Personalized-dose COVID-19 vaccination in a wave of virus *Variants of Concern*: Trading individual efficacy for societal benefit

Patrick Hunziker^{†‡§*}

[†] Intensive Care Unit, University Hospital Basel, Switzerland

[‡] University of Basel, Switzerland

[§] CLINAM Foundation, Basel, Switzerland

Submitted: May 26, 2021

Accepted: July 7, 2021

Published: July 24, 2021

Graphical Abstract

Abstract

Limited vaccine supplies and virus variants of concern threaten to prolong the COVID-19 pandemic. The elderly dies more frequently, but the younger drives disease transmission. Here, we explore strategies that trade individual vaccine efficacy for increased numbers of vaccinations by personalized vaccine dosing during the onset of a wave of virus variants of concern. The model incorporates US demographic and epidemic data and vaccine characteristics. We find that broad, personalized-dose vaccination, trading individual efficacy for vaccination speed and societal benefit, mitigates an infection wave of highly infectious *variants of concern* better and overcomes the pandemic faster than conventional “elderly first” strategies. This strategy implies that on a global scale, tailoring vaccine dose and vaccination strategy to the pandemic phase and demographic characteristics may have significant potential for minimizing deaths and quickly mastering the pandemic.

*Corresponding author: hunzikerp@swissnano.org.

The first version of this manuscript has been deposited to a preprint repository on January 30, 2020, and can be found here: <https://doi.org/10.1101/2021.01.30.21250834>

Keywords

Coronavirus, infection, COVID-19, vaccine, mRNA vaccine, strategy, public health, computer modeling, epidemiology, mortality, USA, variant of concern, mRNA-1273

Rationale and Purpose

COVID-19 is a threat to individuals, local healthcare systems, economies, and global health. Vaccination is one cornerstone of mastering the pandemic. While nanoparticle-based vaccines have been highly successful in clinical trials, their global deployment is a significant challenge, and new waves of virus variants can even arise in the few countries with a high percentage of vaccinated persons. Therefore, this study aims to identify vaccination strategies that make the best use of the limited vaccine stock available to minimize infections and deaths at a continental scale in the fastest possible way.

Introduction

Vaccines against SARS-Cov2 have been developed at “warp speed” and are pillars of managing the evolving COVID-19 pandemic.¹ mRNA vaccines like the Pfizer BNT162b2² (Tozinameran) and the Moderna mRNA-1273³ have shown strong immunogenicity, safety, and efficacy against disease. Emerging data also show protection against infection (and thus, transmission) by the immune response reached in natural infection⁴ and vaccination.^{5,6,7} In addition, antibody levels required for significant protection from infection and severe disease are markedly lower⁸ than average convalescent levels and levels after vaccination.

While a new global peak was observed in January 2021, manufacturing lines cannot cover the vast global demand, calling for optimally effective strategies for vaccine deployment. While phase I-II data have confirmed that elderly people exhibit reduced immune responses to vaccination,⁹ the vaccines have been dose-optimized to achieve excellent immunity even in the elderly, suggesting that for younger people (such as those ≤ 64 years), the standard vaccine dose may be higher than needed, as antibody levels are known to correlate with protective efficacy.¹⁰ To obtain proof of efficacy quickly, pivotal trials were performed at “one

fits all” dose levels. In younger people, sufficient immunity might be reached with lower vaccine doses.¹¹ Faced with the currently severe vaccine availability bottleneck, a lower dose per vaccination would translate into more significant numbers of people receiving the vaccine early. Due to their social contact patterns,^{12,13} younger people drive the pandemic to a large degree. Vaccinating them early while continuing to protect the vulnerable may prove to be a game-changing strategy for stopping the pandemic rapidly. In the younger, even quarter-dose vaccination with the Moderna vaccine elicits immune titers (S-2P antigen antibodies, receptor-binding domain binding antibodies, pseudovirus neutralization assay, and live-virus plaque-reduction neutralization testing assay) that are higher or similar to those seen in convalescent sera and in the elderly vaccinated at full dose, as shown in the supplement.

Virus variants of concern (VOC) are currently spreading fast^{12,13} and may be associated with reduced vaccine efficacy.¹⁴ According to emerging data, infection and transmission are reduced by vaccination^{15,16} and antibody titers after immunization are correlated with protection from reinfection.¹⁷ However, even partial vaccination with an mRNA vaccine still led to vaccine efficacy for symptomatic disease, infection, and transmission to a degree covered by our model.¹⁸

Therefore, we tested the hypothesis that early in a wave, due to highly infectious virus variants of concern, personalized, age-tailored vaccine dosing strategies will allow early vaccination of significantly more persons and translate into a reduction of caseload, deaths, and pandemic duration.

Methods

Detailed methods are described in the supplement.

Scenarios were tested using a pandemic model (Figure 1 and supplement) that is based on the SEIR (susceptible, exposed, infective, recovered) approach with a discrete structure^{19,20} with daily assessment for 100 consecutive days. It includes two age strata that are differentially parameterized for age-specific differences in social interaction, case fatality rate, and vaccine efficacy, including the interaction of the two groups, as described in detail in the online methods.

Figure 1: COVID-19 case numbers, deaths, and “risk contact” propensity during 100 days of a vaccination campaign modeled for the USA. **Panel A:** COVID-19 cases per day, comparing the different scenarios. Note that using a reduced (quarter) dose vaccine reaches a larger proportion of the population faster. Despite a reduced efficacy per individual person, the societal impact, measured as case number reduction, is strongest for a personalized-dose, reduced-dose vaccination strategy, and the strategy with reduced-dose vaccination starting solely in the young. **Panel B:** Death number reduction is initially fastest by an “elderly first,” and to some degree by the “personalized-dose” strategy, while later, the broadest approach, namely vaccinating primarily the young, has the largest impact it stops the pandemic most quickly. **Panel C, D, E:** Risk contact propensities (i.e., a non-immune meets an infectious person) and “semi-risk contacts” (a vaccinated or previously infected meets an infective person, acknowledging that the protection provided is less than 100%) compared to day 1.

We documented the robustness of the model to variations in infectivity, vaccine efficacy, and prevalence of non-documented infections in the community. The model baseline starts with the demographic and epidemiologic situation in the USA in late January 2021.

Vaccination strategies include:

“Elderly first”: starting with regular dose vaccination until 80% of the elderly are covered, then vaccinating the younger at regular dose.

“Young first”: starting with regular dose vaccination in the younger, leaving the elderly aside during the first 100 days.

“Personalized-dose”: in parallel, using half of the stock for each, vaccinate the elderly at full dose and the young at a quarter dose.

“Personalized-dose, the young first”: starting with quarter dose vaccination in the young, leaving the elderly aside until 80% of the young are vaccinated.

We then looked at the impact of vaccination strategies in the context of a rapid spread of a variant of concern on public health outcomes such as case number, deaths, and pandemic wave evolution. Specifically, an initial reduction in case numbers with a reproduction number of 0.8 as observed in the US was paralleled by a rapid spread of a VOC with 1.5-fold infectivity that becomes dominant within 40 days and is also characterized by reduced vaccine protection.

Results

Limitations of “elderly first” and “young first” vaccination strategies

Baseline results in the “elderly first” strategy, using standard vaccine dosing, predict a cumulative death count of 153,000 over 100 days. Case numbers fall below 100,000/day on day 64, and the daily deaths fall below 1,000/day on day 55, as shown in Figure 1.

As in the strategy “elderly first,” unchecked virus propagation in the younger occurs, there is a rapid decay of “risk contacts” within the elderly, but the immunized elderly will encounter large numbers of infected young people, maintaining a residual risk. In contrast, the strategies

that include the younger from the beginning reduce “risk” and “semi-risk” encounters significantly, particularly if the quarter dose vaccination is part of the strategy.

Thus, in the elderly, death rates initially fall fastest compared to other scenarios, but later in the pandemic, the significant exposure of the elderly to the many infectious younger persons in the not yet vaccinated, younger, socially active population segments, and considering that the protective efficacy of the vaccine in the elderly is less than 100%, may lead to continued morbidity and mortality in the elderly compared to other scenarios.

In the “young first” scenario, at standard-dose vaccine, case numbers fall faster in the young, but at the expense of higher mortality in the unprotected elderly cohort throughout most of the study period, yielding a higher overall death count of 184,000, with case rates falling below 100,000/day on day 42 and death rates falling below 1000/day on day 70.

Personalized-dose vaccination

In a “personalized-dose” strategy, including reduced-dose vaccination in the young and full dose vaccination in the elderly, case numbers fall faster than with either prior strategy. While mortality in the elderly is initially slightly higher than in the “elderly people first” strategy, mortality, even in the elderly, quickly falls below the one observed in the other strategies, resulting in markedly lower cumulative deaths of 128,000 in 100 days. The milestones of <100,000 cases/day are reached on day 30, and of <1000 deaths/day on day 49, significantly faster than in the prior scenarios. This improvement is due to the substantial reduction in risk contacts and the “semi-risk” contacts (a partially immune meets an infectious person) in the young and the elderly, compared to the prior scenarios, as shown in Figure 1 panels C-E.

Figure 2: Time-discrete model inspired by the SEIR (susceptible-exposed-infective-recovered) approach, using two age strata that are parameterized differentially for vaccination protection, social contacts, and case-fatality rates. Case rates are used, not infection rates, to render the approach parameterizable with available real-world data. Solid arrows indicate the transition of patients to a different group; dotted arrows indicate risk contacts within and between groups.

Limiting the vaccine campaign to the younger and vaccinating them at quarter dose leads to an even faster reduction of risk contacts and case numbers, but with a similar cumulative number of deaths: 121,000 in 100 days, achieving < 100,000 cases/day in 22 days and <1000 death/day in 45 days. Again, however, this approach might convey a sense of injustice as effective as it is.

The robustness of the model was tested by varying the reproduction number, the protection degree of the vaccination, and the prevalence of unrecognized infection. Assuming a protective efficacy against infection (and transmission) of quarter dose vaccination and natural infection of only 30%, while full dose vaccination yielded infection protection levels

equal to the published disease protection levels, the personalized-dose strategy yielded similar cumulative death numbers (162,000 vs. 163,000) and a shortened time to <100,000 cases (50 vs. 82 days) compared to the “elderly first” strategy, as shown in Figure 3A.

Down to a protection level of quarter dose vaccination against infection above 30%, the personalized-dose strategy remained preferable to the “elderly first” strategy.

The benefit of the personalized-dose vaccination approach was higher when the reproduction number R was >1.0 (Figure 3B), emphasizing its value during the onset of an infection “wave.” The number of unrecognized infections was not a significant confounder for the results (Figure 3C).

Figure 3: Panel A: Impact of the transmission-blocking effect of the vaccine in the younger on the COVID-19 cases/day arising with implementation of different vaccination scenarios in the USA. As stopping transmission in the younger is the key mechanism of success for the personalized-dose strategy, a decreasing efficacy on transmission-blocking in the young was modeled, while transmission blocking in the elderly was maintained at 86.4%, a bias in favor of the “elderly first” strategy. Note that even at low transmission-blocking efficacy down to 30%, the personalized-dose strategy has a substantial impact on case numbers when compared to the “elderly first” strategies. Multiplying early vaccine recipients in the younger, such as choice of the vaccination strategy predominates over transmission protection reduction in an individual person. Labels indicate the transmission-blocking efficacy in the younger for a given strategy in percent. RI is the relative infectivity of the virus, compared to the baseline, wild type. **Panel B:** Impact of virus infectivity on the success of vaccination campaign, comparing the relative infectivity of 1.0 (corresponding to an initial reproduction number of 1.0), with viruses of increased (relative infectivity $RI=1.1$) or decreased ($RI=0.9$) infectivity. In viruses with higher infectivity, differences in vaccination strategy success are amplified. **Panel C:** Impact of the fraction of non-diagnosed infection (FNI) in a population (adding to the number of persons with naturally acquired immunity). Varying the number of undiagnosed infections from 0 to 50% (half of the infections are not confirmed as “cases”) only has a minor impact on strategy outcome.

Variants of Concern taking over during a vaccination campaign

Virus variants like the Alpha (B.1.1.7), Beta (501Y.V2) the Gamma (P.1), and Delta (B.1.617.2) strains are of concern because they showed increased infectivity and potentially reduced coverage by current vaccines; currently, they are becoming the dominant strains in multiple continents. In our model, the choice of vaccination strategy has a significant impact on the evolution of new waves of infections due to VOCs, as shown in Figure 4. The early vaccination of much larger numbers of the younger, highly socially active population segments is predicted to profoundly impact vaccination campaign success even if the protective efficacy of the current mRNA vaccines decreases by 40% (absolute).

Online Methods

The SEIR-inspired model (Figure 1) (susceptible, exposed, infective, recovered) approach with a discrete structure^{21,22} with daily assessment for 100 consecutive days. In addition, it includes two age strata that are differentially parameterized for age-specific differences in social interaction, case fatality rate, and vaccine efficacy, including the interaction of the two groups through risk contact propensity. The model was parameterized based on Moderna vaccine publications on phase I^{23,24,25,26,27} II and III²⁸ studies. The model was initialized using a population size and age structure of the USA with a population of 332,599,000, split into a cohort of 54,303,000, “old” persons > 64 years and of 278,296,000 “young” persons ≤64, according to US government data.²⁹ Covid-19 case numbers were from the US Center for Disease Control,³⁰ the Johns Hopkins University CSSE dataset,³¹ and the Oxford University “our world in data” repository³² and were used to initialize the model to 193,717 cases per day per January 20, 2021. Hospitalization numbers are from the COVID Tracking project³³ and government sources.³⁴ New cases are infectious from day 1 to day 7. Stock for 1 million standard dose vaccinations per day is available. Protection by vaccination occurs from day 10.

In one analysis, protective efficacy against infection transmission of the 100 µg vaccine dose was set to 95.6% in the young and 86.2% in the

elderly as published for protection against disease. Vaccine efficacy of a 25 µg dose in the young was set to 86.2% based on the levels of immunogenicity achieved in the younger compared to the immune response in the elderly vaccinated with 100 µg, as shown in the table. In a further analysis, protective efficacy against virus transmission after vaccination³⁵ and natural infection was varied from 30 to 90% for the younger when using the 25 µg dose. Based on known differences in social contacts between age groups,³⁶ younger persons were set to have 80% of their social contacts with the “younger” and 20% with the “old,” while for the old, contacts to other elderly and the young were each set to be 50% each. Using risk contacts propensities at study start (derived from the numbers of non-immune, of infectious, of new cases, in each age segment) as a reference, we used daily contact propensities to compute transmissions in each age group: encounters of non-immune with infectious persons were “risk contacts,” while encounters of immune with infectious persons were “semi-risk contacts,” weighting infection risk according to the protection afforded by the vaccine in that age segment.

Deaths on a given day were computed from the daily case count 14 days before, using the case fatality rate in the US in January 2021, approximately 1.6%, according to the relatively stable case and death counts in this period. The age-dependent COVID-19 death distribution was derived from the Center for Disease Prevention and Control data,³⁷ indicating a case fatality rate of 0.35% for the younger and 8.9% for the elderly, as supported by others.³⁸ The following scenarios were tested:

“Elderly first”: starting with regular dose vaccination until 80% of the elderly are covered, then vaccinating the young at regular dose.

“Young first”: starting with regular dose vaccination in the young, leaving the elderly aside during the first 100 days.

“Personalized-dose”: in parallel, using half of the stock for each, vaccinate the elderly at full dose and the young at a quarter dose.

“Personalized-dose, the young first”: starting with quarter dose vaccination in the young, leaving the elderly aside until 80% of the young are vaccinated, then vaccinating the elderly at full dose.

The robustness of the model was tested by varying the protection degree of the vaccination, the reproduction number, and the prevalence of unrecognized infection, shown in Figure 3.

A decreasing efficacy on transmission-blocking with reduced-dose vaccination ranging from 90% down to 30% in the younger was modeled, while transmission blocking in the elderly was maintained at 86.4%, a bias in favor of the “elderly first” strategy.

The impact of virus infectivity on the success of a vaccination campaign was analyzed by comparing the relative infectivity (RI) of 1.0 (corresponding to an initial reproduction number of 1.0), with virus strains of increased (relative infectivity RI=1.1) or decreased (RI=0.9) infectivity. In virus strains with higher infectivity, differences in vaccination strategy success are amplified.

The impact of the fraction of non-diagnosed infection (FNI) in a population (that increases the number of persons with naturally acquired immunity) was assessed. Varying the number of undiagnosed infections from 0 to 50% (half of the infections are not counted as confirmed “cases”) only has a minor impact on strategy outcome. In an analysis of the spread of variants of concern (VOC), the spread of a variant of concern with 50% increased infectivity was modeled that has negligible initial prevalence but becomes dominant within 40 days. A baseline reproduction number of 0.8 was chosen, corresponding to the rapid decline of cases in the USA in early February 2021. The VOC was also associated with a reduction of the protective efficacy of vaccination: initial protective efficacy of 85% in full-dose vaccinated elderly fell gradually to 45%, and in reduced-dose vaccinated young people, protective efficacy fell gradually from 65% to 25%. Results are shown in Figure 4.

Figure 4: Impact of the spread of virus variants of concern (VOC) on vaccination campaign success with an “elderly first” or “personalized-dose” strategy. Starting with infectivity corresponding to an initial reproduction number of 0.8 representing “wild type” virus, a VOC becomes predominant within 40 days, leading to an increase in infectivity (RI) from 0.8 to 1.2. A virus with infectivity corresponding to an initial reproduction number of 1.0 is shown as a comparison. Protective efficacy of vaccination for full dose vaccination falls from 85% to 45%, and for reduced dose vaccination from 65% to 25%. The VOC induces a next “wave” of cases, but the “personalized-dose” strategy is particularly effective at society scale despite marked reduction at the individual scale because many more persons receive the vaccination during the rise in infections.

Discussion

In a pandemic wave, protect the vulnerable and society by vaccinating all, fast

The COVID-19 pandemic calls for decisive action to minimize excess deaths and long-term sequelae of the disease, protect healthcare facilities, and minimize the damage to the economy. Vaccination is a cornerstone for mastering the pandemic but identifying the optimal vaccination policies is a prodigious task. Here, we use the demographics and recent epidemiologic data from the United States together with age-related social interaction patterns to build a predictive country-scale model and combine it with age-dependent immunity responses observed in the early clinical studies of the Moderna mRNA vaccine. While a widespread policy is “protect the vulnerable” implemented as “vaccinate the elderly first,”³⁹ we find that the vulnerable are best protected by protecting society through a broad vaccination strategy enabled by personalized vaccine dosing. This was achieved by exploiting the excellent immunogenic properties of the available mRNA vaccine through fractional vaccine dosing in the younger, thereby reaching many more persons early. This approach proved preferable even when a lower efficacy of the reduced dose against infection and transmission is factored in.

Two of the studied scenarios, namely “personalized-dose: split the vaccine stock to vaccinate the elderly at full dose and use it at a quarter dose to vaccinate as many younger as possible,” as well as the scenario “Vaccinate the young first, at quarter dose” excelled in terms of shorting the pandemic, minimizing the number of cases and deaths. As the “justice” of the latter strategy may be challenging to convey to the public because the “vulnerable” seems to be left out (although they even benefit from the approach), the personalized-dose approach seems to be a preferable policy.

Emerging data indicate that the vaccines do not only protect from disease but also to a significant degree from infection and transmission.^{40,41} However, as the exact numbers for the degree of protection are not yet entirely in, we evaluated the impact of varying degrees of infection reduction by the vaccine from 30–90% and found that the strategies proposed here are

valid down to an infection transmission reduction of 30% of a vaccine.

The strong efficacy of the Moderna vaccine already at a moderate immune response level, evident by its effectiveness in preventing disease within 10–14 days after the first standard dose, before the full immune response is achieved, supports these findings. Also, prior infection significantly protects against reinfection,⁴² despite that antibody levels in reconvalescents are lower than those reported with quarter dose vaccination⁴³ and antibody titers correlate with protection against infection.⁴⁴ Emerging data from Israel indicate that the immune response elicited in the elderly, elicited by a single dose of Pfizer’s mRNA vaccine mediates a degree of protection against infection and transmission.⁴⁵ However, the age and the fact of receiving only a single dose in this time window imply less than optimal antibody levels. “Fractional” dose vaccination has proven beneficial in viral poverty diseases^{46,47} further supporting the findings of this study.

The social interaction patterns significantly impact “risk contacts” in COVID-19 and pandemic course, as known from the literature^{48,49} and underlined by this study. Thus, even poor immunity conveyed to a significant proportion of the age groups that fire the pandemic is highly desirable. At the same time, modifications of social interaction patterns like social distancing, personal protective measures like masks, testing and quarantine, indoor ventilation (adapted to local settings like population density) will remain cornerstones of public health until the COVID-19 pandemic is mastered.

Virus mutations and fractional vaccination strategies

Analysis of the current spread of highly infectious VOCs predicts that the early access to vaccination is particularly effective during the onset of a wave due to VOCs, even at reduced vaccine efficacy due to the virus variant, and in the young due to the reduced vaccination dose.

Might this reduced-dose vaccination lead to a risk of the development of new mutant strains? In general, vaccines are considered unlikely causes of resistance development in viruses.⁵⁰ As it is probable that mutants typically arise in persons with impaired immune responses who cannot eliminate the virus, while coronavirus

infection occurring after immunization in the healthy leads to a strong immune system boost;⁵¹ using reduced-dose vaccination is unlikely to lead to more mutants, in contrast, mastering the pandemic as fast as it is possible may be the key to prevent further mutants from emerging. As the Moderna vaccine preserves activity to the prevalent Alpha VOC,⁵² we believe that the strategy delineated here is reasonable. As other mutations that might not be covered by the immune response from prior infection or by the current vaccines are expected soon⁵³ and may require additional shots with modified vaccines, such iterative vaccine “boosters,” again encoding a slightly modified spike protein will further enhance the protection conveyed by prior fractional dose vaccinations. In addition, less strain on the overloaded production lines by a fractional dose approach may free some resources to produce new, optimized vaccine batches that cover VOCs faster.

While we primarily base this analysis on the Moderna vaccine, we note that the Pfizer Tozinomeran vaccine has a similarly flat dose-response relationship for immunogenicity⁵⁴ in the young, in doses from 30 µg down to 10 µg, measured as antibody and T cell response. This suggests that reduced-dose strategies in the young as proposed here may also be considered for the Pfizer vaccine, although generalization to further vaccine types will need an additional in-depth examination of vaccine-specific immune response data.

Future work will integrate the evolving data on emerging new variants and upcoming data on vaccination strategies and dosing in the pediatric vaccination trials. It may go into more detail in modeling social interaction measures like lockdown. The model may further be refined to reflect specifics like social interaction in a city or rural area, although each variable

added to a model has the potential to inject errors related to imprecise knowledge.

Limitations

Study limitations include assumptions that stem from phase I and II studies of limited size and the extrapolation on clinical efficacy based on comparing measured immune titers. Case rate and case fatality rate are not ideal parameters during a pandemic, and mortality rates are phase-shifted to case rates; however, the substantial testing rates and the stagnation at a high level of case rates and mortality in December/January 2021⁵⁵ render their use acceptable, as information on actual infection rates is still sparse. Preferably, the findings of this study are scrutinized by well-designed clinical trials, although such trials would also need to be performed at “warp speed.” The most straightforward way is to allocate cities within a country to the personalized-dose approach proposed and use daily cases, deaths, hospitals, and ICU occupancy as continuously available endpoints, permitting rapid policy adaptation when indicated. The “off-label use” character of this approach calls for acquiring proper permits for its clinical application.

Successful translation to the real world of this approach will also depend on human factors, including the anti-vaxxing movement, although in some countries like England and Israel, high vaccination rates have been shown feasible. The dependence of first-generation mRNA vaccines on a low-temperature cold-chain currently limits the approach’s applicability to world regions with sufficient infrastructure. Suited regulatory processes need to be determined to enable widespread application, such as the recent progress in identifying surrogate laboratory parameters for vaccine efficacy.⁵⁶

Conclusion

This modeling study predicts that personalized-dose vaccination strategies that rely on personalized vaccine dosing of a highly effective mRNA vaccine, applied to all population segments, markedly outperform standard dose regimens that are initially focused on the elderly, within the limitations of this model. This approach is of particular benefit early in a wave caused by virus variants of concern. By multiplying the number of people vaccinated early, this approach limits society-wide transmission faster, shortens the pandemic duration, and markedly lowers case counts and deaths. Thus, from a global perspective, personalized dose vaccination adapted to a country’s demographics may contribute mainly to mastering the COVID-19 pandemic.

Acknowledgments

Author's contributions: PH designed, performed, and wrote this self-funded study.

Conflict of interest

The author declares that there is no conflict of interest. For a signed statement, please contact the journal office: editor@precisionnanomedicine.com

Data and Code availability

Data and Code are deposited at Hunziker Patrick (2021). Impact of personalized-dose vaccination on Covid-19 in the USA during the emergence of virus variants of concern (Version 3.0.0) [Data set] Zenodo. <http://doi.org/10.5281/zenodo.4572448> and will be made available upon publication from the author.

Ethics committee approval

The author has received a Declaration from Ethisches Komitee Nordwestschweiz that computer modeling studies do not fall under its jurisdiction.

Quote this article as Hunziker P., Personalized-dose Covid-19 vaccination in a wave of virus Variants of Concern: Trading individual efficacy for societal benefit, *Precis. Nanomed.* 2021;4(3):805-820, <https://doi.org/10.33218/001c.26101>

Supporting information

Immunogenicity of fractional vaccine doses

Specifically, Moderna vaccine development has explored doses of 25, 50, 100, and 250 µg. Also, 25 µg in the young achieves immunity levels comparable to those seen in reconvalescent plasma in natural infection, with the latter being protected to 83% for at least 5 months.⁵⁷ A dose of 100 µg achieves high immunity levels in all age groups, even in the elderly. The key study populations were protected against infection for at least four months despite reducing the measured immunity parameter in the elderly. Notably, in the younger, a 25 µg dose of the Moderna vaccine elicited an immune response level at day 57 similar to those in patients older than 71 years at day 119 (Table 1), reaching >86% protection.

Table 1: Immune response parameters of the Moderna vaccine by dose and age.

	>71y	<55y	Convalescent plasma
	2× 100µg	2×25µg	
S-2P ELISA		299,751	142,140
RBD ELISA	157,964	183,652	37,857
PsVNA50	109	80·7	109·2
PRNT80	165	339·7 (d43)	158·3

The immune response was observed in convalescent plasma compared to persons < 55 years vaccinated by the Moderna vaccine with 2× 25 µg, day 57,⁵⁸ and the immune response was observed at 119 days in persons >71 years.⁵⁹ S-2P is the antigen encoded by the vaccine mRNA. RBD ELISA: receptor-binding domain binding antibodies. PsVNA₅₀: pseudovirus neutralization assay's 50% inhibitory dilution. PRNT₈₀: live-virus plaque-reduction neutralization testing assay's 80% inhibitory dilution.

GATHER checklist of information that should be included in reports of global health estimates

Item number Checklist item

Objectives and funding

- 1 Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made. [OK \(methods\)](#)
- 2 List the funding sources for the work. [OK \(title page\)](#)

Data inputs

For all data inputs from multiple sources that are synthesized as part of the study:

- 3 Describe how the data were identified and how the data were accessed: [OK \(methods and research in context block\)](#)
- 4 Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.
Provide information about all included data sources and their main characteristics. [\(Not applicable here\)](#)
- 5 For each data source used, report reference information or contact name/institution, the population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant. [OK \(methods, research in context block\)](#)
- 6 Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5). [OK \(age-group differences in figures\)](#)

For data inputs that contribute to the analysis but were not synthesized as part of the study:

Item number	Checklist item
7	Describe and give sources for any other data inputs. (Not applicable here)
<i>For all data inputs:</i>	
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. OK (data inputs referenced data repositories in an extractable format). For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data. (Not applicable here)
<i>Data analysis</i>	
9	Provide a conceptual overview of the data analysis method. OK (in methods and supplement)
A diagram may be helpful.
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s). OK (in methods and supplement)
11	Describe how candidate models were evaluated and how the final model(s) were selected. OK (in methods, supporting information, and figures)
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis. OK (in results)
13	Describe methods of calculating the uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis. OK (uncertainties given as confidence interval for input data)
14	State how analytical or statistical source code used to generate estimates can be accessed. OK (data sharing statement)
<i>Results and discussion</i>	
15	Provide published estimates in a file format from which data can be efficiently extracted. OK (data sharing statement)
16	Report a quantitative measure of the uncertainty of the estimates (e.g., uncertainty intervals). (Not applicable here)
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates. OK (discussion section)
18	Discuss limitations of the estimates. Include a discussion of any modeling assumptions or data limitations that affect the interpretation of the estimates. OK (limitation section)

References

-
- ¹ Skegg D, Gluckmann P, Boulton G. Future Scenarios for the COVID-19 pandemic. *The Lancet* 2021; 397, 777–778.
 - ² Polack F P, Thomas S J, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine *N Engl J Med* 2020; **383**, 2603–15.
 - ³ Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine *N Engl J Med* December 30, 2020. DOI: 10.1056/NEJMoa2035389.
 - ⁴ Lumley S F, O'Donnell D, Stoesser NE, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2034545
 - ⁵ Mallapaty S. Are COVID vaccination programmes working? Scientists seek first clues. *Nature* 2021 ; **589**, 504–5.
DOI: 10.1038/d41586-021-00140-w

- ⁶ Voysey M, Costa Clemens SA, Madhi SA et al. Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. Preprint, available at SSRN: <https://ssrn.com/abstract=3777268>
- ⁷ Hall VJ, Foulkes S, Saei A et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study *The Lancet* 2021; 397: 1725-1735. DOI: [https://doi.org/10.1016/S0140-6736\(21\)00790-X](https://doi.org/10.1016/S0140-6736(21)00790-X)
- ⁸ Khoury DS, Cromer D, Reynaldi A et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; DOI: doi.org/10.1038/s41591-021-01377-8
- ⁹ Varnica Bajaj V, Nirupa Gadi N, Allison P, Spihlman AP et al. Aging, Immunity, and COVID-19: How Age Influences the Host Immune Response to Coronavirus Infections? *Front. Physiol.*, 2021. DOI : doi.org/10.3389/fphys.2020.571416
- ¹⁰ Voysey M, Costa Clemens SA, Madhi SA et al. Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. Preprint, available at SSRN: <https://ssrn.com/abstract=3777268>
- ¹¹ Kim JH, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. *Nature Medicine*. 2021 Jan 19:1-7.
- ¹² Kuppalli K, Gala P, Cherabuddi K et al. India's COVID-19 crisis: a call for international action. *The Lancet* 2021; DOI: [https://doi.org/10.1016/S0140-6736\(21\)01121-1](https://doi.org/10.1016/S0140-6736(21)01121-1)
- ¹³ Plante J A, Mitchell BM, Plante KS, Debbink K, Weaver S , Menachery, VD. The variant Gambit: COVID's next move. *Cell host & microbe* 2021. DOI: <https://doi.org/10.1016/j.chom.2021.02.020>
- ¹⁴ Alona Kuzmina, Yara Khalaila, Olga Voloshin, Ayelet Keren-Naus, Liora Bohehm, Yael Raviv, Yonat Shemer-Avni, Elli Rosenberg, Ran Taube. SARS CoV-2 escape variants exhibit differential infectivity and neutralization sensitivity to convalescent or post-vaccination sera. *medRxiv* 2021; doi: <https://doi.org/10.1101/2021.02.22.21252002>
- ¹⁵ H. De-Leon, R. Calderon-Margalit, F. Pederiva, Y. Ashkenazy, D. Gazit. First indication of the effect of COVID-19 vaccinations on the course of the outbreak in Israel. *medRxiv* 2021; doi: <https://doi.org/10.1101/2021.02.02.21250630>
- ¹⁶ Emary KRW, Golubchik T, Aley PK. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). SSRN. 2021; <https://dx.doi.org/10.2139/ssrn.3779160>
- ¹⁷ Lumley S F, O'Donnell D, Stoesser NE, al. Antibodies to SARS-CoV-2 are associated with protection against reinfection. *medRxiv* 2020; DOI: 10.1101/2020.11.18.20234369
- ¹⁸ Public Health England, COVID-19 vaccine surveillance report, week 26, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/998411/Vaccine_surveillance_report_-_week_26.pdf
- ¹⁹ Ibeas, A., de la Sen, M., Alonso-Quesada, S. *et al.* Stability analysis and observer design for discrete-time SEIR epidemic models. *Adv Differ Equ* **2015**, 122 (2015). <https://doi.org/10.1186/s13662-015-0459-x>
- ²⁰ Hu, Z, Teng, Z, Jiang, H: Stability analysis in a class of discrete SIRS epidemic models. *Nonlinear Anal., Real World Appl.* 2012; **13**, 2017–33
- ²¹ Ibeas, A., de la Sen, M., Alonso-Quesada, S. *et al.* Stability analysis and observer design for discrete-time SEIR epidemic models. *Adv Differ Equ* **2015**, 122 (2015). <https://doi.org/10.1186/s13662-015-0459-x>
- ²² Hu, Z, Teng, Z, Jiang, H: Stability analysis in a class of discrete SIRS epidemic models. *Nonlinear Anal., Real World Appl.* 2012; **13**, 2017–33
- ²³ Jackson L A, Anderson EJ, Roupael NG, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2022483.
- ²⁴ Anderson E J, Roupael NG, Widge AT, al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med* *N Engl J Med* 2020; **383**: 2427–38.
- ²⁵ Widge A T, Roupael NG, Jackson LA, et al. "Durability of responses after SARS-CoV-2 mRNA-1273 vaccination." *N Engl J Med* 2021; **384**: 80–2.
- ²⁶ Supplement to: Jackson LA, Anderson EJ, Roupael NG, et al. An mRNA vaccine against SARS-CoV-2 — preliminary report. *N Engl J Med* 2020; **383**:1920–31. DOI: 10.1056/NEJMoa2022483
- ²⁷ Jacqueline M. Miller. mRNA-1273 Clinical Development Program. Moderna presentation, August 26, 2020, retrieved from <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-08/COVID-02-Miller-508.pdf>
- ²⁸ Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2035389.

- ²⁹ <https://www.census.gov/data/tables/2020/demo/popest/2020-demographic-analysis-tables.html>
- ³⁰ <https://covid.cdc.gov/covid-data-tracker/#demographics>
- ³¹ <https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6>
- ³² Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Coronavirus Pandemic (COVID-19). 2020. Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/coronavirus' on January 25, 2021
- ³³ <https://covidtracking.com/data/national/hospitalization>
- ³⁴ <https://healthdata.gov/dataset/covid-19-reported-patient-impact-and-hospital-capacity-facility>
- ³⁵ Voysey M, Costa Clemens SA, Madhi SA et al., Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. Preprint, available at SSRN: <https://ssrn.com/abstract=3777268>
- ³⁶ Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. *American Journal of Epidemiology*. 2006;164:936–44.
- ³⁷ <https://covid.cdc.gov/covid-data-tracker/#demographics>
- ³⁸ Yang W, Kandula S, Huynh M, Greene SK, Van Wye G, Li W, Chan HT, McGibbon E, Yeung A, Olson D, Fine A. Estimating the infection-fatality risk of SARS-CoV-2 in New York City during the spring 2020 pandemic wave: a model-based analysis. *The Lancet Infectious Diseases*. 2020 Oct 19. DOI: 10.1016/S1473-3099(20)30769-6
- ³⁹ Bubar KM, Reinholt K, Kissler SM, et al. Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. *Science*. 2021 Jan 21. DOI: 10.1126/science.abe6959
- Bubar KM, Reinholt K, Kissler SM, et al. Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. *Science*. 2021 Jan 21. DOI: 10.1126/science.abe6959
- ine-Tiefenbrun, Idan Yelin, Rachel Katz, Esma Herzel, Ziv Golan, Licita Schreiber, Tamar Wolf, Varda Nadler, Amir Ben-Tov, Jacob Kuint, Sivan Gazit, Tal Patalon, Gabriel Chodick, Roy Kishony. Decreased SARS-CoV-2 viral load following vaccination. *medRxiv* 2021; doi: <https://doi.org/10.1101/2021.02.06.21251283>
- ⁴² Lumley S F, O'Donnell D, Stoesser NE, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2034545
- ⁴³ Jackson L A, Anderson EJ, Roupahel NG, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2022483.
- ⁴⁴ Voysey M, Costa Clemens SA, Madhi SA et al. Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. Preprint, available at SSRN: <https://ssrn.com/abstract=3777268>
- ⁴⁵ Mallapaty S. Are COVID vaccination programmes working? Scientists seek first clues. *Nature* 2021; **589**, 504–5. DOI: 10.1038/d41586-021-00140-w
- ⁴⁶ Resik S, Tejeda A, Diaz M, et al. Boosting immune responses following fractional-dose inactivated poliovirus vaccine: a randomized, controlled trial. *The Journal of infectious diseases* 2017, **215**, 175–82.
- ⁴⁷ de Menezes Martins R, Maria de Lourdes S M, de Lima S M B Duration of post-vaccination immunity to yellow fever in volunteers eight years after a dose-response study. *Vaccine* 2018, **36**, 4112–7.
- ⁴⁸ Meehan MT, Cocks DG, Caldwell JM, et al. Age-targeted dose allocation can halve COVID-19 vaccine requirements. *medRxiv* 2020; DOI: 10.1101/2020.10.08.20208108
- ⁴⁹ Brünink SC, Juliane Klatt J, Stange M, et al. Determinants of SARS-CoV-2 transmission to guide vaccination strategy in a city. *medRxiv* 2020.12.15.20248130; DOI: 10.1101/2020.12.15.20248130
- ⁵⁰ Kennedy DA, Read AF. Why the evolution of vaccine resistance is less of a concern than the evolution of drug resistance. *PNAS*. 2018; **115**:12878–86.
- ⁵¹ Callow KA, Parry HF, M. Sergeant M, Tyrrell DAJ. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol. Infect.* 1990, **105**, 435–46
- ⁵² Wu K, Werner AP, Moliva JJ, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. *medRxiv* 2020; DOI:10.1101/2021.01.25.427948
- ⁵³ Faria NR, Morales Claro I, Candido D, et al, on behalf of CADDE Genomic Network. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings. Retrieved Jan 26, 2021 on from <https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586>

-
- ⁵⁴ Sahin U, Muik A, Vogler I, et al. BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans. *medRxiv*. 2020; DOI: doi.org/10.1101/2020.12.09.20245175
- ⁵⁵ https://ourworldindata.org/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..la-test&country=IND~USA~GBR~CAN~DEU~FRA®ion=World&casesMetric=true&interval=smoothed&perCapita=true&smoothing=7&pickerMetric=total_cases&pickerSort=desc
- ⁵⁶ Khoury, D.S., Cromer, D., Reynaldi, A. et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021. DOI: 10.1038/s41591-021-01377-8
- ⁵⁷ Lumley S F, O'Donnell D, Stoesser NE, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2034545
- ⁵⁸ Jackson L A, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2022483
- ⁵⁹ Widge A T, Rouphael NG, Jackson LA, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. *N Engl J Med* 2021; **384**: 80–2.