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COVID-19 vaccine dose sparing: strategies to improve vaccine equity and pandemic preparedness

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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 underway. 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.

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Introduction

The emergence of SARS-CoV-2 has burdened health systems worldwide. COVID-19 still poses a threat to global health, with over 67 000 new fatalities a week, as of February, 2022.[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. New COVID-19 vaccines have been developed, tested, and registered at a remarkable pace. Currently, there are nine COVID-19 vaccines that are used widely, effectively reducing infection, severe disease, and death worldwide.[2] Real-world data from Israel, the UK, Sweden, and the USA, showed that full vaccination with the BNT162b2 (Pfizer–BioNtech) or mRNA-1273 (Moderna) vaccine protected adults from 61% to 92% against infection, 80–87% against hospitalisation, and 85% against death for the viral variants that were prevalent at the time of conducting these studies.[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 number is in stark contrast to high-income countries, in which more than 180 vaccinations per 100 citizens have been given.[4] This leaves a staggering 2·7 billion people still to be vaccinated globally. The COVID-19 Vaccines Global Access (COVAX) initiative 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-income and middle-income countries (LMICs) is a complex challenge with limited supplies of vaccines, vaccine nationalism in high-income countries,[7] vaccine hesitancy, and complications in distribution and registration[6,8] all playing 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 in Angola and the Democratic Republic of the Congo had an estimated 7000 cases.[9] Faced with a substantial global shortage, WHO reviewed the available evidence, and advised on fractionated dosing to combat the epidemic.[10] Together with WHO, the Democratic Republic of the Congo's government launched a vaccination campaign with a one-fifth fractional dose. In 1 week, more than 7 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. In 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 (Moderna),[12] ChAdOx1 nCoV-19 (Oxford–AstraZeneca),[13] and BNT162b2 (BioNTech–Pfizer)[14] vaccines, this meant that the highest dose from the dose-finding trial was used in the phase 3 trial, yet it is probable 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 fractionated 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 Institute

for Immunology, funded by the United States National Institutes of Health, which evaluated immunogenicity in participants 6 months after receiving a one-quarter fractionated primary regimen of the mRNA-1273 vaccine. Despite the fact that neutralising antibody responses after low-dose vaccination were about half as strong as those seen with registered dose vaccination,[16] we can now estimate that even the low-dose would yield a more than 80% efficacy based on the model created by Khoury and colleagues.[17] A second example is the fractional dosing scheme unintentionally introduced in a subgroup 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, which led to a protective efficacy of 90% (95% CI 67–97).[18]

The results of these trials underline that there is no absolute linear correlation between dose and efficacy—eg, a one-fifth fractional dose does not reduce efficacy to one fifth. Consequently, dose fractionation 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 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, intradermal vaccination requires a lower dose than intramuscular vaccination, making it a valid strategy for dose sparing. Intradermal vaccination is already in use for influenza and rabies vaccination whereby non-inferiority for immunogenicity has been demonstrated when administering a 20–60% fractionated dose.[19] For the tuberculosis vaccine (Bacillus Calmette-Guérin [BCG]), intradermal administration is already the standard of care and WHO approves intradermal 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 one-fifth fractionated intradermal vaccination with the mRNA-1273 vaccine. Funded through crowdfunding and philanthropic organisations, we found this strategy to be safe and well tolerated. Both low-dose regimens elicited higher anti-spike and anti-regional binding domain IgG concentrations than in a comparative convalescent serum group and comparable to a group that received the full intramuscular dose.[22] A larger study to compare levels of neutralising antibodies head-to-head with the registered intramuscular dose is underway (EudraCT: 2021-000454-26).

Concerns about the intradermal vaccination technique have been posited as potential drawbacks for large-scale implementation as a dose-sparing method. Although intradermal vaccination is technically more challenging than intramuscular vaccination, the technique can be acquired after some training and is already used extensively for BCG vaccination worldwide. After intradermal 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 programmes 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 (Johnson & Johnson), mRNA-127, and the BNT162b2 vaccines are safe, well tolerated, and immunogenic, sometimes even more immunogenic than homologous regimens.[24–28] A study from the US Institute of Allergy and Infectious Diseases found that homologous regimens increased neutralising antibody titres 4·2–20 fold, whereas heterologous regimens increased titres 6·2-76 fold.[24] In all trials, regimens that contained at least one mRNA vaccine induced higher neutralising antibody titres than did regimens that only contained viral vector vaccines.[24,27,28]

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

Dose stretching

In December, 2020, the UK government decided to prioritise 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).[31] However, upscaling of production capacity takes time and currently there are still not 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 one-fifth 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). Ideally, such dose-sparing approaches are immediately evaluated in parallel with the prelicensure 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 also evaluate dose-sparing 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 process happened 3 to 4 months after the first vaccines got licensed, which 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 a 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.

Currently, there is no infrastructure in place to systematically coordinate and fund post-licensure trials. The Coalition for Epidemic Preparedness Innovations 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] Although 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

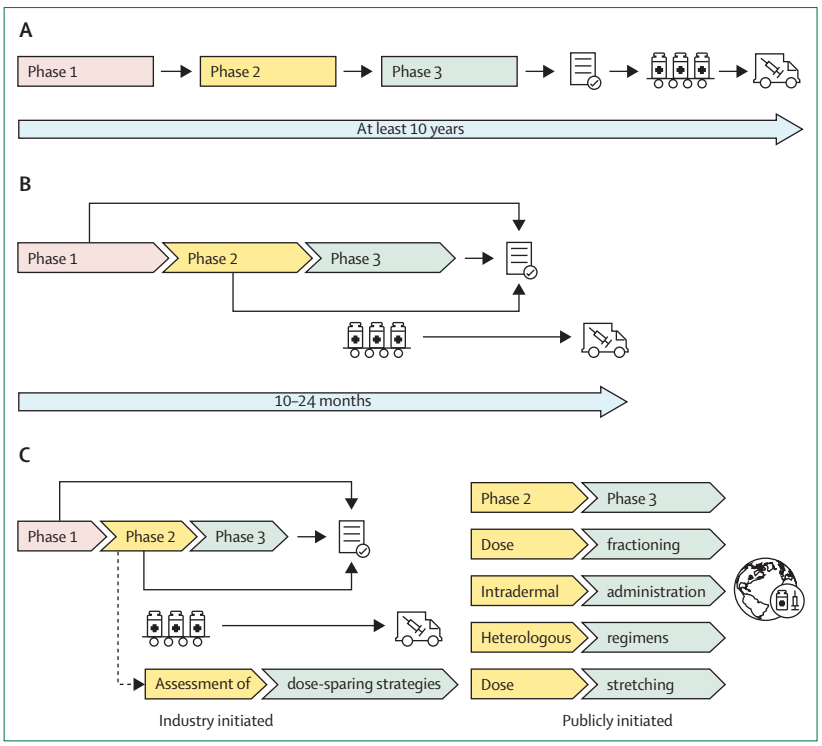

Figure: **Vaccine development: conventional, COVID-19, and future pandemics**
(A) Conventional vaccine development with sequential clinical trial phases followed by regulatory review, production, and distribution. (B) Vaccine development during COVID-19 pandemic whereby clinical trial phases overlap, regulatory authorities apply rolling review procedures, and pharmaceutical companies start production before approval (financial risk partly covered by governments). (C) Optimal future pandemic preparedness with 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. Parts A and B of this figure are conceptually inspired by Krammer 2020.[31]

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.

Contributors

GVTR and MR conceptualised the manuscript. GVTR wrote the original draft of the manuscript. All authors reviewed and edited the manuscript.

Declaration of interests

We declare no competing interests.

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