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

Linda Marchioro, Karen Huber, Benjamin Hofner, Bernhard Kerscher, Rakel Arrazuria, Igor Stojkov, Isabelle Bekeredjian-Ding

Paul-Ehrlich-Institut

Zoonoses 2023 - Berlin, 9-11 October 2023
Acknowledgements and Disclaimers

COMBINE has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 853967. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

www.imi.europa.eu

This presentation reflects the author’s view and does not represent the views of the Paul-Ehrlich-Institut, the European Medicines Agency, IMI, EFPIA or the European Union.
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](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?
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.

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

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

- Published literature
- Clinical trial data
- Expert opinions
- EMA Scientific Advice letters

EMA: European Medicines Agency
1: Review of Published Literature

„Which challenges have been publically reported so far?“
2: Expert Opinions (Vaccine Expert Workshop)

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

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

- 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.

Preliminary results

Bacterial vaccine candidates with SALs (n=83)

First screening excluded:
- No ESCAPE pathogens (n=72)

Relevant bacterial vaccine candidates with SALs (n=11)

Second screening excluded:
- Post-marketing (2)
- Immunobridging (1)
- Non-clinical/Quality (1) (n=4)

Included vaccine candidates (n=7 with in total 12 SALs)

Primary endpoint
- Clinical definition
- Laboratory
- Time frame
- Effect estimation
- Target vaccine efficacy
- Age
- Risk exposure (past)
- Risk exposure (planned)
- Antibiotic treatment (past)
- Antibiotic treatment (planned)
- Comorbidities (inclusion)
- Comorbidities (exclusion)
- Stratification
- Randomization
- Comparator
- Blinding
- Study location
- Single pivotal trial
- Power
- Interim analyses
- Multiplicity/Type 1 error

Study population

Statistical analysis

0 2 4 6 8 10 12
- Fully endorsed
- Silently endorsed
- Partially endorsed
- Not endorsed
4: Clinical Trial Data

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