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

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Background. Only few of the currently marketed vaccines have the potential to limit antimicrobial resistance (AMR), and no vaccines against ESCAPE pathogens are licensed. The COMBINE project, part of the IMI AMR Accelerator, aims to identify factors associated with late development failures of vaccine candidates and to improve translation and clinical trial design. In February 2021, the Paul-Ehrlich-Institut, on behalf of COMBINE, organised a two-day Vaccine Expert Workshop to collect typical problems in the development of vaccines against AMR infections.

Methods. The workshop focused on *S. aureus, C. difficile, K. pneumoniae,* extraintestinal pathogenic *E. coli* (ExPEC) and aspects of clinical trial design. Seventeen project-external chairs and speakers active in the field of vaccine research and development participated in the workshop.

Results. The experts repeatedly mentioned the gaps in our understanding of the pathogenesis of the disease, the role of pre-colonisation and the optimal targets as the greatest obstacles to pre-clinical development. The speakers pointed to the limitations of current animal models in predicting vaccine efficacy. The three most common problems hindering clinical development were the lack of robust correlates (surrogates) of protection, the uncertainties around risk factors, and the relatively low incidence of ESCAPE infections. The latter issues are particularly problematic, as they make it necessary to conduct large, often unfeasibly so, pivotal clinical trials.

Conclusions and future perspectives. COMBINE is planning an integrative, data-driven analysis in order to inspect and validate the hypotheses generated in the workshop. We are interested in investigating clinical trial design, subpopulations and endpoints across different vaccine candidates. For this scope, we are looking for efficacy and immunogenicity clinical data from completed and terminated vaccine development programs. The open data call is published on the COMBINE website (https://amr-accelerator.eu).