Comparative cost-effectiveness of SARS-CoV-2 vaccine dose fractionation in India: a modelling study

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Brief Communication

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Abstract

Given constrained vaccine supplies globally, fractionation of vaccine doses may be an effective strategy for reducing disease and healthcare burdens, even with the emergence of COVID-19 variants. Using a multi-scale model that incorporates population-level transmission and individual-level vaccination, we estimate the costs associated with hospitalization, vaccine costs, and the economic benefit of reducing COVID-19 deaths associated with dose-fractionation strategies. Assuming a willingness-to-pay of US$10,517 per averted year of life lost (YLL) and a price of $12 per vaccine, under various transmission scenarios, with effective reproduction numbers ranging from 1.1 to 5.0 and with vaccine efficacy against transmission from 52% to 91%, the optimal vaccination strategy would always involve fractional doses of vaccines. Vaccine dose fractionation is a cost-effective strategy for mitigating the COVID-19 pandemic and could save a large number of lives, even after the emergence of variants with higher transmissibility.

Main

Coronavirus disease 2019 (COVID-19) still poses a major public health threat, with the potential to overwhelm fragile health care ecosystems, especially in developing countries. COVID-19 cases have risen sharply in Africa in July 2021 [1], and potentially introduce new vaccine-evasive variant seeds in countries, such as India, in the near future. As of August 28, 2021, India has reported 33 million COVID-19 confirmed cases and 437 thousand deaths. Globally, there have been over 216 million reported cases and 4.49 million deaths[2].

To control COVID-19 transmission, a number of public health and social measures (e.g., border entry restrictions, quarantine and isolation of cases and contacts) have been implemented, but are difficult to sustain on a longer term basis given the huge impacts on local social and economic development [3]. Worldwide, 94 vaccine candidates have been tested in humans and 31 have made it to final phases of clinical trials by June 19, 2021[4]. Currently, there are 18 COVID-19 vaccines approved for limited or full use to prevent morbidity and mortality globally [4]. But the global supply shortage and inequity of vaccines is a particular problem without a well-established global procurement mechanism [5], especially for low-income countries which collectively received only 0.2% of the global vaccines despite accounting for roughly 10% of the world population by March 2021 [6].

India began administration of COVID-19 vaccines on 16 January 2021, and administered 263 million doses overall with 15% of the population partly vaccinated and 3.5% fully vaccinated by June 27, 2021 [7]. Three COVID-19 vaccines (Covishield, Covaxin and Sputnik V) have received emergency-use authorization in India after completion of Phase III trials by June 2021, covering only 0.2% of the population daily [4].

Given limited global supplies of vaccine antigen, the use of fractional dosing of vaccines has been proposed in order to provide at least partial protection to a larger number of people [8]. Assuming that the efficacy of vaccines approved in India is concave in dosage, here we explore the potential value of dose fractionation in India. Studies of COVID-19 mRNA vaccines indicate that fractional doses could still provide a robust immune response against COVID-19 [9–11]. For the mRNA-1273 vaccine, two doses of 25μg elicited about half the geometric mean PRNT80 titers at 14 days, compared to two doses of the standard dose (100μg) [10]. Recent modelling studies suggested this strategy reduces the burden of disease from COVID-19 [12–14]. Moreover, strategy of using fractional doses has been used in the past successfully by the WHO to address vaccine shortages for inactivated poliovirus vaccines [15] and meningococcal conjugate vaccines in outbreaks [16]. One fifth of the standard dose of the 17DD yellow fever vaccine was used in Angola and the Democratic Republic of Congo in 2016 to save lives during an outbreak [17].

With the limited supplies of COVID-19 vaccines, the impact of global shortages are greatest in low and middle income countries [5]. This is made worse by the emergence of COVID-19 variants (e.g., B.1.1.7, B.1.351, P.1, and B.1.617.2), which may result in lower vaccine effectiveness [18]. Fractionation of vaccine doses may be an effective strategy for mitigating risks while the virus continues to spread, especially under the transmission of variants as long as vaccination provides protection against escape variants [19]. Here, we identify cost effective strategies for fractional doses of vaccines. We assess the costs and benefits of vaccine dose fractionation using an individual-based mathematical model that incorporates household-specific and age-stratified SARS-COV-2 transmission rates, and a vaccination rollout. We consider the costs associated with hospitalization and vaccine costs, and the economic benefit of preventing COVID-19 deaths despite a potential reduction in vaccine efficacy.

Using an individual-based model of SARS-CoV-2 infection dynamics, we compare vaccination strategies with fractionation or not, lowering different levels of both susceptibility to infection and severity once infected (**Table S3**). For twelve different transmission scenarios, with reproduction numbers ranging from 1.1 to 5, we performed stochastic simulations to identify the cost and benefit of specific vaccination strategy (**Table S1**, **Figure 1.A**). Assuming a vaccine cost of US$12 and willingness to pay per YLL averted of US$10,517, the optimal strategy under various transmission scenarios would always be doses of vaccines with more fractionations over vaccine efficacy of transmission (**Figure 1.B**, **Figure S1**).

For each scenario, we estimate the health and economic outcomes of each dosing fractionation strategy. Taking a quarter dose fractionation strategy with 91% vaccine efficacy after the second dose for transmission, at reproduction numbers between 1.2 and 3, the median incremental cost is expected to be negative by averting more hospitalization costs than vaccine costs (**Table S1**). Under a high transmission scenario (R_e=3), the optimal strategy of vaccine dose fractionation would be expected to avert 7.7 (95% CrI:-7.19, 23.02) million YLL and exact a cost of 1.31 (95% CrI:-0.5, 2.99) billion USD (**Table S1**). Under a low transmission scenario (R_e=1.2), the optimal strategy still suggests vaccine dose fractionation, with the expectation to avert 10.32 (95% CrI:-3.8, 21.72) million YLL and exact a cost of 0.56 (95% CrI:-0.91, 1.83) billion USD. We also assessed robustness of the results with respect to $3 per dose of vaccines [20], which denote slightly lower cost and higher averted YLL (**Table S2**), and with reduced vaccine efficacy of transmission perhaps for variants (**Figure S2**), which denotes slightly lower net monetary benefit averted.

Fractional dosing of vaccines in the context of a global supply shortage can substantially reduce transmission and mitigate the burden on healthcare systems. Our cost-effectiveness analysis provides an indication of potential benefit gained for people vaccinated with the fractional dose in a community. We provide a data-driven approach to tailoring fractional dosing to local epidemiological conditions. Across a range of SARS-CoV-2 transmission scenarios, the optimal strategy under various transmission scenarios would always be fractional doses of vaccines.

Worldwide, six variants of concern have already been identified [21]. Some of these variants are thought to spread more easily or cause more severe infection than the wild-type SARS-CoV-2 virus [21]; some may be able to evade immunity provided by prior infection or vaccines [22]. With only 0.2% of the global vaccines for roughly 10% of the world population by March 2021 [6], the global supply shortage and inequity of vaccines will be continually a public health problem in next months or even years.

As such threats arise, vaccine dose fractionation will be a cost effective strategy for reducing risks and avoiding the socio-economic burden of public health and social measures. The fractionated dosing effort can be adapted to balance the costs associated with vaccine roll-out with the benefits of averting COVID-19 related morbidity and mortality. The UK and Canada have adopted a “first dose first” strategy that prioritizes administering first doses of SARS-CoV-2 vaccines widely by delaying second doses [19]. People vaccinated may prefer two doses to one, whereas the supply of

vaccines remains short, the benefits of reducing COVID-19 public health can be greater when first doses are more widely distributed, when the protection of fractional dosing is larger than a full regimen [23].

Although we believe our qualitative results are robust and can be implemented, we underline a number of simplifying presumptions. Our model does not explicitly include sub-groups with anomalously high contact rates, for example home caregivers, which may serve as viral reservoirs to spread viruses. Our economic analysis results only consider vaccine costs and the benefits of hospitalizations and death averted. Future analysis would take into account additional non-pharmaceutical interventions. The duration of immunity after infection or immunization with SARS-CoV-2 is still not clear, which may last for at least six months [24].

To sum up, fractionation of vaccine doses for SARS-CoV-2 in India is expected to provide a cost effective strategy for mitigating the lingering threat of the COVID-19 pandemic. If COVID-19 remains a persistent threat, especially with multiple SARS-CoV-2 variants escaping, fractional dosing of vaccines for SARS-CoV-2 might provide additional public health and economic benefits, especially when the global supply is limited or in the early period of a new vaccine developed targeting variants in future.

Methods

Epidemic model

We simulate the transmission of COVID-19 in a typical Indian community for 150 days using a stochastic agent-based model, with the parameters given in **Table S5**. At any time, each individual can be in one of 10 possible compartments (**Figure 2**). Following infection, an individual remains in the exposed compartment for an average of $1/\sigma$ days, and then become pre-symptomatic with a probability of p_{sym} or asymptomatic with a probability of $1-p_{sym}$. Asymptomatic cases recover after a period of $1/\hat{\gamma}$ days on average. Pre-symptomatic cases become symptomatic at a rate ϵ, and recover at a rate γ.

The infectiousness of a case depends on the infection status (i.e., asymptomatic, pre-symptomatic, or symptomatic) and the type of contact (i.e., household or non-household). Compared to symptomatic cases, the infectiousness of asymptomatic and pre-symptomatic cases are scaled by factors of $\hat{\omega}$ and ω, respectively. We use an interior-point algorithm that minimizes the mean square error between the targeted value of effective reproduction number (R_e) and the mean estimate of R_es across 100 *in silico* pandemic trajectories simulated using our agent-based model initialized with 10 randomly exposed individuals. The effective reproduction number at the start of a simulation is estimated as the average number of secondary infections from the first 100 cases. To compare the epidemiological impact of vaccination under each transmission and vaccination scenario, simulations initiate both a vaccine rollout and a *status quo* strategy (in which no vaccines) with 2% randomly exposed population (the positive rate of India on January 16, 2021, when Indian vaccination program began) [25] at beginning.

SARS-CoV-2 vaccination

We model the two-dose vaccine with d_{dose} denoting the time interval between doses (**Table S5**). Let ω_1 and ω_2 denote the vaccine efficacy achieved by the first and second doses, respectively (**Table S3**). The susceptibility of acquiring infection for vaccinated individuals is reduced after a period d_{immunity} by a factor 1-ψ_1 after the first dose and by 1-ψ_2 after the second dose; if infected, they also have a reduced probability of developing symptoms with probabilities of of 1-ω_1 and 1-ω_2, respectively. We assume that people are vaccinated nationwide per day following the daily vaccination rate of first dose starting from 0.01% on January 16, 2021 [25] in an Indian population of 1366 million people [26]. We

assign the daily vaccination courses (v) in the individual-based network over weeks w_v to individuals across all compartments. We prioritize adults over age 65 with vaccines.

Individual-based network

The SARS-CoV-2 infection dynamic model assumes that the virus spreads through a fixed contact network consisting of 47,568 individuals in 10,000 households. The size and age composition of each household is parameterized using the distributions (mean: 4.76; standard deviation: 1.74) of household sizes collected from the 2011 Census Data in India [27]. We assume that the individual members of each household are fully connected (i.e., all individuals in the same household are linked by edges). We assume that our model represents the household structure, contact patterns, and SARS-CoV-2 transmission dynamics of a contact network, and directly scale our results from the 47,568 individuals in the model to the 1366 million residents of India. Following Du et. al. [28], we randomly connect individuals from different households, according to the Indian data about age-specific contact rates [29] in which all people are divided into five age groups: 0-5, 6-17, 18-49, 50-64, and > 65. Specifically, to determine the number of contacts between an individual of age group a_i and individuals of age group a_j, we draw a random variable from the Poisson distribution with rate equaling the mean number of contacts between age groups a_i and a_j. The resulting network has 10,000 households and 47,568 individuals.

Estimating the Years of Life Lost (YLL) Averted and Monetary Costs

Given each transmission and vaccination scenario, we simulate 100 random realizations for each of the three candidate vaccination strategies (including the status quo). For each round, we determine the years of life loss (*YLL*) averted for each strategy τ, as follows:

1. Calculate the difference in incidence by age group as $\Delta_{a,\tau} = D_{a,0} - D_{a,\tau}$, where $D_{a,0}$ and $D_{a,\tau}$ are the numbers of total death in age group a produced by the status quo and strategy τ simulations, respectively.
2. Estimate the YLL prevented by the vaccination strategy τ as

$$B_\tau = \sum_a (\lambda_a - a)\Delta_{a,\tau}$$

where λ_a denotes the future-discounted life expectancy for individuals of age a.

Similarly, we determine the incremental monetary costs for each strategy τ as given by

$$C_\tau = (T_\tau - T_0)\, c_T + \sum_a c_{H,a}\,(H_{\tau,a} - H_{0,a})$$

where T_τ and T_0 are the total number of vaccines administered in the strategy (τ) and status quo simulations, respectively, c_T is the price of administering one dose of vaccines, $H_{\tau,a}$ and $H_{0,a}$ are the total number of hospitalizations in age group a in each simulation, and $c_{H,a}$ is the median COVID-19 hospitalization cost for age group a. The cost parameter values are given in **Table S6**.

Estimating the Cost-Effectiveness Acceptability Curve

The willingness to pay per YLL averted is the maximum price a society is willing to pay to prevent the loss of one year of life. The GDP per capita, purchasing power parity (PPP) in 2020 is 6,454.3 USD and 63,543.6 USD for India and the US, respectively [30]. Health economists have inferred from healthcare expenditure that the US is willing to pay US$100,000 per quality-adjusted life-year [31], of which YLL is one component. We thus assume the willingness to pay in India is US$10,517 per YLL, estimated from that in the US with the scaling factor of their values of GDP per capita, PPP. For a given willingness to pay for a YLL averted (θ), we calculated the net monetary benefit (NMB) of a strategy as

$$\mathrm{NMB}_\tau = \theta \cdot B_\tau - C_\tau.$$

We determined the optimal strategy across a range of scenarios, each defined by the effective reproduction number (R_e), willingness to pay, and cost of a vaccine. For each transmission scenario coupled with each of the three candidate vaccination strategies (including the status quo), we simulate 100 random realizations of our stochastic model. For each of the 100 rounds of three simulations, we identify the strategy giving the highest NMB. We then estimate the probability that a particular strategy has the greatest net benefit of all strategies by the proportion of simulation rounds in which it gives the highest NMB. For a given scenario, the strategy with the highest probability of having the highest NMB is considered optimal. Using this approach, we assume a price of US$12 per vaccine and a US$10,517 willingness-to-pay per YLL averted and find the optimal strategy with the greatest net benefit.

Declarations

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Author Contributions

ZD, LW, and BJC: conceived the study, designed statistical and modelling methods, conducted analyses, interpreted results, wrote and revised the manuscript; AP, WWL, MC, APP, EHYL, PW, AM. and SC: interpreted results and revised the manuscript.

Competing interests

BJC is supported by the AIR@innoHK program of the Innovation and Technology Commission of the Hong Kong SAR Government.

Data availability

All data are collected from open source with detailed description in Section Method.

Code availability

Code used for data analysis is freely available upon request.

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Figures

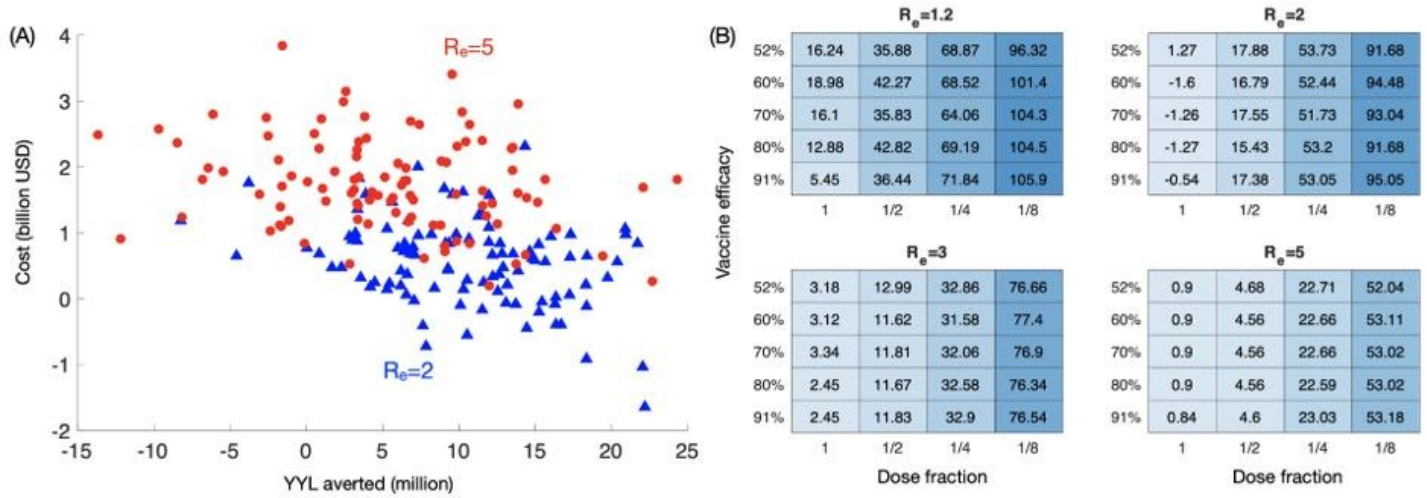

Figure 1

Estimated net monetary benefit of fractionated dose strategies averted. (A) Estimated costs of fractionated dose strategies and YLLs averted. Each data point corresponds to one of 100 stochastic simulations for the specified quarter dose fractionation strategy (circle and triangle denotes strategies with 91% vaccine efficacy of transmission under two Re scenarios, respectively), under parameters given in the appendix. Costs include admission to hospital due to COVID-19; YLLs averted considers mortality due to COVID-19. The costs and YLLs averted are all scaled assuming an Indian

population of 1366 million individuals. Re=effective reproduction number. YLLs=years of life lost. VE =vaccine efficacy of transmission. (B) Projected net monetary benefit averted ($ billion) in the India individual network with proportions of vaccine efficacy and dose fractionation. Assuming a vaccine cost of US$12 and WTP per YLL averted of US$10,517, these projections are mean estimates of net monetary benefit (NMB) based on 100 stochastic simulations of COVID-19 transmission over vaccine efficacy of transmission from 52% to 91% over 4 synthetic scenarios of transmission, under parameters given in the appendix. The optimal strategy under various transmission scenarios would always be doses of vaccines with more fractionations over vaccine efficacy of transmission.

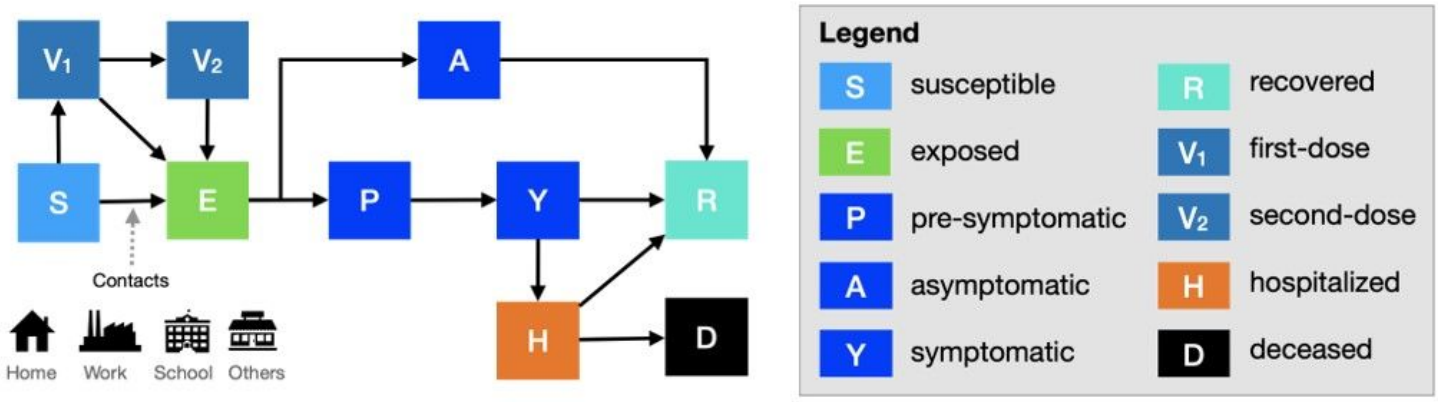

Figure 2

Schematic of the individual-based mathematical model of COVID-19 transmission and vaccination. Following infection from age-specific contacts in home, work, school or others, susceptible individuals (S) become exposed (E), during which they are infected but not yet infectious or symptomatic. After the incubation period, each infected case becomes asymptomatic (A), in which the asymptomatic case has a reduced infectiousness before recovery (R). The remaining infected cases progress to be pre-symptomatic (P), during which they have a moderate infectiousness with no symptoms. The pre-symptomatic cases progress to symptomatic infectious (Y), with a subset becoming hospitalized (H) or deceased (D). Recovered individuals remain permanently protected from future infection. Vaccinated individuals progress to a one dose (V1) followed by a two dose compartment (V2) with different efficacies.

Supplementary Files

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- V4SIVaccinationstrategieswithfractionateddose.docx