Recurring Issues in the Development of Vaccines Against Antimicrobial Resistant (AMR) Infections: Results from the COMBINE Vaccine Expert Workshop

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Annual Meeting of the Vaccine Working Group (DGfI AK Vakzine)
13th January 2022
IMI AMR Accelerator

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.

IMI: Innovative Medicine Initiative
Acknowledgements and disclaimer

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Why vaccines against AMR?

• Antimicrobial Resistance (AMR) is on the rise worldwide:
  • ESCAPE pathogens are particularly affected

• To slow down AMR and prepare for the future:
  • 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

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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 (so far)

• WHY?
• Are there recurring problems across pathogens/infections?
• COMBINE focus: Translation and clinical trial design?
Vaccine Expert Workshop

„Which recurring problems have you 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>
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| 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 |
Focus on \textit{S. aureus}

- 3 vaccine candidates failed after phase 2b/phase 3

- Recurring issues:
  - Gaps in knowledge of pathogenesis and identification of optimal antigen combination
  - Lack of reliable and predictive animal models
  - Endpoint definition (clinical manifestations), lack of surrogates of protection
  - Selection of study population (≠ target population?)
Focus on *C. difficile*

• 2 vaccine candidates reached phase 3 (one failed, one ongoing)

• Recurring issues:
  • Gaps in knowledge of pathogenesis (role of toxins, role of precolonisation)
  • Lack of reliable and predictive animal models
  • Selection of trial population

• Additional issues:
  • First vs. recurrent infections
  • Technological improvements to improve understanding of pathogenesis
Focus on *E. coli* (ExPEC) and *K. pneumoniae*

- One ExPEC vaccine currently in phase 3, no *K. pneumoniae* past phase 2

- Recurring issues:
  - Role of microbiome (incl. vaccine-related perturbances) and precolonisation
  - Large variability of antigens, cross-protection
  - Lack of surrogates of protection

- Additional issues:
  - ExPEC: Definition of endpoint (which clinical manifestations)
  - *K. pneumoniae*: Low incidence ➔ Pivotal clinical trials unfeasible
Focus on Clinical Trial Design

- Bottlenecks: Endpoint definition, Sample size (feasibility)

- Adaptive Study Designs should be considered (e.g. group sequential design, population enrichment)

- Controlled Human Infection Models *likely* not suited for these infections (weakened strains, ability to treat infection)

- Role of Regulators:
  - Company speaker: „Seek early advice“
  - Non-standard regulatory pathways (high unmet medical need)
Summing up: Yes! There are recurring problems:

- **Basic knowledge:**
  - Gaps in the knowledge of the pathogen/pathogenesis
  - Lack of knowledge about the optimal antigen combination

- **Preclinical tests:**
  - Lack of reliable animal models
  - Translation issues

- **Clinical tests:**
  - Endpoint definition (clinical manifestations), lack of surrogates of protection
  - Low incidence, selection of study population → Feasibility
Next step

Integrative data-analysis to investigate bottlenecks and propose solutions for translation and clinical trial design

Can you share clinical and matched preclinical data through our open data call (data from antibiotics, vaccines, mAbs, successes or failures)?

Contact: IMI-COMBINE@pei.de
Stay up to date: https://amr-accelerator.eu/
Old slides
IMI AMR Accelerator

- Foster a wide-ranging series of projects that address many of the scientific challenges in AMR
  - Capability building scope

- Progress a pipeline of potential medicines to treat patients with resistant bacterial infections
  - 10 preclinical candidates
  - 5 Phase II-ready assets
  - Phase II clinical trials
Why NO Vaccines against AMR?
(Scientific perspective)

- Approximately a dozen vaccines against ESCAPE pathogens have reached clinical phase 2 or 3 and failed
- Why failed? Which areas should be improved?
Why NO Vaccines against AMR?
(Scientific perspective)

• Approximately a dozen vaccines against ESCAPE pathogens have reached clinical phase 2 or 3 and failed

• Why failed? 3 groups of possible reasons:
  • Vaccine did not correctly tackle the target pathway(s), or the target pathway was not causative of the disease
  • Inadequate animal models, translation issues
  • Inadequate clinical trial(s) or development program
Expert Workshop on Vaccines for AMR pathogens

- 7.5 h workshop, 17 external speakers, 60-100 people in the audience (most from speakers’ affiliations)

- Question: “Why have clinical trials for AMR vaccines been failing?”
  - Some sessions/talks very focused
  - Some others vague, missing the point

- Take home messages:
  - Questions have been asked for years (endpoints, target population, low prevalence for hospital-acquired infections)
  - Option: Bad vaccines → how to model it?
  - Gap: Correlates/surrogates of protection, epidemiology
Acknowledgement

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IMI AMR Accelerator
Public-Private collaboration with the shared goal of progressing the development of new medicines to treat or prevent resistant bacterial infections
The COMBINE project
Coordination, support and capability building within the IMI AMR Accelerator

Coordination and support of the Accelerator projects

WP4 - Collection, sharing and analysis of vaccine and antibacterial data to **improve the design and analysis of clinical trials**

WP5 - Improved understanding of **animal infection model reproducibility and translation to clinical efficacy**
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