Improving Clinical Trials for Candidate Vaccines Against Antimicrobial Resistant (AMR) Infections: Perspectives from the COMBINE Project

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Paul-Ehrlich-Institut

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www.imi.europa.eu

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Why Vaccines Against AMR?

- Antimicrobial Resistance (AMR) is on the rise worldwide[1]
  - ESCAPE pathogens are particularly affected
    - *E. faecium, S. aureus, C. difficile, A. baumannii, P. aeruginosa, Enterobacteriaceae* (including *K. pneumoniae*) - mostly linked to hospital-acquired infections
- To slow down AMR and prepare for the future[2]:
  - Non-pharmaceutical interventions (surveillance systems, antibiotics stewardship, WASH measures, etc.)
  - Novel therapeutic and preventive agents (new antibiotics, vaccines, monoclonal antibodies, etc.)
- Vaccines and vaccination have great potential to contain AMR[3]

[1] https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
[2] OECD, WHO, FAO and OIE, "Tackling Antimicrobial Resistance - Ensuring Sustainable R&D", 29 June 2017
[3] Micoli et al, 2021; Jansen & Anderson, 2018; Lipsitch & Siber, 2016

Why NO Vaccines Against AMR?

- Several vaccine candidates against ESCAPE pathogens have been developed, but they all failed to prove efficacy (so far)

- Why have they failed?
- Are there recurring problems across pathogens/infections?
- How can we improve future vaccine development?

COMBINE
Part of IMI AMR Accelerator

IMI AMR Accelerator

A public-private collaboration to progress the development of new medicines to treat or prevent resistant bacterial infections

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

COMBINE Scientific Objectives

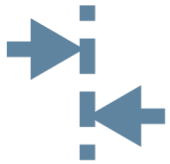
A data-driven, hands-on approach to:

- Standardize and optimize protocols for preclinical infection models
- Identify better ways to translate preclinical know-how into clinical predictions
- Investigate novel strategies to analyze clinical data and optimize trial designs

INPUT

Relevant data originating from the AMR community

COMBINE



Inter- and intra-study analyses

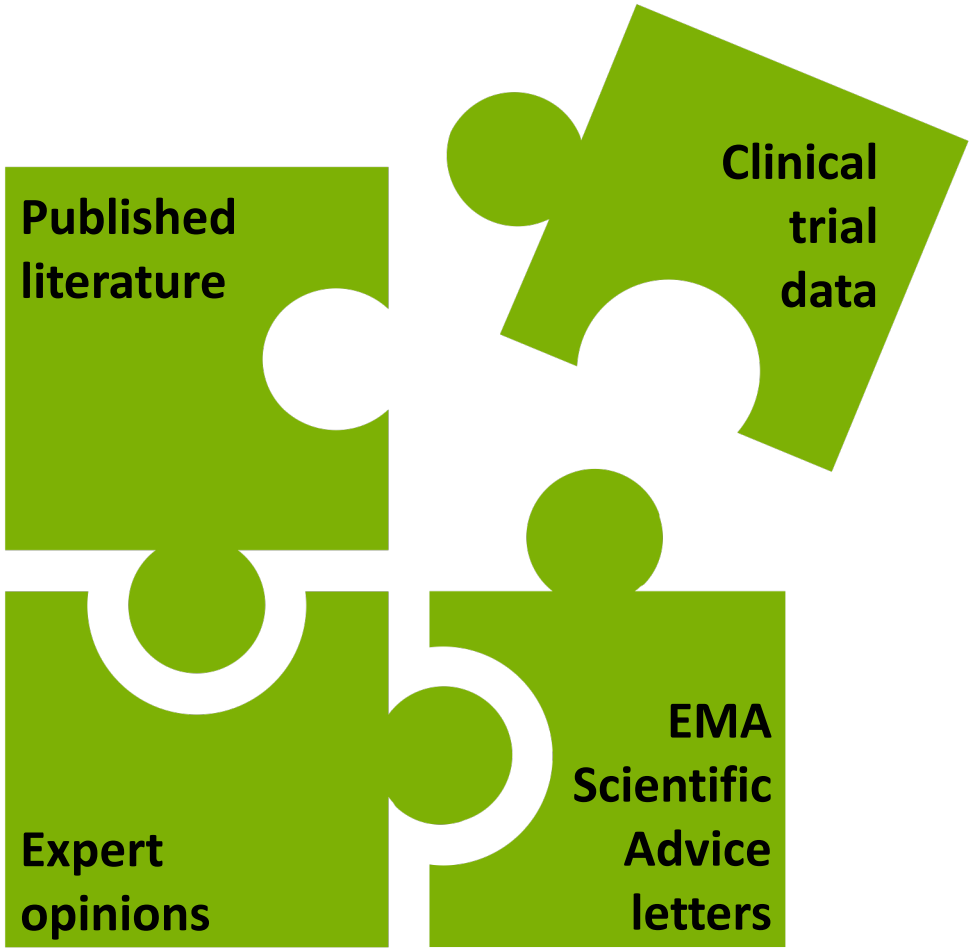
Experimental studies to validate findings

Preclinical to clinical translation

OUTPUT

- Optimized & validated **standard protocols for preclinical** infection models
- Factors that **influence outcome** of the clinical trial
- Proposed **improvements** to study design and analysis

(Meta-)Data Sources



1: Review of Published Literature

„Which challenges have been publically reported so far?“

frontiers in Immunology

REVIEW
published: 05 August 2020
doi: 10.3389/fimmu.2020.01755

Check for updates

Challenges for Clinical Development of Vaccines for Prevention of Hospital-Acquired Bacterial Infections

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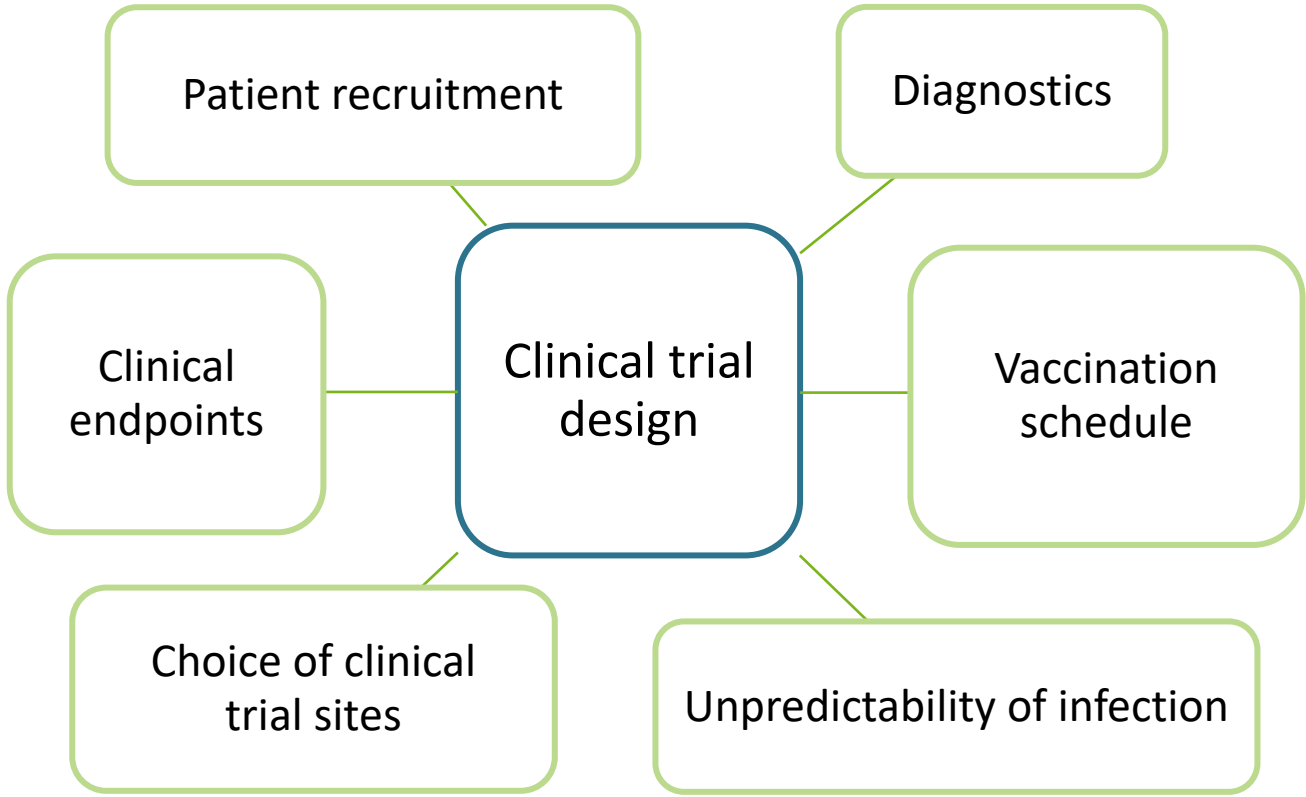
OPEN ACCESS



2: Expert Opinions (Vaccine Expert Workshop)

„Which recurring problems have experts been encountering in the development of vaccines against AMR infections?“

Day 1 (Monday, February 8th, 2021):		Day 2 (Tuesday, February 9th, 2021)	
Introduction, *S. aureus, C. difficile*		*K. pneumoniae, E. coli,* Clinical trial design	
15.00 - 15.45	Welcome and introduction to nosocomial AMR pathogens	15.00 - 17.00	Focus on *K. pneumoniae* and *E. coli*
15.45 - 17.30	Focus on *S. aureus*		
Biobreak		Biobreak	
18.00 - 19.00	Focus on *C. difficile*	17.30 - 19.00	Clinical trial design
19.00 - 19.15	Wrap-up	19.00 - 19.15	Wrap-up and farewell

- 17 external speakers and chairs (industry, academia and public health bodies)
- 60-100 attendees

2: Expert Opinions (Vaccine Expert Workshop)

Recurring problems

Gaps in basic knowledge

- Role of precolonisation, microbiome and other risk factors
- Pathogenesis
- Optimal targets

Issues in preclinical development

- Lack of reliable animal models
- Translation issues

Issues in clinical development

- Endpoint definition
- Optimal population
- Feasibility

3: EMA Scientific Advice Letters

„Have these issues been discussed in the interactions between developers and regulators?“

How scientific advice works

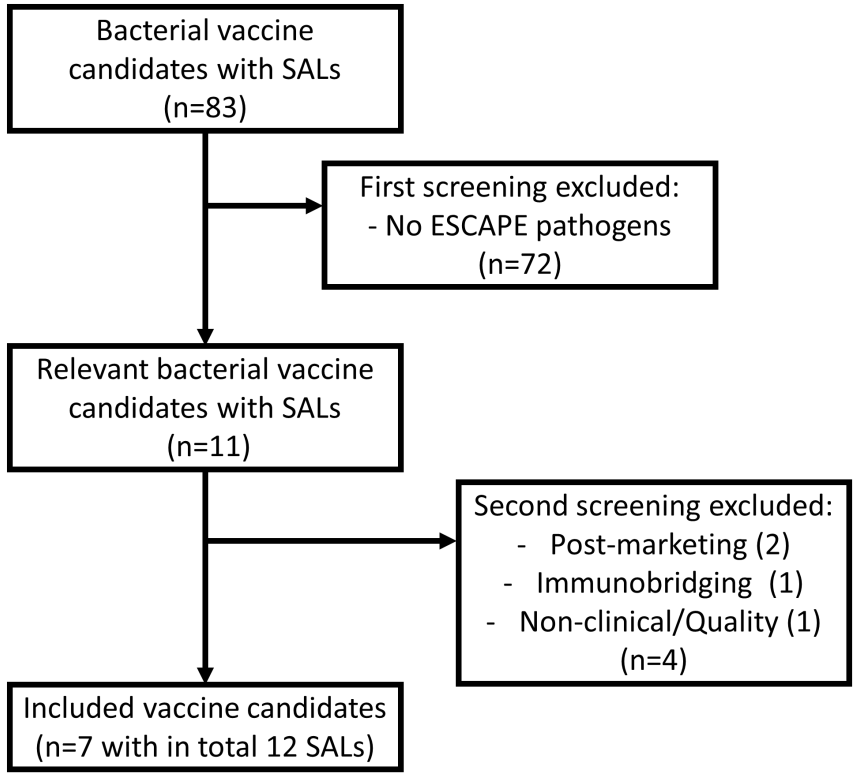
EMA gives scientific advice by **responding to specific questions** posed by the medicine developer on the development of a particular medicine.

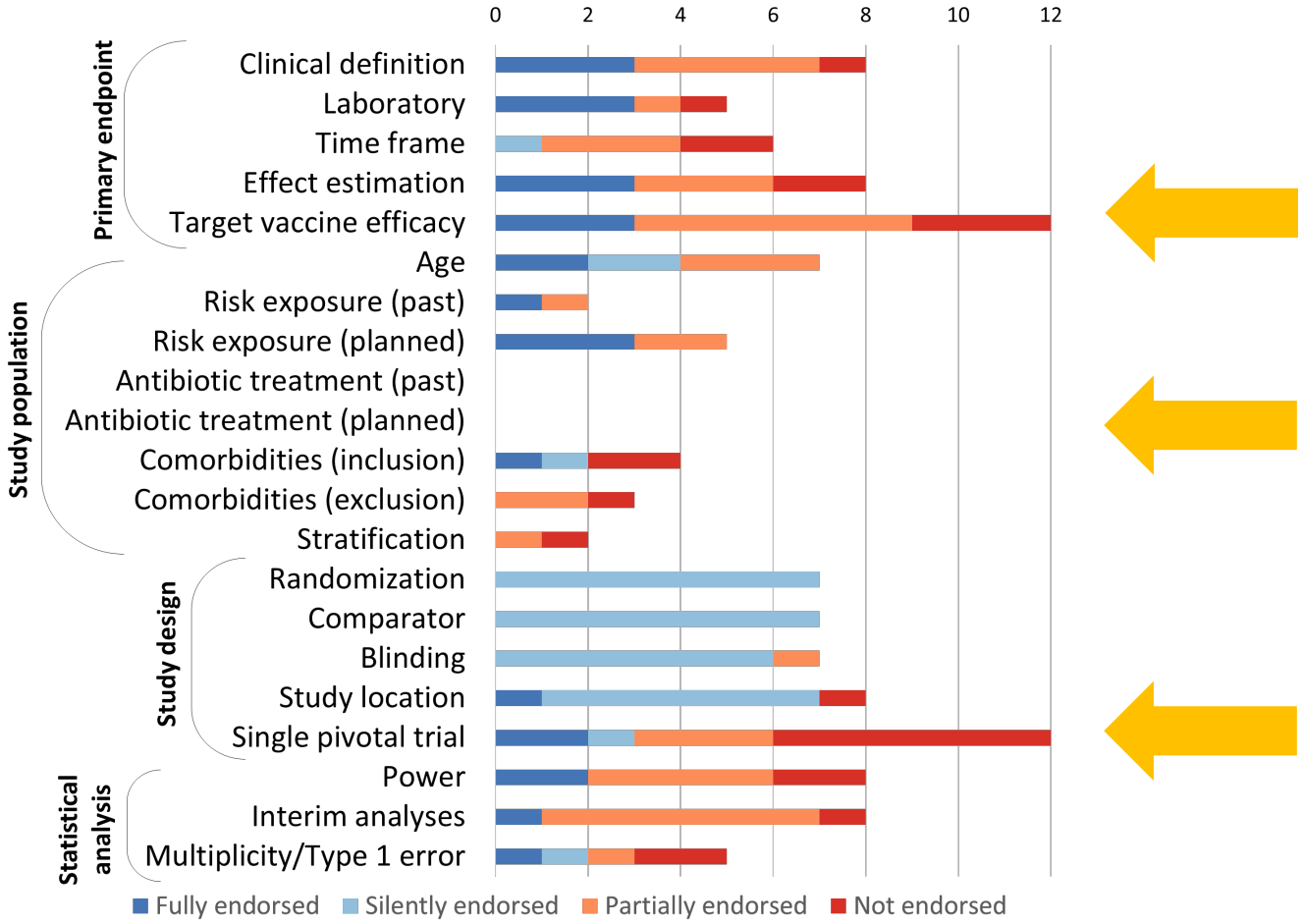
The developer of a medicine presents the way it plans to develop its medicine and identifies questions and possible solutions. EMA then gives advice on the developer's proposals.

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

3: EMA Scientific Advice Letters (SAL)

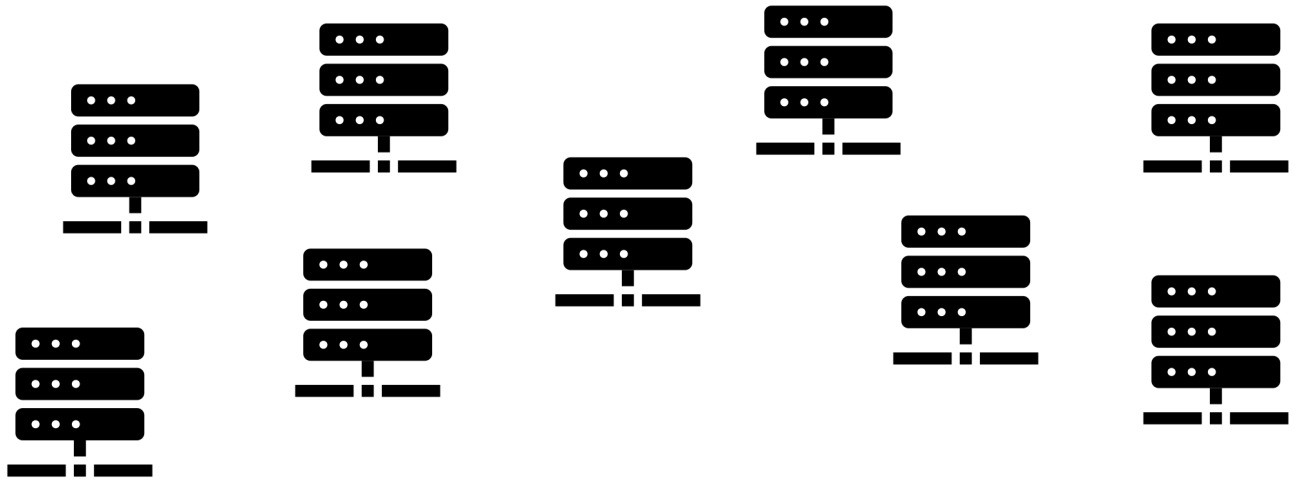
Preliminary results





4: Clinical Trial Data

„Can we learn from failed trials and improve future trial design?“



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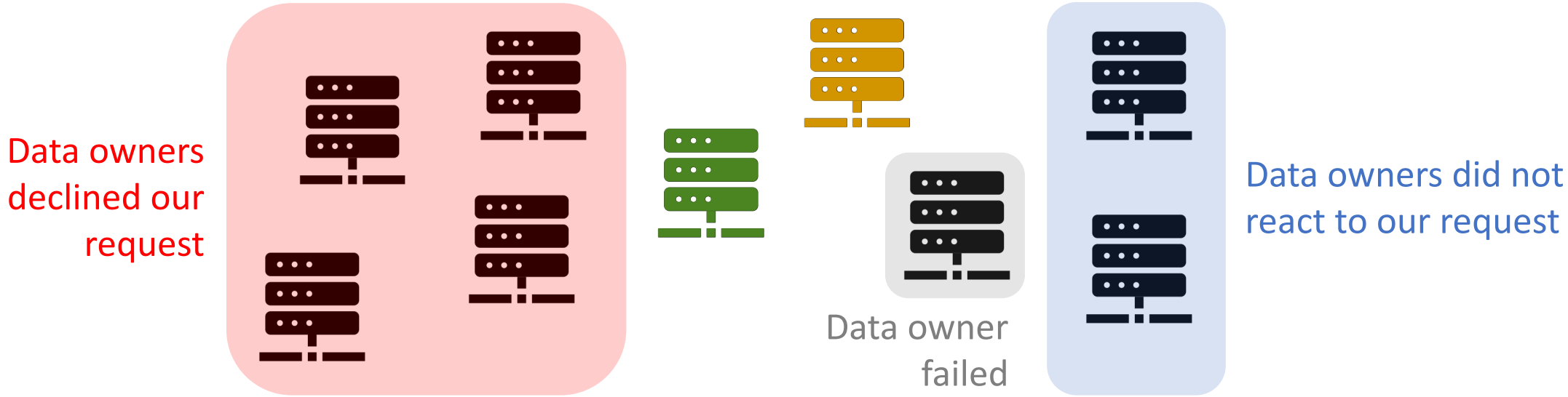

Major challenges in clinical data sharing in the AMR space!

Key Messages

- Bottlenecks in clinical development: definition of the optimal **primary endpoint**, of the **study population**, and **feasibility** of the (pivotal) trials
- Controversial issues in regulatory interactions: **target vaccine efficacy**, generation of pivotal evidence via a **single pivotal trial**
- Major challenges in **clinical data sharing** in the AMR space!

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