The sharpest tool in the shed: question-based clinical development of vaccines to address global health priorities

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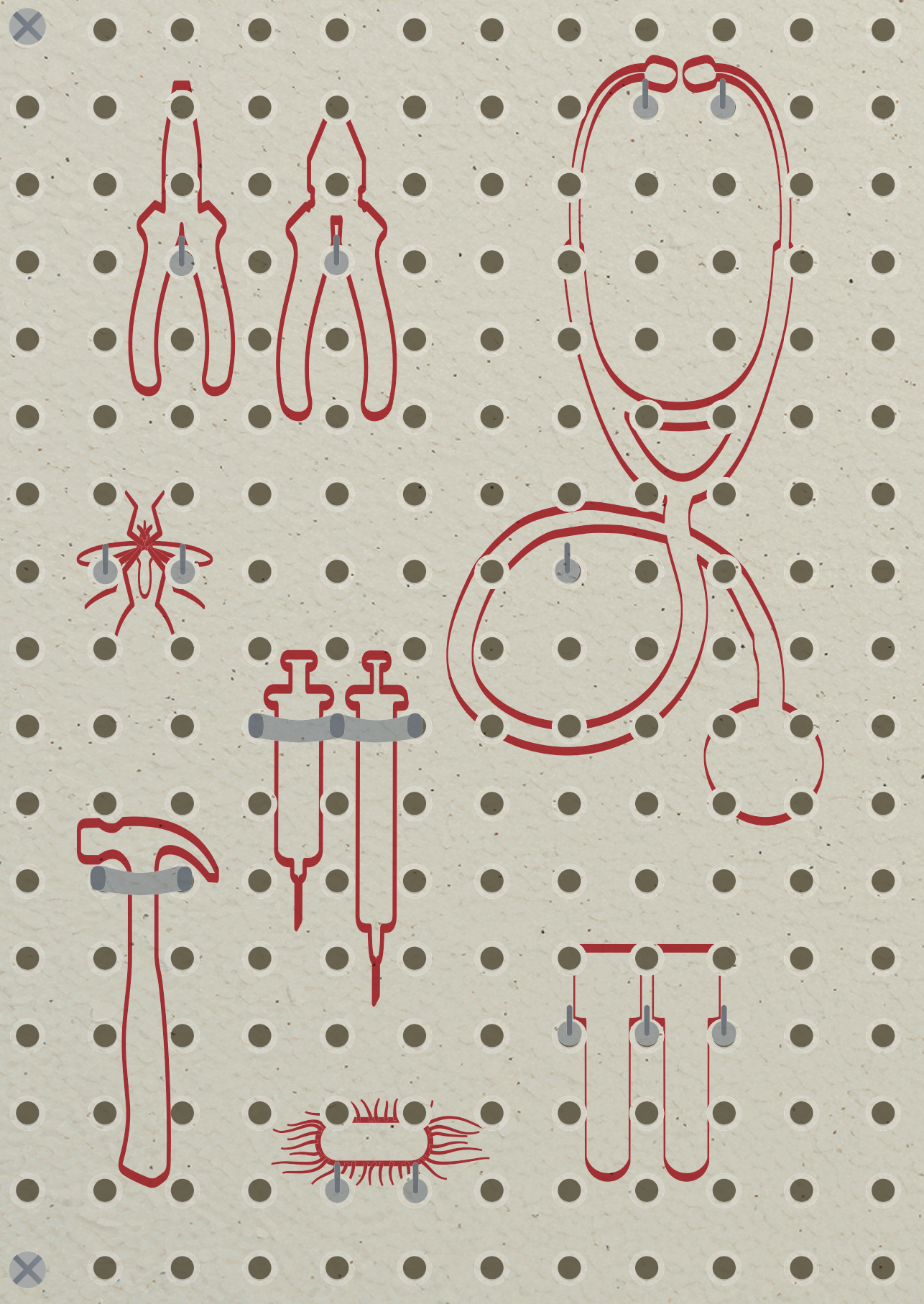

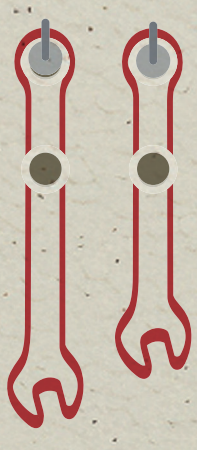

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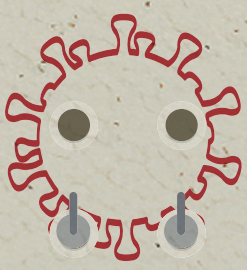
General Introduction



Infectious diseases have been the predominant cause of death throughout human history.[1] Epidemics have decimated ancient civilizations[2], and in many wars, more people died of infections than by bullets or bombs.[3] In 2021, more than twice as many people died from an infectious disease like malaria (1.1% of the global population) as all deaths from conflicts (0.14%), natural disasters (0.0014%), and malnutrition (0.32%) combined.[4]

Vaccines have played a significant role in the global fight against infectious diseases in recent decades. In 1974, the World Health Organization (WHO) introduced the Expanded Program on Immunization (EPI) to make life-saving vaccines available to the entire world population. Since the introduction of EPI, vaccination has averted an estimated 154 million deaths, including 146 million among children below the age of five.[5] Since vaccines have an immense potential to positively impact global health, developing new vaccines is a top scientific priority.

The most critical vaccines to develop or improve are those with the greatest potential to prevent mortality and safe life years on a global scale, as they offer the highest impact on global health (Fig. 1).[6] Two important scenarios where high-impact vaccine are especially needed include:

1. A poorly contained infectious disease with high mortality in a low-resource setting: developing a vaccine for a disease that currently lacks preventive measures or effective containment, can have a substantial positive impact. This scenario is more likely to occur in low- and middle-income countries (LMICs) where healthcare systems may struggle to provide adequate treatment, elevating mortality rates of a disease which increases the importance of preventive vaccines;
2. An outbreak of a novel pathogen: in case of an epi- or pandemic in a population with limited or no pre-existing immunity, introducing a new and effective vaccine can dramatically reduce the disease's impact.

Both scenarios present distinct challenges regarding vaccine development and implementation. Commercial vaccine developers typically allocate more resources to developing vaccines with higher revenue potential, resulting in limited funding for vaccines targeting diseases that predominantly burden low-resource settings. Additionally, in the case of a pandemic vaccine, there will always be a scarcity of vaccine doses at its moment of introduction, complicating the availability and distribution of the novel vaccine.

Challenges for the development and implementation of new high-impact vaccines are multifaceted and complex, encompassing not only scientific but also societal, economic, and logistical dimensions. Addressing them requires collaboration and insights from policymakers and industry stakeholders. Nonetheless, scientists in non-commercial institutions can also play an import role in developing these new vaccines. Certain biomedical and scientific aspects can be addressed by designing and conducting optimized clinical trials initiated by academia or other not-for-profit research organizations. Such trials can focus on facilitating the

advancement of vaccine development and implementation, even when resources are limited. In this thesis, some of the most pressing challenges associated with vaccine development will be addressed and an evaluation will be made on how publicly initiated clinical trials can contribute to overcoming them.

The next section will begin with a brief description on how pharmaceutical companies generally manage clinical vaccine research, followed by an exploration of a new approach to clinical development. This approach will then be assessed for its potential to support publicly funded researchers in advancing vaccine development that holds significant global health relevance. In subsequent sections, reasons for the typical underfunding of this research by commercial vaccine producers will be discussed, along with ways in which academia and other non-commercial organizations can help to fill this gap.

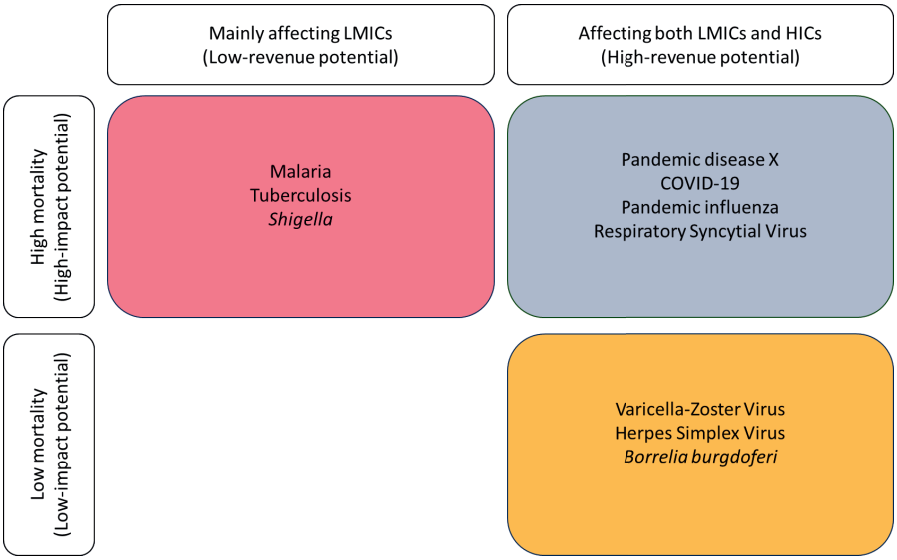


Figure 1. High-impact potential versus high-revenue potential

Vaccines targeting diseases with a high disease burden, do not necessarily have a high-revenue potential. Non-commercial organizations should strive to address vaccine development for these diseases, as they may be of less interest to the pharmaceutical industry.

Clinical vaccine development

Conventionally, new potential drugs, including vaccines, identified during preclinical development undergo three phases of clinical trials. In Phase I, approximately 10 to 100 participants receive the new vaccine, with several doses tested based on preclinical animal studies. The primary objective of Phase I is to assess safety and dosage. In Phase II, about 50 to 500 individuals are vaccinated to evaluate immunogenicity and tolerability. This phase may involve testing two or three dosing regimens and may include specific target groups, such as

older adults or minors. Phase III trials aim to gather the majority of safety and efficacy data, typically involving 1000 to 10 000 participants, depending on the disease's incidence and transmission rates. Generally, only one dose, dosing regimen, or route of administration is assessed in Phase III.

Clinical trials are expensive, particularly Phase III trials. As a candidate vaccine progresses through clinical development, the number of participants increases, leading to longer processing times and requiring a larger staff to conduct the trials, which further escalates costs. Although trial expenses can vary substantially depending on the setting, the disease and the product being tested, Phase I trials cost around $3 million, while Phase III trials can reach $20 to $75 million.[7] Consequently, only major pharmaceutical companies generally have the resources to conduct these large clinical trials necessary for market approval of a candidate vaccines.

A major downside of the three-phases paradigm is that that it does not take the specific properties of a candidate drug and the target disease into account. This increases the risk of advancing candidate drugs with low potential into late-phase development. As an alternative, the Question-Based Clinical Development (QBCD) method has been proposed.[8] Rather than rigidly adhering to the three standard phases of clinical development, QBCD proposes the identification of so-called key questions that are essential for the specific drug being developed, drawing from, but not limited to, the five general QBCD questions:

1. Does the biologically active compound reach the site of action?
2. Does the compound produce its intended pharmacological effect?
3. Does the compound have beneficial effects on the disease or its pathophysiology?
4. What is the therapeutic window of the new drug?
5. How do the sources of variability in drug response within the target population affect product development?

Taking these scientific key questions into account, the QBCD method evaluates them together with development risks and financial considerations to determine the optimal development path for the new drug.[8] In QBCD, clinical trials are not designed to follow the three phases, but to answer key questions in the most effective order.

QBCD does not bypass the need for a clinical trial evaluating efficacy and safety in a large population. However, it does help answer the questions resulting from the specific biomedical properties of the vaccine, the target disease, and the target population. Having these insights early in the research process, accelerates vaccine development and reduces vaccine development costs. When a well-designed clinical trial already reveals significant flaws in a candidate vaccine early in the development process, costly and unsuccessful trials later on can be prevented. This so-called fail-fast principle ensures efficient funding allocation to candidate vaccines with highest potential for success.

While the three-phase paradigm primarily focuses on advancing a candidate vaccine from early-phase clinical trials to market approval, QBCD better allows for the identification of key questions that are relevant for global health and equitable vaccine access. Therefore, QBCD is particularly well-suited for academia or other non-commercial organizations aiming to contribute to the development or improvement of high-impact vaccines. Even with limited funding, these institutions can use QBCD to initiate non-commercial research that expedites the development of high-impact vaccines and enhances vaccine equity and accessibility by identifying and answering key questions.

The next two sections aim to identify relevant key questions for publicly initiated development of high-impact vaccines. First, challenges for vaccine development for diseases predominantly prevalent in LMICs will be evaluated. This includes outlining financial and immunological challenges and pinpointing knowledge gaps that can be addressed by non-commercial research. Second, challenges for vaccine dose-finding and optimization during a pandemic will be discussed. This section will explain how publicly initiated research can address these key questions, especially those that are not addressed by vaccine produces, even after a vaccine has received market approval.

Vaccine development for low- and middle-income countries

Limited vaccine research is conducted in LMICs, and much of it is led by external stakeholders. In 1990 the term "90/10 gap" was introduced to highlight that less than 10% of global research funding was allocated to health issues prevalent in LMICs, even though these countries bear over 90% of the global burden of preventable mortality.[9] Although the nature of the 90/10 gap has changed, a large inequality in research funding persists to this day (Fig. 2). Diseases with low morbidity but a high revenue potential in high-income countries (HICs) receive disproportionately more funding, while research into diseases that impose a high global burden remains severely underfunded.[9]

Historically, most vaccines were developed for a dual market, where profits would be maximized by selling at high prices in HICs, enabling pharmaceutical companies to offer the same vaccines for a lower price in LMICs.[10] However, this model fails for vaccines targeting diseases predominantly affecting LMICs. Pharmaceutical companies in HICs are often reluctant to invest in these vaccines due to their limited revenue potential. As a result, manufacturers from LMICs started to enter the market in the 1980s.[10] These manufacturers, united in the Developing Countries Vaccine Manufacturers Network (DCVMN), generate their income through the high-volume sale of low-cost vaccines in LMICs, rather than through high-margin sales in HICs.[11] Although DCVMN members now represent 18% of the vaccine market by volume, their share in revenue remains only 5% (and even 49% and 6%, respectively, when excluding COVID-19 vaccines).[12] This high-volume, low-revenue business model substantially limits DCMVN members to invest in product innovation, resulting in less vaccine research aimed at LMIC populations. Of the 94 vaccines and biologicals that got market approval between 2000 and 2011, only eight were directed at diseases affecting populations in low-income countries, and

only 1% of the clinical trials in 2011 were researching these diseases.[13] In the entire period from 2012 to 2018, only one vaccine for a disease mainly affecting low-resource settings got market approval.[14]

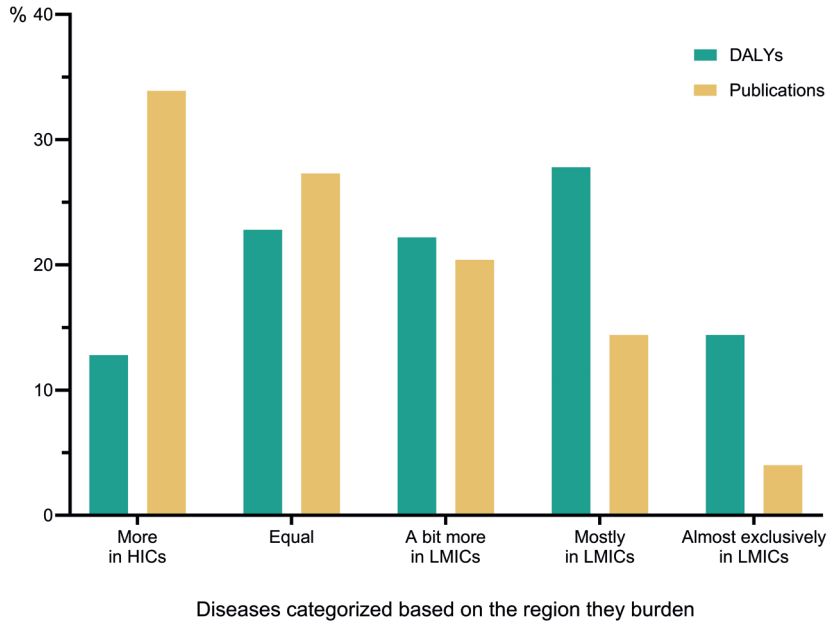


Figure 2. Global disease burden (DALYs) in relation to global research output (scientific publications)

The nature of the 90/10 gap has changed but a large inequality still exists. Globally, 34% of research addresses diseases that cause more burden in HICs, while causing only 13% of the global burden. Vice versa, only 4% of research focusses on diseases that exclusively burden LMICs, but attribute to 14% of the global burden.

DALY = disability-adjusted life year, HIC = high-income country, LMICs = low-and-middle-income countries.

Figure based on data from: Yegros-Yegros A, van de Klippe W, Abad-Garcia MF, et al. Exploring why global health needs are unmet by research efforts: the potential influences of geography, industry and publication incentives. Health Research Policy and Systems. 2020;18(1):47.

Given that the vaccine market incentivizes the development for HICs, there exists a gap in vaccine development for low-resource settings. Until LMICs establish the capacity to develop their own vaccines, (semi-)public institutions funded by HICs (and upper-middle income countries) should strive to compensate this unbalance. To use their funding optimally, these institutions must focus on identifying the right key questions that will help design trials that enable fast failure of vaccine candidates with low potential and accelerate the development of those with high potential.

An additional difficulty resulting from the fact that most vaccines are developed in and for HICs is vaccine hyporesponsiveness: lower performance of vaccines in specific populations. For

example, the BCG vaccine and vaccines targeting yellow fever virus, Ebola virus, and rotavirus are known to induce lesser immune responses in populations from LMICs than in populations in HICs.[15] Although genetic differences play a role here, about 70% of the hyporesponsiveness is thought to be caused by environmental factors such as differences in food intake, microbiome and exposure to different micro-organisms and parasites.[15]

Key question 5 of QBCD ("How do the sources of variability in drug response within the target population affect product development?") encourages vaccine developers to address the issue of hyporesponsiveness. Evaluating varying doses of different antigen and adjuvant combinations to determine the most immunogenic options is typically conducted early in clinical development. If a vaccine targets a disease in LMICs, but these initial developmental decisions are solely based on trials in HIC populations, it risks suboptimal performance in its intended population. For this reason, tailoring vaccines to LMIC populations early on is crucial. While regulatory or risk considerations may sometimes necessitate initial trials in HICs (especially if the vaccine has been developed there), moving vaccine development to LMICs as early as possible will lead to better vaccine development.

Beyond addressing hyporesponsiveness, numerous other key questions can be formulated regarding vaccine properties specifically relevant for LMICs. Examples are improved storage stability, and reduced production costs, and easier administration methods. To further tailor new vaccines to LMICs needs, expanding local scientific capacity and strengthened local regulatory and ethical oversight in LMICs are essential. This would support the conduct of high-quality clinical trials and allow for context-specific research by local scientists. Despite considerable progress, continued support from international academic and public initiatives, aided by global health organizations, can further advance infrastructure and training for local scientists and regulators.[16] Increased scientific capacity would empower local researchers to initiate non-commercial research that aligns vaccine development with local needs.

Part I of this thesis will discuss two trials that aim to contribute to addressing key questions on vaccine development for LMICs.

Dose optimization during a pandemic

With the majority of the world population living in cities, the ever-increasing number of international flights, and the proximity in which high numbers of people and livestock live together, it is inevitable that new epidemics, and potentially pandemics, will arise, albeit hard to predict when and where they will strike. The COVID-19 pandemic has shown that we now have more tools than ever to respond to emerging infectious diseases quickly: the new mRNA and viral vector vaccines (together with established technologies like protein vaccines) have proven very effective for the rapid development of vaccines that have saved an estimated 14 million lives in the first year after their introduction alone.[17] The pandemic showed that when Phase I, II, and III studies run overlapping, regulatory authorities conduct their reviews as soon as new evidence comes in ("rolling review"), and large-scale production of new vaccines starts

before approval (with the financial risks covered by governments), pharmaceutical companies can develop, market and mass produce new vaccines in about two years, instead of the usual 10-plus year process.[18-21]

When developing a vaccine, it is challenging to determine the most fit dose. Generally, developers have information on toxicity and immunogenicity in animal models and extrapolate this, with a safety margin, to a first-in-human dose for the Phase I trial. Then, the dose is escalated until the maximum tolerated dose has been identified. Based on these results, two or three candidate doses are selected for Phase II. Based on Phase II results, the most immunogenic dose that is still tolerable is chosen for Phase III.

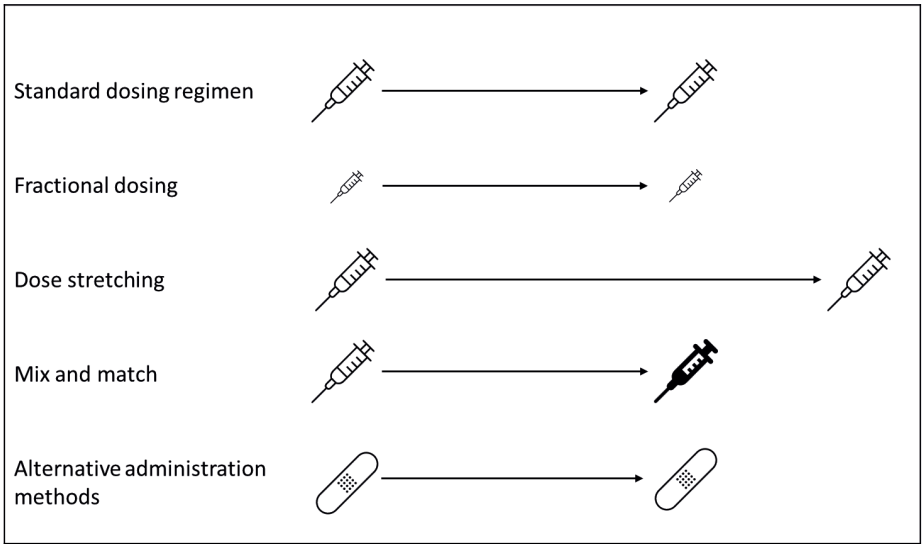


Figure 3. Different strategies for dose optimization

Although this is the fastest method to identify a tolerable and effective dose, it often results in a dose that exceeds the minimally required amount to elicit sufficient immune levels to prevent most morbidity and mortality on a population level. For optimal future vaccine implementation, it is essential to gather additional information on strategies that enhance vaccine availability ("dose sparing"), such as the reducing vaccine doses ("fractional dosing"), extending intervals between doses ("dose stretching"), employing alternative administration methods (e.g. intradermal delivery), and adopting immunization regimens that combine different types of vaccines ("mix and match") (Fig. 3). Addressing these additional key questions on dose optimization is usually not a priority for vaccine manufacturers, as it requires additional trials that are not strictly necessary for market approval. Since clinical development costs typically contribute more to vaccine production expenses than the costs of raw materials[22], there is often little commercial incentive to incorporate elaborate dose optimization in the standard development process. However, such efforts can be very valuable

for society as a whole. Determining the minimal dose required to provide sufficient protection against a novel pathogen is particularly relevant in the context of a pandemic, when vaccine shortages will inevitably occur. From a global health perspective, rapidly increasing herd immunity with lower doses in a larger population is preferable to inducing higher immunity in a smaller group of people.

Part II of this thesis will discuss publicly initiated clinical trials that addressed these issues on vaccine dose-optimization during the COVID-19 pandemic. Other examples of key questions regarding pandemic vaccines that are important for society as a whole, but are not profitable and therefore not addressed by industry, will also be discussed.

Outline

Part I (**Chapter 2** and **Chapter 3**) will discuss trials for developing vaccines for diseases with a (primary) target population of children in LMICs, particularly malaria and shigellosis. **Chapter 2** reports on a controlled human malaria study conducted at LUMC that assessed the protective efficacy of a single immunization with a genetically attenuated malaria parasite. **Chapter 3** describes a study protocol for a trial to evaluate the safety, tolerability, and immunogenicity of a novel *Shigella* vaccine and adjuvant combination in Dutch and Zambian adults.

Part II (**Chapters 4-8**) will focus on how publicly funded clinical trials can contribute to research into dose-sparing strategies and innovation, particularly for COVID-19 mRNA vaccines. This part will discuss a Viewpoint article and four post-licensure studies into dose optimization conducted during the pandemic. In the Viewpoint article in **Chapter 4**, we describe which locally initiated publicly funded initiatives were researching COVID-19 vaccine dose-optimization. We propose more centralized coordination and stimulation of this research to fully harness its potential. **Chapter 5** describes a proof-of-concept trial for fractional intradermal administration of the mRNA-1273 COVID-19 vaccine (Moderna Spikevax®). In **Chapter 6,** this concept is tested in a larger non-inferiority study design, and the trial reported in **Chapter 7** evaluates its potential as a booster dose. In **Chapter 8**, fractional intradermal dosing of mRNA-1273 is assessed as a pragmatic approach to vaccinating patients with a suspected allergic reaction to their first mRNA COVID-19 vaccine.

Chapter 9 summarizes the findings and aims to situate them within a broader context. This chapter assesses whether and how the studies presented in **Part I** and **Part II** contributed to the formulation and answering of key questions that were unlikely to have been addressed by commercial developers.

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