Paul-Ehrlich-Institut

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

COMBINE
part of IMI AMR Accelerator

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Vaccines Against Antimicrobial Resistant (AMR) Infections: Introduction and Problem Statement
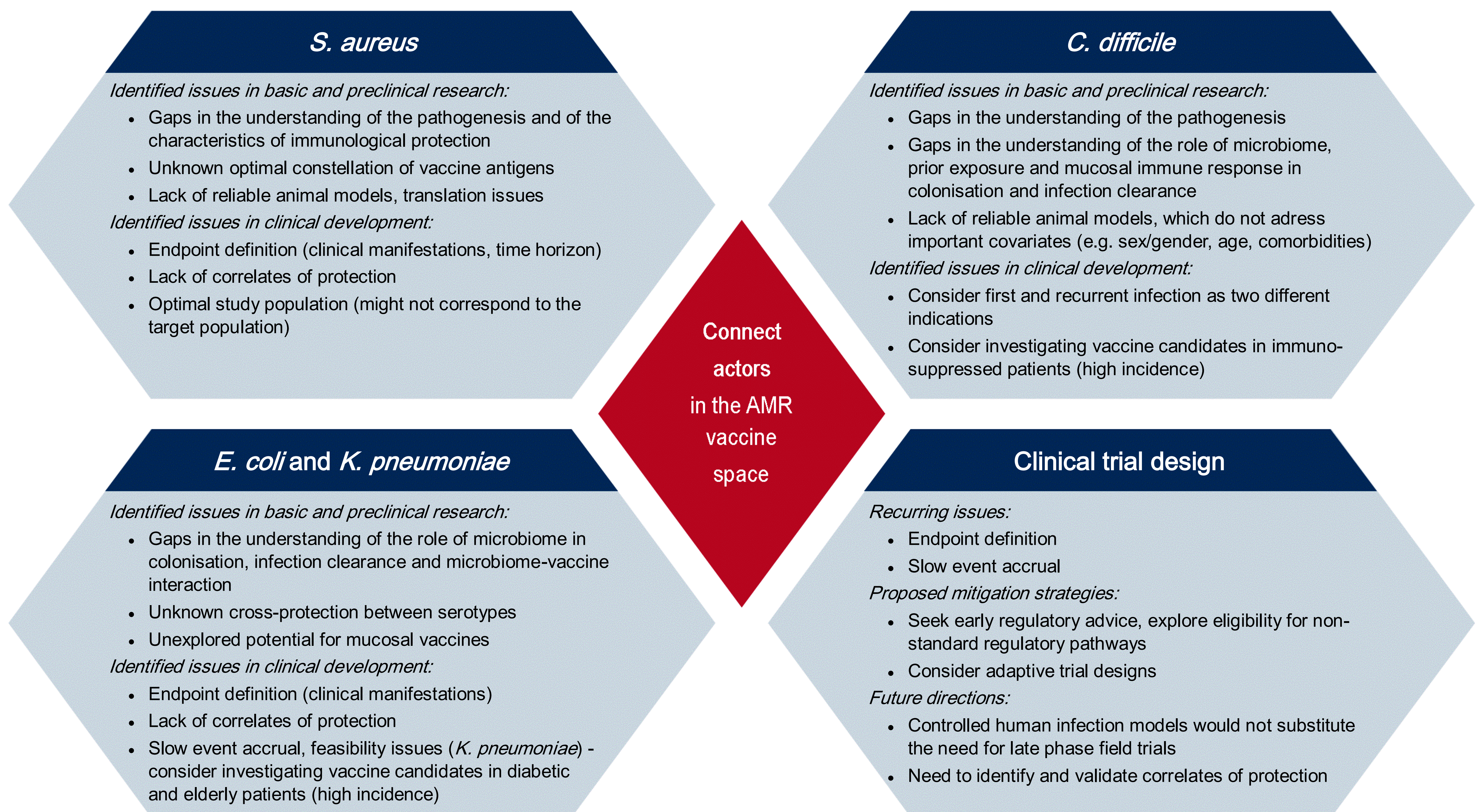
- AMR is on the rise worldwide and affects prominently ESCAPE pathogens (see box).
- Vaccines and vaccination have great potential to contain AMR.
- Several vaccine candidates against ESCAPE pathogens have been developed, but so far they have all failed to show efficacy in late stage clinical trials.
- One of the objectives of the COMBINE project, part of the IMI AMR Accelerator, is to identify factors associated with these failures and to propose improvements in translation and clinical trial design.

ESCAPE pathogens

E. faecium
S. aureus
C. difficile
A. baumannii
P. aeruginosa
Enterobacteriaceae spp.
(including *E. coli* and *K. pneumoniae*)

COMBINE Vaccine Expert Workshop: Main Messages

- The workshop brought together experts on vaccines against AMR from industry, academia, regulatory agencies and public health bodies to discuss overarching as well as pathogen-specific issues.
- The following bottlenecks in the preclinical and clinical development of vaccines against AMR pathogens were identified:
  - ► Gaps in basic knowledge: pathogenesis, role of precolonisation and microbiome, optimal target(s);
  - ► Preclinical issues: lack of reliable animal models, translation issues;
  - ► Clinical trial design: endpoint definition, lack of correlates of protection, slow event accrual and feasibility issues.

S. aureus

Identified issues in basic and preclinical research:
- Gaps in the understanding of the pathogenesis and of the characteristics of immunological protection
- Unknown optimal constellation of vaccine antigens
- Lack of reliable animal models, translation issues

Identified issues in clinical development:
- Endpoint definition (clinical manifestations, time horizon)
- Lack of correlates of protection
- Optimal study population (might not correspond to the target population)

C. difficile

Identified issues in basic and preclinical research:
- Gaps in the understanding of the pathogenesis
- Gaps in the understanding of the role of microbiome, prior exposure and mucosal immune response in colonisation and infection clearance
- Lack of reliable animal models, which do not adress important covariates (e.g. sex/gender, age, comorbidities)

Identified issues in clinical development:
- Consider first and recurrent infection as two different indications
- Consider investigating vaccine candidates in immuno-suppressed patients (high incidence)

Connect actors in the AMR vaccine space

E. coli and K. pneumoniae

Identified issues in basic and preclinical research:
- Gaps in the understanding of the role of microbiome in colonisation, infection clearance and microbiome-vaccine interaction
- Unknown cross-protection between serotypes
- Unexplored potential for mucosal vaccines

Identified issues in clinical development:
- Endpoint definition (clinical manifestations)
- Lack of correlates of protection
- Slow event accrual, feasibility issues (*K. pneumoniae*) - consider investigating vaccine candidates in diabetic and elderly patients (high incidence)

Clinical trial design

Recurring issues:
- Endpoint definition
- Slow event accrual

Proposed mitigation strategies:
- Seek early regulatory advice, explore eligibility for non-standard regulatory pathways
- Consider adaptive trial designs

Future directions:
- Controlled human infection models would not substitute the need for late phase field trials
- Need to identify and validate correlates of protection

About the workshop
- The workshop, hosted by the Paul-Ehrlich-Institut, took place online on the 8th and 9th February, 2021. The following sessions were organised: Introduction, Focus on *S. aureus*, Focus on *C. difficile*, Focus on *E. coli* and *K. pneumoniae*, Clinical trial design (including aspects of project management).
- The workshop was held under the Chatham House Rule, which prevents participants from disclosing the identity or the affiliation of the participants.
- Between 60 and 100 attendees participated in each session.
- The workshop organisers, on behalf of the COMBINE consortium, would like to thank the 21 experts (17 of which not affiliated with COMBINE) who participated as panelists and chairs.

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