Exploring Challenges in Vaccine Development for ESCAPE Pathogens: A Study of Regulatory Interactions between Developers and Regulators

Igor Stojkov[1], Linda Marchioro[1], Pham Kim Hue Kästel[1], Benjamin Hofner[1], Isabelle Bekeredjian-Ding[2,3]

[1]Section Data Science and Methods, Paul-Ehrlich-Institut, Langen, Germany; [2]Division of Microbiology, Paul-Ehrlich-Institut, Langen, Germany;
[3]Institute for Medical Microbiology and Hospital Hygiene, Philipps-University Marburg, Marburg, Germany

Introduction

The European Medicines Agency (EMA) together with national regulatory agencies provide non-binding scientific advice (ScA) to medicine developers on their medicine's development plan. The goal is to assist in the generation of robust evidence for the marketing authorization of medicines.

The aim of our study is to analyze ScAs, as valuable and unique source of information, in order to identify, assess, and summarize the most prominent challenges discussed with respect to the development of vaccines against ESCAPE pathogens (*E. faecium, S. aureus, C. difficile, A. baumannii, P. aeruginosa, Enterobacteriaceae).*

The analysis is carried out within the COMBINE project, as part of the AMR Accelerator, a cluster of public-private partnership projects funded by the Innovative Medicines Initiative.

Methods

We have identified relevant EMA ScAs from the Paul-Ehrlich-Institut's internal database and developed a standardized extraction table. Two independent researchers extracted relevant information on clinical efficacy across 21 subcategories related to the main groups of primary endpoints, study population, study design, and statistical analyses. Quality, non-clinical, or safety aspects were beyond the scope of this study. This research expands the outcomes of a previous Vaccine Expert Workshop organized by the COMBINE project.

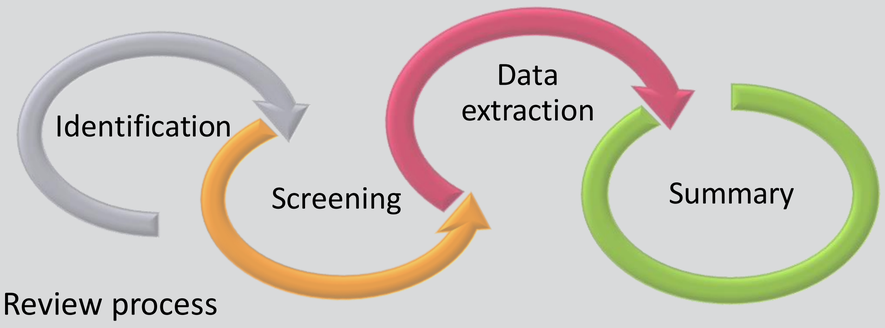

Figure 1. Review process

Preliminary Results

We identified 83 bacterial vaccine products, of which seven products, associated with four pathogens (*C. difficile, E. coli, P. aeruginosa, S. aureus*), met the inclusion criteria, containing twelve ScAs (Figure 2). From these ScAs, we categorized 123 efficacy-related questions relative to four categories and 21 subcategories. Most frequent were questions regarding the study design (41) and primary endpoint category (38), followed by study population (23) and statistical analyses category questions (21). From the subcategory questions, target vaccine efficacy and single pivotal trial questions to support marketing authorization were the most frequent ones. Frequency and level of endorsement are shown in Figure 3.

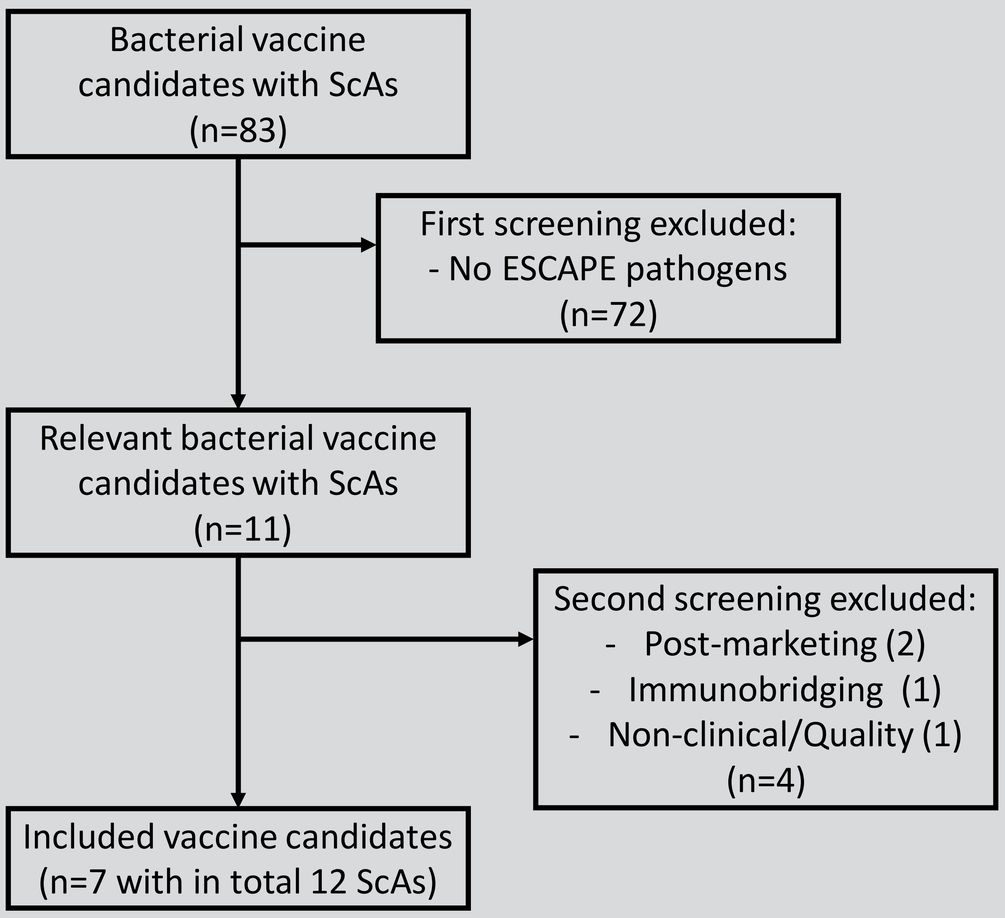

Figure 2. Flowchart of the screening process

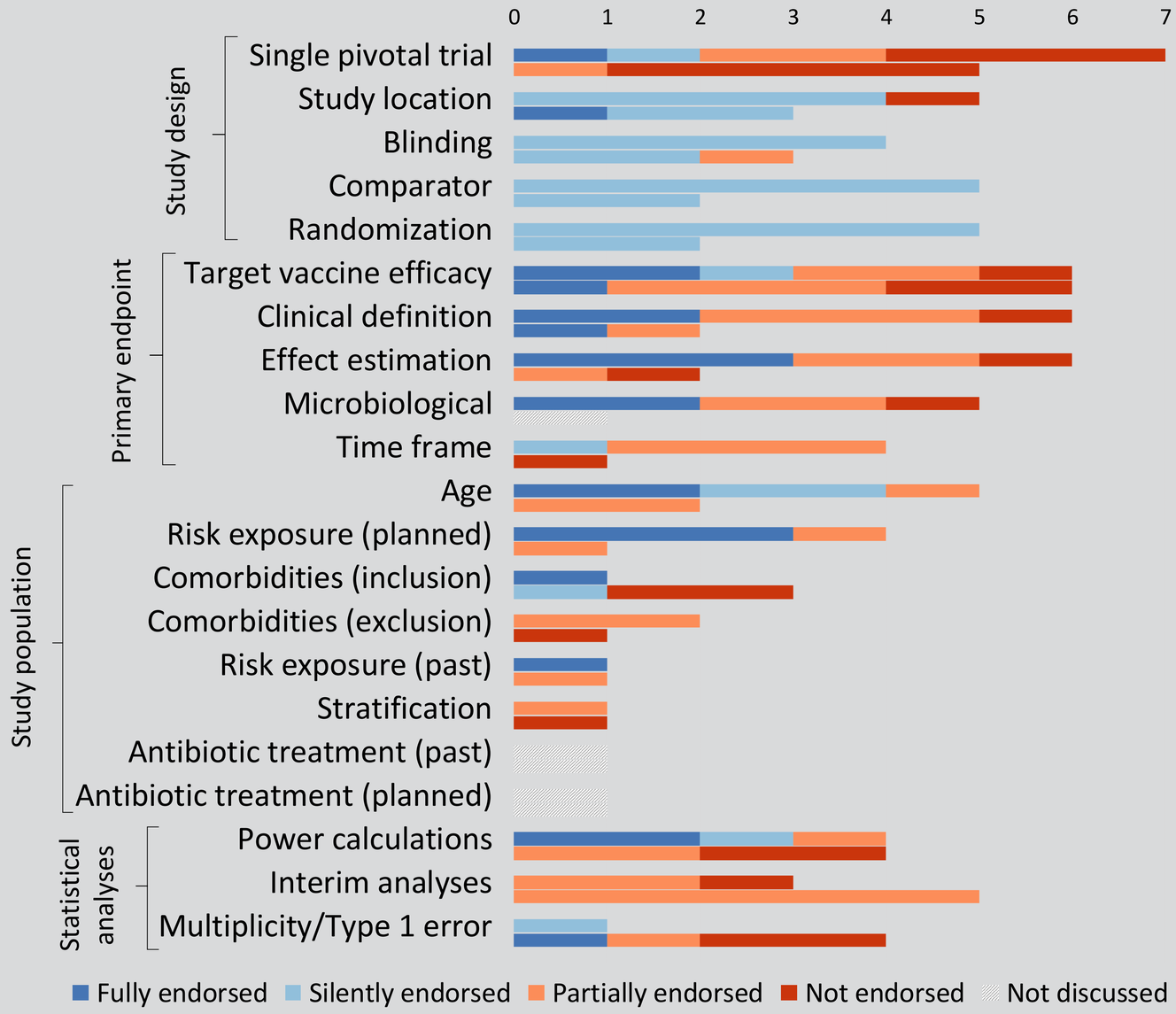

Figure 3. Questions per subcategory for initial (1st row) and follow-up (2nd row) ScAs

Conclusion

The development and availability of bacterial vaccine products targeting ESCAPE pathogens remains deficient, also visible in the low number of associated ScAs. While most of the proposed sub-categories have been addressed and supported, important aspects like past risk exposures, antibiotic interventions, or comorbidities are notably underrepresented in the initial discussions. This may result in new positions not being endorsed in later discussions about the trial requirements, vaccine efficacy, and statistical analyses.

www.imi.europa.eu

Correspondence to: IMI-COMBINE@pei.de

This project 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 companies' in kind contribution.