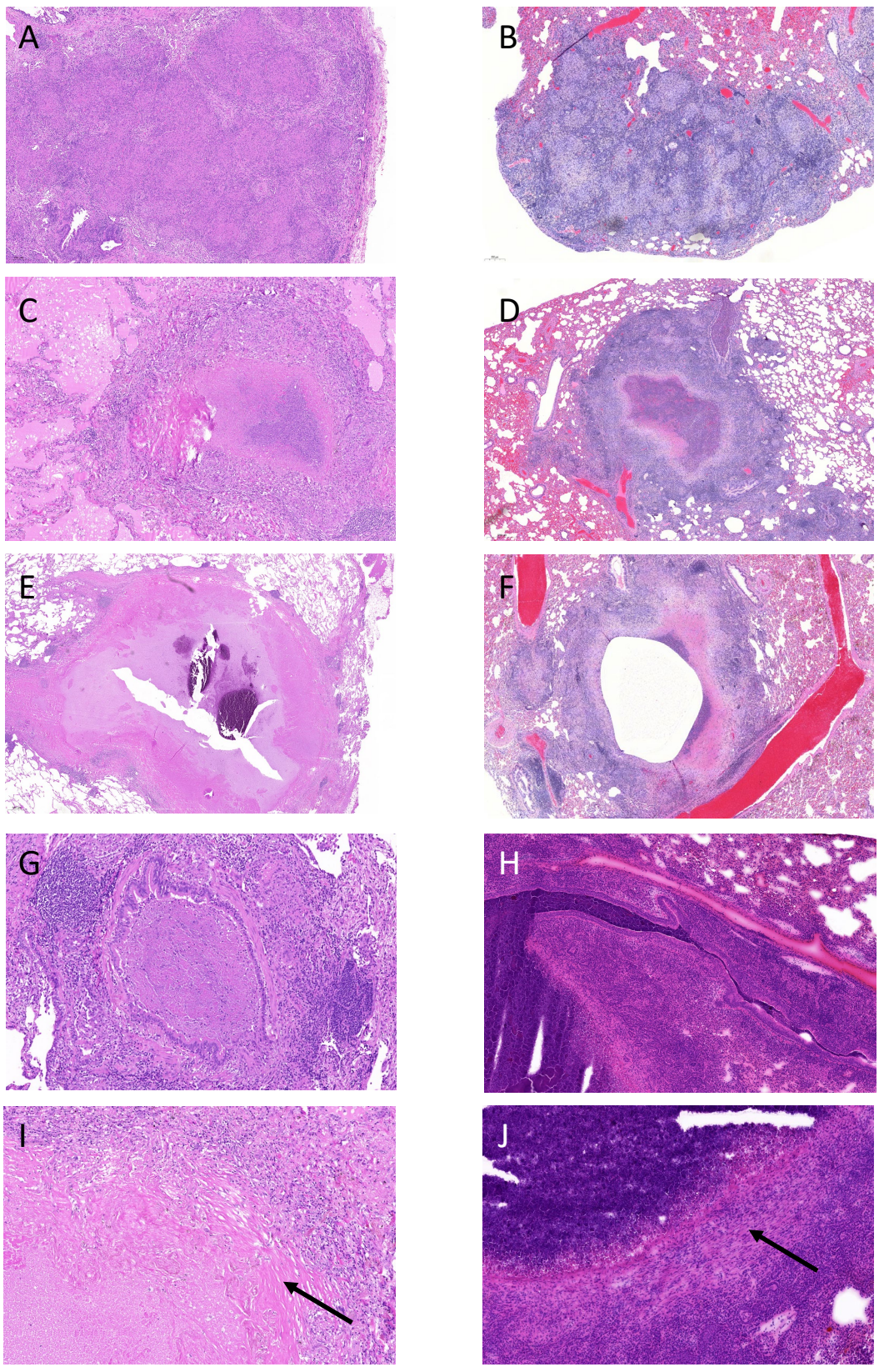

Figure S2. Common histopathological features seen in human NTM-PD and active rabbit TB, shown side-by side. (A-B) Coalescing non-necrotic granulomas. (C-D) Necrotic granuloma with mixed cellularity seen in caseous foci. (E-F) Cavitating

lesion. (G-H) Bronchiole filled with necrotic caseum (G) and cavity caseum oozing into a connected airway (H), both indicative of bronchogenic spread. (I-J) Areas of fibrosis (arrows) surrounding caseous necrosis. Sections shown in panel H and J are from flash-frozen lesions and appear slightly different from all other tissue sections, which are from formalin fixed tissues.

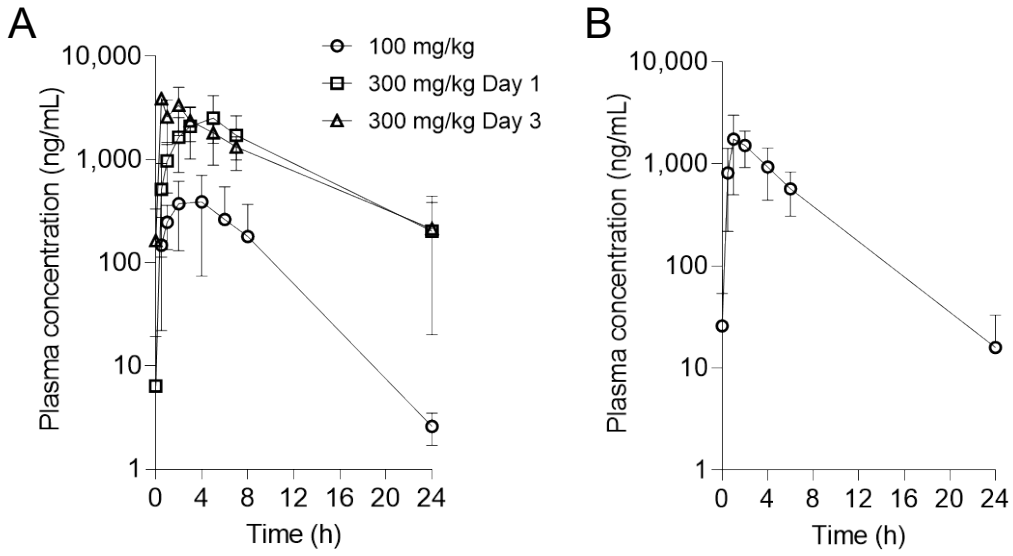

Figure S3. Plasma pharmacokinetic profile of clarithromycin in rabbits. (A) Plasma concentration time profiles of clarithromycin dosed via the oral route to disease-naïve rabbits as indicated. (B) Plasma concentration time profile of clarithromycin after 3 oral daily doses of 200 mg/kg to TB-infected rabbits. Mean and SD (error bars) are shown (n = 6 rabbits except for the 24h time point where n = 3).

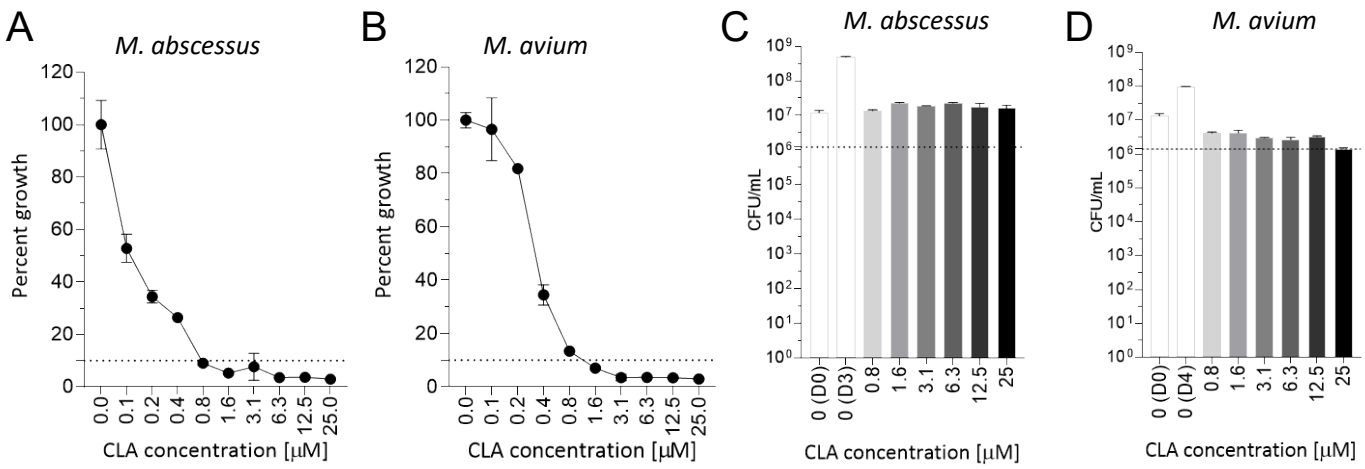

Figure S4. Dose-response activity of clarithromycin (CLA) against clinical isolates *M. abscessus* bamboo and *M. avium* 11. (A-B) Growth inhibition curves: mid-log phase cultures (OD_{600} ~ 0.05) were exposed to increasing concentrations of CLA for 3 days (*M. abscessus* bamboo) or 4 days (*M. avium* 11) in 96-well flat-bottom Corning Costar microplates in a final volume of 200 µL. Percentage of growth was calculated relative to cell density in the drug-free culture. The dotted line indicates 90% growth inhibition compared to the untreated control. (C-D) Bactericidal activity: cultures were grown as described in (A-B). At the end of the experiment, 10 µL were collected from the first clear well onward and plated at different dilutions on 7H10 agar for CFU enumeration. The MBC_{90} is the concentration of CLA that results in a 90% reduction in CFU/ml of the treated culture compared to untreated control at time zero (D0), indicated by the horizontal dotted line. D3 and D4 in (C) and (D) indicate the untreated control at the end of the drug incubation period. Each experiment was performed twice independently. The average and standard deviations of 3 technical replicates of one representative experiment are shown.

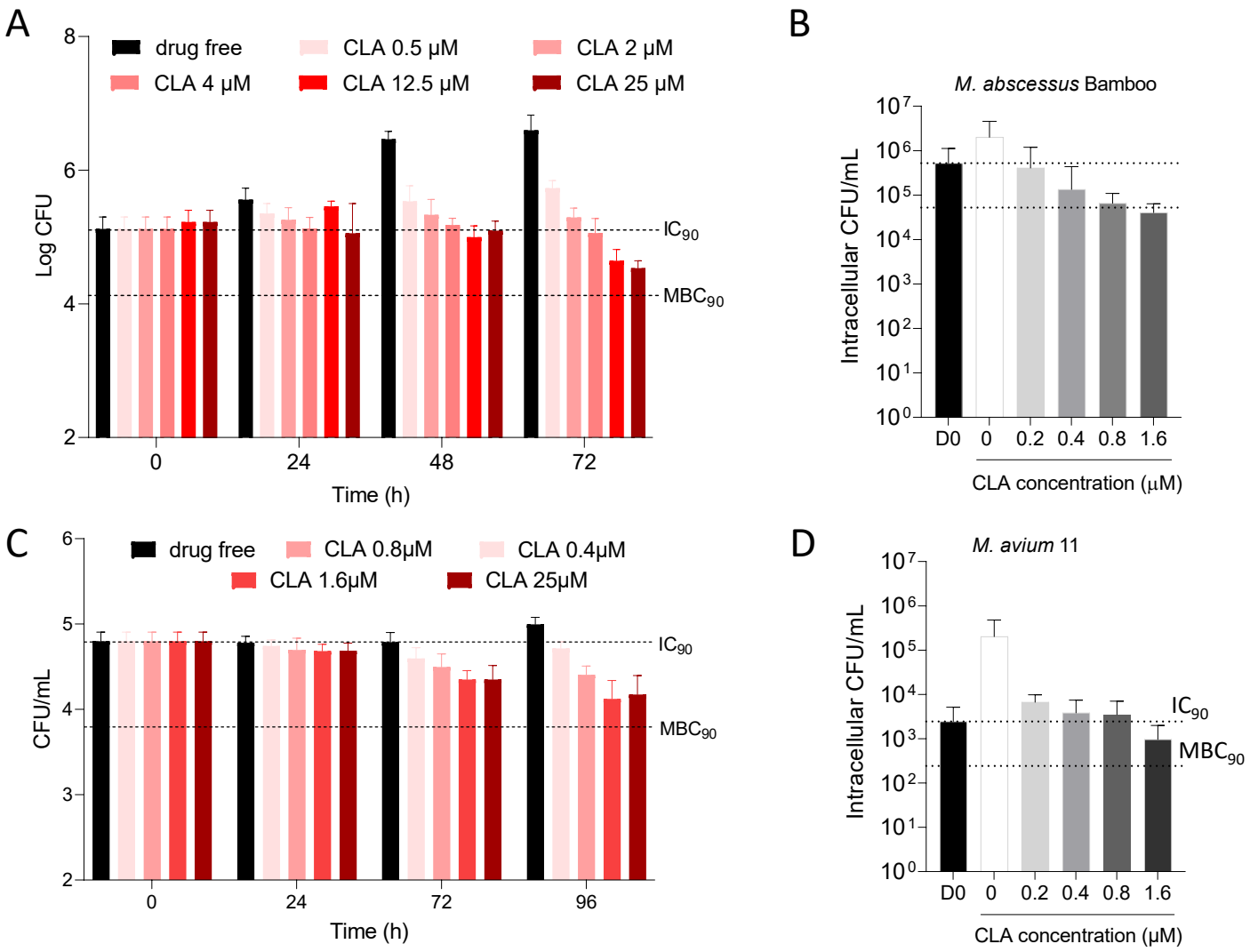

Figure S5. Dose-response activity of clarithromycin (CLA) against intracellular *M. abscessus* bamboo (A-B) and *M. avium* 11 (C-D) in THP-1 derived macrophages. Differentiated THP-1 cells were infected with each strain at a multiplicity of infection of 1:10 for 2h and treated with clarithromycin as indicated for 3 days (*M. abscessus*) and 4 days (*M. avium*) prior to CFU enumeration on solid medium. Concentrations in excess of 25 µM were not tested due to the immunomodulatory activity of clarithromycin and macrolides in general at higher concentrations. The reported IC_{90} is the concentration that reduced intracellular growth by 90% compared to untreated controls. Due to the poor intracellular growth of *M. avium* in panel C, the $MacIC_{90}$ was derived only from the data shown in panel D. The reported MBC_{90} is the concentration that reduced intracellular bacterial viability by 90% compared to the starting inoculum on Day 0. Each experiment was performed twice independently. The average and standard deviations of 3 technical replicates (4 replicates in panel A) of one representative experiment are shown, except for panel C where both datasets were pooled.

M. abscessus - lower 5th percentile	macIC90	MIC90	ECOFF	BiofilmMIC 90	MBC90	macMBC 90	BiofilmM BC90
Cellular	33,274.0	6,654.8	831.9	1,512.5	166.4	133.1	44.4
Lung	22,146.0	4,429.2	553.7	1,006.6	110.7	88.6	29.5
Outer caseum	4,272.3	854.5	106.8	194.2	21.4	17.1	5.7
Inner caseum	932.7	186.6	23.3	42.4	4.7	3.7	1.2
Plasma	326.1	65.2	8.2	14.8	1.6	1.3	0.4

M. abscessus - median	macIC90	MIC90	ECOFF	BiofilmMIC 90	MBC90	macMBC 90	BiofilmM BC90
Cellular	61,359.9	12,272.0	1,534.0	2,789.1	306.8	245.4	81.8
Lung	40,855.8	8,171.2	1,021.4	1,857.1	204.3	163.4	54.5
Outer caseum	7,880.3	1,576.1	197.0	358.2	39.4	31.5	10.5
Inner caseum	1,720.2	344.0	43.0	78.2	8.6	6.9	2.3
Plasma	601.7	120.3	15.0	27.4	3.0	2.4	0.8

M. avium - lower 5th percentile	macIC90	MIC90	ECOFF	BiofilmMIC 90	MBC90	macMBC 90	BiofilmM BC90
Cellular	16,637.0	6,654.8	1,663.7	1,663.7	166.4	166.4	166.4
Lung	11,073.0	4,429.2	1,107.3	1,107.3	110.7	110.7	110.7
Outer caseum	2,136.1	854.5	213.6	213.6	21.4	21.4	21.4
Inner caseum	466.4	186.6	46.6	46.6	4.7	4.7	4.7
Plasma	163.1	65.2	16.3	16.3	1.6	1.6	1.6

M. avium - median	macIC90	MIC90	ECOFF	BiofilmMIC 90	MBC90	macMBC 90	BiofilmM BC90
Cellular	30,679.9	12,272.0	3,068.0	3,068.0	306.8	306.8	306.8
Lung	20,427.9	8,171.2	2,042.8	2,042.8	204.3	204.3	204.3
Outer caseum	3,940.2	1,576.1	394.0	394.0	39.4	39.4	39.4
Inner caseum	860.1	344.0	86.0	86.0	8.6	8.6	8.6
Plasma	300.9	120.3	30.1	30.1	3.0	3.0	3.0

Figure S6. Ratios between area under the concentration time curve (AUC) in tissue or plasma, and the bacteriostatic and bactericidal potency values. The analysis was performed for simulated *M. abscessus* and *M. avium* patients with either average pharmacokinetic exposure or at the lower end (5th percentile) of the drug exposure spectrum. Color coding spans from dark green (top 10th percentile of ratios) to dark red (90th percentile or lower 10th percentile of ratios).