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

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Introduction: The urgent need for vaccines against antibiotic-resistant ESCAPE pathogens (*E. faecium, S. aureus, C. difficile, A. baumannii, P. aeruginosa*, and *Enterobacteriaceae*) is hindered by a history of unsuccessful clinical trials, highlighting the need for a better understanding of the underlying difficulties. These challenges are often discussed between developers and EU regulators in scientific advice (ScA) procedures, which provide valuable, non-binding guidance and recommendations by the European Medicines Agency to generate robust evidence for marketing authorization. By examining these ScA procedures, our study aims to identify, assess, and summarize the main challenges encountered during the development of vaccines targeting ESCAPE pathogens.

Methods: We have identified relevant 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 analysis. Quality, non-clinical, or safety aspects are beyond the scope of this study. This research expands the outcomes of a previous Vaccine Expert Workshop organized by the COMBINE project.

Results: We identified 83 bacterial vaccine products with ScAs. Seven products, targeting four pathogens (*C. difficile, E. coli, P. aeruginosa, S. aureus*), met the inclusion criteria with a total of twelve ScAs (initial and follow-ups). From the twelve ScAs, we assessed 123 efficacy-related questions relative to nine different phase IIb/III clinical trials. Discussions regarding the study design (n= 41) and primary endpoints (n = 38) were the most frequent, followed by discussions on study population (n = 23) and statistical analysis (n = 21). From the subcategories, discussions on target vaccine efficacy associated with sample size calculations and single pivotal trial questions to support market access authorization were the most frequent ones.

Conclusion: The development and availability of bacterial vaccine products targeting ESCAPE pathogens remains deficient, with challenges in vaccine development and recurring issues that have not been appropriately discussed in ScA procedures. While proposals for most of the subcategories were made by the developers and subsequently endorsed by EMA, important aspects like previous risk exposures, antibiotic interventions, or comorbidities are notably underrepresented in the discussions.