CORRESPONDENCE

Fractionation of vaccine doses could extend limited supplies and reduce mortality

Benjamin J. Cowling[1,2], Wey Wen Lim[1], Sarah Cobey[3]

Affiliations:

1. WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

2. Laboratory of Data Discovery for Health Limited, Hong Kong Science and Technology Park, New Territories, Hong Kong Special Administrative Region, China

3. Department of Ecology and Evolution, University of Chicago, Chicago, IL

Corresponding author: bcowling@hku.hk

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ABSTRACT

Fractionation of vaccines, i.e. reducing the amount of antigen in each dose so that more people can be vaccinated, has been successfully used to control yellow fever outbreaks in Africa and South America. Published data on immunogenicity and efficacy of partial doses of COVID-19 vaccines support the potential for fractionation of COVID-19 vaccines to make the most of available antigen supply and maximise the number of lives protected by vaccination in this pandemic.

Coronavirus disease 2019 (COVID-19) continues to pose a major threat to public health. Public health and social measures have been implemented to control transmission, but they are emergency measures that are difficult to sustain in the longer term. There are now 15 COVID-19 vaccines being used worldwide. However, shortages in the supply of vaccines have been a particular problem for low-income countries, which have collectively received only 0.2% of all vaccines delivered worldwide for approximately 10% of the world population. Fractionation of vaccine doses, illustrated in the Figure, is a potential solution to this global shortage of vaccines that has not been given sufficient attention and consideration.

In 2015, emergency yellow fever vaccination was needed to mitigate epidemics in Angola and the Democratic Republic of Congo. However, there were limited supplies of the vaccine, and a 6-month minimum manufacturing process [1]. The World Health Organization's Strategic Advisory Group of Experts on Immunization reviewed the evidence on immunogenicity and safety of fractional dosing of yellow fever vaccines, and recommended dose fractionation down to one fifth of the standard dose [2]. This was put into practice in Angola and the Democratic Republic of Congo in 2016, with millions vaccinated with the fractional dose, and subsequently in Brazil in 2017/18 [3]. Fractional dosing was predicted to substantially reduce population infection attack rates and save lives [1]. Vaccine dose fractionation has also been recommended by the WHO for inactivated poliovirus vaccines and meningococcal conjugate vaccines as an alternative mass-vaccination strategy, particularly when vaccine shortages occur during outbreaks in resource-limited locations.

Dose-finding studies indicate that fractional doses of mRNA vaccines could still provide a robust immune response against COVID-19 [2, 3]. In a non-randomized open-label phase I/II trial of the BNT162b2 vaccine, doses as low as one-third (10μg) produced comparable antibody and cellular immune responses to the full dose of 30μg [4]. Specifically, the geometric mean titer of neutralizing antibodies 21 days after the second vaccine dose was 166 for the group who received 10μg, almost the same as the geometric mean titer of 161 for the group who received 30μg, and 63 days after the second dose, titers were 181 and 133, respectively [4]. For the mRNA-1273 vaccine, 25μg doses conferred geometric mean $PRNT_{80}$ titers of 340 at 14 days after the second dose, compared to 654 in the group who received the standard dose of 100μg [5]. According to the model proposed by Khoury et al. [6], if vaccine efficacy at full dose is 95%, a reduction in dose that led to as much as a halving in the post-vaccination geometric mean titer could still be in the range of 85%-90%. While other components of the immune response may also contribute to efficacy, these dose-finding data are at least indicative of the potential for further exploration of fractionation as a dose-sparing strategy. Durability of responses after fractional doses should also be explored.

We are only aware of one trial reporting data on the clinical efficacy of a fractionated dosing strategy for COVID-19, which was a trial of the AZD1222 vaccine in the United Kingdom [7]. As part of a larger multicentre trial, Voysey et al. reported a vaccine efficacy of 90% (67% to 97%) among a subgroup of participants that were primed with a half dose instead of a full dose, followed by a full dose boost after a median of 12 weeks. While only a small number of participants were included in this subgroup, the lower bound of 67% for the efficacy estimate is very reassuring.

Concerns about the evolution of vaccine resistance have been posited as a potential drawback of dose-sparing strategies. However, vaccines that protect against clinical disease appear also to reduce transmission, implying that expanding partial vaccination coverage could reduce the incidence of infection. As described in a recent paper, lower prevalence should slow, not accelerate, the emergence and spread of new variants [8]. Within-host dynamics are unlikely to overcome these population-level effects. In contrast to some chronic infections such as human immunodeficiency virus, infections with SARS-CoV-2 in healthy individuals do not select readily for immune escape variants. Such rapid selection has only been reported in immunocompromised individuals, who might have better access to vaccines if doses were fractionated in the general population. One other potential concern of fractionation would relate to vaccine hesitancy, if fractionated doses are viewed as inferior. However, the "first dose first" strategy applied in the United Kingdom and elsewhere has been well accepted as a strategy to provide at least partial protection to a greater number of individuals [8].

In conclusion, fractionated doses could provide a feasible solution to extend limited supplies of COVID-19 vaccines, which is a major challenge for low- and middle-income countries. We identified several ongoing dose-finding studies listed in clinicaltrials.gov that will provide important evidence to support fractionation policies. While most dose-finding studies focus on immune responses with relatively smaller sample sizes, larger trials to estimate the efficacy of fractionated doses would also be worthwhile. The mRNA vaccines may be particularly suited for fractionation because of their high levels of efficacy in comparison to other vaccine types, while the favourable clinical trial results on fractionation of the first dose of AZD1222 should encourage further investigations [7]. Even though some locations are reaching higher levels of vaccine coverage, many parts of

the world with low vaccination rates could benefit from fractionation if it were determined to be an advantageous strategy. Of course, vaccination rates are restricted not only by antigen supply but also by the availability of vaccinators and clinical supplies such as syringes. Nevertheless antigen supply remains the greatest restriction for COVID-19 vaccines, and strategies which make the most of available antigen supply would maximise the number of lives saved by vaccination. More generally, in future pandemics we should consider identifying the appropriate vaccine dosage that can save the most lives for a limited amount of antigen, rather than just a dosage which balances efficacy and reactogenicity for the individual.

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AUTHOR CONTRIBUTIONS

B.J.C. conceived of this Comment; B.J.C. wrote the original draft of the manuscript with contributions from all authors; and all authors reviewed and approved the final version of the manuscript.

POTENTIAL CONFLICTS OF INTEREST

BJC has consulted for GSK, Sanofi Pasteur, AstraZeneca, Roche and Moderna. The authors report no other potential conflicts of interest.

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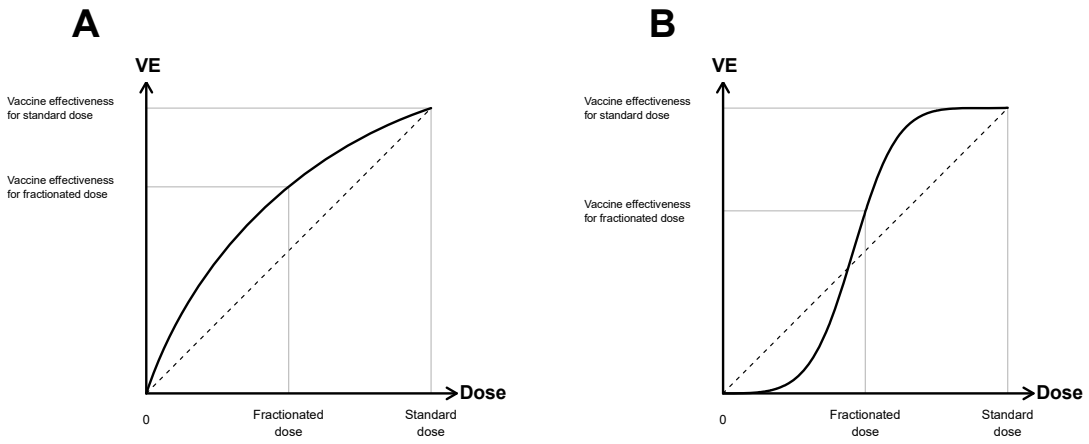

Figure. Illustration of the rationale for dose fractionation to make more effective use of limited supplies of vaccine antigen. The solid line in Panel A shows a concave relationship between vaccine efficacy and dosage, where a fractionated dose (say approximately half of a standard dose) could provide considerably more than half the effectiveness of the standard dose, where a dashed diagonal line is included for reference. If the concave relationship holds, it indicates that providing half-doses to a certain number of people could provide a greater level of population immunity than providing standard doses to half as many people. For reference, we could estimate the population immunity conferred by vaccination via the vaccination coverage multiplied by vaccination effectiveness. Panel B illustrates another scenario where very low fractionated doses might not provide any clinical benefit, but fractionation would still provide population benefits above a certain threshold. In Panel B, the solid line crosses the diagonal dashed line at doses approaching half a standard dose, and at the fractionated dose indicated (approximately half a standard dose) there would be an advantage for population immunity to use half doses.