Assessing Regulatory Communications in Vaccine Development Against Emerging Pathogens: A Pilot Study

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Introduction

Scientific advice letters (SALs) are non-binding documents issued by regulatory agencies to medicine developers, offering guidance and recommendations to assist in the generation of robust evidence for the marketing authorization of medicines.

The aim of our study is to analyze SALs, as valuable and unique source of information, in order to identify, assess, and summarize the most prominent challenges associated with 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 (Collaboration for Prevention and Treatment of Multi-Drug Resistant Bacterial Infections) project, a public-private partnership aiming to develop new medicines for drug-resistant infections.

Methods

This pilot analysis was conducted on the SALs from the European Medicines Agency, available at the Paul-Ehrlich-Institut's database until July 2023. We extracted information on 21 key subcategories related to primary endpoints, study population, study design, and statistical analysis, which were previously identified as relevant during the COMBINE expert workshop on recurring issues in vaccine development. Information from the included SALs were extracted by two independent reviewers using pre-defined extraction tables.

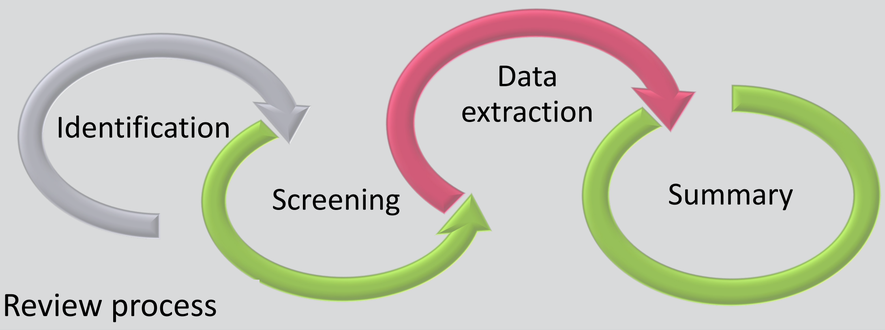

Figure 1. Review process

Preliminary Results

We identified 83 bacterial vaccine products with SALs, of which seven associated with four pathogens (*C. difficile, E. coli, P. aeruginosa, S. aureus*) met the inclusion criteria and contained twelve SALs (Figure 2). From these SALs, we categorized 124 efficacy-related questions relative to nine different phase IIb/III clinical trials. Most frequent were questions regarding the study design and primary endpoint category (41 & 39), followed by study population and statistical analysis category questions (23 & 21). From the subcategory questions, target vaccine efficacy associated with sample size calculations and single pivotal trial questions to support market access authorization were the most frequent ones. Frequency and level of endorsement are shown in Figure 3.

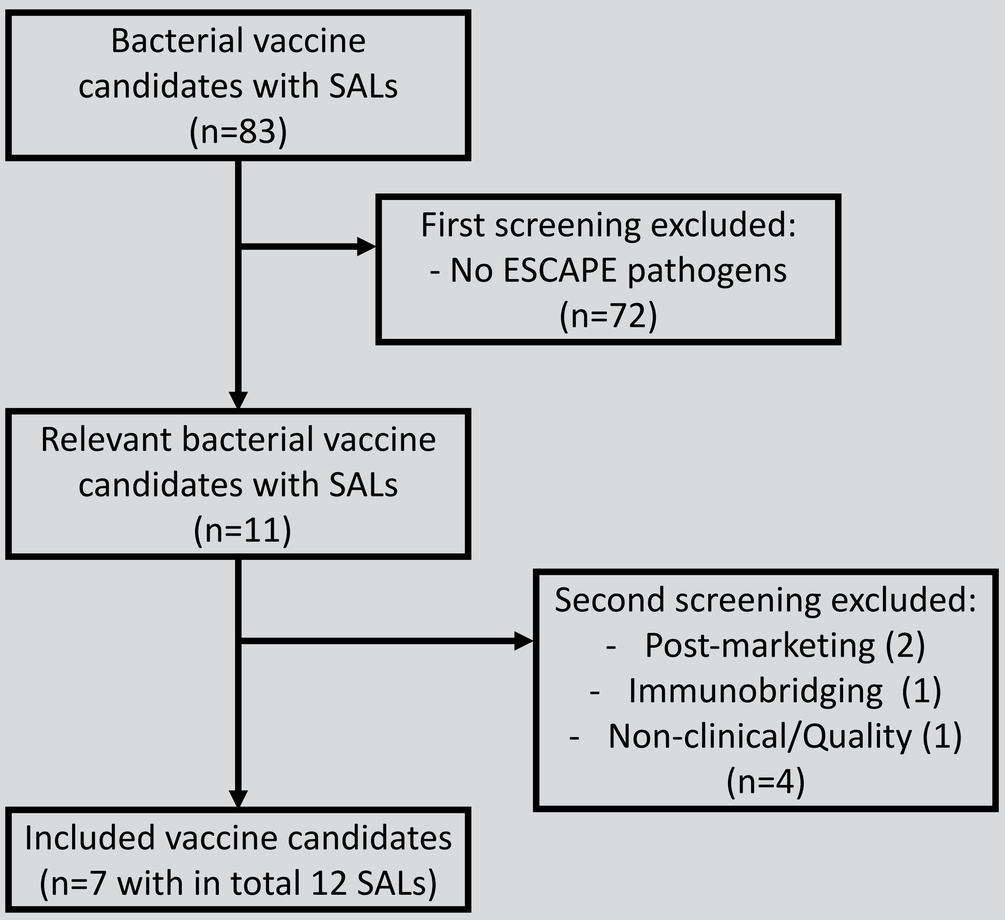

Figure 2. Flowchart of the screening process

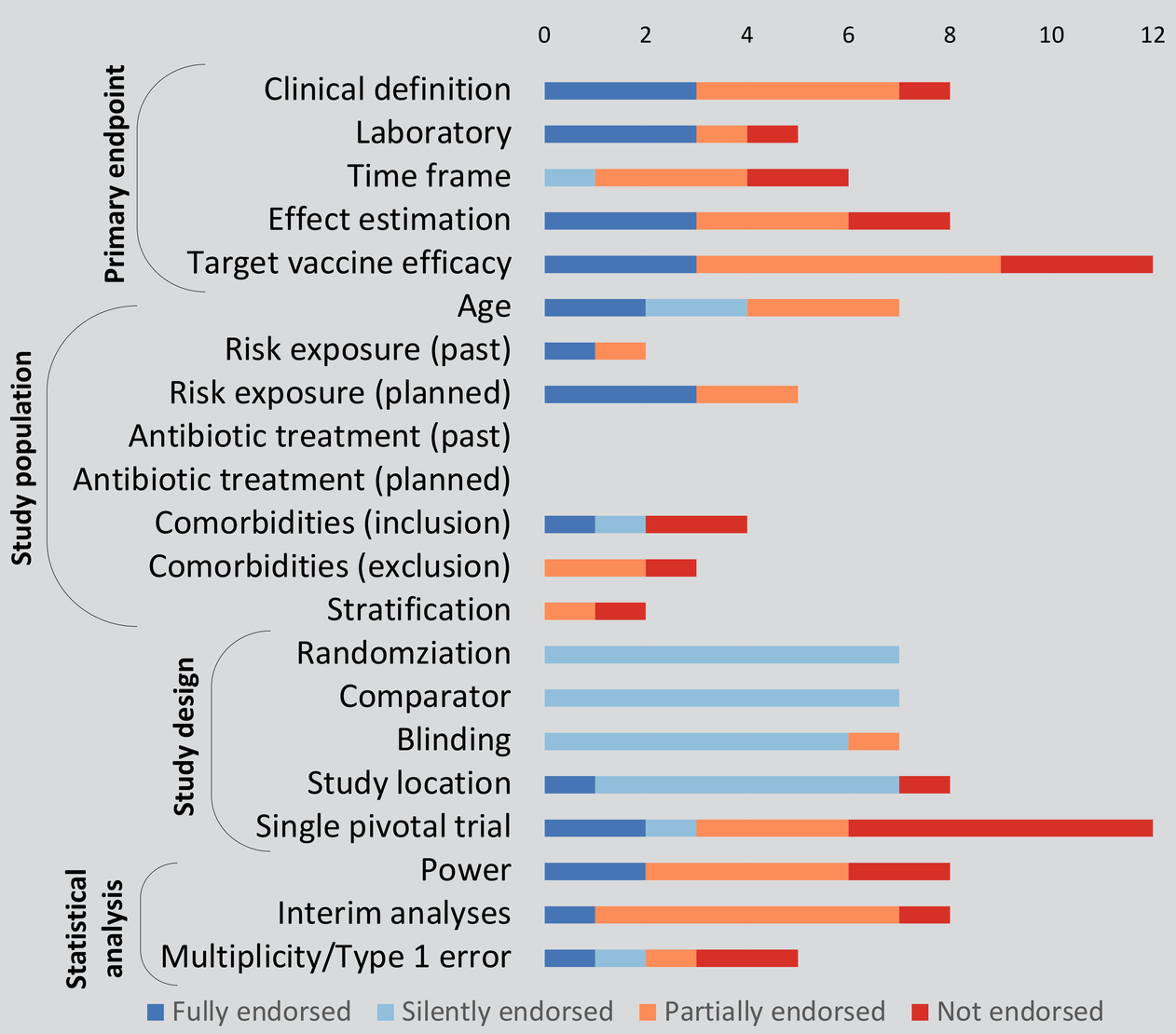

Figure 3. Number of questions per subcategory with level of endorsement

Conclusion

The development and availability of bacterial vaccine products targeting ESCAPE pathogens remains deficient, corroborated also by the low number of associated SALs. While most of the proposed sub-categories have been addressed and supported, important aspects like past risk exposures, antibiotic interventions, or comorbidities were notably underrepresented in the discussions. We plan to further study and organize the SALs and related queries in a timely manner, aiming to structurally anticipate the potential challenges.

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