IMI AMR Accelerator

Tackling antibiotic resistance together

COMBINE WP5:

Improving animal models and preclinical-to-clinical translation

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Scientific Director, GSK

AMR Accelerator: Public-Private collaboration with the shared goal of progressing the development of new medicines to treat or prevent resistant bacterial infections (www.amr-accelerator.eu)

Who are we?

3 topics within the AMR Accelerator

TUBERCULOSIS & NTM

Accelerating scientific discoveries and advancing the R&D pipeline of new and innovative agents to treat TB and NTM lung disease.

TRIC-TB Part of IMI AMR Accelerator

UNITE 4TB Part of IMI AMR Accelerator

RESPIRI TB

RESPIRI NTM

ERA 4TB EUROPEAN REGIMEN ACCELERATOR FOR TUBERCULOSIS Part of IMI AMR Accelerator

GRAM-NEGATIVES

Advancing the R&D pipeline of new and innovative agents to address AMR in Gram-negative bacteria.

AB-Direct Antibiotic Distribution & Recovery Part of IMI AMR Accelerator

GNA NOW IMI AMR ACCELERATOR

CAPABILITY BUILDING

Accelerating and validating scientific discoveries in AMR. Coordinating and supporting projects across the AMR Accelerator.

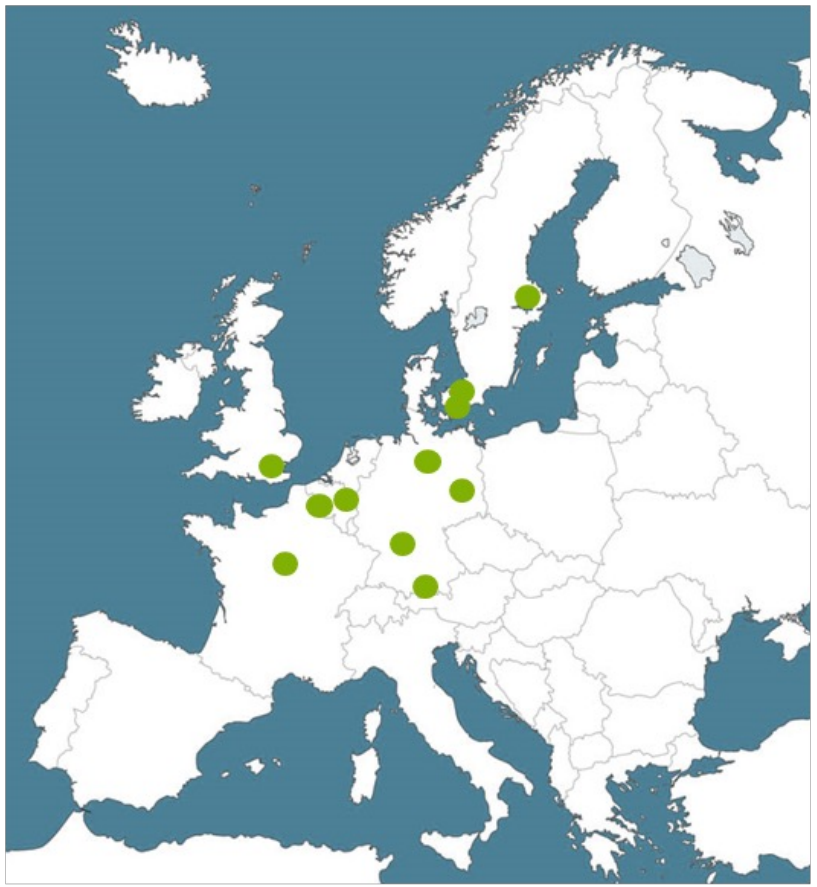
COMBINE Part of IMI AMR Accelerator

PrIMAVeRa

IMI AMR Accelerator Tackling antibiotic resistance together

Collaboration for prevention and treatment of MDR bacterial infections (COMBINE)

➢ *6-year project from Nov 2019 – Nov 2025*



Universities, research organisations, public bodies, non-profit groups:

- Uppsala University (UU) Sweden Coordinator
- Paul-Ehrlich-Institut (PEI) Germany
- Fraunhofer Gesellschaft (FRAUNHOFER) Germany
- Statens Serum Institut (SSI) Denmark
- BEAM Alliance (BA) France

Small and medium-sized enterprises (SMEs) and mid-sized companies (<€500 m turnover):

- Asclepia (AC) Belgium
- GRIT42 (G42) Denmark
- BIOCOM (BC) Germany

EFPIA companies:

- GlaxoSmithKline (GSK) United Kingdom Project Lead
- Evotec (EVT) Germany
- Janssen (JNJ) Belgium

https://amr-accelerator.eu/project/combine

WP5: Animal Models & PK/PD

Improve understanding of animal infection model reproducibility and translation to clinical efficacy

Problem:

- Animal infection models are excellent tools, yet translational gaps remain
- Methods used for study conduct & analyses impact results
- Lack of standardization hinders interpretation & comparison

Our ambitious goals:

- Develop standardised animal infection model protocol
- Benchmark standard model using relevant control compounds
- Establish in vivo reference strain bank supported by data from the model
- Provide framework for PK/PD analysis & mathematical modelling
- Improve understanding of preclinical-to-clinical translation

Two main workstreams

Establish Reference Strain Bank

- Identify candidate strains that perform well in the standard model
- Evaluate performance of selected strains across labs and studies
- Provide benchmark data for the selected strain-antibiotic combinations
- Ensure reference strains and data are available to AMR community

Improve Preclinical-to-Clinical Translation

- Investigate how response in our standard model translates to the clinic
- Learn how to appropriately interpret the data from our standard model
- Explore variability in drug response across strains and between labs
- Demonstrate how to best use the data for PK/PD modeling
- Provide preclinical data for further translational analyses

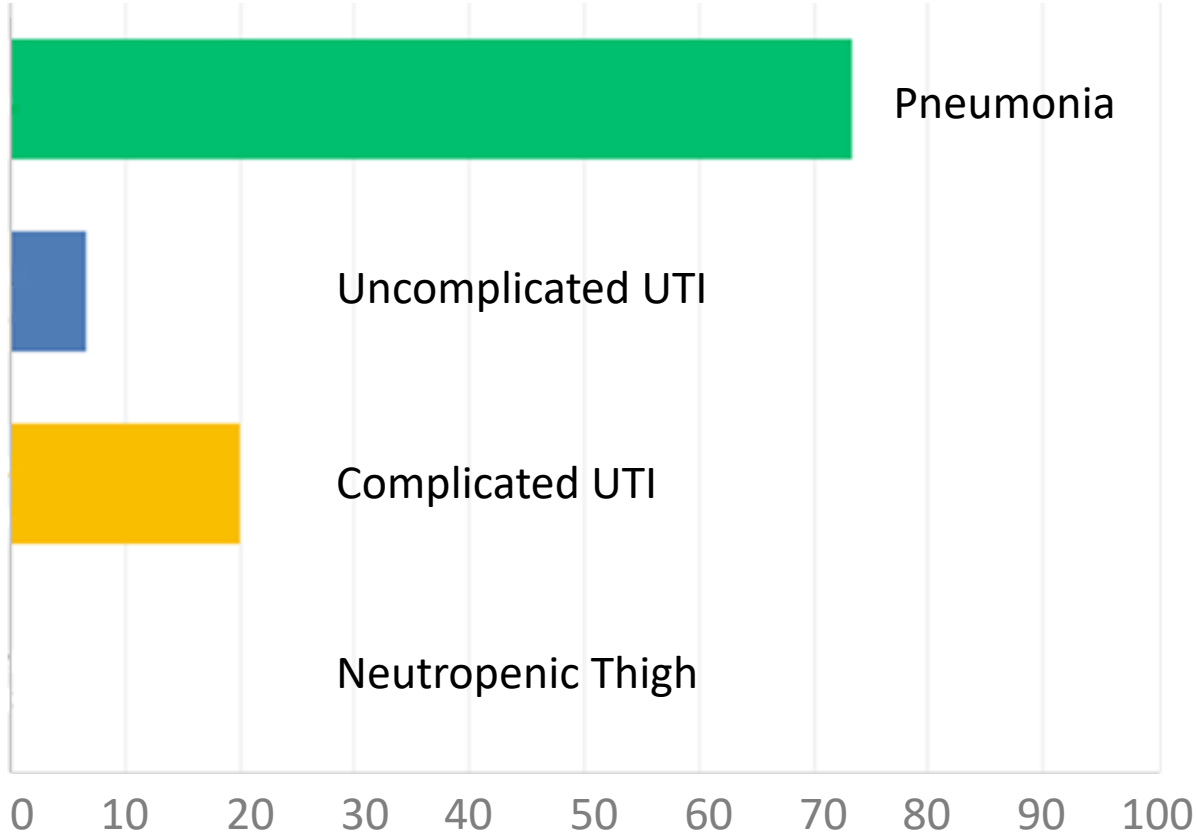
Selection of model and assessment of methods in literature

AMR Animal Models Webinar

- Presentations on models to study antibiotics vs. Gram-neg pathogens
- Survey of participants to identify greatest need for model improvement

Results of Literature Review

- Substantial differences in study methods
  - ➢ Mouse strain, sex, age, etc.
  - ➢ Bacterial strains/inoculum
  - ➢ Infection procedure
  - ➢ Treatment time, route, etc.
  - ➢ Study endpoints and timing



Model with greatest translational gap (% of survey participants)

Identification of key variables and selection of standards

EXPERT WORKSHOP: Develop standardized murine model to evaluate treatments for AMR lung infections

Day 1 (Tuesday, April 27th 2021): 15:00-19:00 CEST

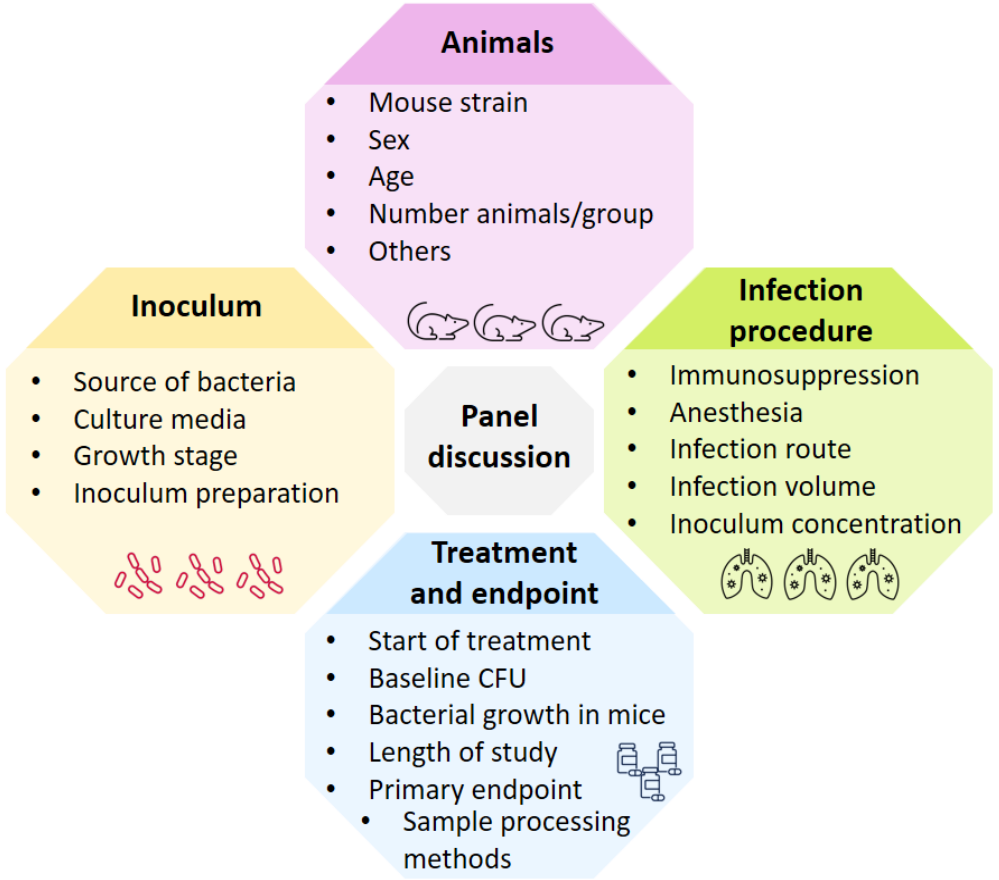
Developing a standardized murine pneumonia model to characterize PK/PD of antibiotics

Day 2 (Wednesday, April 28th 2021): 15:00-19:00 CEST

Standard protocols for murine pneumonia models - beyond PK/PD

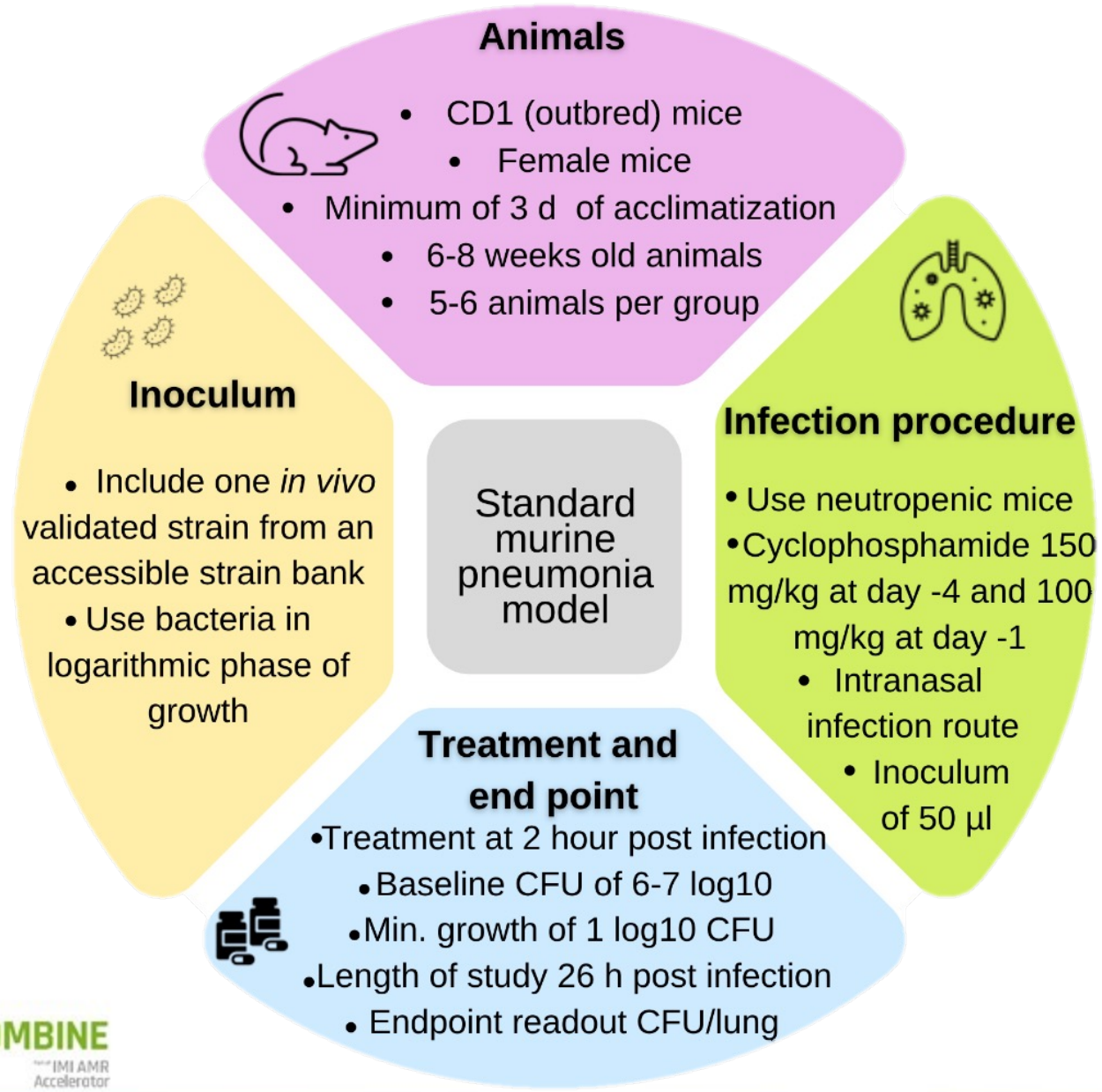
Expert Panel & Participant Survey

Variables discussed/standardized



Watch for our upcoming publications!

Standard lung model established for PK/PD



What's next?

1. Select bacterial strains

- Characterized for resistance profile
- That are shareable via an accessible repository

2. Validate strains in model

- To ensure consistent growth

3. Choose reference compounds

- Examples of different classes
- Reasonable to work with in vivo
- Maximize collaborative efforts

4. Generate in vivo data

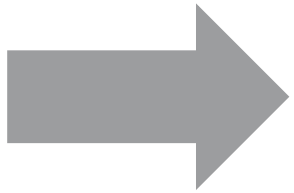
- PK from infected mice
- PD for ≥3 strains of *P. aeruginosa* and *K. pneumoniae*

5. Analyses/reporting

Our goal in WP5 is to move the AMR community

FROM:

1. Variability in animal models employed for pneumonia
2. Inconsistent strain use
3. Lack of consensus on interpretation
4. Varying application of mathematical modeling
5. Greater translational risk



TO:

1. Standardized & validated pneumonia model
2. Benchmarked in vivo reference strains
3. More informed interpretation
4. Clear PK/PD modeling framework
5. Greater confidence moving to clinic with new antibacterials

COMBINE aims to identify better ways to *translate preclinical know-how into clinical predictions*

Let's collaborate! Can you…

Share **expertise** and strains

***Contact** us:*
IMI-COMBINE@pei.de

Support our **data quest**

***Share** your preclinical and/or clinical pneumonia data*

Combine effort on common interests

***Conduct** validation studies in your lab or CRO*

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Acknowledgement

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