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

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Citation

Roozen, G. V. T. (2025, November 7). *The sharpest tool in the shed: question-based clinical development of vaccines to address global health priorities*.

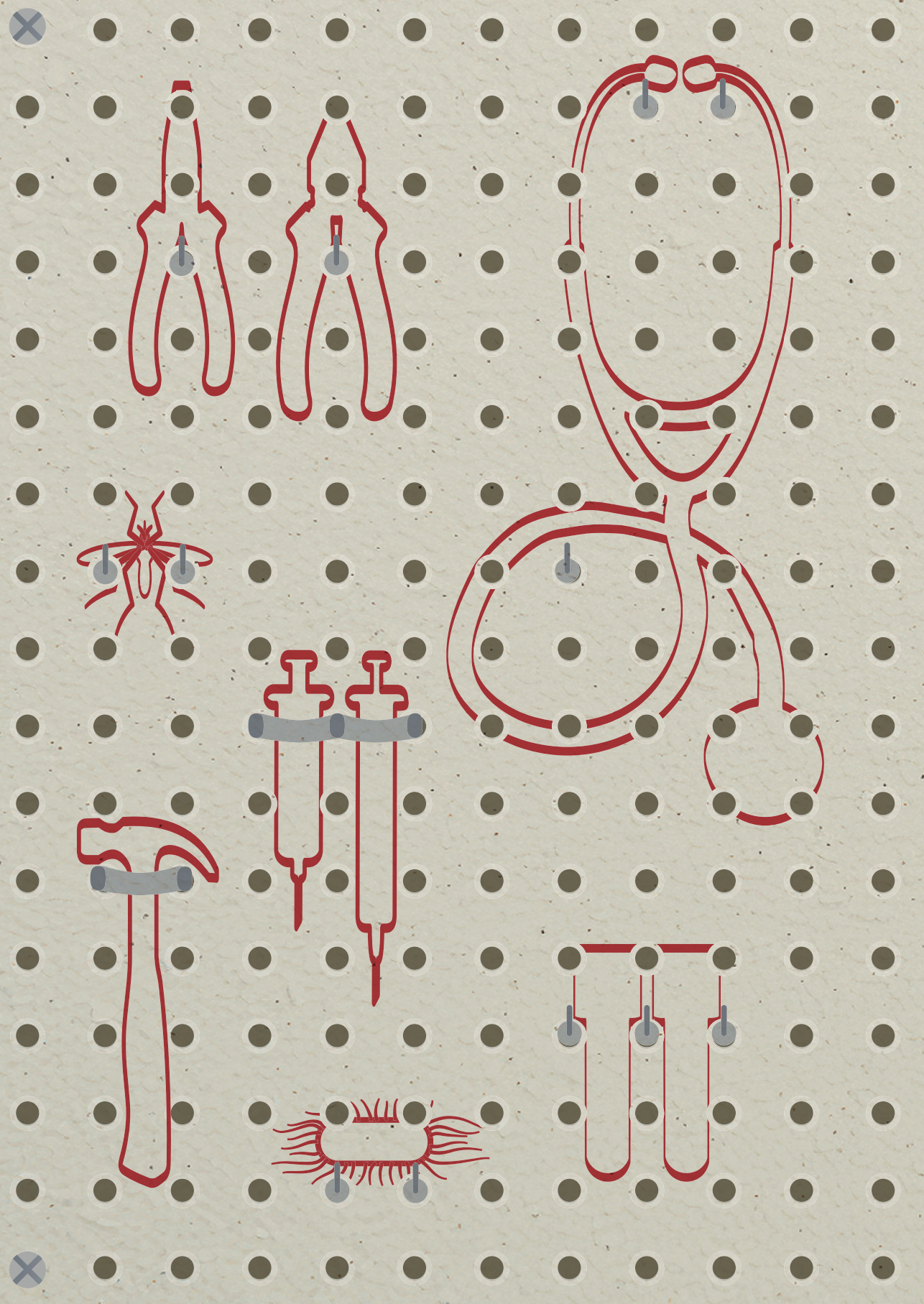
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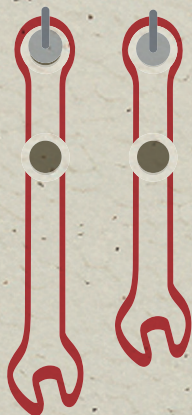
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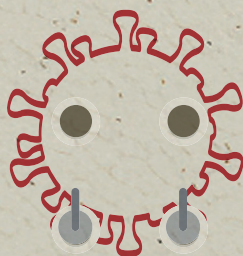




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English summary

Vaccines are crucial to global health, preventing millions of deaths each year. Newly developed vaccines can have the greatest impact in preventing mortality and saving life years when targeting a deadly disease primarily affecting children or against an international outbreak of a novel pathogen (or variant). Given their importance, development of these vaccines together with strategies to ensure equitable vaccine access should be considered a top scientific priority. Because these priorities do not always align with commercial interests, pharmaceutical companies hardly ever address these issues. Therefore, vaccine development should not be left solely to the commercial sector, but public bodies and academia must actively participate, with governments closely monitoring and supporting these efforts, directly or indirectly.

In general, clinical vaccine development adheres to the three-phase paradigm. First, a Phase I study evaluates the first-in-human vaccine administration, followed by a Phase II study in which the highest tolerated dose is established. Then, a large Phase III study is conducted to assess the protective efficacy of that dose.

This thesis argues that stepping away from this paradigm can positively influence the development process through decreasing time and costs, and that public bodies and academia can play a pivotal role here. Instead of rigidly following the three-phase model, vaccine development should be guided by identifying key questions based on the biomedical properties of the vaccine and the target disease. Based on scientific and financial arguments, the most optimal order for answering these questions must be determined. Trials should then be designed to address these questions in this most efficient sequence, a concept termed Question-Based Clinical Development (QBCD).

QBCD does not eliminate the need for expensive late-stage clinical trials to evaluate safety and efficacy in a broad population. However, early identification and answering of key questions can minimize the risk of advancing unsuccessful candidate vaccines to late-stage development. Early termination of the development of candidates with low potential has been described as the “fail-fast approach.” This strategy can help save resources, which is particularly important for developing vaccines targeting diseases primarily affecting low- and middle-income countries (LMICs) with limited funding. In a pandemic setting, not only development speed should be prioritized, but also key questions that facilitate widespread vaccine availability after market approval.

This thesis is divided in two parts. In **Part I**, two studies are presented that are designed with the QBCD principles in mind and aim to advance the development of a vaccine against malaria and *Shigella*. **Part II** consists of four chapters that describe studies that aimed to increase the availability of COVID-19 vaccines during the pandemic by addressing key questions on dose optimization.

Part I

Chapter 2 presents findings of a controlled human malaria infection (CHMI) study. In a CHMI study, healthy study participants are deliberately infected with malaria parasites under controlled conditions; they are tested for malaria daily and receive antimalarial treatment immediately once they test positive. A CHMI study is an efficient way to test the protective efficacy of a vaccine in early-stage clinical development without the need for a large clinical trial in a malaria-endemic area. The trial in **Chapter 2** examined the protective efficacy of the GA2-parasite, a genetically attenuated malaria parasite that can infect the liver but does not cause malaria. Previous work found that three immunizations by mosquito bite protected 8 out of 9 participants from a CHMI. The current study revealed that after only one immunization with the GA2-parasite by mosquito bites, 9 out of 10 participants were protected against a controlled infection. This has never been shown before for malaria immunization and could substantially benefit vaccine implementation and traveler's vaccination.

Before this immunization method can be developed into a vaccine ready for late-stage development, it will be critical to investigate key questions on the longevity of the protection, performance in pre-exposed populations living in malaria-endemic areas, and whether similar efficacy can be achieved when using an injectable form of the GA2-parasite.

Chapter 3 reports on a study protocol for a trial that will be conducted by an international consortium with African, European, and North American partners. The trial will assess the safety and immunogenicity of a new *Shigella* vaccine (Invaplex_{AR-Detox}) and adjuvant (dmlT). The vaccine has previously proven safe and immunogenic in adults in the United States. However, previous *Shigella* vaccines were ineffective in the target population (infants and young children in LMICs). Therefore, the study will assess whether the vaccine's immunogenicity can be improved further by adding an adjuvant, an immunostimulant compound. Once the first-in-human and dose-escalation part of the trial has been completed in Dutch adults, the rest of the study will be conducted in Zambia to test the immunogenicity of the vaccine and adjuvant in a *Shigella*-endemic setting. The most important key question for this vaccine and adjuvant combination will be its immunogenicity in children and young adults. To address this, the study consortium aims to perform an age-de-escalation study if the trial described in **Chapter 3** generates promising results.

Part I

Chapter 4 reviews clinical COVID-19 vaccine trials from the early stage of the pandemic. These trials evaluated dose optimization strategies to increase the number of people who could be vaccinated with the same amount of vaccine. To improve pandemic preparedness, we argue that such publicly funded clinical trials should be initiated by international public bodies and governments. Moreover, these institutions should oversee and coordinate all post-licensure vaccine research to ensure effective research and implementation of dose optimization and other strategies that can improve equitable distribution of vaccines. Ideally, pharmaceutical companies are incentivized to integrate dose optimization into vaccine development as well.

Chapters 5-8 present the results of four studies with the mRNA-1273 COVID-19 vaccine (Moderna Spikevax®) conducted soon after the vaccine's market approval in the European Union. We showed that a 1/5th dose can safely be administered intradermally (**Chapter 5**) and that this method induces sufficient immunogenicity for both the primary vaccination series (**Chapter 6**) and the booster vaccination (**Chapter 7**). **Chapter 8** demonstrates that intradermal administration is a pragmatic solution for (suspected) allergy to mRNA COVID-19 vaccines.

Conclusion

Part I highlights the broader issue of vaccine development for diseases endemic to LMICs, where market failure often leads to underinvestment. The studies on malaria and *Shigella* vaccines exemplify how publicly initiated research can fill this gap by addressing key questions that pharmaceutical companies may not prioritize. The ultimate goal is for LMICs to independently develop, test, and license vaccines, reducing their reliance on developers in high-income countries. Until this ideal is achieved, partnerships between researchers from the Global North and the Global South can help build capacity and foster knowledge exchange.

Part II underlines the importance of dose optimization strategies for vaccine development and the role that publicly initiated research can play in this regard. Stronger public oversight and more research into dose optimization can improve equitable vaccine access, particularly during a pandemic.

In conclusion, this thesis demonstrates how academic institutions and publicly funded research can expedite vaccine innovation. By addressing research areas and knowledge gaps that are of little interest to the commercial sector they can play a critical role in advancing the development of vaccines for global health priorities.

