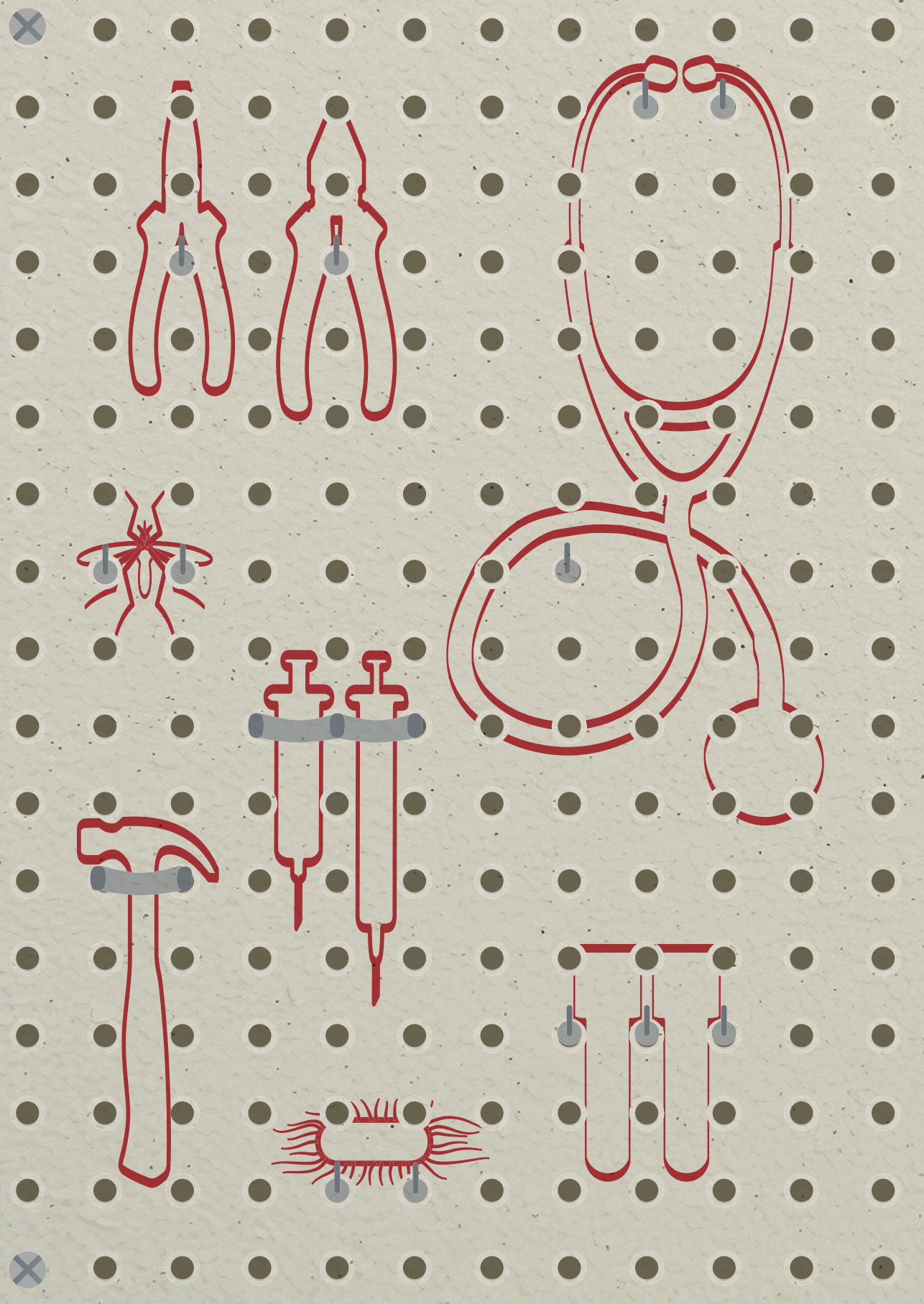
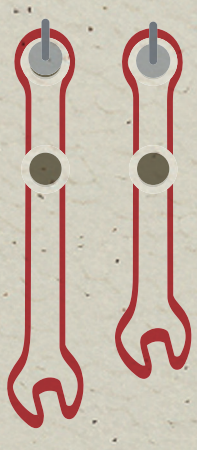
# The sharpest tool in the shed: question-based clinical development of vaccines to address global health priorities

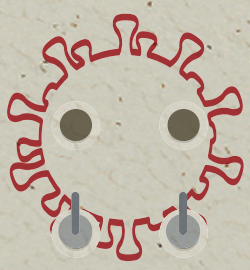
Roozen, G.V.T.





# 9

# Discussion



This final chapter summarizes the findings presented in the previous chapters and situates them within the broader context of vaccine development for malaria (**Chapter 2**) and shigellosis (**Chapter 3**), as well as dose optimization of COVID-19 vaccines during the pandemic (**Chapter 4-8**). Furthermore, it evaluates the contributions of these publicly initiated trials to enhancing vaccine accessibility and development. Finally, this chapter examines how the principles of Question-Based Clinical Development (QBCD), introduced in **Chapter 1**, can drive the ongoing advancement of these vaccines.

## Whole-sporozoite malaria vaccine development

**Chapter 2** presents a study on dose optimization of a whole-sporozoite (WSp) immunization approach for malaria. Malaria is a disease caused by the *Plasmodium* parasite, which is transmitted between humans by mosquitoes. Each year, approximately 600 000 people die from malaria, mostly children below the age of five.[1] The *Plasmodium falciparum* (*Pf*) parasite is the leading cause of malaria-related mortality.[1] To date, *Pf* is the only parasite for which a vaccine has been developed and broadly implemented outside of clinical research settings.

RTS,S and R21 are the two malaria vaccines that currently have received prequalification by the World Health Organization (WHO). Both are subunit vaccines that consist of nanoparticles covered with the circumsporozoite protein (CSP) in combination with an adjuvant to increase immunogenicity.[2, 3] In regions with moderate to high seasonal transmission where seasonal malaria chemoprevention is provided, a three-dose regimen of either of the two vaccines prevents approximately 75% of clinical malaria episodes for about one year when administered to young children at the start of the malaria season.[2-4] However, protective efficacy is substantially lower when the vaccinations are given outside of this timing (50-70%), when given to infants (approximately 40%), in areas with high perennial transmission (20-35%), or in the second year after receiving a booster dose (40-60%).[2-4] As of February 2024, nearly 10 000 children in Cameroon and Burkina Faso have received the RTS,S vaccine, and RTS,S and R21 are planned for introduction in a total of 19 African countries.[5]

The development and implementations of these two vaccines mark important milestones in the fight against malaria. Current immunization regimens result in a decrease of morbidity and mortality among vaccinated individuals. However, achieving a substantial reduction in community-level transmission requires next-generation malaria vaccines capable of inducing robust and durable protection from blood-stage disease (e.g. 90% for more than a year), preferably with simpler dosing schemes.[6]

Since malaria predominantly affects LMICs, a new malaria vaccine holds limited revenue potential (**Chapter 1**). As a result, a substantial part of research into the development of next-generation malaria vaccines is not conducted by the pharmaceutical industry but by public and other non-commercial research institutions. Adhering to QBCD and the fail-fast principle ensures an efficient use of limited available funding.

A specific strategy to facilitate this process is the evaluation of experimental malaria vaccines through small-scale trials using a controlled human malaria infection (CHMI). In CHMI trials, participants are randomized to receive either the vaccine or a placebo and then exposed to wild-type malaria parasites via infected mosquito bites or intravenous inoculation with sporozoites. Participants are monitored daily and receive antimalarial treatment as soon as parasites are detected in their peripheral blood (parasitemia). The proportion of participants in the vaccinated group who are protected against infection as well as the time-to-parasitemia in those who are unprotected provides valuable insights into how the vaccine may perform in larger, late-stage field trials in malaria-endemic regions.[7] The use of CHMI allows for early down selection of ineffective vaccine candidates, thereby reducing the financial burden associated with unsuccessful late-stage development.[8]

A promising approach to develop the next generation of malaria vaccines is immunization with attenuated WSp, which may improve both the efficacy and durability of protection against malaria. WSp are metabolically active *Pf* parasites that expose the immune system to a broader range of antigens comparted to subunit vaccines.[9] Strong supportive evidence for this idea comes from immunization with chemoprophylaxis and sporozoites (CPS), in which infective sporozoites are administered under the cover of a prophylactic drug that is only effective against the erythrocytic stage of the disease.[9] When evaluated in a CHMI, CPS is found to elicit high levels of protective efficacy,[10-13] which is durable as well.[14]

Through genetic modification, the Leiden University Medical Center (LUMC) has developed a *Pf* parasite in which the *mei2* gene, vital for the parasite's intrahepatic development, has been removed. This genetically attenuated *PfΔmei2* parasite (GA2) demonstrates complete growth arrest in the liver after approximately 6 days,[15] thus mimicking the CPS method but without inducing symptoms associated with blood-stage disease. Three administrations of GA2 to human participants, delivered through the bites of 50 mosquitoes, were safe and did not cause breakthrough parasitemia. Three weeks later, eight out of nine participants were protected against a subsequent CHMI.[16] While these results supported the potential for further development of a three-dose regimen, the key question arose whether a single immunization could induce similar high-level protection. A next-generation vaccine with a single-immunization regimen would vastly simplify implementation in vaccination campaigns, compared to the current vaccines that require three vaccinations and a booster.

To address this, the trial described in **Chapter 2** was conducted, evaluating the efficacy of a single-dose regimen. The findings demonstrated that a single immunization with GA2 provided protection against CHMI. Six weeks post-immunization, 90% of participants (9/10) in the GA2 group were protected, compared to non in the control (0/5).

These results mark an important step forward in the development potent vaccines based on genetically attenuated parasites. In line with QBCD, several key questions can be identified that require an answer to effectively advance this concept into late-stage development:

1. What is the optimal dose? Can a lower dose also induce sufficient immunity?
2. How durable is the immunity?
3. What is the protective efficacy of a vialed genetically attenuated WSp vaccine that can be administered parenterally?[17]
4. Can a genetically attenuated WSp vaccine induce equivalent efficacy in pre-exposed populations in malaria-endemic regions?

The first question aligns with general question 5 of the QBCD framework: "What is the therapeutic window of the drug?" (**Chapter 1**). To address this, an ongoing trial at LUMC is investigating the protective efficacy of GA2 immunization at a lower dose (NCT05468606). Additionally, another trial will address protection durability by rechallenging participants at least one year post-immunization (NCT06293339).

It is important to note that the current administration method, relying on mosquito bites, is not feasible for large-scale implementation. Another genetically attenuated WSp vaccine has been developed that can be stored in liquid nitrogen and administered through intravenous injection.[18] This vaccine, termed LARC2, has the same *mei2* gene deletion as GA2 and an additional knockout of the *linup* gene.[18] A first-in-human trial with LARC2 is planned and its results will be pivotal for the future of genetically attenuated WSp malaria vaccine development.

The fourth key question formulated above pertains to the issue of vaccine hyporesponsiveness.[19] Previously tested WSp approaches that used radiation-attenuation instead of genetic attenuation reported lower efficacy and lower humoral and cellular immune responses in pre-exposed African populations compared to malaria-naive adults in the United States.[17] Despite this knowledge, radiation-attenuated WSp vaccines were subsequently tested in multiple large-scale clinical trials in malaria endemic regions.[17] This strategy arguably deviated from the principles of QBCD and the fail-fast approach, suggesting that research funds could have been allocated more optimally. While formulating key question is central to QBCD, the framework also emphasizes the importance of addressing these questions in a prioritized, optimal sequence; often the most challenging aspect of the strategy. According to QBCD, both financial and scientific factors must guide the selection of the optimal development path.[20] There are financial and environmental barriers that complicate the conduction of CHMI trials in malaria-endemic regions, but genetically attenuated WSp vaccines developed in the Global North should eventually be tested target populations. Assessing the efficacy and immune responses in pre-exposed African populations should be a priority early in the development process, to avoid the missteps made with previous WSp vaccine candidates.

If hyporesponsiveness in the target population is identified, a potential solution could be the identification of potent adjuvants to enhance the immunogenicity of WSp immunization. While substantial research has been conducted on adjuvants for subunit malaria vaccines, little is known about adjunvating WSp vaccines. Preliminary rodent studies have yielded

promising results,[21-23] but further research in humans is needed to determine the viability of this approach.

If the key questions discussed here could successfully be addressed, a genetically attenuated WSp malaria vaccine candidate could progress to large-scale clinical trials to evaluate safety and efficacy in populations in malaria-endemic regions. Achieving this goal would represent a major step toward the development of a highly effective next-generation malaria vaccine.

### Development of a new Shigella vaccine

Shigellosis is an enteric infection caused by *Shigella* bacteria, which induces inflammation that can lead to gut enteropathy, malnutrition, and stunting in children. Symptoms typically include fever, malaise, anorexia, vomiting, and most prominently, (bloody) diarrhea. Shigellosis is estimated to be the second leading cause of diarrhea-associated mortality in LMICs. Currently, there is no licensed *Shigella* vaccine available, but modelling suggests that the introduction of an effective vaccine could avert 43 million cases of stunting and 590 000 deaths over a 20-year period.[24]

**Chapter 3** outlines the protocol for an upcoming study to evaluate the safety and immunogenicity of a candidate *Shigella* vaccine and adjuvant. The vaccine candidate, Invaplex$_{AR\text{-}Detox}$, has previously been proven safe and immunogenic in adults in the United States (NCT03869333). According to the WHO Preferred Product Characteristics (PPC) for *Shigella* vaccines, the target population are infants and young children under five living in LMICs, where the disease burden is highest.[25] However, prior studies with *Shigella* vaccine candidates have shown low or absent immune responses in children under three.[26, 27] Vaccine hyporesponsiveness, due to different genetic and environmental factors, may further limit the immune response in LMIC populations. Addressing these challenges will require optimization of the vaccine to overcome variability in the target population, in line with general key question 5 of QBCD (**Chapter 1**)

The study protocol described in **Chapter 3** is specifically designed to address this question. The safety and immunogenicity of Invaplex$_{AR\text{-}Detox}$ will be assessed both with and without dmLT, a candidate adjuvant shown to significantly enhance immune responses to *Shigella* antigens in mice.[28, 29] To address hyporesponsiveness, the third study cohort will involve Zambian adults, following two dose-escalation cohorts in Dutch adults to confirm safety and tolerability.

This early evaluation in the target setting ensures rapid conformation of dmLT's adjuvating potential or, alternatively, facilitates the termination of this strategy if dmLT added benefits are minimal ("fail fast"). If Invaplex$_{AR\text{-}Detox}$ combined with dmLT proves to be safe and immunogenetic, a subsequent age-descending study is planned to evaluate the vaccine and adjuvant in adolescents, young children, and infants in a country with a high *Shigella* disease burden (either Burkina Faso or Zambia). This trial will ultimately answer the key question on immunogenicity in the target population.

Beyond advancing the vaccine pipeline for shigellosis, the study is part of a broader project that aims to strengthen the capacity of ethical reviewing and clinical research in the African countries participating in the consortium. While most countries in the WHO African region have national ethical committees installed, more than halve indicate a need for capacity strengthening on health research ethics, including clinical trials.[30] International collaborations for vaccine development (both between HICs and LMICs and among LMICs) can enhance this development. National regulatory authorities can be strengthened in clinical trial evaluation and authorization through an exchange of knowledge and best practices with experienced foreign regulators.[31]

The study protocol described in **Chapter 3** exemplifies how publicly funded initiatives can foster partnerships between scientific organizations in the Global North and the Global South, facilitating the exchange of expertise. A parallel submission process of the study protocol to the Dutch and Zambian review boards proved efficient and provided valuable insights to researchers in both countries on local regulatory priorities on study design, ethical principles and good manufacturing practices of investigational products. To further promote knowledge sharing, a two-day capacity building program was organized to bring together researchers from Burkina Faso, Zambia, and The Netherlands, as well regulators from Zambia, to exchange experiences on vaccine trials and discuss ethical and regulatory principles of clinical trials with Dutch regulators.

### Intradermal administration and fractional dosing of mRNA COVID-19 vaccines

In early 2020, the world was hit by the COVID-19 pandemic, the largest since the 1918 influenza outbreak. By the end of 2024, more than 7 million confirmed COVID-19-related deaths have been reported[32], though the true death toll is likely substantially higher.

The pandemic demonstrated that when the need for a vaccine in high-income countries (HICs) is high, pharmaceutical companies are willing and capable of accelerating the development and production of vaccines, particularly when HIC governments cover most financial risks.[33-36] Clinical trials were quickly rolled out, addressing key questions (**Chapter 1**) required to acquire (emergency) licensure, like “What is the highest tolerated and safe dose?”, “Is the vaccine immunogenic?” and “Does the induced immune response protect against infection and/or severe disease?” However, other key questions were not addressed, particularly those relevant to advancing vaccine equity but less directly beneficial to the vaccine producer.

In **Chapter 4,** we described that questions like “Which reduced dose can induce sufficient immunity levels to vaccinate more people with the same amount of vaccine?” or “Can the interval between vaccinations be stretched in the initial stage of the vaccination campaign?” are typically not addressed by vaccine producers, but by publicly funded research institutes. Although these studies generated important insights, they were primarily local initiatives and relied on the enthusiasm and dedication of individual research groups rather than being coordinated in a centralized effort. To address this gap, we proposed establishing a pandemic

preparedness vaccine development pipeline, coordinated by an international public body, such as the World Health Organization (WHO) or the Coalition for Epidemic Preparedness Innovations (CEPI). Under this framework, post-licensure trials should systematically evaluate reduced doses, alternative dosing methods, and revised vaccination regimens as soon as pharmaceutical companies successfully completed a late-phase clinical trials for vaccines targeting pandemic pathogens. Furthermore, governments investing in vaccine candidates and guaranteeing their purchase should require producers to assess at least some dose optimization during large pre-licensure trials.

**Chapters 5** - **7** present findings from post-licensure studies on the mRNA-1273 COVID-19 vaccine (Moderna Spikevax®). These trials evaluated the safety, tolerability, and immunogenicity of an intradermally administered dose as a dose-sparing strategy. The rationale for these trials is based on two principles.

First, it was assumed that the registered vaccine dose may be excessive and that a reduced dose could still elicit sufficient immune responses. Determining the optimal dose during vaccine development is challenging because the dose-response relationship is usually not linear but concave or S-curved (Fig. 1). This means that a major reduction of the dose often leads to a minor reduction in effectiveness.[37] Fractionating doses to vaccinate five or ten times more individuals, even with slightly lower immune responses, could greatly enhance herd immunity, reducing mortality and morbidity on a population level.[38] As discussed in **Chapter 1**, during clinical vaccine development, often the highest tolerated dose instead of the lowest necessary dose is selected. As a result, a lot of the vaccine is effectively wasted.

Second, the studies were based on the hypothesis that the dermis, which contains more immune cells than muscle tissue, might produce a stronger immune response to vaccine antigens (Fig. 2). Intradermal administration could therefore induce a stronger immune response than intramuscular administration.[39] A review comparing immune responses from intradermally and intramuscularly administered vaccines at equivalent doses found this hypothesis holds true for some vaccines.[40] For others, equivalent doses administered intradermally produced similar immune responses as intramuscularly administered doses.[40]

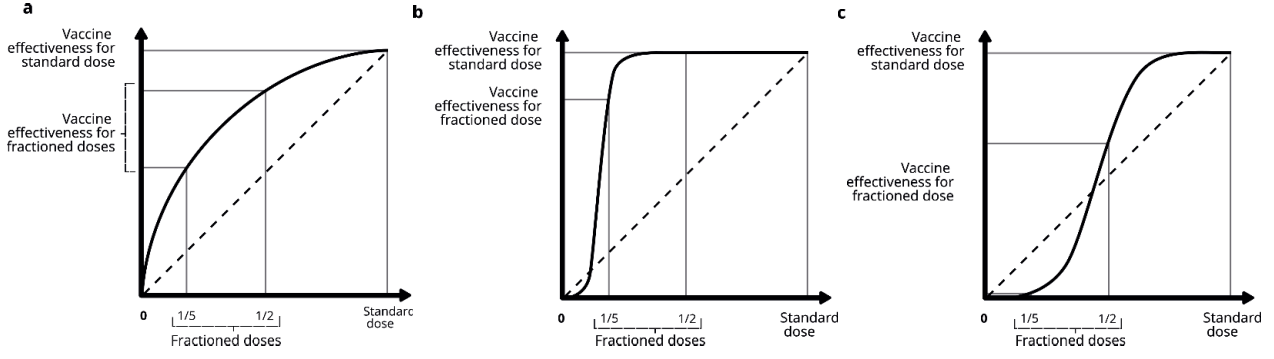



**Figure 1. Relationship between vaccine dose and effectiveness is not linear**

Three scenarios with different vaccine dose-effectiveness relationships. In all three examples, providing halved doses to a certain number of people could provide a greater level of population immunity than would providing standard doses to half as many people. For reference, the population immunity conferred by vaccination could be estimated via the vaccination coverage multiplied by vaccination effectiveness. Horizontal axis represents vaccine dose, and vertical axis represents vaccine efficacy. The dashed diagonal line is included for reference.

**A.** Solid line indicates a scenario in which there is a concave relationship between vaccine efficacy and dosage, whereby a half dose could provide considerably more than half the effectiveness of the standard dose. In this example a 1/5$^{th}$ fractioned dose leads to considerably less effectiveness in the individual but would still be beneficial on a population level if twice as many people receive a vaccination. **B.** A different scenario: in this example there is an S-curved relationship between dose and effectiveness. Here, a halved dose has the same effectiveness as the standard dose and a 1/5$^{th}$ fractioned dose still has an effectiveness of approximately 80%. **C.** Another scenario in which there is an S-curved relationship between dose and efficacy. Here, a 1/5$^{th}$ fractioned dose does not provide any protective effectiveness. A halved dose will still provide population benefits if it leads to twice as many people getting vaccinated but would come with a substantial reduction in effectiveness on the individual level.

*Used with permission, adapted from: Cowling BJ, Lim WW, Cobey S. Fractionation of COVID-19 vaccine doses could extend limited supplies and reduce mortality. Nature Medicine. 2021;27(8):1321-3. Figure adaptation by Jori Jansen.*

The trials described in **Part II** were conducted using the mRNA-1273 vaccine shortly after it received market approval in the European Union. This vaccine was selected because it was the first COVID-19 vaccine available for research purposes and among the first ever mRNA vaccines to receive market approval in the Netherlands.

**Chapter 5** presents the first ever study to report on intradermal administration of a mRNA vaccine. Forty participants were assigned to receive either an intradermal administration of 10 µg (1/10$^{th}$ fractional dose) or 20 µg (1/5$^{th}$ fractional dose), or a 20 µg intramuscular dose as the control group. Although the small sample size prevented definitive conclusion about whether intradermal administration yields superior immune responses compared to intramuscular administration, the trial demonstrated that reduced doses elicited antibody levels correlating with high levels of protection as observed in the mRNA-1273 Phase III trial conducted by Moderna.[41]

**Chapter 6** reports on a trial involving 150 participants comparing the 20 µg intradermal dose, delivered either with a conventional small-gauge needle or a novel microneedle that enables easy perpendicular administrations (Bella-mu® needle), to the standard-of-care 100 µg intramuscular dose. Both intradermal methods induced robust antibody responses that were slightly lower than those observed in the intramuscularly vaccinated control group. Analysis of cellular immune responses revealed comparable or slightly better T-cell responses in intradermally vaccinated participants (standard needle) compared to the control group, although B-cell responses were somewhat reduced.

**Chapter 7** presents the findings from a trial of 129 participants, including 80 who had participated in the trial described in **Chapter 6**. This study demonstrated that robust antibody levels could also be induced by administering a fractional intradermal dose as a booster. Furthermore, participants who received their primary vaccination series intradermally showed similar booster responses to those in the control group.



The results from **Chapters 5 - 7** highlight the immunogenic potential of intradermally administered mRNA-1273 and represent the first step toward new administration methods for mRNA vaccines. Microneedles, such as the Bella-mu needle used in the trial in **Chapter 4**, could facilitate efficient intradermal mass vaccination campaigns. However, even greater progress may be achieved with needle-free innovations like jet injection or permeabilization techniques, which could reduce vaccine hesitancy associated with fear of needles.[42] Moreover, international global health organizations like UNICEF, PATH, CEPI, and GAVI are mobilizing efforts to develop dermal patches covered with microneedles, a so-called vaccine-containing microarray patch (VMAP) that can be stored outside the fridge for a few days.[43-46] VMAPs could directly contribute to increasing global immunization coverage, especially in low-resource settings where problems with maintaining the cold chain make it challenging to complete the last mile of vaccine distribution.[46] However, developing new VMAPs for different vaccines requires addressing specific key questions for each type of vaccine. In a recent study assessing

a VMAP loaded with the mRNA-1273 COVID-19 vaccine, the dermal patch failed to induce an immune response, possibly because the mRNA lipid nanoparticles were too large to diffuse from the ceramic VMAP.[47]

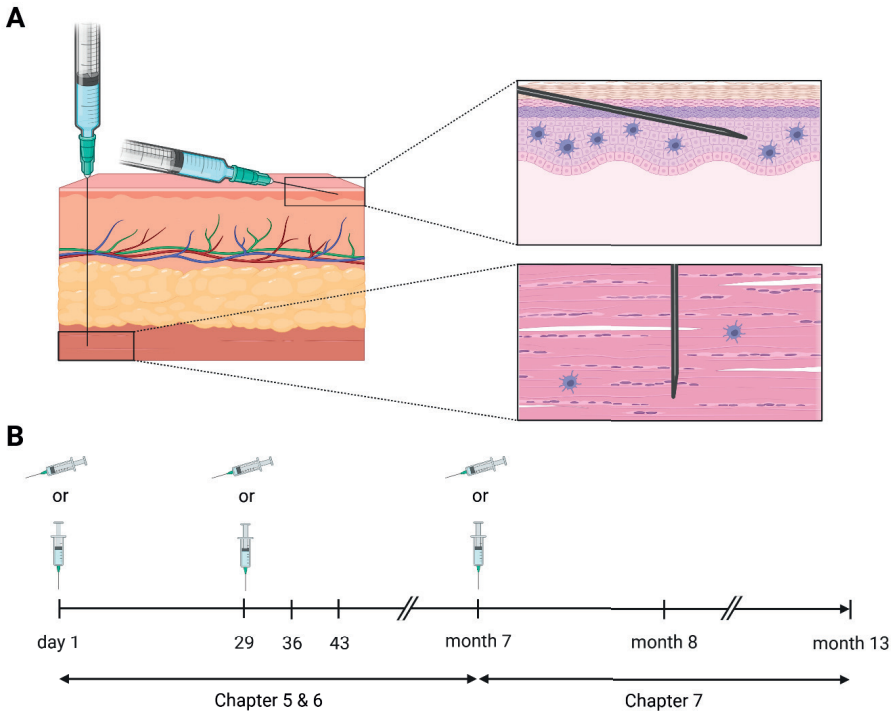



**Figure 2. Rationale and design of the intradermal vaccination trials described in Part II**

**A.** Intradermal vaccination requires administration of a fractional dose in the stratum spinosum of the dermis, which is rich in antigen-presenting cells. Intramuscular vaccination requires administration is in the muscle tissue which is low in antigen-presenting cells. **B.** In the primary series, two vaccinations were given at a one-month interval, with additional blood collections 1 week, 2 weeks and 6 months after the second dose. The booster dose was administered 6 months after the second dose, with additional blood collections 1 month and 6 months after the booster.
*Figure created with BioRender.*

**Chapter 8** focuses on a post-licensure study evaluating intradermal administration of the mRNA-1273 in individuals with suspected allergies to mRNA COVID-19 vaccines. This study included 56 patients who were referred to the vaccination outpatient clinic of LUMC after experiencing suspected allergic reactions to their first mRNA COVID-19 vaccination. At the clinic, these patients received a 20 µg intradermal dose of mRNA-1273 to simultaneously assess their allergic response in a controlled setting and complete their primary immunization regimen. Antibody levels measured in 47 patients after intradermal vaccination were comparable to those in a historical reference group that received the standard intramuscular regimen. Importantly, none of the 56 patients experienced anaphylaxis or a severe allergic

reaction, suggesting that intradermal vaccination could offer a pragmatic solution for individuals with suspected allergies to mRNA COVID-19 vaccines.

The studies in **Part II** highlight the importance of post-licensure vaccine research to evaluate dose-optimization strategies and improve global vaccine access during a pandemic. Addressing these challenges asks for a question-based development approach focused on improving equity and accessibility, extending beyond the Phase I-III paradigm that prioritizes rapid market approval. Even after a vaccine receives (preliminary) market approval, key questions can be formulated that address gaps in vaccine equity and accessibility. While commercial incentives to tackle these issues are often lacking, the studies presented here exemplify how publicly initiated and socially driven research can bridge knowledge gaps that pharmaceutical companies do not address.

## Conclusion

Most vaccines continue to be clinically developed through standardized steps: small early-phase clinical trials to establish first-in-human administration and identify the highest tolerated dose, followed by large, late-phase clinical trials to assess protective efficacy. Clinical development can be improved by the QBCD framework: formulating key questions critical for development, prioritizing these questions based on scientific and economic arguments, and then designing trials to optimally address these questions.[20] Strategies to answer these fundamental questions more efficiently include involving target populations in early-phase clinical trials and utilizing controlled human infection models to evaluate protective efficacy earlier in the development process.

In times of vaccine shortages, key questions regarding dose optimization, such as fractional dosing, dose stretching, or alternative administration methods become particularly relevant. However, there are currently no incentives for pharmaceutical companies to pursue dose optimization once a vaccine has received market approval. Such studies require additional financial investments and could reduce revenues if findings suggest that one dose is sufficient to immunize multiple people. Consequently, investigators from academia and not-for-profit organizations play a pivotal role in addressing these important questions.

The studies presented in **Part II** of this thesis are among numerous publicly funded initiatives that investigated optimal dosing strategies, demonstrating that a rapid scientific response is feasible. These studies highlight how publicly initiated trials can successfully formulate and answer vaccine-related key questions, ultimately contributing to pandemic response efforts and enhancing preparedness. Nevertheless, these initiatives were not centrally coordinated. Even when substantial evidence supporting fractional dosing strategies emerged, policymakers remained hesitant to implement these findings. This reluctancy likely stems from

concerns about deviating from registered doses and regimens unless more systematically structured and large-scale evidence supporting dose-sparing strategies is presented.

Such evidence can only be generated if governments or international public bodies take control for overseeing and coordinating the post-licensure research. This would allow for the identification of knowledge gaps and ensure that all dose-optimization questions are addressed. During the COVID-19 pandemic, governments covered the financial risks associated with vaccine development.[34-36] Governments should use this position of influence as leverage to demand the evaluation of fractional doses and alternative administration methods in large, late-phase trials. Furthermore, central coordination of post-licensure research would ensure oversight by identifying knowledge gaps, prioritization, distribution of research question across institutions, and consolidation of findings. These efforts would create a robust framework to rapidly deliver scientific sound evidence on dose optimization aiding policymakers in effectively rolling out vaccination campaigns during pandemics.

During periods of vaccines shortages, it is especially difficult for LMICs to acquire pandemic vaccines. Vaccine nationalism of HICs drives up the price during a pandemic, putting LMICs at the back of the queue for vaccine distribution. During the COVID-19 pandemic, initiatives like COVID-19 Vaccines Global Access (COVAX) aimed to counter these inequities to and promote fairer vaccine allocation, achieving considerable but limited success.[48] If similar disparities occur in future pandemics, dose-sparing strategies will hold even greater significance for LMICs than for HICs, since vaccine shortages will exacerbate due to their resource constraints.

For diseases primarily affecting LMICs, vaccine development faces challenges by market failure. Pharmaceutical companies prioritize diseases with a predominant burden in HICs due to their higher potential to generate profits.[49-51] To address this, the international scientific community should strive to establish a sustainable system in which researchers from the Global South develop, test and deploy vaccines tailored to diseases and the needs in their regions. This will reduce dependency on pharmaceutical companies in the Global North as it will empower LMICs to address their own public health priorities more effectively. Currently, this ideal is far from realized. Until then, academic institutions in HICs can support vaccine development for resource-limited settings by addressing key questions relevant for diseases with high prevalence in LMICs. Rather than conducting trials as external researcher from the Global North, collaborations with local researchers from the Global South should be forged to create equitable partnerships.[52] Such collaborations contribute to capacity building, which is essential for enabling researcher in the Global South to independently develop, test, and license future vaccines for disease that impose high burdens on their populations.

Every newly developed vaccine represents a valuable asset for humanity. However, vaccines targeting diseases with high pediatric mortality or those with significant pandemic potential have the greatest impact to transform global health outcomes.[53] Historically, vaccine development priorities haven been driven by economic incentives and opportunities for

profit.[49] Academia and other non-commercial research institutes can counterbalance these market forces. They can ensure optimal allocation of their limited resources by designing clinical trials that address the most pressing key questions. By doing so, they foster innovative vaccine development that prioritizes global health needs.

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