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Variability in murine bacterial pneumonia models used to evaluate new antimicrobial drug candidates

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Introduction

Standardization of *in vivo* models is required to improve the robustness and reproducibility of preclinical studies and thus translational research. The “Collaboration for prevention and treatment of MDR bacterial infections” (COMBINE) consortium, funded by the European Innovative Medicines Initiative (IMI), aims to develop a standardized murine pneumonia model for the preclinical efficacy testing of novel anti-infective candidates against Gram-negative pathogens and develop improved tools for the translation of preclinical data to the clinic. Here we describe the results of a literature search which highlights the variability of murine pneumonia model protocols employed in antimicrobial efficacy studies.

Methodology

Fifty-three pertinent studies mined from scientific literature that focused on the assessment of antimicrobials against *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter baumannii* were systematically identified and reviewed.

Results

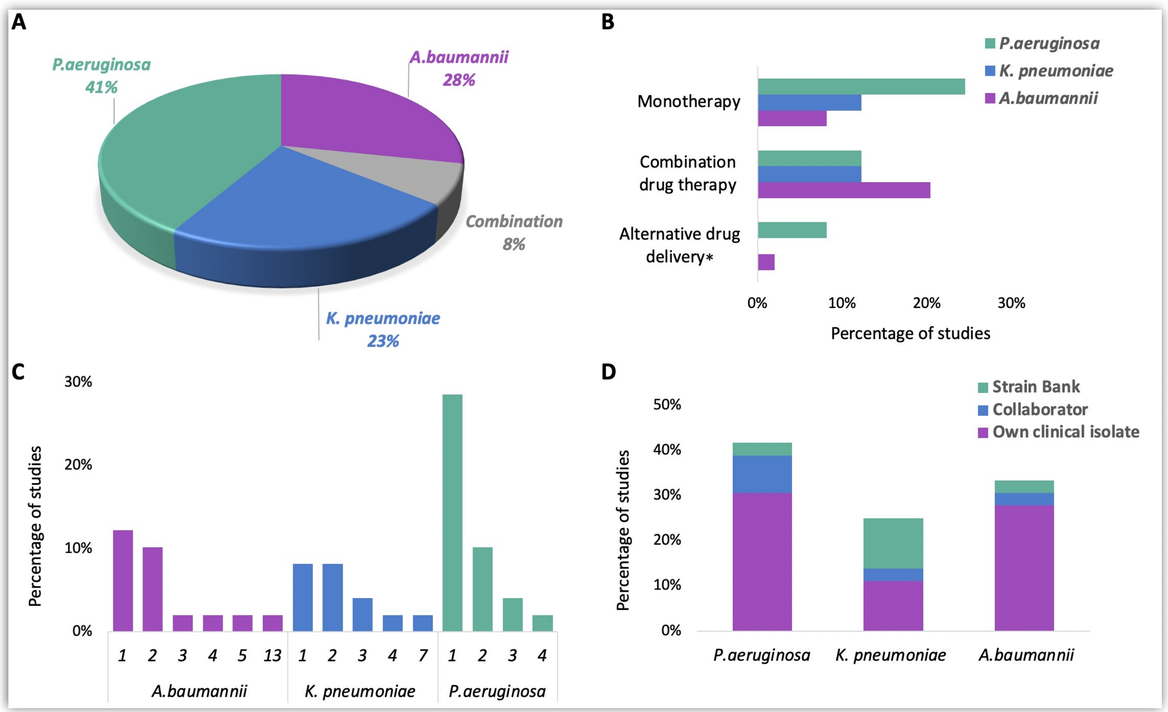

Figure 1. (A) Percentage of studies employing selected bacterial species for *in vivo* antimicrobial assessment, (B) type of antimicrobial intervention, (C) number of strains tested and (D) source of employed bacterial strains. * Alternative or non-traditional treatment such as aerosol, liposome, etc.

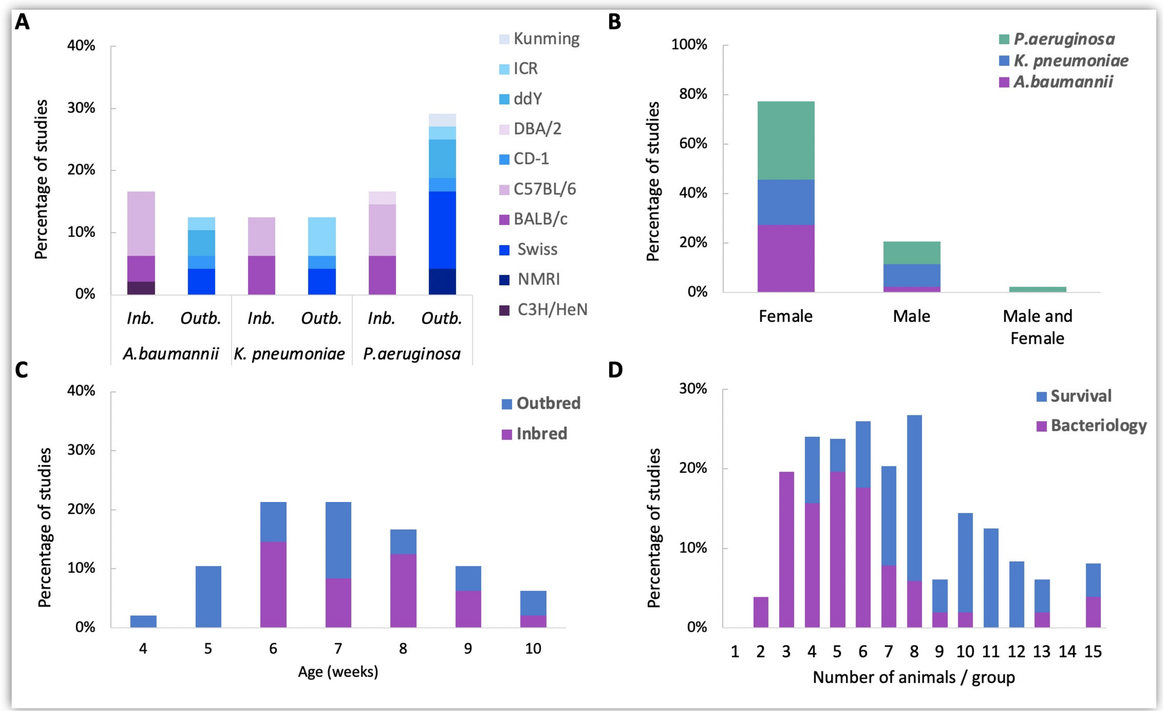

Figure 2. Mouse characteristics in antimicrobial efficacy studies. (A) Mouse strains in relation to bacterial infection, (B) sex of mice, (C) age of mice and (D) number of animals per group. *Inb:.* Inbred, *Outb.*: Outbred.

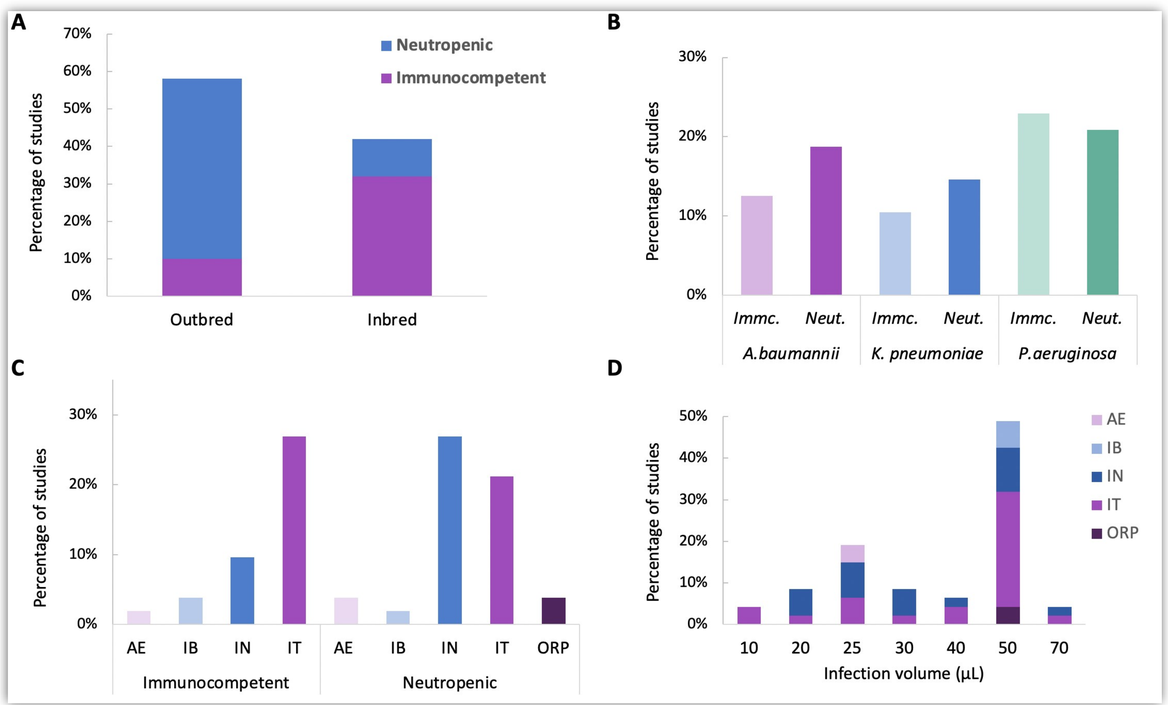

Figure 3. (A) Immune status of mice in relation to mouse strain, (B) bacterial infection and (C) route of infection. (D) Infectious route in relation to the employed infection volume. Immc: Immunocompetent, Neut: neutropenic, IT: intratracheal, IN: intranasal, ORP: oropharyngeal, IB: intrabronchial, AE: aerosolization.

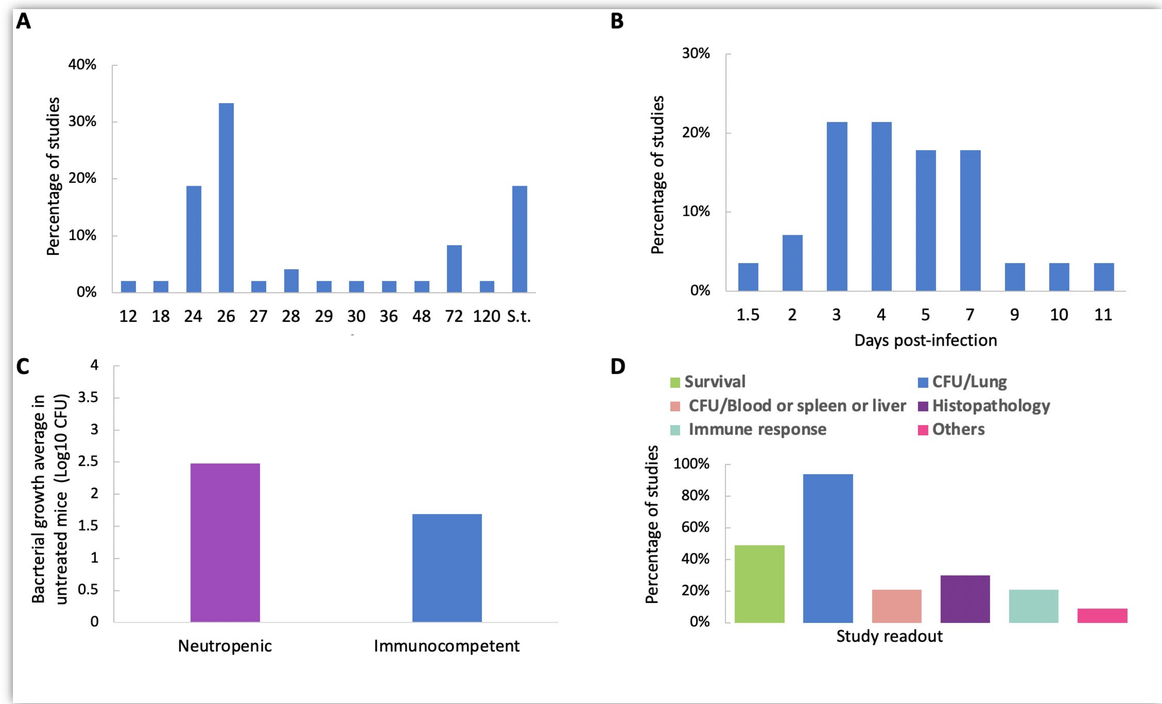

Figure 4. Experimental time period for (A) bacteriology and (B) survival endpoints. (C) Average of lung bacterial growth (Log_{10} CFU / lung) over the study period in untreated neutropenic and immunocompetent animals. (D) Study outcomes employed in the reviewed studies. S.t: several time points.

Conclusion

The observed variability in murine pneumonia model protocols used for evaluating antimicrobials highlights the need for standardization to strengthen the reproducibility and comparability of data generated during the evaluation of novel antibiotics. These results were shared and discussed in an expert workshop organized by the COMBINE consortium. A consensus murine pneumonia model protocol has been proposed (detailed in a complementary poster by Vingsbo Lundberg *et al.*) and will be further benchmarked and validated within the consortium.

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