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

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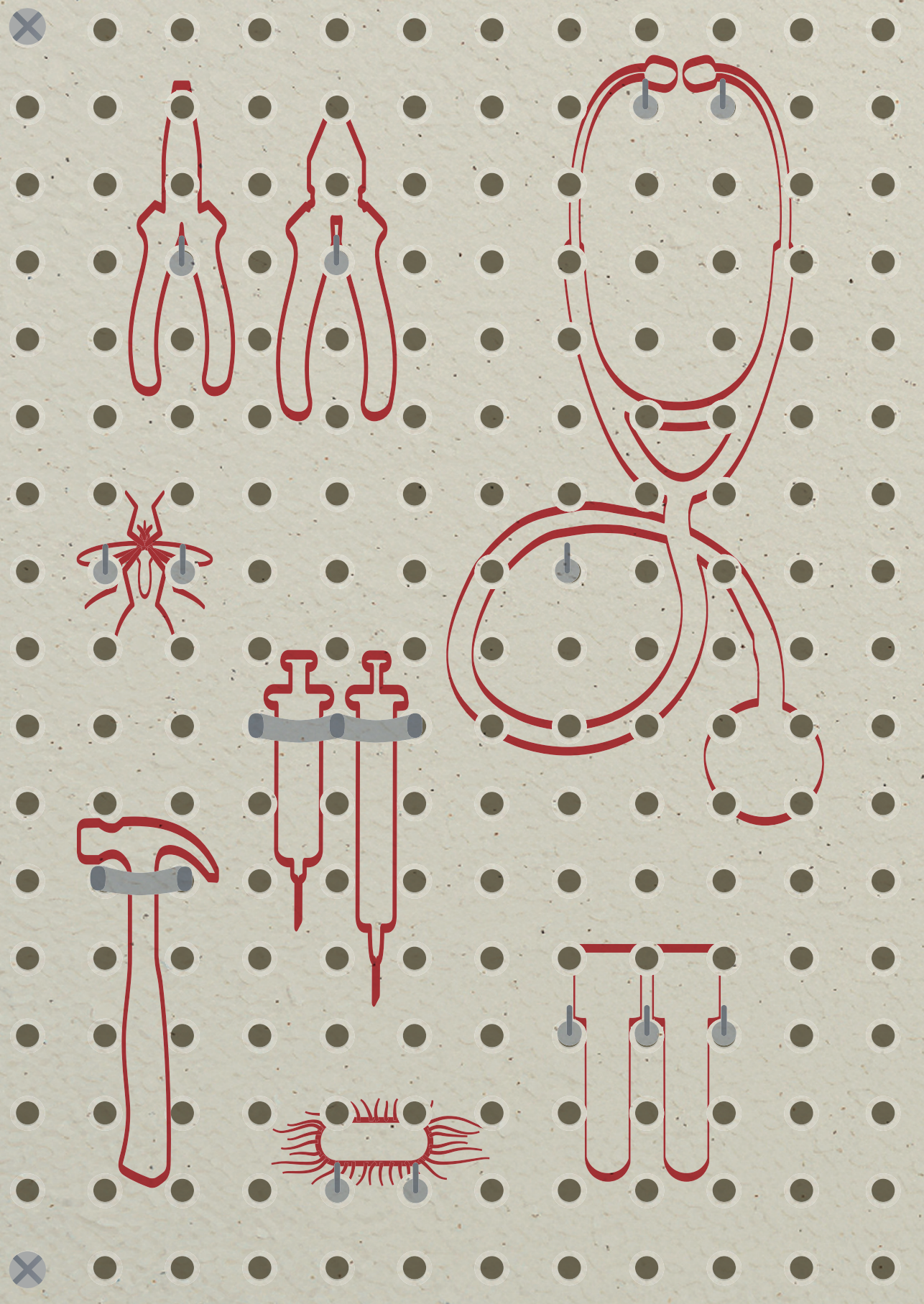
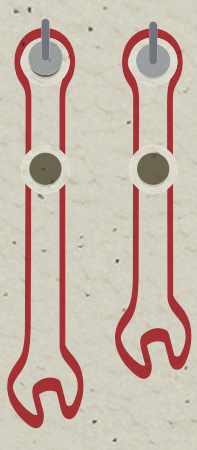
Part II

Dose-Optimization Strategies During a Pandemic





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COVID-19 Vaccine Dose Sparing: Strategies to Improve Vaccine Equity and Pandemic Preparedness

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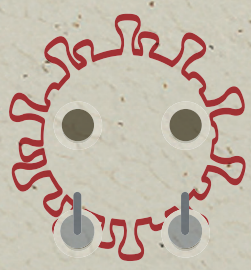

Abstract

Despite tremendous efforts, worldwide COVID-19 vaccination coverage is lagging. Dose-sparing strategies for COVID-19 vaccines can increase vaccine availability to address the global crisis. Several clinical trials evaluating dose sparing are currently under way. However, to rapidly provide solid scientific justification for different dose-sparing strategies, joint coordinated action involving both public and private parties is needed. In this Viewpoint, we provide examples of approaches to vaccine dose-sparing that have previously been evaluated in clinical trials to improve vaccine availability and reflect on the origin of their funding. With a focus on the current COVID-19 pandemic, we stress the need for expedited testing of vaccine dose-sparing strategies in endemic or epidemic infectious diseases. However, we argue that the establishment of a mechanism through which dose-sparing opportunities are systematically identified, scientifically tested, and ultimately implemented will prove to be valuable beyond the current pandemic for infectious diseases product development and pandemic preparedness in the future.

Introduction

The emergence of the SARS-CoV-2 coronavirus has burdened health systems worldwide. COVID-19 still poses a threat to global health, with nearly 67 000 new fatalities a week, as of February.[1] Additionally, the measures to contain COVID-19 take an enormous social and economic toll.

Vaccination is a highly cost-effective tool to curtail cases in epidemic and pandemic infectious diseases. At a remarkable pace, new COVID-19 vaccines have been developed, tested and registered. Currently, there are nine vaccines that are used widely, effectively reducing infection, severe disease and death worldwide.[2] Real world data from Israel, the United Kingdom (UK), Sweden and the United States, showed that full vaccination with the BNT162b2 (Pfizer-BioNTech Comirnaty®) or mRNA-1273 (Moderna Spikevax®) vaccine protected adults for 61-92% against infection, 80-87% against hospitalization and 85% against death for the viral variants that were prevalent at the time these studies were conducted.[3]

Although highly effective vaccines are available and have a proven effect on pandemic control, less than 15% of people in low-income countries have been (partially) vaccinated so far.[4] This is in stark contrast to high-income countries (HICs), where more than 180 vaccinations per 100 citizens have been given.[4] This leaves a staggering 2.7 billion people still to be vaccinated globally. COVID-19 Vaccines Global Access (COVAX), aimed to provide enough vaccines to vaccinate 40% of the adult population of 92 lower income economies participating in the COVAX Advance Market Commitment by the end of 2021, but reached only 20% by the end of the year.[5] The delay in vaccination leads to enormous preventable morbidity and mortality and puts more strain on health care systems that were already heavily burdened before the pandemic.[6]

Increasing access to vaccines in low- and middle income countries (LMICs) is a complex challenge: limited supplies in vaccines, HIC vaccine nationalism,[7] vaccine hesitancy, and complications in distribution and registration[6, 8] all play a part. Although these problems require societal, political, logistical and infrastructural solutions, scientific justification for alternative dose-sparing strategies are needed to facilitate resolution of shortages.

New approaches to dose sparing and vaccination regimens

Fractional dosing

Fractional dosing, administering only a part of a registered dose, has been an important strategy to provide more vaccine doses in epidemic circumstances in the past. In 2016, a yellow fever epidemic plagued Angola and the Democratic Republic of Congo (DRC) with an estimated 7 000 cases.[9] Faced with a substantial global shortage, the World Health Organization (WHO)

reviewed the available evidence, and advised on fractional dosing to combat the epidemic.[10] Together with the WHO, the DRC government launched a vaccination campaign with a one fifth fractional dose. In one week, more than seven million people were vaccinated, preventing the spread of the disease in the capital Kinshasa.[11]

In most dose-finding studies for COVID-19 vaccines, several doses (based on results from animal testing) were evaluated for tolerability and immunogenicity. During that initial period of vaccine development in early 2021, it was unclear whether antibody concentrations and T cell responses would correlate to protective efficacy, so the most certain strategy was to continue with the highest tolerated dose from the Phase 2 trial into the Phase 3 trial. For the mRNA-1273,[12] ChAdOx1 nCoV-19 (AstraZeneca Vaxzevria®)[13] and BNT162b2[14] vaccines, this meant that the highest dose from the dose-finding trial was used in the larger efficacy trial. This makes it likely that some of these vaccines are actually over-dosing and that lower doses would probably lead to comparable, or overall acceptable protective efficacy.[15]

Whereas fractional doses have been investigated to booster fully vaccinated populations, trials comparing fractional versus full dose priming regimens are scarce. One such a study has been conducted by La Jolla Centre for Immunology funded by the United States National Health Institute, which evaluated immunogenicity in participants 6 months after receiving a 1/4th fractional primary regimen of the mRNA-1273 vaccine. Despite the fact that neutralizing antibody responses in the low-dose vaccine group about half of those vaccinated with the registered dose,[16] we can now estimate that even the low-dose would yield a more than 80% efficacy base on the model created by Khoury et al.[17] A second example is the fractional dosing scheme unintentionally introduced in a sub-group of the Phase 3 study of the ChadOx1 nCoV-19 vaccine. Participants in this group were primed with a half dose, followed by a regular dose booster. This led to a protective efficacy of 90% (95% confidence interval: 67% to 97%).[18]

The results of these trials underline that there is no absolute linear correlation between dose and efficacy, e.g. a one fifth fractional dose does not reduce efficacy to one fifth. As a consequence fractional dosing will yield higher levels of cumulative immunity with the same amount of vaccine.[15] In times of an outbreak, fractionation can thus provide an immediate solution which should be considered when dealing with vaccine shortages.[15]

Intradermal vaccination

Intradermal (ID) vaccination provides opportunities to further increase vaccine efficacy of fractioned doses by administering the vaccine into the dermis, which is rich in antigen-presenting cells. Consequently, ID vaccination requires a lower dose than intramuscular (IM) vaccination, making it a valid strategy for dose sparing. ID vaccination is already in use for influenza and rabies vaccination where non-inferiority for immunogenicity has been demonstrated when administering a 20% to 60% fractional dose.[19] For the tuberculosis vaccine (Bacillus Calmette-Guérin [BCG]), ID administration is already the standard of care

and the WHO approves ID vaccination as a way of dose sparing for rabies and inactivated polio vaccine.[20, 21]

We have previously assessed the safety and immunogenicity of both a one tenth and a 1/5th fractional ID vaccination with the mRNA-1273 vaccine. Funded through crowdfunding and philanthropic organizations, we found this strategy to be safe and well tolerated. Both low-dose regimens elicited higher anti-spike (anti-S) and anti-regional binding domain (anti-RBD) IgG concentrations than in a comparative convalescent serum group and comparable to a group that received the full IM dose.[22] A larger study to compare levels of neutralizing antibodies head-to-head with the registered IM dose is on its way (EudraCT: 2021-000454-26).

Concerns about the ID vaccination technique have been posited as potential drawbacks for large scale implementation as a dose-sparing method. Although ID vaccination is technically more challenging than IM vaccination, the technique can be acquired after some training and is already used extensively for BCG vaccination worldwide. After ID vaccination, the appearance of a wheal provides immediate feedback on correct administration of the vaccine, facilitating training and quality control. Additionally, novel application devices such as intradermal applicators or needle-free injection devices can further facilitate mass vaccination campaigns.[23]

Heterologous vaccine regimens

To increase flexibility of vaccination programs in times of vaccine shortage, knowledge about "mix and match" strategies is crucial when different vaccines are available. Various publicly funded studies have shown that combinations of ChAdOx1 nCov-19, Ad26.CoV.S (Janssen Jcovden®), mRNA-1273 and the BNT162b2 vaccines are safe, well tolerated and immunogenic, sometimes even more immunogenic than homologous regimens.[24-28] A study from the United States Institute of Allergy and Infectious Diseases found that homologous regimens increased neutralizing antibody titers 4.2-20 fold, whereas heterologous regimens increased titers 6.2-76fold.[24] In all trials, regimens that contained at least one mRNA vaccine induced higher neutralizing antibody titers than regimens that only contained viral vector vaccines.[24, 27, 28]

Early knowledge on heterologous regimens can assure continuation of vaccination programs when supplies of certain vaccines are delayed and others are still available. The use of heterologous regimens can also aid campaigns where one vaccine is temporarily not given due to safety concerns.

Dose stretching

In December 2020, the UK government decided to prioritize giving the first COVID-19 vaccine to as many people in at-risk groups as possible, rather than providing second vaccinations. A study funded by the National Institute for Health Research, AstraZeneca and others evaluated the dose stretching approach. The study found that a longer interval between two doses of the ChAdOx1 nCov-19 vaccine led to higher antibody levels than shorter intervals. Antibody levels

were 923 ELISA Units with an 8–12 week interval; 1860 ELISA Units with a 15–25 week interval, and 3738 ELISA Units with a 44–45 week interval.[29] Concerns were raised that expanding the fraction of the population with partial immunity could increase selection for vaccine-escape variants. However, others argued that the corresponding reduction in prevalence and incidence reduced the rate at which new variants are generated and the speed of adaptation.[30] The dose stretching approach enabled the UK to provide at least one vaccine to almost half of its population in the first 3 months of its vaccination campaign.[4] This example illustrates how central coordination and rapidly launched trials can aid in making policies that improve vaccine access.

Pandemic preparedness

During the COVID-19 pandemic, new vaccines were developed at an unprecedented pace. The development process was accelerated in multiple ways: running the different clinical testing phases in parallel, rolling reviews by the regulatory authorities, and starting large-scale production before regulatory approval (Figure 1).[31] However, upscaling of production capacity takes time and currently there are still not nearly enough vaccines to meet global needs. As of December 2021, COVAX has distributed 1.2 billion doses to LMICs.[5] If these doses had been administered with a 1/5th fractionation, the entire eligible population of countries receiving COVAX vaccines could have already been fully vaccinated with these vaccines.[32]

In future pandemics, it is inevitable that we will be confronted with vaccine shortages once again when new vaccines become available. That is why dose-sparing mechanisms should be identified and tested as soon as new vaccines have demonstrated to be safe (Figure 1). Ideally, such dose-sparing approaches are immediately evaluated in parallel with the pre-licensure Phase 2 and 3 trials. However, in this stage of development it is still unclear whether a vaccine will be licensed at all and it therefore stands to reason to evaluate dose sparing only after licensure. In post-licensure Phase 2 trials, promising dose-sparing strategies could be quickly evaluated, followed by larger post-licensure Phase 3 trials to assess efficacy of these strategies. With the identification of immunological correlates of protection, these Phase 3 trials would not necessarily have to be as large-scale as the initial Phase 3 trials.[17]

By the time pharmaceutical companies have registered and marketed a new vaccine, there is little financial incentive to evaluate dose-sparing mechanisms. As the aforementioned trials illustrate, dose-sparing trials are typically initiated in the public scientific domain.

In the current COVID-19 crisis, dose-sparing trials eventually came to be as governments rolled out their national vaccination campaigns, which provided access to vaccines for public institutions to conduct trials with. In most places, this happened 3 to 4 months after the first vaccines got licensed. This is a considerable delay given the only very short timelines of clinical development to licensure (around 10 months). Ideally, dose-sparing strategies are

tested immediately after licensure as part of coordinated effort between industry and public parties to improve global access. Research funding bodies that use public money to fund the development of vaccines should use these financial investments as leverage to demand trial designs that assess dose-sparing regimens, not only in Phase 1 but also in the later stages of clinical development.

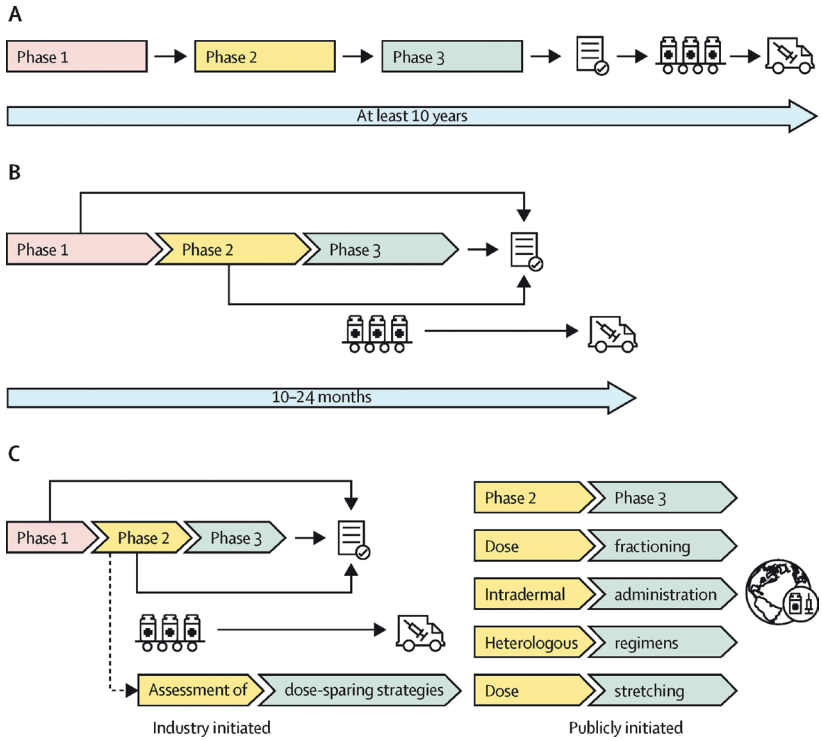

Figure 1. Vaccine development: conventional, COVID-19 and future pandemics

A. Conventional vaccine development: sequential clinical trial phases followed by regulatory review, production and distribution. **B.** Vaccine development during COVID-19 pandemic: clinical trial phases overlap; regulatory authorities apply rolling review procedures and pharmaceutical companies start production before approval (financial risk partly covered by governments). **C.** Optimal future pandemic preparedness: pre-approval phases as in B, after which international public body stimulates and coordinates new trials to evaluate strategies to improve global vaccine access. Promising strategies are evaluated in Phase 2/3 trials. Ideally, this evaluation already starts as soon as industry-initiated Phase 2 is completed.

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Currently, there is no infrastructure in place to systematically coordinate and fund post-licensure trials. CEPI has made a first attempt by launching a funding opportunity for trials assessing fractional dosing, but again this application of dose-sparing vaccination is intended as a way of boosting immunity in fully vaccinated populations.[33] Albeit important, insights

gained by this initiative will only benefit countries whose populations have for the most part been fully vaccinated, and not those countries that are still at the beginning of their vaccination campaigns. We thus argue that joint, coordinated efforts are needed to provide the infrastructure for rapid testing of dose sparing.

Improving worldwide immunity against COVID-19 is a multifaceted challenge involving limited vaccine supplies, vaccine hesitancy and logistical problems. Overcoming these difficulties requires coordination, collaboration and a globalist view on health. Creative scientific innovations can provide a solid foundation to a comprehensive approach that includes societal, political, logistical and infrastructural solutions to improve the availability of vaccines. At the same time, these innovations require robust scientific evidence to avoid providing substandard vaccines to LMICs.

We believe that in times of shortage, the scientific community and the pharmaceutical industry have a moral obligation to rapidly identify and test dose-sparing strategies and unleash the full potential of available vaccine doses to save lives. Creating the infrastructure to collaboratively conduct post-licensure trials will not only help address one of the biggest global health challenges so far, but also contribute to our preparedness for new pandemics that will undoubtedly follow.

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