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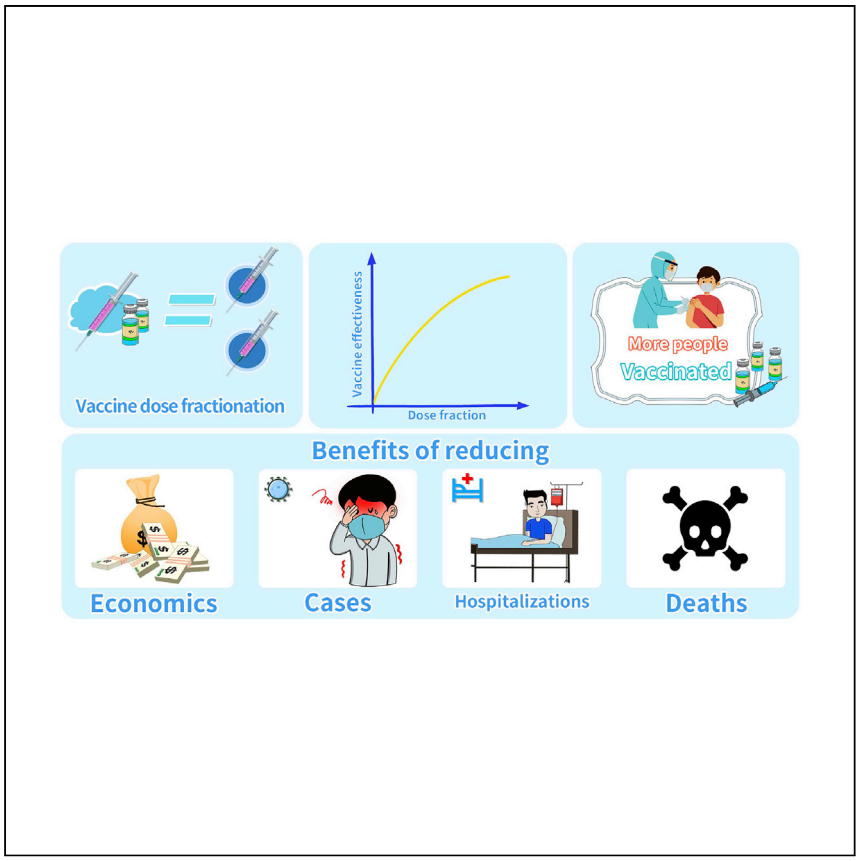
Cost effectiveness of fractional doses of COVID-19 vaccine boosters in India



This analysis demonstrated that the use of fractional dosing could offer greater net monetary benefit in both moderate and rapid transmission scenarios given the epidemiological and socioeconomic conditions in India in 2022. In the face of a vaccine shortage, the fractional dosage of vaccinations would have additional beneficial public health benefits.

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Highlights

Booster vaccination can improve waning immunity and reduce community epidemics

Epidemiological model that incorporates transmission and waning immunity is developed

Booster vaccination with fractionated doses as a cost-effective strategy in India

Translation to Population Health

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Cost effectiveness of fractional doses of COVID-19 vaccine boosters in India

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SUMMARY

Background: Coronavirus disease 2019 (COVID-19) continues to be a major global public health crisis that exacts significant human and economic costs. Booster vaccination of individuals can improve waning immunity and reduce the impact of community epidemics.

Methods: Using an epidemiological model that incorporates population-level severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission and waning of vaccine-derived immunity, we identify the hypothetical potential of mass vaccination with fractionated vaccine doses specific to ChAdOx1 nCoV-19 (AZD1222 [Covishield]; AstraZeneca) as an optimal and cost-effective strategy in India's Omicron outbreak.

Findings: We find that the optimal strategy is 1/8 fractional dosing under mild (Re ~ 1.2) and rapid (Re ~ 5) transmission scenarios, leading to an estimated $6 (95% confidence interval [CI]: −13, 26) billion and $2 (95% CI: −26, 30) billion in health-related net monetary benefit over 200 days, respectively. Rapid and broad use of fractional dosing for boosters, together with delivery costs divided by fractionation, could substantially gain more net monetary benefit by $11 (95% CI: −10, 33) and $2 (95% CI: −23, 28) billion, respectively, under the mild and rapid transmission scenarios.

Conclusions: Mass vaccination with fractional doses of COVID-19 vaccines to boost immunity in a vaccinated population could be a cost-effective strategy for mitigating the public health costs of resurgences caused by vaccine-evasive variants, and fractional dosing deserves further clinical and regulatory evaluation.

Funding: Financial support was provided by the AIR@InnoHK Program from Innovation and Technology Commission of the Government of the Hong Kong Special Administrative Region.

CONTEXT AND SIGNIFICANCE

The global supply shortage of COVID-19 vaccines was a major challenge in low-income countries before 2022. Here, researchers at The University of Hong Kong, University of Cambridge, University of Oxford, University of California San Diego, and University of Chicago assessed the potential economic benefit and cost of using fractions of the standard dose of SARS-CoV-2 booster vaccines based on a data-driven model of SARS-CoV-2 transmission that incorporates waning immunity induced by vaccination or infection. Given the epidemiological and economic conditions in India in 2022, this study showed that the use of fractional dosing could provide more net monetary benefit under both mild and rapid transmission scenarios. Fractional dosing of vaccines would provide additional public health benefits in the face of a vaccine shortage.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been a global public health and medical crisis for more than 2 years since the start of 2020, resulting in 462 million reported cases and 6.05 million deaths as of March 16, 2022, globally.[1] Mass vaccination has been a key measure to mitigate the COVID-19 pandemic, and the global supply shortage of COVID-19 vaccines was a major challenge of supply rather than demand in low-income countries, which collectively received only 0.2% of all vaccines delivered worldwide for approximately 10% of the world's population as of July 2021[2] but not in 2022 as supply and donations have ramped up. From December 2021, many high-income countries actively deployed massive vaccination of booster doses to mitigate the unprecedented Omicron wave, which exacerbated vaccine supply

shortages in low- and lower-middle-income countries, perhaps due to the expectation of waning immunity against variants.[3,4] Recent clinical studies suggest that robust, highly effective immune protection against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and less reactogenicity[5] could be achieved with fractional doses of booster vaccines. Indeed, third doses of the Moderna vaccine are provided with a fractional (half) dose.[6]

Dose fractionation of COVID-19 vaccines could help accelerate vaccine rollout and expand vaccination coverage regardless of vaccine supply constraints. Modeling studies suggest that dose fractionation of COVID-19 vaccines could substantially accelerate vaccination coverage and reduce the disease and economic burden of COVID-19.[7,8] Therefore, hypothetically, the dose fractionation of COVID-19 booster vaccines might be a cost-effective strategy to accelerate vaccination in low- and lower-middle-income countries, which can enhance their population immunity by compensating for waning of immunity over time and immune escape of emerging variants.[2]

India is among the countries worst hit by the COVID-19 pandemic, with 43 million confirmed cases and 0.5 million deaths as of March 16, 2022.[1] The COVID-19 vaccination program was started in India on January 16, 2021. As of January 9, 2022, more than 60% of the Indian population had received at least one dose of the COVID-19 vaccine. The relatively slow pace of COVID-19 vaccination in India was partially due to vaccine shortages and inequity of vaccine distributions. Given the Omicron wave started from early January 2022, the COVID-19 booster vaccination was initiated in India on January 10, 2022.[9] Although 1.4% of the Indian population received the booster doses in the 2 months that ensued, the Omicron wave recorded 8 million reported cases (0.5% of the Indian population).[9] The maximum capacity of the healthcare systems in India allows 150 million of the Indian population to be vaccinated per month, requiring over 10 months to vaccinate the entire Indian population with booster doses. Assuming that vaccines approved in India face a shortage in the total number of full doses available for booster, we evaluated the hypothetical economic costs and benefits of fractionated booster doses of COVID-19 vaccines. Here, we use an age-stratified, individual-based model that explicitly incorporates the waning efficacy of COVID-19 vaccines ChAdOx1 nCoV-19 (AZD1222 [Covishield]; AstraZeneca), waning immunity of natural infection, and vaccination rollout rates to assess the costs and benefits of fractional-dose vaccines (Figure 1).

RESULTS

We examined the expense of hospitalization and booster doses, as well as the economic benefits of reducing COVID-19 mortality using dose-fractionation strategies, informed by willingness-to-pay per age group (STAR Methods). We explored a wide range of possible disease transmissibility, waning vaccine efficacy, and waning immunity from natural infection (Figure 1; Figure 2; Table S1). By comparing several potential fractional-dose strategies with an alternative of full-dose vaccination, we found that booster doses with higher-fold fractionations will increase the cost effectiveness even if the interval between the second dose and booster is long (Figures 3 and 4).

We find that the optimal strategy with undivided delivery cost (cost of administering each *1/f* fractionated dose of vaccination is $12/*f*) is 1/8 fractional dosing under mild ($R_e \sim 1.2$) and rapid ($R_e \sim 5$) transmission scenarios, leading to an estimated $6 (95% confidence interval [CI]: −13, 26) billion and $2 (95% CI: −26, 30) billion in health-related net monetary benefit over 200 days, respectively, compared with

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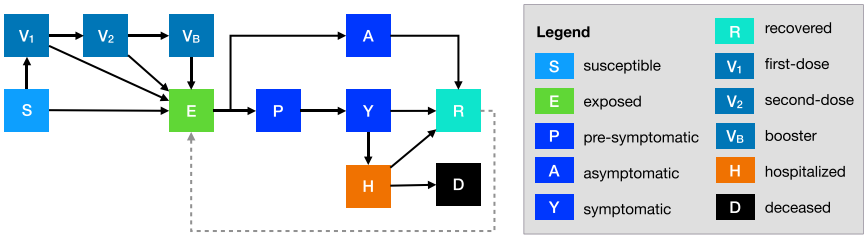

Figure 1. Schematic of the individual-based mathematical model of COVID-19 transmission and vaccination

Following infection, susceptible individuals (S) enter an exposed state (E), where they are not yet infectious or symptomatic. A fraction of cases then progress to a moderately infectious asymptomatic state (A). The remaining progress first to a moderately infectious pre-symptomatic state (P) before becoming highly infectious and symptomatic (Y). A fraction of symptomatic cases will be hospitalized (H), and a subset of those will die (D). Eventually, asymptomatic and symptomatic individuals recover (R) and remain protected from future infection for the duration of the simulation. Vaccinated individuals progress to a one dose (V_1) followed by a two-dose state (V_2) and booster (V_B). Individuals who have been exposed to the virus go through a non-infectious incubation period (on average of $1/\sigma$ days) before becoming pre-symptomatic of the disease with probability p_{sym} or asymptomatic with probability $1 - p_{sym}$. At a rate ε, the pre-symptomatic cases develop symptoms and recover at a rate γ (Table S3). The degree to which an infected person is contagious is determined by the severity of the infection. The relative infectiousness $\hat{\omega}$ and ω are used to scale the infectiousness of asymptomatic and pre-symptomatic cases, respectively.

unfractional dosing for booster over 200 days (Figures 3 and 4). If the use of fractional dosing for boosters can be shortened from 9 to 3 months, the net monetary benefit of 1/8 fractional dosing would increase to \$8 (95% CI: −14, 29) billion and \$−1 (95% CI: −27, 24) billion, respectively (Figures 3 and 4). If the delivery costs can be divided by fractionation (cost of administering each *1/f* fractionated dose of vaccination is \$[3/*f* + 9]), the net monetary benefit could substantially increase to \$11 (95% CI: −10, 33) and \$2 (95% CI: −23, 28) billion, respectively, under the mild and rapid transmission scenarios. These results hold for weaker vaccine efficacy of fractional dosing (Figure 5).

The strategy of 1/8 fractional dosing would also avert 1 (95% CI: −0, 2) and 0 (95% CI: −1, 2) million of hospitalizations under mild ($R_e \sim 1.2$) and rapid ($R_e \sim 5$) transmission scenarios, respectively, over 200 days (Figure S1). With a shorter time interval to use the fractional dosing for boosters, the number of hospitalization (million) averted by 1/8 fractional dosing would increase to 2 (95% CI: 1, 3) and 1 (95% CI: −1, 2). For the number of deaths (thousand), 1/8 fractional dosing would avert 195 (95% CI: −236, 625) and 91 (95% CI: −557, 739) under mild and rapid transmission scenarios, respectively. The shortened time interval to use boosters would significantly increase the number averted to 193 (95% CI: −278, 665) and 45 (95% CI: −549, 639) under the mild and rapid transmission scenarios, respectively.

DISCUSSION

About 2 years into 2020 and 2021 of the COVID-19 pandemic, many parts of the world struggled with outbreaks attributed to immune-escape variants, waning population immunity, and the opening of borders coinciding with the rollback of social distancing measures in many locations, encouraging a greater mixing of individuals with varying exposure to vaccination and infection. While countries previously grappled with limited supplies of vaccines and effective treatment, improvements in vaccine availability and effective treatment have largely mitigated the severe morbidity and mortality seen in the pre-vaccine period. The emergence of immune-escape

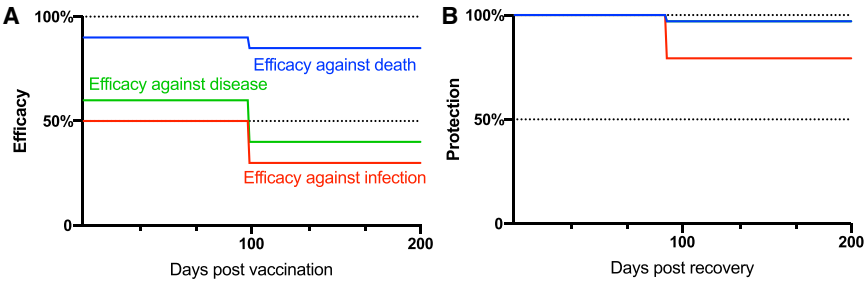

Figure 2. Protection efficacy of the booster dose and natural infection

(A) Vaccine efficacy (Omicron) against symptomatic disease, infection, and death.

(B) Protection efficacy of natural infection against disease, infection, and death. More details can be found in Table S1.

variants threatened healthcare systems as breakthrough infections among vaccinated and/or recovered populations caused significant, albeit milder, disease.

The use of fractionated vaccine doses to boost population immunity could be a cost-effective strategy to mitigate COVID-19 disease burden and healthcare costs. Our cost-effectiveness analysis using a data-driven epidemiological model of the ChAdOx1 vaccine as an example indicates that switching to fractional dosing of vaccines for booster doses could mitigate the healthcare and economic burdens by accelerating vaccination in the context of vaccine shortages in the past. Compared with the alternative full-dose vaccination for booster shots, the fractional dosing of ChAdOx1 vaccines would be an economically optimal vaccination strategy, even if fractional doses are less effective than full doses. In our estimation, the net monetary benefit of fractional dosing has a wide 95% CI, perhaps attributable to the low vaccination rate, which can only result in a small number of individuals vaccinated per day in contrast to the daily number of new infections. The impact of vaccines is weakened in the high-transmission scenario. Specifically, most populations are infected over a short period, during which only a small proportion of the population is vaccinated for booster doses. Since the clinical data to support this approach are currently limited, regulatory approval of fractional doses is unlikely in the short term. This is a missed opportunity.

There is good evidence that fractionated doses can elicit comparable levels of antibodies against ancestral strains[2,7] and protection against immune-escape variants.[11] Also, fewer COVID-19 antigens may be required to generate protective immune responses against COVID-19 infection. Therefore, fractionated doses of booster vaccines could not only be a cost-effective strategy but it would also be more cost efficient, potentially conserving valuable resources that could be redirected to the development, manufacturing, and distribution of newer vaccines that could address immune-escape variants.

Concerns about ethics, politics, and vaccine hesitancy or resistance have also been raised as a potential disadvantage of dose-sparing strategies,[12] which may have resulted in no low-income countries currently adopting dose-sparing strategies for COVID-19 vaccines. However, vaccine manufacturers have sponsored dose-sparing trials for both children and boosters[13,14] and approved a one-third-dose mRNA vaccine made by Pfizer-BioNTech for children aged 5–11[15,16] and half-dose booster mRNA vaccines by Moderna for adults.[6] And clinical trials have indicated that fractional doses could provide a robust, highly effective immune response[17] and fewer side effects (e.g., fever).[5]

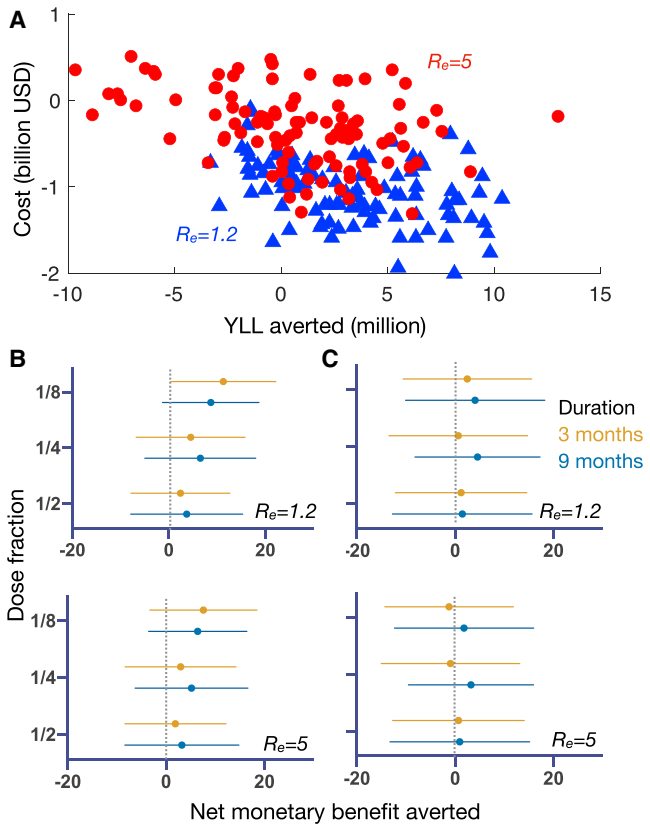

Figure 3. Expected net monetary benefit (NMB) averted for each fractional-dose strategy

(A) An example for the estimated costs of fractionated dose strategies versus the averted years of life lost (YLLs) with reference to the standard booster vaccine strategy. Each dot indicates one realization of the 100 stochastic simulations given the use of 1/8 dose fractionation strategy with 3 months for the duration of booster dose post-second dose in two transmission scenarios.

(B) Estimated mean and standard deviations for the expected gain in the NMB (billion USD) over two durations of booster dose post-second dose given the cost of administering each *1/f* fractionated dose of vaccination as $12/*f* and willingness to pay (WTP) per YLL averted of USD 1,097, USD 1,251, USD 2,977, USD 3,150, and USD 3,205 for five age groups (0–5, 6–17, 18–49, 50–64, and >65), respectively.

(C) Same as (B) but setting the cost of administering each *1/f* fractionated dose of vaccination as $(3/*f* + 9).

As of January 2022 and prior to the Omicron surge, the COVID-19 Delta pandemic wave in India during March and June 2021 exposed large portions of the unvaccinated and vaccinated to COVID-19,[18] which would acquire immunity through natural and breakthrough infection. And over 60% of individuals have received at least one dose as of January 2022. Immunity following natural infections and vaccinations reduced the impact of the Omicron outbreak during January and February 2022, which was smaller than that of the Delta pandemic, although the Omicron variant has a triple effective reproduction number compared with that of the Delta variant.[19] The next variant may be less severe but have a higher transmissibility than Omicron. Although vaccine-derived immunity is expected to wane quickly, vaccines have changed the course of the COVID-19 pandemic.[20] However, a highly vaccinated population is still not enough to combat Omicron's spread, as variants have been able to escape the immunity conferred by vaccinations or prior infections.[21] A booster dose can temporarily increase the protection against symptomatic infection

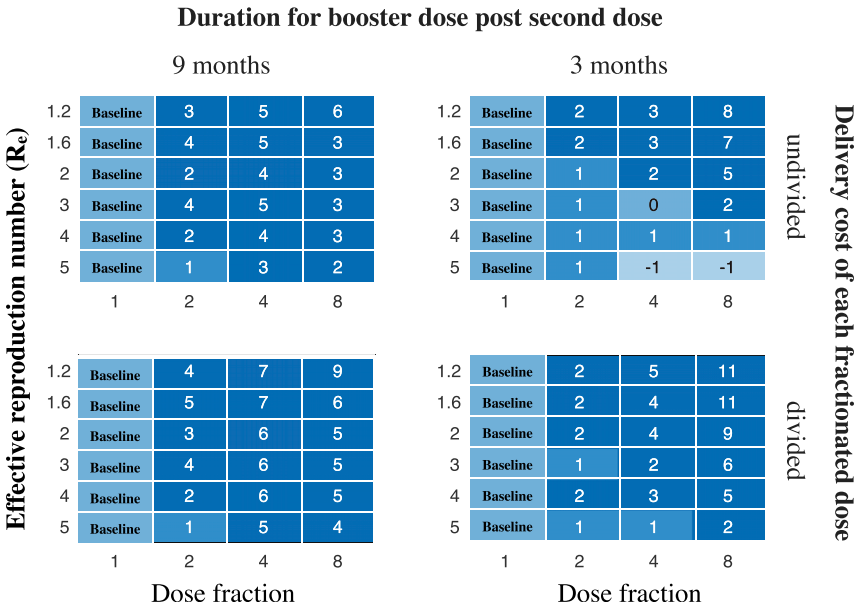

Figure 4. Projected mean estimation (in 2021 billion USD) of the expected gain in the NMB for each fractional-dose strategy compared with the status quo strategy (i.e., standard vaccination) in India

The estimation examines a wide range of possible transmission (with effective reproduction number R_e increasing from 1.1 to 5) and waning vaccine efficacy (Table S1) scenarios. Given each R_e, the duration of booster dose post-second dose is considered as 9 months in the left column and 3 months in the right column (SARS-CoV-2 vaccination program in India). Cost of administering each *1/f* fractionated dose of vaccination is $12/*f* (bottom panels) or $(3/*f* + 9) (top panels), which indicates that the delivery cost can also be divided or not. $3 is the vaccine procurement price per dose, and $9 accounts for the vaccination delivery costs including delivery, distribution, and potential wastage[10] (Table S4). The WTP per YLL averted values are USD 1,097, USD 1,251, USD 2,977, USD 3,150, and USD 3,205 for five age groups 0–5, 6–17, 18–49, 50–64, and >65, respectively. Under different transmission scenarios, the optimal strategy would always be the vaccination with fractionations, even if the duration for booster dose post-second dose is 9 months.

by either subvariant back to 30%–60%[22] and likely provide more sustained protection against severe COVID. In India, 27% of the population received second or booster vaccine doses between January and March 2022, of which 1.5% were vaccinated with booster doses at the end of March 2022.[9] The fractional dosing strategy would offer a choice to supply such as these.

Countries can time the ramp up of their booster campaign as close to the nation's full reopening as possible, to account for waning immunity, when there is a supply shortage of COVID-19 vaccines. However, low- and middle-income countries (LMICs) have the highest burden of endemic infectious diseases (e.g., HIV) and had to reallocate limited resources against COVID-19,[23] facing considerable obstacles to raising necessary financing in both receiving and distributing vaccines. As of March 19, 2022, over 11 billion vaccine doses had been administered. However, nearly 70% of them benefited high- and upper-middle-income countries,[24] in which 79% of people in high-income countries had received at least one dose compared with just 14% in low-income countries.[24] This would put substantial pressure on the healthcare providers in LMICs, who have faced vaccine shortages and delays.

In conclusion, fractionation of booster doses for SARS-CoV-2 vaccination could be more efficacious than the current standard as a cost-effective strategy to mitigate

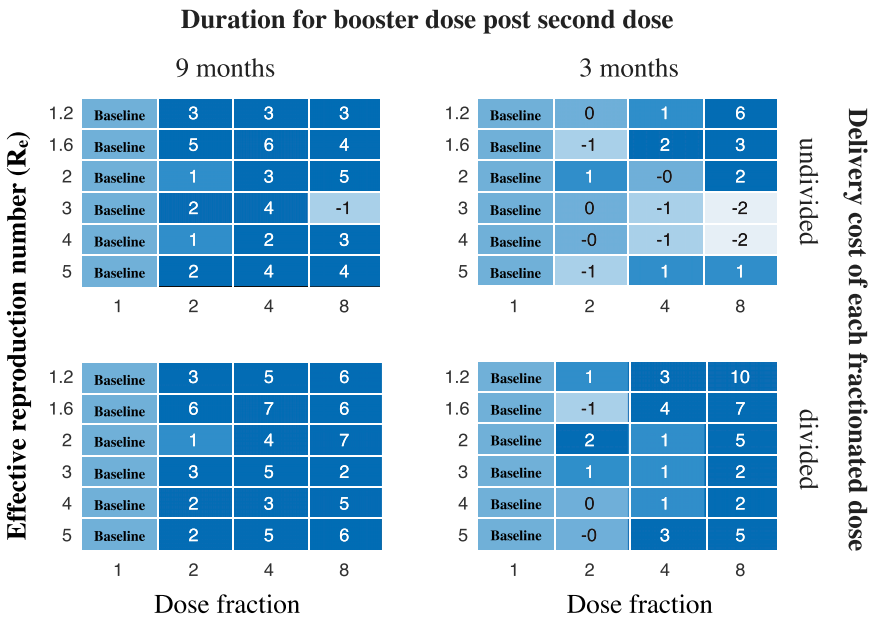

Figure 5. Sensitivity analysis of projected mean estimation (in 2021 billion USD) of the expected gain in the NMB for each fractional-dose strategy compared with the status quo strategy (i.e., standard vaccination) in India

The estimation examines a wide range of possible transmission (with effective reproduction number R_e increasing from 1.1 to 5) and waning vaccine efficacy (Table S1) scenarios. We set the waning vaccine efficacy of fractional dosing boosters beginning from the 141st day of that of standard dose. Given each R_e, the duration of booster dose post-second dose is considered as 9 months in the left column and 3 months in the right column (SARS-CoV-2 vaccination program in India). Cost of administering each *1/f* fractionated dose of vaccination is $12/*f* (bottom panels) or $(3/*f* + 9) (top panels), which indicates that the delivery cost can also be divided or not. $3 is the vaccine procurement price per dose, and $9 accounts for the vaccination delivery costs including delivery, distribution, and potential wastage[10] (Table S4). The WTP per YLL averted values are USD 1,097, USD 1,251, USD 2,977, USD 3,150, and USD 3,205 for five age groups 0–5, 6–17, 18–49, 50–64, and >65, respectively. Under different transmission scenarios, the optimal strategy would always be the vaccination with fractionations, even if the duration for booster dose post-second dose is 9 months.

transmission of SARS-CoV-2 in India. If SARS-CoV-2 variants escaping immunity emerge in the coming future, fractional dosing of vaccines might provide additional public health and economic benefits to reformulate the population in the face of a vaccine shortage in the early stage of outbreaks. We strongly encourage more investment in clinical research on fractional dosing of COVID-19 vaccines.

Limitations of the study

Currently, we have no definitive data to tell the epidemiological and economic impact of fractional vaccine dosing on disease spreading given that it was not applied in the world when there was a vaccine shortage in 2020 and 2021. Mathematical models can provide epidemiological insights. Individual-based epidemic models are a general framework, as an alternative to traditional epidemiological compartmental models, to simulate events subject to individual stochasticity and heterogeneity. The projected results in the individual-based model, including thousands of households, would be expected to have little difference with increased population size.[25]

There are several assumptions in our study. First, our model does not explicitly include contact patterns with high contact rates (e.g., home caregivers). Second, our study only considers vaccination and hospitalization and the averting of

hospitalizations and deaths via vaccination without explicitly incorporating related non-pharmaceutical interventions but captured by different values of R_e. Third, we mainly considered the economic expense of vaccines and hospitalization in the private sector, which may vary widely depending on both types of hospitals[26] and vaccines.[27]

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
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  - Materials availability
  - Data and code availability
- METHOD DETAILS
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  - Individual-based epidemic model
  - Estimating the willingness to pay per averted YLL and the cost-effectiveness

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.medj.2023.02.001.

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AUTHOR CONTRIBUTIONS

Z.D., L.W., Y.B., and B.J.C. designed the overall experiments and had unrestricted access to all data and performed the experiments. S.F., S.R., W.W.L., E.H.Y.L., and A.M. performed statistical analyses and wrote the article. All authors read and approved the final article and take responsibility for its content.

DECLARATION OF INTERESTS

B.J.C. consults for AstraZeneca, GlaxoSmithKline, Moderna, Pfizer, Roche, and Sanofi Pasteur. B.J.C. is supported by the AIR@innoHK program of the Innovation and Technology Commission of the Hong Kong SAR Government.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
Matlab R2021b	The MathWorks, Inc.	https://www.mathworks.com/
Keynote version 12.2	Apple Inc.	https://www.apple.com/hk/en/keynote/

RESOURCE AVAILABILITY

Lead contact

Further information and request should be directed to the lead contact, Benjamin J. Cowling (bcowling@hku.hk).

Materials availability

This study did not generate new unique reagents.

Data and code availability

All data were collected from open-access sources with detailed description in the section Method. All data used in this study are publicly available, including the daily vaccination rate of the first dose in India (https://ourworldindata.org/covid-vaccinations), and the 2011 Census Data in India (https://censusindia.gov.in/Tables_Published/HH-Series/hh_series_tables_20011.html). All Matlab codes used in this study would be accessed at github.com/ZhanweiDU/VaccineBooster (*Zenodo*. doi.org/10.5281/zenodo.7323432). We use Keynote (version 12.2) to combine figures generated by Matlab. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

METHOD DETAILS

SARS-CoV-2 vaccination program in India

We considered the COVID-19 vaccination with two standard doses and an additional booster dose using ChAdOx1 (Covishield, AstraZeneca) vaccine manufactured by the Serum Institute of India. We considered dose fractionation for the booster dose. Let $\omega_1(t_{V1})$ be the vaccine efficacy against Omicron infection at t_{V1} days after the first standard dose (i.e., *V1*), $\omega_2(t_{V2})$ the vaccine efficacy against Omicron infection at t_{V2} days after the second standard dose (i.e., *V2*), and $\omega_B(t_{VB})$ the vaccine efficacy against Omicron infection at t_{VB} days after the booster dose (i.e., *VB*). The vaccine efficacy declines over time and depends on the time post vaccination (Table S1). Let $\omega_N(t_R)$ describe the protective effect of pre-existing immunity against Omicron infection for individuals who recovered from previous infection, which also declines over time and depends on the time post recovery (Table S2). As the Delta variant dominated the SARS-CoV-2 transmission in India during March to June 2021, we assumed that the prior infections were primarily driven by the Delta variant before the initiation of booster vaccination on 13 January 2022. The immunity elicited by vaccine or natural infection reduces the individual susceptibility in acquiring Omicron infection by a factor $\omega_1(t_{V1})$ for the first dose, by $\omega_2(t_{V2})$ for the second dose, and by $\omega_N(t_R)$ for natural infection.

Similarly, we considered the vaccine efficacies against symptomatic disease and against death after an Omicron infection for each dose of vaccination, which decline over the time post vaccination (Table S1). We also considered the protective effect of

pre-existing immunity against symptomatic disease and against death of the Omicron infection for individuals who recovered from previous infection, which change over the time post recovery (Table S2). To reflect the effect of vaccine breakthrough, we assumed that if vaccinated individuals acquire infection, they have the same transmission rate as those unvaccinated.

Let d_2 be the time interval between the first and second doses, and d_B the time interval between the second and booster doses (Table S3). Individuals receive the second dosing when it is d_2 days after the first dosing, and they receive the booster dosing when it is d_B days after the second dosing. We assigned the vaccines available per day to individuals taking their first, second or booster dose according to the empirical data about the daily number of individuals that can receive each dose[24] (Table S3). Based on the COVID-19 vaccination agenda in India, only individuals over age 18 could be vaccinated before 2 January 2022, after which individuals between 15 and 18 were also allowed to be vaccinated.[28]

We conducted a sensitivity analysis on the vaccine efficacy of the booster dose by assuming that efficacy against infection (ω_B), symptomatic disease (ψ_B), hospitalization (κ_B), and death (θ_B) have values of vaccine efficacy after 20 weeks since the first day post vaccination for different settings of dosing (Figure 5).

Individual-based epidemic model

In our individual-based model, we built an Indian community with 10,000 households comprising 47,568 individuals. Community members from different households are connected through a static contact network using the 2011 Census Data in India[29] and members of each household are fully connected. We stratified all individuals into five age groups: 0–5, 6–17, 18–49, 50–64 and >65 years. Following Du et al.,[8,25] we used the age-specific contact rates data in India[30] to develop the connection network for individuals from different households. By scalarizing a single community of 47,568 individuals to the entire population of 1,366 million Indians, we obtain economic evaluation results for the whole country. In other words, we run each simulation for 47,568 individuals, and get the net monetary benefit in the population by scaling the 47,568 individuals to the entire population of 1,366 million.

Using this individual-based model of a single Indian community, we simulated the spread of SARS-CoV-2 over 200 days from 13 January to 31 July 2022. Our model considers the changes in health status over 10 possible states for each individual, including susceptible, vaccination with a single dose, with two doses, and with a further booster dose, exposed, asymptomatic, pre-symptomatic, symptomatically infectious, recovered, hospitalized, and deceased (Figure 1). The transmissibility of Omicron variant of SARS-CoV-2 is quantified by the effective reproduction number R_e, which denotes the mean number of secondary infections per infector that is averaged over the first 5,000 infectors in each simulation realization. We used an interior-point algorithm[31] to calibrate the transmission rate per contact β by minimizing the mean square error between the target value of R_e and our simulated estimation of Re that is averaged over 100 realizations of the simulated pandemic. Each simulation realization is performed with two steps: (1) simulation with the status quo strategy (booster vaccination with standard doses); and (2) simulation with the rollout of fractional booster vaccines. We compared the public health and economic impacts between the fractional vaccination strategy and status quo strategy.

We consider one possible initialization scenario for the simulated pandemic in India, assuming that 1% of the Indian population had been randomly exposed to the

Omicron infections at the start of the simulations. The start time of our simulation corresponds to 13 January 2022, when the COVID-19 booster vaccination program began in India. To account for the Indian population who had received COVID-19 vaccines before13 January 2022, we collected the vaccination data each day from the start of COVID-19 vaccination program in India[24] on 16 January 2021 to 12 January 2022. This provides the number of Indian population receiving the first standard dose ϑ_1 (d) and receiving the second standard dose ϑ_2 (d) on each day d. As of 12 January 2022, 64.5% of the Indian population had received at least one standard dose. According to the sixth Delhi seroprevalence survey conducted in April 2021, 97% of the population in Delhi had antibodies reacting to the SARS-CoV-2 virus.[32] There were eight million cases in India's Delta outbreak during December 2021 and February 2022.[24] We thus assumed that 32.5% of the Indian population were infected by the Delta variant as of 13 January 2022. The time at which each of these 32.5% Delta cases was recovered is assigned according to the temporal distribution of daily new cases reported over the period between 16 January 2021 and 12 January 2022.[24]

Estimating the willingness to pay per averted YLL and the cost-effectiveness

Our simulations include the status quo as well as 100 random realizations of each potential vaccination strategy, accounting for the COVID-19's vaccination and hospitalization costs as well as the years of life lost (YLLs) as a result of mortality. We calculate YLL averted following each strategy τ for each realization. We estimate the YLL averted by the vaccination strategy τ as

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

where λ_a denotes the future-discounted life expectancy for individuals of age a. $\Delta_{a,\tau} = D_{a,0} - D_{a,\tau}$ is the difference in deaths for age group a, where $D_{a,0}$ and $D_{a,\tau}$ are the total number of deaths in age group a for the status quo and strategy τ, respectively. And the incremental monetary costs averted for each strategy τ is given:

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

where $(T_\tau - T_0)$ and $(H_{\tau,a} - H_{0,a})$ are the differences in administered vaccines and hospitalizations, respectively, between the strategy τ and status quo. c_τ and $c_{H,a}$ are the cost per dose delivered for each dose and hospitalization cost for age group a, respectively (Table S5).

The willingness to pay (WTP) per averted YLL (θ_a for age group a) is set as vUS$1,097, US$1,251, US$2,977, US$3,150, and US$3,205 for five age groups 0–5, 6–17, 18–49, 50–64, and >65, respectively.[8] The net monetary benefit (NMB) of a strategy is given by

$$\mathrm{NMB}_\tau = \sum_a \theta_a * B_{\tau,a} - C_\tau$$

A population of 1366 million people in India is used to scale all costs and YLLs reduced in this analysis. We first simulate 100 stochastic realizations of each candidate vaccination strategy for each set of disease transmissibility and vaccine efficacy (including the status quo). We then use the above formulas to calculate the expected gain in the net monetary benefit for each candidate strategy τ in contrast with the status quo strategy. For each measure (e.g., net monetary benefit), we estimate the mean and SD of the 100 values, each from a stochastic realization, and evaluate the 95% confidence interval by mean $\pm$ (1.96 $\times$ SD).