

A standard protocol for the murine pneumonia model to evaluate treatments for AMR lung infections

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BACKGROUND & METHOD

Preclinical *in vivo* PK/PD models play a crucial role in antimicrobial efficacy investigations and provide the basis for the selection of dosing regimens in clinical applications. Differences in the methodology in the preclinical *in vivo* models used are extensive, thus limiting the results' comparability and reproducibility and possibly impeding successful translation to the clinic. To facilitate translation, and to accelerate the development of new antibiotics, the COMBINE consortium aims to establish a reliable and globally harmonized preclinical *in vivo* mouse pneumonia model. Supported by a systematic literature review, we identified important experimental variables and discussed the relevance of these parameters through a workshop with experts in the field. Using a small panel of reference and contemporary clinical *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* isolates we report a first test of the application of the standard mouse lung infection protocol.

Figure 1

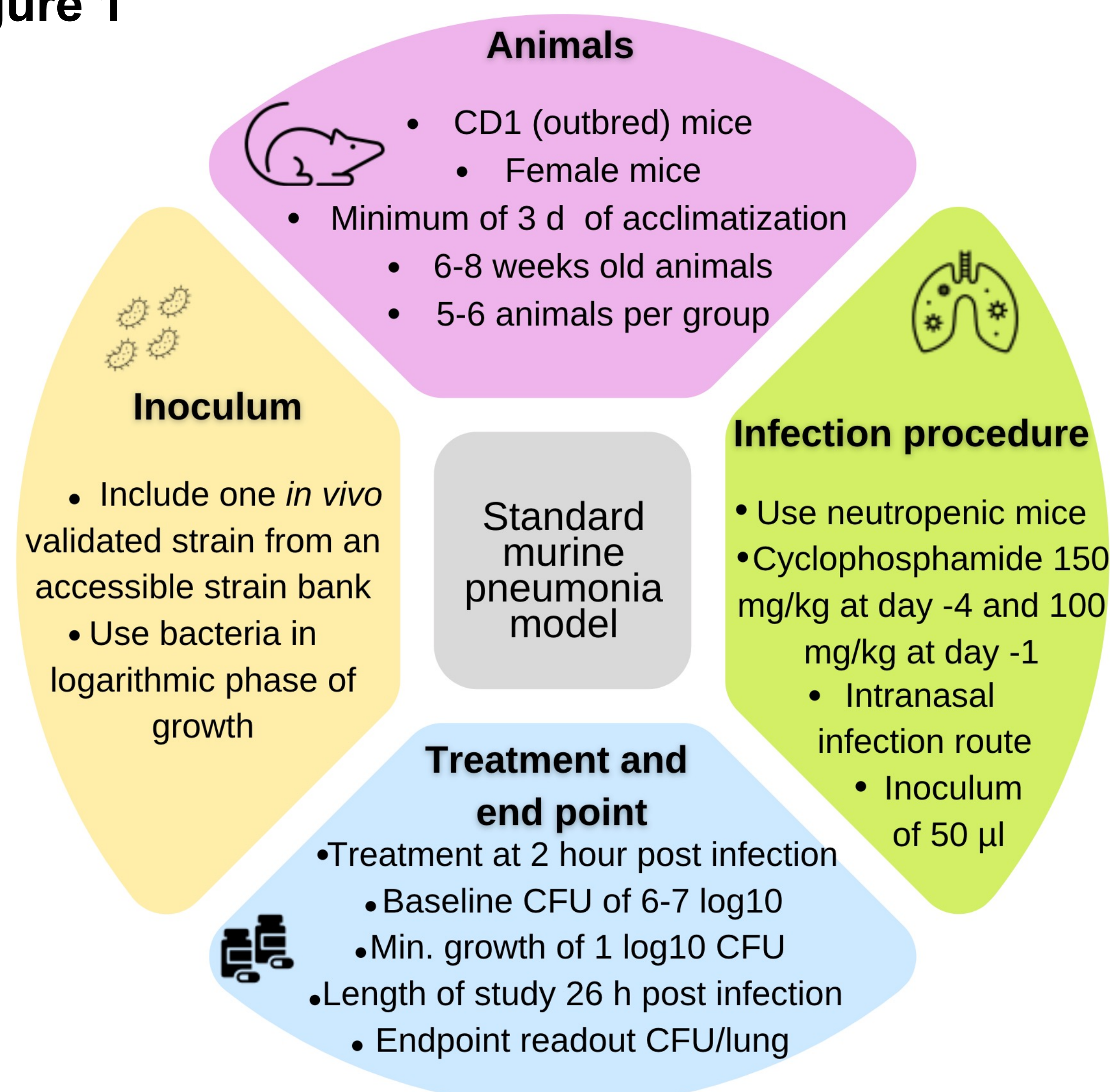


Table 1

Species	No. of isolates tested	Increase in bact. load < 1 log from 2 hrs to endpoint	Lethal ≤12hrs	Suitable strains identified
<i>P. aeruginosa</i>	12	2	8	2
<i>K. pneumoniae</i>	11	2	0	9

RESULTS

A standard mouse pneumonia protocol was established (figure 1) and applied to test susceptible as well as AMR isolates of species *K. pneumoniae* and *P. aeruginosa* isolates (table 1), to identify strains that meet the criteria for use in the COMBINE standard protocol (exemplified in figure 2). Overall, the majority of the tested *K. pneumoniae* strains met the established virulence criteria whereas the majority of *P. aeruginosa* strains were either lethal in less than 12 hrs or did not grow *in vivo*. Ultimately, a selection of isolates that perform appropriately in the model, together with PK/PD data for reference antibiotics vs. these isolates, will be made available to the community for bench-marking new small molecule antibiotics in preclinical development.

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Figure 2

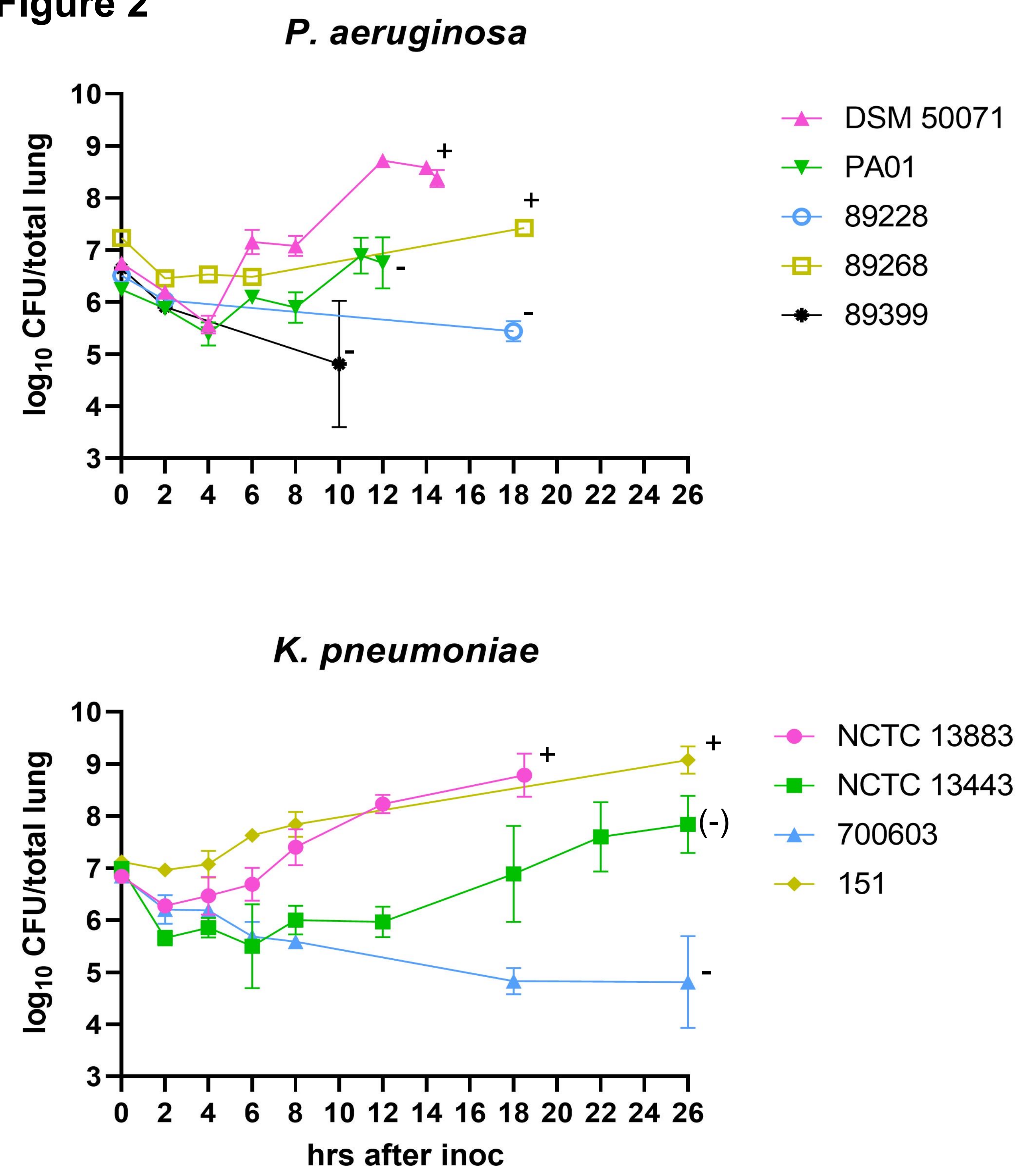


Figure 2. Mean \pm SD CFU values of examples of *P. aeruginosa* and *K. pneumoniae* isolates that meet (+) or fail (-) the criteria of the model. CFU values at t=0 were quantified from the inoculum, not mouse lungs; isolates with endpoints before 26 hrs were euthanized due to clinical score