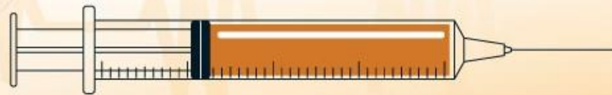

Probability of success and timelines for the development of vaccines for emerging and reemerged viral infectious diseases

Bibliography

MacPherson A, Hutchinson N, Schneider O, et al. *Probability of Success and Timelines for the Development of Vaccines for Emerging and Reemerged Viral Infectious Diseases*. Ann Intern Med. 2020;174(3):326-334. doi:10.7326/M20-5350.

Critical Opinion

This study is methodologically rigorous and offers a sobering counterpoint to politically optimistic vaccine development promises, particularly those made early in the COVID19 pandemic. Its strength lies in relying exclusively on public, non-proprietary data, ensuring transparency and reproducibility. However, because the dataset heavily features influenza and HIV vaccines—fields with unique developmental dynamics—the aggregate probability of success (POS) may underestimate or overestimate prospects for other pathogens. A more substantive limitation is the manuscript's focus on FDA approvals, which excludes vaccines licensed elsewhere (e.g., in Europe, China or India). The U.S. centric outcome measure unintentionally conflates scientific failure with jurisdictional regulatory pathways. Moreover, while the authors acknowledge preclinical and manufacturing timelines, their exclusion likely understates the full developmental burden. Nonetheless, the article succeeds in illustrating the structural barriers that have long constrained vaccine innovation and provides an invaluable empirical baseline against which the extraordinary speed of COVID19 vaccine development can be contextualized.

Summary

MacPherson et al. present one of the most comprehensive empirical assessments to date of clinical development outcomes for vaccines targeting emerging and reemerging viral infectious diseases (EVIDs). Motivated by the uncertainty surrounding COVID19 vaccine development timelines in 2020, the authors evaluate success probabilities and development durations across 23 viral diseases using publicly available data from ClinicalTrials.gov, WHO databases, FDA records, and supplementary literature. Their core objective is to estimate the likelihood that a vaccine entering phase 2 trials will achieve FDA licensure within ten years, offering a realistic benchmark against which pandemic era expectations can be measured.

The authors identify 606 eligible clinical trials representing 220 distinct development "trajectories" initiated between 2005 and March 2020. Only 76 of these trajectories advanced beyond phase 1 and were therefore included in the primary probability of success (POS) analysis. The results reveal starkly modest success rates: just 10% of vaccine candidates entering phase 2 achieved FDA approval within the subsequent decade. When influenza vaccines—beneficiaries of mature platforms—are excluded, the probability drops to 3.2%, underscoring the substantial difficulty of bringing non-influenza viral vaccines to market.

Timelines are similarly long and variable. Among approved vaccines, the average time from phase 2 initiation to FDA approval was 4.4 years, with outliers ranging from six weeks (rapid

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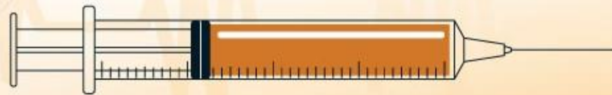

approvals of H1N1 pandemic vaccines) to nearly 14 years (the H5N1 vaccine Audenz). The study identifies only nine approvals among the 220 trajectories, most of which were pandemic influenza vaccines, along with Ervebo (Ebola) and Dengvaxia (dengue). These findings reinforce that regulatory licensure represents only a narrow apex in a wide pyramid of failures, attrition, and stalled development.

Phase transition probabilities offer additional insight: 38.2% of phase 1 candidates advanced to phase 2, 38.3% of phase 2 candidates advanced to phase 3, and 61.1% of phase 3 candidates ultimately obtained approval. Even so, the absolute number of vaccines approaching licensure remained small. A sensitivity analysis examined whether discontinuations coincided with "outbreak quelling"—periods in which disease incidence fell to zero for twelve months. Although roughly oneq uarter of failed trajectories ended during such quiescent periods, overall, POS changed minimally when these were excluded. This suggests that biological, technical, commercial, and logistical hurdles—not merely diminishing disease incidence—explain most vaccine failures.

The study's stratified analyses reveal substantial heterogeneity across vaccine types. Split-virus influenza vaccines had by far the highest success probability (56.4%), reflecting their reliance on well established production platforms. Nucleic acid vaccines—representing early predecessors to mRNA COVID19 vaccines—showed a low but nonzero approval probability (5.9%). Whole pathogen and subunit vaccines in this dataset failed to produce a single FDA approval within ten years of phase 2 initiation. Sponsorship also mattered: trajectories involving large pharmaceutical companies exhibited considerably higher success probabilities (30.5%) than those led by government, small companies, or philanthropic organizations.

MacPherson et al. emphasize that their POS estimates represent historically observed rates, not forecasting tools for COVID19 development. Nonetheless, their findings highlight why expectations for pandemic speed vaccine development should be tempered by an appreciation of systemic obstacles. Most EVIDs lack the robust scientific groundwork, prior vaccine platforms, or strong commercial incentives that supported the historically accelerated development of pandemic influenza vaccines. Furthermore, the biological novelty of pathogens like SARSCoV2 compounds uncertainty, particularly concerning immune responses, safety risks such as vaccine dependent enhancement, and the performance of novel platforms like mRNA and viral vectors.

The authors also note that global collaboration, unprecedented funding, and parallelized clinical trial phases may accelerate pandemic-era vaccine development beyond historical norms. Even so, foundational limitations remain: regulatory requirements for safety, the time needed to accrue trial endpoints, and the high attrition intrinsic to immunobiology.

Brought to you by Assistant Editor ***Dr. Mohammad Daniel Nikdel*** *- Supported by AI*

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