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Sustainable vaccine development: a vaccine manufacturer's perspective

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Vaccination remains the most cost-effective public health intervention after clean water, and the benefits impressively outweigh the costs. The efforts needed to fulfill the steadily growing demands for next-generation and novel vaccines designed for emerging pathogens and new indications are only realizable in a sustainable business model. Vaccine development can be fast-tracked through strengthening international collaborations, and the continuous innovation of technologies to accelerate their design, development, and manufacturing. However, these processes should be supported by a balanced project portfolio, and by managing sustainable vaccine procurement strategies for different types of markets. Collectively this will allow a gradual shift to a more streamlined and profitable vaccine production, which can significantly contribute to the worldwide effort to shape global health.

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Introduction

Vaccination remains one of the most cost-effective public health interventions to address the world-wide health economic (HE) burden associated with infectious diseases. Indeed, for every US$ 1 spent on vaccination against diseases associated with 10 antigens in low-income and middle-income countries (LMICs), the estimated return on investment for society is US$16 due to direct savings on healthcare and increased productivity, and nearly three times higher (US$44) when broader economic and social benefits are considered [1••]. From 2001 to 2020, the broader benefits could amount to a staggering US$ 820 billion in the 73 countries supported by the Global Alliance for Vaccines and Immunization (GAVI) [2], a public–private partnership (PPP) involving amongst others the UN, the vaccine industry and the Bill and Melinda Gates Foundation (BMGF). Due to the higher disease burden and more limited medical infrastructure, the HE gain from introducing a vaccine in LMICs will be greater than in higher-income countries (HICs), where the gain will largely be determined by competition between the different health options on offer [3].

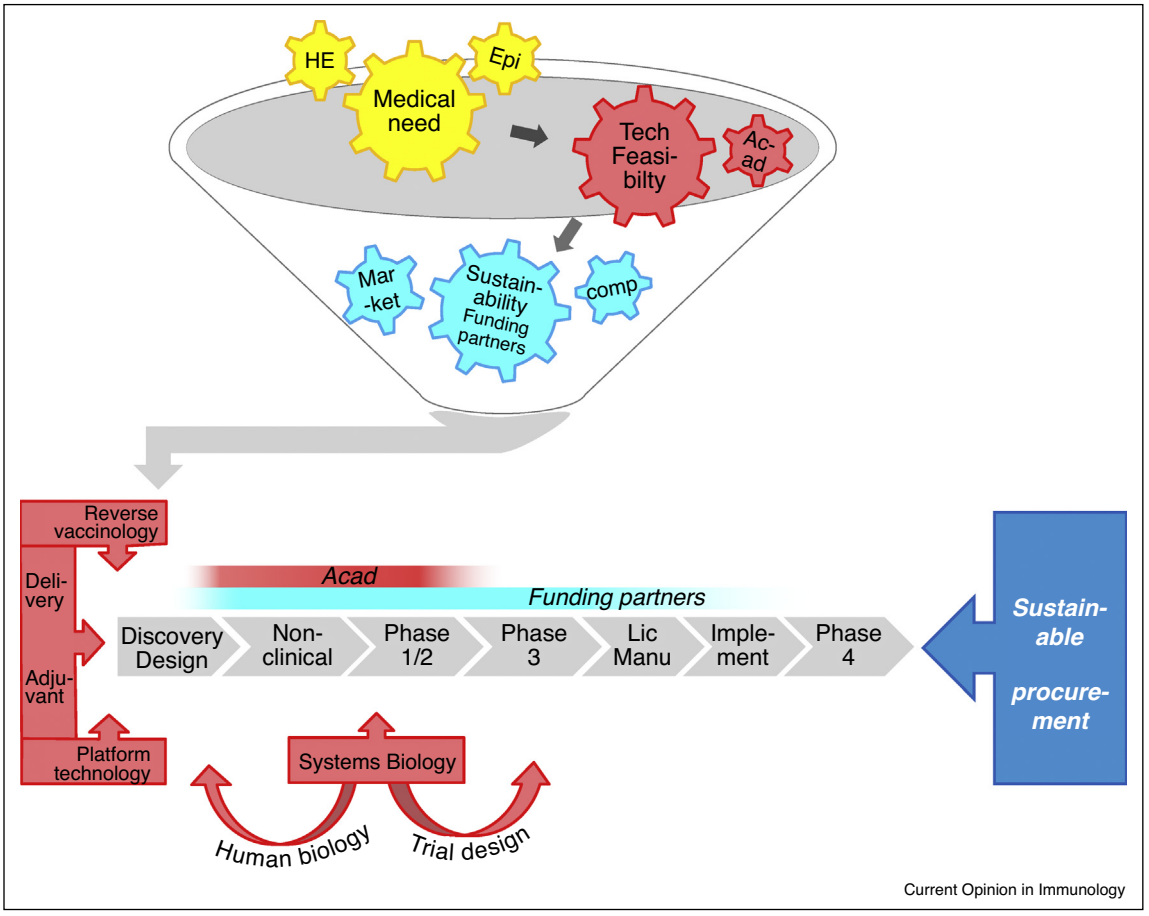
The global demand for vaccines is growing due to a host of factors, such as global population growth, future implementation of newly licensed or advanced-stage vaccines into health-care systems, and ongoing global immunization campaigns. The latter is illustrated by GAVI's aim to reach an additional 300 million children for routine childhood vaccination by 2020. Also, the pressure is mounting to deliver improved or new vaccines against challenging infectious diseases (e.g. tuberculosis, HIV/AIDS), new zoonotic pathogens, and therapeutic vaccines against non-communicable chronic diseases such as cancer and neurodegenerative diseases. They are also needed to address the scourge of antibiotic-resistant bacteria [4] and the varying vaccine needs across a person's life-span (vaccine 'life-cycle management to support life-course immunization' [5]).

To meet the increasing demands, there is a continuous quest for innovation of vaccine design and manufacturing technologies. Traditionally, the multiphase vaccine development process, which typically progresses over a 10–15-year period from vaccine discovery to advanced clinical development in Phase 3 efficacy trials, can require investments of US$ 0.5–1 billion [6–8]. This, combined with the slim (<10%) probability of candidates to enter the market, has negatively impacted the number of investing vaccine manufacturers and has contributed to the current productivity gap in vaccine development. The selection criteria supporting prioritization of a vaccine project must therefore be increasingly stringent. Here we discuss the key considerations in this decision-making process from a vaccine manufacturer's perspective.

Toward sustainable vaccine development

Medical need is a key factor for project prioritization, as illustrated by the spurred development of vaccines against the globally emerging threat posed by *Clostridium difficile* infections, or by the accelerated clinical development periods during the devastating Ebola crisis in West Africa in 2014, which for some vaccines could be

Figure 1



Sustainable vaccine development and collaborations. *Funnel*: Guiding criteria for vaccine project prioritization are, first, the unmet medical need, as supported by health-economical ('HE') and epidemiological ('Epi') evaluations; second, technical feasibility, often benefitting from partnerships with academia ('Acad'), and third, the sustainability of its development, which depends on the availability of funding partners for collaborative development, as well as on the competitive landscape ('comp') and the economic development status of the market for which the vaccine is intended ('Market'). While the development of vaccines with a market that includes high-income countries is often predominantly industry-funded, trials evaluating vaccines for predominantly low-to-middle-income markets, or prepandemic vaccines, are typically co-funded by public–private partnerships including industry, governments and international non-governmental organizations. *Bars*: Red and blue bars indicate the development stages typically benefitting from involvement/support by academia and international funding organizations, respectively. Academic partners mostly contribute by providing immunological insights in late preclinical and Phase 1/2 clinical phases. Funding partners can provide support throughout the whole process, including the licensing ('Lic') phase, and the post-licensing phases comprising vaccine manufacturing ('Manu') and implementation ('Implement'), for example the supply chain management support provided by the public–private partnership (mVacciNation). Post-marketing Phase 4 studies monitoring vaccine usage, adverse effects (pharmacovigilance), and long-term immunity are typically industry-funded. Red arrowed bars indicate the technologies used to guide antigen discovery and/or vaccine design (reverse vaccinology, delivery, adjuvants and platform technologies), while systems biology data, often generated in industry-academic partnerships, can guide during the discovery phase, as well as in later clinical phases, by supporting adaptive trial designs to expedite progression to Phase 3 clinical evaluations. Finally, strategies to manage the sustainable procurement of new vaccines, such as tiered pricing policies, will also majorly drive the vaccine development process.

shortened to less than a year. In the prevailing business model, other key guiding criteria are the technical feasibility, as well as the expected return on investment. The latter is largely determined by competitive landscape analyses, and is dependent of the economic development status of the market in question (Figure 1). To nurture and sustain the R&D processes, manufacturers' business strategies will strive to maintain a project portfolio that is balanced between projects offering a solid business case, and higher-risk, longer-term and/or lower-feasibility projects. The considerable financial risks inherent to the latter category, combined with a pressing immediate need or expected future medical need, has been prompting industry to seek strategic funding partners such as governments and/or non-profit international vaccination foundations. Indeed, nearly every vaccine available in resource-poor settings today has been developed through combinations of public and private efforts. Underpinning