

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.



Acknowledgements and disclaimer

The AMR Accelerator projects have received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 853976 | 853967 | 853979 | 853932 | 853903 | 853800 | 853989 | 101007873 | 101034420. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. ERA4TB has received additional support from Global Alliance for TB Drug Development, Bill & Melinda Gates Foundation and University of Dundee. UNITE4TB has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 101007873. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA, Deutsches Zentrum für Infektionsforschung e. V. (DZIF), and Ludwig-Maximilians-Universität München (LMU). EFPIA/AP contribute to 50% of funding, whereas the contribution of DZIF and the LMU University Hospital Munich has been granted by the German Federal Ministry of Education and Research.

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Why vaccines against AMR?

- Antimicrobial Resistance (AMR) is on the rise worldwide¹
 - ESCAPE pathogens are particularly affected
- To slow down AMR and prepare for the future²:
 - 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 AMR³

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?“

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

Focus on *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 (\neq 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

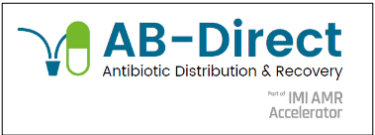
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IMI AMR Accelerator

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



IMI AMR Accelerator
Tackling antibiotic resistance together



COMBINE
Part of IMI AMR Accelerator



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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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The COMBINE Project

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