22 billion in the hole: Omicron’s implications for global mRNA vaccine needs in 2022

1: James Krellenstein, PrEP4All, Brooklyn, NY USA (james@prep4all.org)*†
2: Garrett Wilkinson, MSPH, MSc, Partners In Health, Boston, MA USA †
3: Joseph Osmundson, PhD, New York University, New York, NY USA
4: Salmaan Keshavjee MD, PhD, ScM, Harvard Medical School, Boston MA USA
5: Angela L. Rasmussen, PhD, Vaccine and Infectious Disease Organization, University of Saskatchewan, Saskatoon, SK Canada
6: Wafaa El-Sadr, MD, MPH, MPA, Columbia University, New York, NY USA

*: Author to whom correspondence should be addressed.
†: These authors contributed equally to this work
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**Executive summary**

The best evidence available to date suggests the world needs up to 22 billion doses of mRNA vaccine to bring the pandemic under control in 2022

*mRNA vaccines are essential for blunting SARS-CoV-2 infections and bringing Omicron under control*

COVID-19 vaccines are important for two reasons: Firstly, they reduce the risk of getting infected with SARS-CoV-2 and the risk of vaccinated individuals transmitting the virus to others; secondly, they reduce the risk of severe COVID-19 disease and death among those who become infected despite being vaccinated.

Recent research has shown that the two modified mRNA COVID-19 vaccines currently being made and administered—Comirnaty and Spikevax, hereafter referred to as the Pfizer-BioNTech and NIAID-Moderna vaccines, respectively—are among the only widely used vaccines that have been clearly demonstrated to provide significant protection against Omicron infection as an initial two-dose series, with a third dose of mRNA vaccine being necessary to further recover protection against infection. Preliminary clinical data suggest that an mRNA booster dose can also dramatically recover protection against infection in individuals initially vaccinated with two doses of the adenoviral vector-based Oxford-AstraZeneca vaccine.¹ Even before Omicron, research showed that mRNA vaccines elicit a superior antibody response when given as a single dose booster, regardless of the type of vaccine individuals were previously inoculated with.² ³ ⁴

While it is likely that individuals vaccinated with non-mRNA vaccines will be partially protected from severe disease and death due to Omicron infection, the apparent dramatic loss of protection from infection raises serious concerns. Real-world experience and mathematical modeling demonstrate that loss of protection from infection results in a significant increase in hospitalizations and deaths in the community at large, even when protection against severe disease and death is largely preserved in most vaccinated individuals.⁵ Protection from infection

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⁴ Angkasekwinai N et al. “The immunogenicity and safety of different COVID-19 booster vaccination following CoronaVac or ChAdOx1 nCov-19 primary series” *medRxiv* 2021.11.29.21266947; doi: 10.1101/2021.11.29.21266947
also reduces the chance that new viral variants will emerge. Future viral variants may become even more transmissible, immune evasive, and virulent than Delta or Omicron.

The scientific evidence is clear: only by universally deploying the vaccines currently most effective against infection – which for now appear to be mRNA vaccines – will we be able to blunt the virus’s evolution and begin to bring the pandemic under control globally. This has implications for the need to expand production of mRNA vaccines.

Current mRNA production capacity is now insufficient to meet global needs

Public health authorities in many high-income countries, including the United States,\(^6\) Israel,\(^7\) Singapore,\(^8\) and South Korea,\(^9\) as well as the European Union,\(^10\) are increasingly recommending that adults vaccinated with a one or two dose initial vaccine series receive at least one additional “booster” dose of an mRNA vaccine to protect against Omicron. Just meeting single dose “booster” needs for the global population already vaccinated will require 4.1 billion doses of mRNA vaccine. However, current evidence suggests that individuals vaccinated with Johnson & Johnson\(^11\) or an inactivated vaccine\(^12\) (e.g. Sinovac, Sinopharm, Covaxin) may need two additional mRNA vaccine doses to achieve maximum protection against Omicron infection. Meeting global mRNA “booster” needs in this more likely scenario would require 10.5 billion doses of mRNA vaccine. This would require one and a half times the most optimistic forecast of currently planned global mRNA vaccine production in 2022.

Additionally, based on present global vaccination coverage, providing mRNA doses to individuals who are unvaccinated (or only partially vaccinated) will require 11.5 billion doses of mRNA vaccine if three mRNA doses are required to confer maximum protection, as is anticipated.

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In summary, the world presently needs a total of 22 billion doses of mRNA vaccine to bring the pandemic under control in 2022. Pfizer-BioNTech and Moderna, neither of which is likely to meet its 2021 projections, claim they will make 4 billion and 3 billion mRNA vaccine doses, respectively, in 2022. Assuming Pfizer-BioNTech and Moderna meet these production goals (an optimistic assumption), the world will face a shortfall of 15 billion doses per year of mRNA vaccine production capacity in 2022. Based on the best available evidence, we therefore recommend that policymakers aim to produce an additional 15 billion doses of mRNA vaccine in 2022.

Absent dramatic scale-up of mRNA vaccine production, the global vaccine inequity the world has experienced since late 2020 will persist through 2022, with people in wealthy countries triply or even quadruply vaccinated with the world’s most efficacious vaccines, while people in low- and middle-income countries are left with limited access to vaccines overall and, if they are fortunate to access vaccines, they are likely to be vaccines that provide minimal protection against infection, merely (yet unproven) protection against severe disease and death.

Ongoing research offers the possibility that a multivalent mRNA vaccine targeting both Omicron and other variants (likely Delta) will be developed and demonstrated to be as effective in a two-dose series as three doses of the current wild-type-targeting mRNA vaccines. In such a scenario, only 7.4 billion additional doses will be required for individuals who have not completed their primary vaccination series. A highly efficacious multivalent mRNA vaccine may also mean that single-dose mRNA boosting can restore maximum protection in individuals vaccinated with Johnson & Johnson or inactivated vaccines, in which case just 4.1 billion doses would be needed to meet present “booster” needs. In this “best case” scenario, the global mRNA vaccine dose needs would fall to 11.5 billion doses in 2022, with the shortfall being 4.5 billion doses per year of mRNA vaccine production capacity, assuming Pfizer and Moderna meet their production targets in 2022.

How to rapidly scale up mRNA production capacity to meet the global shortage

Scaling mRNA production capacity to produce 15 billion additional mRNA vaccine doses in 2022 will require significant—yet imminently achievable—concerted actions by the United States government. Based on real world experience at facilities in both the U.S. and Switzerland, we estimate the construction of manufacturing capacity needed to produce this quantity of vaccine doses will cost less than $12 billion in capital expenses and can be accomplished in under 4-6 months. One recommendation is for the U.S. federal government to own and control these manufacturing lines via a “Government Owned, Contractor Operated” (GOCO) model, under which the government would pay one or more contract manufacturing organizations with experience in mRNA vaccine production to operate these lines. This model holds the greatest potential for the most rapid and reliable scale-up of manufacturing, given economies of scale, the elimination of the need for bridging trials, and the maximization of U.S. government oversight and control, which is needed to quickly resolve logistical challenges that may arise. A GOCO approach could also be the first step in enabling technology transfer to achieve globally distributed manufacturing to many countries around the world (e.g. Rwanda, South Africa, South
Korea), similar to the approach that the U.S. Biomedical Advanced Research and Development Authority (BARDA) has taken for influenza pandemic preparedness.

This “Government Owned, Contractor Operated” approach has been utilized extensively and successfully by the U.S. government since the Manhattan Project by the Department of Energy (and its predecessor agencies) for both cutting edge scientific research and the production of critical, high-technology national security assets. There is every reason to believe this approach, which the U.S. government has taken to build the U.S. Navy’s nuclear reactors, perform cutting edge nuclear fusion research, help sequence the human genome, and produce munitions, can be used to expeditiously manufacture the number of COVID-19 vaccines the world needs to end the most severe public health threat and biosecurity crisis in a century.

The U.S. government consistently spends hundreds of billions of dollars annually to manufacture (and maintain) technologies deemed essential to U.S. national security and to distribute those technologies among some proportion of approximately 750 U.S. military bases in at least 80 countries worldwide. Bringing the same sense of scale and purpose to bringing the pandemic under control is imperative to the national security of the United States. We urge the Biden administration to harness the productive and logistical capacity of the U.S. Government to produce billions of additional mRNA vaccine doses, support distribution of them to the entire global population through regional and national networks, and monitor outcomes. Such an effort, which would cost a fraction of annual U.S. defense spending, could save millions of lives, preserve billions of livelihoods, generate trillions of dollars in economic growth, and prevent the generation of potentially more dangerous coronavirus variants. The time to act is now.
1. Introduction

The rapid spread of the Omicron variant of SARS-CoV-2, the virus that causes COVID-19, represents a profound global biomedical emergency. Preliminary data demonstrates the variant’s ability to evade the antibody response elicited by both vaccines and prior infections.13 Equally concerning is the Omicron variant’s ability to spread dramatically faster than previous variants of concern, even in relatively vaccinated and previously infected populations.14 Even if this variant is associated with less severe disease than other variants, the increased transmissibility of this variant threatens to overwhelm healthcare systems at levels previously unseen.15 Omicron threatens billions of people’s lives and livelihoods globally.

The political failure to scale production of highly efficacious COVID-19 vaccines and administer them globally, allowing SARS-CoV-2 to spread unchecked throughout 2021 in most of the global population, all but guaranteed the development of a variant like Omicron. Pandemic control will only be achieved when we have flexible, well-funded, equitable vaccine production, distribution, and administration programs that allow everyone in the world to access the most highly efficacious COVID-19 vaccines. With the evolution of highly infectious SARS-CoV-2 variants like Delta or highly infectious and immune evasive variants like Omicron, only vaccines with high efficacy are sufficient to control the spread of this virus.16

For over a year, activists and scientists have warned the Biden administration that limited mRNA vaccine production capacity poses a critical weakness in the world’s ability to control the coronavirus pandemic and prevent the emergence of dangerous new variants.17,18,19 Despite these repeated warnings, and an over $16 billion allocation from the U.S. Congress in March 2021 that could have been used to address this weakness, the Biden administration failed to

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13 See, e.g. Rössler A et al. “SARS-CoV-2 B.1.1.529 variant (Omicron) evades neutralization by sera from vaccinated and convalescent individuals” medRxiv 2021.12.08.21267491 [preprint]; doi:https://doi.org/10.1101/2021.12.08.21267491
14 See, e.g. Grabowski F, Kocharczyk M, Lipniacki T. “Omicron strain spreads with the doubling time of 3.2—3.6 days in South Africa province of Gauteng that achieved herd immunity to Delta variant”. medRxiv 2021.12.08.21267494 [preprint]; doi:https://doi.org/10.1101/2021.12.08.21267494
15 Neil Ferguson et al. Growth, population distribution and immune escape of the Omicron in England. Imperial College London (16-12-2021), doi: https://doi.org/10.25561/93038
17 Krellenstein JB to Fauci AS. “The Urgent Need for U.S. Government Scale-Up of Production of the NIAID/Moderna Vaccine”. (Personal Correspondence). 15 Dec 2020
act, spending almost nothing on scaling vaccine manufacturing capacity.\textsuperscript{20, 21} The world now must face the consequences of these policy failures. Because the companies that co-developed the two available modified mRNA vaccines, Moderna and Pfizer, are both based in the US, and because the US federal government co-owns intellectual property on the U.S. National Institute of Allergy and Infectious Disease-Moderna (NIAID)-Moderna mRNA vaccine\textsuperscript{22}, the United States Government is uniquely positioned to ensure sufficient production of mRNA vaccines for the world.

As this paper explains, the emergence of the Omicron variant has only further increased the world’s need for mRNA vaccines. Essentially, the efficacy of all vaccines (at least in prevention of symptomatic infection) against Omicron has fallen dramatically compared to previous viral variants. However, the efficacy of the Pfizer-BioNTech and NIAID-Moderna vaccines appears to be the best preserved against Omicron relative to that of other vaccines. Importantly, early evidence suggests that a third or “booster dose” of mRNA vaccine can restore partial efficacy against infection to individuals vaccinated with both mRNA and non-mRNA vaccines. While it is encouraging that non-mRNA vaccines may continue to reduce the risk of the most severe COVID-19 outcomes, including hospitalization and death, high levels of coronavirus transmission will still perpetuate the evolution of viral variants. Only by using the vaccines that are most effective at reducing transmission and controlling infection – currently, mRNA vaccines – will we be able to blunt the virus’s ability to continue to evolve and bring the pandemic under control globally.

This paper reviews the current state of knowledge surrounding the efficacy of existing vaccines against the Omicron variant, estimates the world’s need for mRNA vaccine doses in 2022, and provides recommendations for how the U.S. Government can scale mRNA vaccine production to expeditiously meet these needs.

\textsuperscript{20} Krellenstein JB. “Playing Fiddle While The World Burns: The $16 Billion Dollars the Biden Administration Hasn’t Used to End the Pandemic”. PrEP4All. 25 Aug 2021. URL: https://www.prep4all.org/s/Final-PDF-25-Aug-v2.pdf
\textsuperscript{22} See, e.g. Rizvi Z. “The NIH Vaccine” Public Citizen. 25 June 2020. URL: https://www.citizen.org/article/the-nih-vaccine/
2. What we know about vaccine efficacy against Omicron: an overview

This section provides a summary of available data as of Saturday, December 18, 2021, including their relevance to global vaccine production and pandemic response policy. Extensive discussion of illustrative data can be found in the Appendix.

The evidence we reviewed suggests the following:

1) The mRNA vaccines from Pfizer-BioNTech and NIAID-Moderna are likely the only vaccines to provide any significant humoral neutralization against Omicron as an initial two-dose series.\(^{23}\)

2) A third dose of these mRNA vaccines is necessary for those previously dually vaccinated with mRNA vaccines to recover humoral neutralization capacity against Omicron to near levels seen with previous strains.\(^{24} \quad 25\)

3) Preliminary clinical data suggest that protection from symptomatic infection from the Omicron variant conferred by a two-dose series of Pfizer-BioNTech and presumably NIAID-Moderna is severely degraded and likely all but nonexistent for Oxford-AstraZeneca. However, these data suggest that a third dose of mRNA vaccine partially recovers protection against symptomatic infection from Omicron for those vaccinated with either two doses of the Oxford-AstraZeneca adenoviral vector vaccine or the Pfizer-BioNTech mRNA vaccine (and presumably the NIAID-Moderna vaccine).\(^{26}\)

4) Modified mRNA vaccines (i.e. Pfizer-BioNTech, NIAID-Moderna) elicit immunologically superior responses compared to all other types of vaccines when used as a third or subsequent dose to "boost" the immune response in previously vaccinated individuals (with the sole exception of a 3rd dose of Johnson and Johnson's Ad26.COV2.S for individuals previously vaccinated with 2 doses of modified mRNA vaccines), regardless of the type of vaccine they were originally vaccinated with.\(^{27}\)

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5) The immunity conferred by a single dose of Johnson & Johnson’s Ad26.COV2.S or a two dose whole virus inactivated vaccine series (e.g. Sinovac’s CoronaVac, Sinopharm’s BBIBP-CoRV, Bharat’s Covaxin) is likely inferior in both antibody level breadth than those induced by two dose modified mRNA vaccine or adenoviral vector series. Nearly half of the global vaccine supply relies on inactivated vaccines, which even prior to the emergence of Omicron, were considered to have significantly lower efficacy than modified mRNA vaccines, including for protection against severe disease and death. Given the extensive immune evasion of Omicron, it is likely that these vaccines will have an even more limited efficacy against this variant. Thus, for those who have received these vaccines, at least two subsequent modified mRNA vaccine doses may be warranted to achieve sufficient protection against Omicron.

Evidence is not yet available regarding how effective any vaccine is at preventing severe disease or death from Omicron infection. In the absence of clinical data, and with a pressing need to immediately respond to an ongoing emergency, we must consider how a variety of emerging findings all point to one answer: that Omicron is likely able to evade vaccine-induced immune response and that mRNA vaccines are the best available tools in our ongoing global vaccination efforts. Prior research provides support for the value of antibody response as a surrogate marker for vaccine clinical efficacy, thus lending support for assuming that the available antibody responses noted with mRNA vaccines will translate into protection against Omicron. Two mRNA or adenoviral vector doses followed by an mRNA booster seem critically important to achieving protection against infection with the Omicron variant. While other vaccine regimens may prevent the most severe outcomes, their efficacy against infection appears, at this point, clearly diminished.

Limited evidence suggests that much of the residual protection against severe COVID-19 disease may be dependent on T-cell based immunity, although this is unknown. The ability of the Omicron variant to evade T-cell response is likely significantly lower than its ability to evade

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B cell and antibody response due to the strong T-cell epitopes across the SARS-CoV-2 proteome\textsuperscript{34}, although some preliminary in vitro evidence suggests a reduction in CD4+ T-cell immune response for Omicron virus compared to wild type\textsuperscript{35}.

\textbf{In light of the evidence available, mRNA vaccines are currently our best vaccine technology to bring the coronavirus pandemic under control globally.} This conclusion can be made even though protection against severe disease and death is critically important for evaluating any vaccine technology, we must not underestimate the importance of protection from infection at an individual and population level. Given every infection offers the opportunity for both transmission and viral mutation, as well as may be associated with long-term symptoms, prevention of infection is essential to controlling the global coronavirus pandemic. Furthermore, mathematical modeling indicates that even if protection against severe disease is preserved, but effect on prevention of infection is degraded, ongoing transmission results in significantly more deaths in a community than a scenario in which a vaccine is widely deployed that protects against severe disease, death and infection.\textsuperscript{36}

Based on the evidence described above, it is clear we must dramatically scale mRNA vaccine production.

\textsuperscript{34} Redd AD et al. “Minimal cross-over between mutations associated with Omicron variant of SARS-CoV-2 and CD8+ T cell epitopes identified in COVID-19 convalescent individuals.” bioRxiv 2021.12.06.471446; doi: https://doi.org/10.1101/2021.12.06.471446

\textsuperscript{35} Burgers W. “Preliminary experimental data on T cell cross-reactivity to Omicron.” [Presentation at “WHO Global Consultation - What evidence do we have that omicron is evading immunity and what are the implications?”, 15 December 2021] URL: https://cdn.who.int/media/docs/default-source/blue-print/wendy-burgers_c19_whoconsultation_15dec2021.pdf?sfvrsn=2a2a7479_7

3. Estimating 2022 global mRNA vaccine dose needs

3.1 Overview of current global COVID vaccine manufacturing capacity

According to a forecast by Airfinity Ltd., modified mRNA vaccines will make up just 27% of
global COVID vaccine dose production in 2021 by year end. The remaining 73% of forecasted
production consists of adenoviral vector vaccines (27%), whole virus inactivated vaccines
(45%), and protein subunit vaccines (<1%). 37 A breakdown of 2021 vaccine production by
manufacturer is shown in Figure 1 (mRNA vaccines are “exploded” out of the pie chart).

Figure 1 Vaccine production in 2021 by manufacturer

The distribution of mRNA vaccines is skewed by region and income classification. Europe and North America have received 58% of mRNA doses produced so far, despite these regions comprising under 17% of the world’s population (Table 1). High-income countries have received 72% of mRNA doses, while low-income countries have received just 16% (Table 2).

### 3.2 Estimating global mRNA dose needs to achieve maximum vaccine-elicited protection in 2022

As public health officials in multiple countries have already made clear, a minimum of one mRNA booster dose is necessary for almost all currently dual-vaccinated individuals to achieve more robust protection from both symptomatic infection and possibly severe disease from the Omicron variant. As a result, global mRNA dose needs are markedly higher than previously anticipated.

First, we examine the booster needs for individuals worldwide who have already been vaccinated. As of December 18, 2021, approximately 4.47 billion people worldwide have received at least one dose of a COVID-19 vaccine and only 411.4 million booster doses have been administered.38

As a baseline, if we assume, a) all registered booster doses were mRNA doses, b) all individuals who received a single booster dose do not need any further boosting, and c) no further doses are required among those who have received a single dose of COVID-19 vaccine to complete their primary (i.e. 2 dose) series, at least 4.1 billion additional mRNA doses are needed to boost just the existing vaccinated population. This number is likely an underestimate, as a

#### Table 1 Delivery of mRNA vaccines in 2021 by region

<table>
<thead>
<tr>
<th>Region</th>
<th>NIAID-Moderna</th>
<th>Pfizer-BioNTech</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>29,798,100</td>
<td>101,953,528</td>
</tr>
<tr>
<td>Asia</td>
<td>124,236,900</td>
<td>653,865,859</td>
</tr>
<tr>
<td>Australia and Oceania</td>
<td>200,480</td>
<td>34,246,470</td>
</tr>
<tr>
<td>Europe</td>
<td>164,265,097</td>
<td>685,120,585</td>
</tr>
<tr>
<td>Latin America</td>
<td>36,361,920</td>
<td>294,681,679</td>
</tr>
<tr>
<td>North America</td>
<td>330,297,820</td>
<td>575,806,811</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>677,160,317</strong></td>
<td><strong>2,345,674,932</strong></td>
</tr>
</tbody>
</table>

#### Table 2 Delivery of mRNA vaccines in 2021 by income classification

<table>
<thead>
<tr>
<th>Income Classification</th>
<th>NIAID-Moderna</th>
<th>Pfizer-BioNTech</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-income countries</td>
<td>530,497,617</td>
<td>1,643,663,781</td>
</tr>
<tr>
<td>Upper-middle-income countries</td>
<td>5,403,700</td>
<td>20,961,220</td>
</tr>
<tr>
<td>Lower-middle-income countries</td>
<td>106,305,140</td>
<td>236,010,507</td>
</tr>
<tr>
<td>Low-income countries</td>
<td>34,953,860</td>
<td>445,039,424</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>677,160,317</strong></td>
<td><strong>2,345,674,932</strong></td>
</tr>
</tbody>
</table>

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proportion of individuals who have received “at least” a single dose of COVID vaccine have received just one dose of COVID vaccine, and need both their second dose and third dose of an mRNA vaccine.

This figure alone exceeds the total number of mRNA vaccine doses projected to be manufactured in 2021 by more than one third. Meeting this need would take up 57% of total global mRNA production capacity in 2022 if Pfizer-BioNTech’s and Moderna’s most optimistic manufacturing scenarios are borne out in 2022 (4 billion\textsuperscript{39} and 3 billion doses\textsuperscript{40}, respectively).

Regional estimates for additional mRNA booster needs per region under these assumptions are listed in Table 3 below.

\textit{Table 3 Minimum number of mRNA booster doses needed for the previously vaccinated by region}

<table>
<thead>
<tr>
<th>Continent</th>
<th>People with at least one vaccine dose administered\textsuperscript{41}</th>
<th>Boosters already administered\textsuperscript{42}</th>
<th>mRNA booster doses needed for the previously vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>3,054,921,588</td>
<td>170,624,925</td>
<td>2,884,296,663</td>
</tr>
<tr>
<td>Africa</td>
<td>177,104,083</td>
<td>663,869</td>
<td>176,440,214</td>
</tr>
<tr>
<td>Europe</td>
<td>481,193,363</td>
<td>132,581,132</td>
<td>348,612,231</td>
</tr>
<tr>
<td>Oceania</td>
<td>26,148,089</td>
<td>1,488,235</td>
<td>24,659,854</td>
</tr>
<tr>
<td>North America</td>
<td>401,159,091</td>
<td>64,832,975</td>
<td>336,326,116</td>
</tr>
<tr>
<td>South America</td>
<td>328,398,340</td>
<td>41,184,604</td>
<td>287,213,736</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4.5 billion</strong></td>
<td><strong>411 million</strong></td>
<td><strong>4.1 billion</strong></td>
</tr>
</tbody>
</table>


\textsuperscript{42} Ibid.
However, given the insights from available recent immunological data, at least two doses of mRNA vaccine will likely be necessary (absent an Omicron-specific mRNA booster) to confer maximum protection in individuals vaccinated with either the Johnson & Johnson vaccine or inactivated vaccines (e.g. Sinovac, Sinopharm, Covaxin). Unfortunately, inactivated vaccines represent the largest proportion of vaccines manufactured to date (over 5 billion doses).

To explore the potential ramifications of needing to give two doses of mRNA vaccine to individuals who have received a primary series of Johnson & Johnson or inactivated vaccines, including Sinovac, Sinopharm, and Covaxin, we used the number of COVID-19 vaccines that have been delivered by their manufacturers to simulate the number of doses administered, by type. We assume 80% of delivered doses have been administered to individuals.

We calculated global mRNA booster needs for individuals vaccinated with vaccines from 8 manufacturers who collectively represent over 98% of estimated COVID vaccine production in 2021. We note that we are unable to distinguish between doses delivered as third-dose boosters versus two-dose primary vaccination series; however, the number of doses delivered as third doses is negligible (~400 million). We estimate that 10.5 billion mRNA “booster” doses will be needed in this scenario just to provide maximum protection in the currently vaccinated population (Table 4). Meeting this need for just booster doses would require one and a half times the most optimistically forecasted production capacity of Pfizer-BioNTech and Moderna for 2022.

Table 4 Estimated number of mRNA vaccine boosters needed for previously vaccinated global population, after factoring in need for two booster doses in individuals who received a J&J or inactivated vaccine primary series

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Estimated doses administered</th>
<th>mRNA booster doses required</th>
<th>mRNA booster doses required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson &amp; Johnson</td>
<td>180 million</td>
<td>2</td>
<td>360 million</td>
</tr>
<tr>
<td>Oxford-AstraZeneca</td>
<td>1.8 billion</td>
<td>1</td>
<td>900 million</td>
</tr>
<tr>
<td>Sinovac, Sinopharm, and Covaxin</td>
<td>3.7 billion</td>
<td>2</td>
<td>7.2 billion</td>
</tr>
<tr>
<td>Pfizer-BioNTech, NIAID-Moderna</td>
<td>2.2 billion</td>
<td>1</td>
<td>1.1 billion</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>190 million</td>
<td>1</td>
<td>95 million</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>10.5 billion</td>
</tr>
</tbody>
</table>
To date, there are still over 3.3 billion people globally who have not received a single dose of a COVID-19 vaccine. At this point it makes little sense for the world to continue to rely on vaccine production technology that is unlikely to result in a potent of a humoral immune response against Omicron — and will provide little to no protection against symptomatic infection. Furthermore, the unique, cell-free production process of the mRNA vaccine platform allows far more rapid commercial production of a variant targeting vaccine than other, cell-culture production-dependent vaccine platforms. Given the current make-up of global vaccine production, the majority of unvaccinated individuals will likely be receiving a primary series of vaccines that will afford them little protection against symptomatic infection and potentially limited protection against severe disease and death for the foreseeable future, absent a dramatic and rapid increase in mRNA vaccine production.

While an mRNA booster dose will at least partially restore this protection, it is certain that absent a rapid increase in production, many individuals will be waiting months, if not years, for that subsequent third dose.

Given the demonstrated in vitro superiority of two dose mRNA series compared to two dose Oxford-AstraZeneca series, and the likely clinical superiority of the mRNA series, it becomes more important than ever to provide mRNA vaccines as the primary series for unvaccinated individuals worldwide. Although three doses are presently needed for mRNA vaccination to preserve protection against Omicron, the availability of a variant-targeting mRNA vaccine could once again reduce the need for protection from three doses to two doses. Given the antigenic distance between still-circulating Delta and other non-Omicron strains, a multivalent mRNA vaccine encoding antigens for both Omicron and non-Omicron (e.g. Delta and other strains) spike protein should be used. As such, we have simulated two scenarios: one where a three dose series of existing mRNA vaccines encoding pre-fusion stabilized wild type spike protein is necessary to achieve full protection, and one where a two dose series of an Omicron-targeting multivalent mRNA vaccine is able to confer full protection. These scenarios demonstrate the need for an additional 11.45 billion and 7.45 billion doses of mRNA vaccine, respectively (Table 5).

**Table 5 Estimated mRNA vaccine doses needed to vaccinate individuals who have not completed their primary vaccination series**

<table>
<thead>
<tr>
<th>Global population fully vaccinated</th>
<th>Global population partially vaccinated</th>
<th>mRNA doses needed for full vaccination</th>
<th>Total mRNA doses needed per scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3 billion</td>
<td>775.3 million</td>
<td>2</td>
<td>7.4 billion</td>
</tr>
<tr>
<td>3.3 billion</td>
<td>775.3 million</td>
<td>3</td>
<td>11.5 billion</td>
</tr>
</tbody>
</table>
To provide mRNA boosters to previously vaccinated individuals and to provide mRNA primary series vaccination to unvaccinated individuals in 2022, global mRNA dose needs will be between 11.5 billion and 21.6 billion doses of mRNA vaccine next year.

Pfizer-BioNTech claims they will produce 4 billion doses in 2022, while Moderna claims they will produce 3 billion doses of mRNA vaccine in 2022. While this would represent an almost doubling of Pfizer-BioNTech’s projected annual production of 2.5 billion doses in 2021\textsuperscript{43}, it would represent a dramatic, six-fold increase over Moderna’s projected production of just under 600 million doses for 2021\textsuperscript{44}. At this projected level of global mRNA production in 2022, there will be a staggering gap of between 4 and 15 billion doses per year of mRNA vaccine production capacity.

\textsuperscript{44} Airfinity Ltd. Dose Projection for 31 December 2021 for mRNA-1273. Access on 20 Dec 2021.
4. How to produce 15 billion additional doses in 2022

Scaling mRNA production capacity to produce 15 billion additional mRNA vaccine doses in 2022 will require significant—yet imminently achievable—concerted actions by the United States government. For extensive analysis of the likely cost, speed, and viable models for scaling capacity see Krellenstein & Urrutia 2021.\(^{45}\) The findings are summarized below.

4.1 Cost

Although scaling production capacity by 15 billion doses per year may seem dramatic, the cost of building such mRNA vaccine drug substance capacity would be relatively modest. Peer-reviewed estimates from engineers at Imperial College London indicate that capital costs for this level of drug substance production capacity would cost under $4 billion assuming 100µg modified mRNA per dose (i.e. a single full dose equivalent to NIAID-Moderna’s mRNA1273).\(^{46}\) Real-world experience confirms the reasonableness of this estimate. Lonza Group AG, Moderna’s primary contract manufacturing organization (CMO), spent an average of 70 million Swiss Francs (approx. US $78 million) per line capable of producing 100 million doses annually.\(^{47}\) At this production line cost, scaling to 15 billion doses per year would cost less than $12 billion. Costs would likely be significantly lower, not only due to economies of scale, but also because Lonza’s lines were the first of a kind (FOAK) for producing mRNA vaccine drug substance.

4.2 Speed

Real-world experience has demonstrated that large scale mRNA vaccine drug substance manufacturing capacity can be built quickly. For example, BioNTech’s Marburg, Germany facility was brought into commercial operation in less than 6 months after the company acquired the facility from another pharmaceutical manufacturer, Novartis Group AG.\(^{48}\) Critically, this facility, when purchased on September 18, 2020, had no mRNA manufacturing capability when purchased. Rather, it was originally used to produce monoclonal antibodies for cancer therapies.\(^{49}\) Similarly, Lonza was able to build drug substance production lines for Moderna’s

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\(^{47}\) Lonza Group SE. Investor Update: Lonza’s Blueprint for the Future (15 Oct 2020). PDF Page 4.. URL: https://www.lonza.com/investor-relations/-/media/38ADC8E8FB834519B5E7FDA0EC1DC15E.ashx


vaccine in 4 months from tech transfer commencement to commercial drug substance production. \(^50\) \(^51\) It is important to note that Lonza’s facilities were built when there was no previous experience in producing mRNA vaccine drug substance at commercial scale. It is likely that today, given the extensive experience of manufacturers producing these doses, more rapid scale up is possible.

4.3 The Government Owned, Contractor Operated (GOCO) model

Extensive prior experience has demonstrated that simply giving U.S. Government funding to vaccine manufacturers without adequate government control and ownership fails to achieve production at speed and scale. For example, hundreds of millions of dollars were poured into Emergent Biosolutions Inc.’s Baltimore facility as part of the U.S. Biomedical Advanced Research and Development Authority’s (BARDA) Centers for Innovation in Advanced Development and Manufacturing (CIADM) program, only for this contract to eventually be canceled after the facility botched contract manufacturing production of both Oxford-AstraZeneca’s and Johnson & Johnson’s vaccines, dealing a significant blow to global vaccination programs. \(^52\) Similarly, the Biden administration’s inexplicable enlistment of Merck & Co. Inc. in the production of Johnson & Johnson’s vaccine in early March of 2021 has resulted in no expected commercial operation until over one year later in April of 2022.

A Government Owned, Contractor Operated (GOCO) model allows explicit government ownership and control while still enlisting the expertise and skills of private industry. Critically important, a GOCO approach would allow the use of an experienced, pure-play contract manufacturing organization like Lonza (i.e. they just manufacture drugs on behalf of originator companies and do not sell drugs of their own). This model allows the Biden administration to operate under the existing authorization or biological license application of the originator manufacturer (i.e. Pfizer-BioNTech and Moderna). Critically, this circumvents the need for bridging immunogenicity trials, vastly accelerating the time from beginning of construction to doses into arms. A GOCO approach could also be the first step in enabling technology transfer to achieve globally distributed manufacturing to many countries around the world (e.g. Rwanda, South Africa, South Korea), similar to the approach that BARDA took for influenza pandemic preparedness.

The GOCO approach has been utilized extensively and successfully since the Manhattan Project by the Department of Energy for both cutting edge scientific research and the

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widespread production of critical, high-technology national security assets. There is no reason that the GOCO approach the U.S. Government has taken to build the Navy’s nuclear reactors, sequence the human genome, perform cutting edge nuclear fusion research, and produce munitions for the military cannot be used to manufacture COVID vaccines.

5. Conclusion

Almost exactly one year ago, two of the co-authors of this report, along with Peter Staley, wrote an editorial for The New York Times calling on the Biden administration to scale mRNA vaccine production capacity to 16 billion doses per year. At that time, U.S. Government and private sector scientists had seemingly achieved the impossible: developing vaccines 95% effective against symptomatic SARS-CoV-2 infection. It was the responsibility of the U.S., we argued, to ensure global access to this remarkable technology to stem the acute COVID-19 crisis as quickly as possible.

Unfortunately, these warnings were not heeded. As we predicted, ongoing SARS-CoV-2 infection allowed the evolutionary space for a novel immune-evasive variant, Omicron, to emerge. Now, all available vaccines have reduced efficacy, at least against symptomatic infection. In order to stop the generation and proliferation of new viral variants that undoubtedly will threaten lives and livelihoods in the United States and around the world, it is critical that the United States Government act now to ensure the rapid production of 15 billion additional mRNA vaccine doses and ensure full funding for programs to administer them into the arms of people who want them, to provide maximum immunological protection against SARS-CoV-2 to every person on earth. This is essential to the economy and biosecurity of the United States of America and the globe.
Appendix: Review of illustrative evidence

“SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection” 53

This study used sera from 19 participants who had all been vaccinated with two doses of Pfizer-BioNTech, 6 of whom had been infected previously. Sera was collected from participants a median of 24 days after their second dose of vaccine. A live virus neutralization assay was used to determine the ability of vaccine-elicited humoral immunity to neutralize both live Omicron and wild type (D614G) variants. The end-point of the neutralization assay was 50% reduction in viral infection-specific foci, compared to a control assay containing no serum (focus reduction neutralization test, or FRNT$_{50}$).

The ability of serum to neutralize viral replication from participants dually vaccinated with Pfizer-BioNTech dropped from a FRNT$_{50}$ 1963 when wild type virus was tested to a FRNT$_{50}$ of 89 when Omicron virus was tested — a 22-fold drop (95%CI 16-30). Interestingly, the relative change, or fold change, in neutralizing titre between type and Omicron was the same among participants who were previously infected (22-fold drop, 95% CI 16-34) and participants who were not previously infected (22-fold drop, 95%CI 15-32). However, the absolute neutralizing capacity of vaccinated and previously infected participants was significantly greater for both Omicron and wild type neutralization than that of participants who had no prior infection (Figure 2).

This suggests the ability of the Omicron variant to significantly evade existing humoral immunity elicited by recent vaccination with two doses of Pfizer-BioNTech, regardless of previous infection history.

Of note, the authors also estimated that this drop in neutralization capacity could translate to a large drop in the ability of dual vaccination with Pfizer-BioNTech to protect against symptomatic Omicron infection. However, they estimate protection against severe disease caused by Omicron infection may be preserved by dual vaccination with Pfizer-BioNTech.

53 Cele S et al. "SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection." medRxiv 2021.12.08.21267417; doi:https://doi.org/10.1101/2021.12.08.21267417
Figure 2 “Neutralization of Omicron virus compared to D614G ancestral virus by plasma from participants vaccinated with BNT162b2 and previously SARS-CoV-2 infected (green) or vaccinated only (orange)” (Cele S et al., 2021)
“Reduced neutralization of SARS-COV-2 Omicron-B.1.1.529 variant by post-immunisation serum” 54

This study evaluated sera from participants vaccinated with either two doses of the Oxford-AstraZeneca adenoviral vector vaccine (n=22 participants) or two doses of the Pfizer-BioNTech modified mRNA vaccine (n=21). All participants were presumed to have never been infected with SARS-CoV-2 as determined by the lack of the presence of anti-nucleocapsid antibodies (IgG isotype). Following the protocol of the Com-CoV-2 study, the second dose of vaccine was administered 8-11 weeks (median 9) after the first dose. Serum samples were obtained four weeks after the second dose was administered.

A live virus neutralization assay was used to determine the ability of vaccine-elicited humoral immunity to neutralize four SARS-CoV-2 variants: Victoria (an early wild type strain), Omicron, Beta, and Delta. The end-point of the neutralization assay was 50% reduction in viral infection-specific foci (FNRT50), compared to a control assay containing no infection foci detecting antiviral antibodies (focus reduction neutralization test).

Similar to the results reported by the Sigal group, in individuals dually vaccinated with Pfizer-BioNTech, neutralization capacity against Omicron dropped 29.8-fold—from an FNRT50 1609 (Victoria strain) to 54 (Omicron variant). In the Pfizer-BioNTech group, neutralizing activity above the detection threshold was present in 20 out of 21 samples when live Omicron virus was used.

However, in patients dually vaccinated with Oxford-AstraZeneca, the relative change in neutralization capacity from wild type strain to Omicron was impossible to calculate, as no neutralization activity above the detection threshold (50% reduction in viral infection foci) was present in 21 out of 22 samples when live Omicron virus was used (Figure 3). Some residual neutralization capacity below the 50% reduction in infection specific foci threshold was present in most samples. This is a marked contrast with neutralization against wild type live virus, where significant neutralization capacity (median FRNT50 of 133) above the detection threshold was present.

This paper supports the findings of the Sigal group regarding the significant reduction in neutralization capacity in sera from individuals dually vaccinated with Pfizer-BioNTech. Disturbingly, this paper suggests that the neutralization capacity in sera from individuals dually vaccinated with Oxford-AstraZeneca may be even more dramatically compromised than sera from individuals dually vaccinated with Pfizer-BioNTech. This is an early suggestion of the superiority of modified mRNA vaccines against the Omicron variant.

Figure 3 “Neutralizing antibodies against Omicron: 1 month post second dose (uninfected at enrolment)” (Dejnirattisai W et al., 2021)

Figure 4 Detectable neutralizing activity by vaccine type

**Dual AstraZeneca Vaccinated**
- 21/22 had no neutral activity detected against Omicron

**Dual Pfizer/BioNTech Vaccinated**
- 20 out of 21 samples had neutralizing activity detected
This study tested sera from 239 participants who were fully vaccinated with either the NIAID-Moderna, Pfizer-BioNTech, or Johnson & Johnson vaccines. Of the 239 participants, 70 participants had received an mRNA (NIAID-Moderna or Pfizer-BioNTech) booster over 6 months after completing their primary vaccination series.

Unique among the studies detailed so far, this study examined neutralization potency of sera from participants who were single-dose vaccinated with Johnson & Johnson (n=32), double dose vaccinated with NIAID-Moderna (n=55), double dose vaccinated with Pfizer-BioNTech (n=81), as well as potency of sera of “boosted” participants including those who were triple-dosed with NIAID-Moderna (n=33), triple-dosed with Pfizer-BioNTech (n=30), and double-dosed with a single-dose of J&J and a single dose of NIAID-Moderna (n=8). *The dose of the booster doses (100µg vs 50µg) for NIAID-Moderna is not known to study investigators per personal correspondence between J. Krellenstein and G. Wilkinson with W.F. Garcia-Beltran.

Distinct from the studies covered in detail above, this study utilized pseudovirus rather than live, SARS-CoV-2 virus. A pseudovirus is a genetically constructed replication-deficient virus that is unable to replicate itself, but contains the same cell entry machinery (i.e. spike protein) as virus being studied (i.e. SARS-CoV-2). Critically, constructing a pseudovirus allows experimentation to be performed in a laboratory with a lower biosafety level than studies using live infectious virus.

In this study, the pseudovirus contained a “reporter gene” (luciferase) that allows virus neutralization to be quantified. The end-point of the neutralization assay was 50% reduction in luciferase expression as quantified by luminescence (pNT50), compared to a control well that contained no luciferin-containing buffer.

Similar to previously published studies, this study found the neutralization capacity of sera from individuals vaccinated with modified mRNA vaccines was dramatically higher than those vaccinated with just Johnson & Johnson (Figure X). Similar to the previously reviewed work, this study found that primary vaccine series resulted in dramatically weaker neutralizing capacity of participant sera against Omicron pseudovirus compared to wild type and Delta pseudovirus. Uniquely, this study demonstrated that boosting not only increased the concentration of antibodies in patients serum it also increased the “breadth” of the antibody response. That is, not only did the concentration of antibodies increase, their relative ability to neutralize Omicron also increased. This means that following boosting, serum neutralization capacity increased three-fold against Delta pseudovirus for NIAID-Moderna, and nine-fold for Pfizer-BioNTech, it increased 19- and 27-fold against Omicron, respectively.

This study found that sera from participants who received a primary series of mRNA doses and an mRNA booster exhibited potent neutralization against Omicron pseudovirus. Concerningly, among mRNA-boosted participants whose primary series consisted of one dose of Johnson & Johnson, while the overall humoral neutralizing ability increased (versus Johnson & Johnson recipients without an mRNA vaccine booster), it did not achieve the same recovery of neutralization capacity as those vaccinated with three doses of mRNA vaccine. (Figure X)

Taken together, this study demonstrates the clear superiority of serum from individuals vaccinated three times with mRNA doses over any other vaccination regime recommended in the United States, at least using antibody titer and pseudovirus neutralization as proxies for vaccine-induced immunity.

Note: Only participants who received completed their primary vaccination series less than three months prior to serum collection were used as the baseline comparator.

*Figure 5* Cross-reactivity of neutralizing antibody response is increased by mRNA vaccine booster relative to primary vaccination series and can be predicted by anti-spike antibody levels (Garcia-Beltran et al., 2021)
Summary of evidence on inactivated vaccines

Similar to the finding of Garcia Beltran et al. that two doses of mRNA vaccine may need to be administered to individuals who have received one dose of the Johnson & Johnson vaccine to confer maximum protection against Omicron, there is also significant evidence suggesting the need to give a two-dose mRNA series to individuals doubly vaccinated with whole virus inactivated vaccines. Briefly, we think there are at least three distinct reasons to think that these individuals may need two doses of mRNA vaccine.

First, after completing the initial two-dose series, the observed decline in antibody titres and even detectable wild type seropositivity is remarkable for inactivated vaccines. According to a study by Sinovac itself, on average anti-wild type virus antibody titres declined below the detection limit 6-8 months after the second dose was administered in individuals.\textsuperscript{56} This shows a remarkable immunogenic fade, even absent an immune evasive variant. Furthermore, data has demonstrated that the concentration of the antispoke antibody elicited by dual Sinovac vaccination is statistically significantly lower than what dual Oxford-AstraZeneca vaccination elicits.\textsuperscript{57} Given the fact that sera from individuals doubly vaccinated with Oxford-AstraZeneca maintains little to no neutralizing activity against Omicron, this suggests profoundly little neutralizing capacity of Sinovac against Omicron.

Second, Thai research published on August 26, 2021 argues immunogenic fade is even more pronounced when sera from dual-vaccinated Sinovac individuals was assessed using a neutralization assay against live Delta virus rather than live wild type virus. In fact, sera from individuals who had previously recovered from wild type infection and had not been vaccinated showed dramatically more neutralization potential against Delta than individuals vaccinated with Sinovac. This is extremely concerning considering the immune evasiveness of the Delta variant is dramatically lower than what is currently being observed with Omicron. Further supporting this concern, in a recently published study from the university of Hong Kong, in a live virus neutralization assay in sera from 25 individuals doubly vaccinated with Sinovac (who had significant neutralization activity against wild type virus), no neutralization activity was detected against not only Omicron, but also the Beta variant, which shows significantly less antigenic distance than Omicron. This suggests that not only is the \textit{amount} of antibody is significantly decreased for Sinovac compared to Pfizer, but also the \textit{breadth} of the antibody response may be lower as well.


\textsuperscript{57}Angkasekwinai N et al. "The immunogenicity and safety of different COVID-19 booster vaccination following CoronaVac or ChAdOx1 nCoV-19 primary series" \textit{medRxiv} 2021.11.29.21266947; doi: 10.1101/2021.11.29.21266947
Third, even before the emergence of Omicron, Delta, and other variants of concern, multiple comparative studies showed statistically significant inferiority of inactivated vaccines compared to modified mRNA vaccines with respect to clinically relevant endpoints including protection from severe disease and death. This may suggest that the inferior in vitro results discussed above may be translating into clinically observed inferior protection. Unfortunately, Omicron is likely to only exacerbate these disparities in efficacy compared to other vaccines.

The purpose of this paper is not to offer medical advice. Rather, it is to assist policymakers in making vaccine production and pandemic suppression policy. Unfortunately, inactivated vaccines represent the largest proportion of vaccines manufactured to date. While further investigation is warranted, we believe it is prudent to plan for the possibility that at least two additional modified mRNA vaccine doses are needed to achieve maximum protection in populations vaccinated with inactivated vaccines.
“Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial”

The ability of boosters to possibly restore humoral neutralizing protection against Omicron depends on both being able to increase the overall concentration of SARS-CoV-2 antibodies, and their ability to increase the breadth and avidity of vaccine-elicted antibodies to neutralize the Omicron variant, and any changes they elicit to cellular adaptive immunity. Although some data is available on the ability of mRNA vaccines to increase neutralizing capacity against Omicron in previously vaccinated individuals, as of December 17 no immunogenicity data has been published on other vaccines’ ability to do so. The COV-BOOST study group is currently evaluating previously collected boosted sera for neutralization potential against Omicron.

In their study published on December 2nd, the COV-BOOST study group evaluated antibody fold changes as well as neutralizing titres to live wild type virus, wild type pseudovirus, and Delta pseudovirus. Seven vaccines were studied as boosters in participants who were either doubly vaccinated with Oxford-AstraZeneca (n=1,287) or Pfizer-BioNTech (1,270). Together, the vaccines studied as boosters represent the four major vaccine platforms used to make all of the world’s widely authorized or approved COVID-19 vaccines: Oxford-Astrazeneca (adenoviral vector), CureVac (non-modified mRNA), Valnova (whole virus inactivated), Pfizer-BioNTech, Moderna (modified mRNA), J&J (adenoviral vector), and NOVAVAX (protein subunit).

With the exception of the Valnova whole virus vaccine, the antigen expressed by the various platforms was the same, pre-fusion stabilized full-length spike protein for all but the Oxford Astra-Zeneca which used wild-type non-stabilized full-length spike protein.

Study participants were at minimum 84 days post second dose of Pfizer-BioNTech or at minimum 70 days post second dose of Oxford-Astrazeneca. Further details on the methodology can be found in the original paper.

The results of this study were dramatically clear: except for boosting dually vaccinated Pfizer-BioNTech participants with Johnson & Johnson, boosting with modified mRNA vaccines, i.e. NIAID-Moderna and Pfizer-BioNTech, was statistically superior to boosting with any other vaccine evaluated in all humoral end-points including antibody concentration, pseudovirus neutralizing capability regardless of variant, and live virus neutralizing capability. Figure 5

These findings are critical. Not only are mRNA vaccines likely superior as a primary series, they are likely dramatically superior compared to other vaccine technologies as boosters as well. The findings of this study, when interpreted vis-a-vis those of the previously reviewed studies, suggest that modified mRNA vaccine boosters will be far superior to other types of vaccines used as boosters against the Omicron variant.
There is also a suggestion in the data that, among individuals dually vaccinated with Oxford-AstraZeneca, a 100ug Moderna booster dose may be superior to a 30ug Pfizer dose. Superiority was statistically significant in measured immunogenic response in geometric mean fold rise of antispike IgG, antibody neutralization of wild type and Delta pseudovirus, but not statistically significant when measuring antibody neutralization of live wild type virus. However, differences between mRNA vaccines were negligible compared to the differences between each mRNA vaccine and all other vaccine types when used as a booster.

*Figure 6* Anti-spoke IgG in patients dually vaccinated with Oxford-AstraZeneca pre- and post-boost with different types of vaccines as boosters
The previously described studies on Omicron’s immune evasive abilities use in vitro methods, namely antibody titer and virus or pseudovirus neutralization by sera from vaccinated individuals. These experiments do not necessarily translate to vaccine effectiveness in individuals and populations. Vaccine effectiveness, however, is much more difficult and time consuming to measure experimentally and requires complex biostatistics to correct for confounding variables in complex human populations.

In the case of determining which vaccines and how many doses are superior against an immune evasive variant such as Omicron, the in vitro titer and neutralization closely match the initial estimates for vaccine efficacy in human populations.

The UK Health Security Agency used a test-negative case-control design to estimate vaccine effectiveness against symptomatic disease caused by the Omicron and Delta variants in a large population sample of 56,439 Delta cases and small population sample of 581 Omicron cases. Effectiveness against symptomatic disease was estimated in both individuals dually vaccinated with Oxford-AstraZeneca or Pfizer-BioNTech, and individuals boosted with Pfizer-BioNTech. Omicron cases were determined either by whole viral genome RNA sequencing or S-gene drop out on real-time reverse transcription PCR utilizing an S gene taqman probe on a multiplex assay. Omicron cases from 14+ days post booster occurred a median of 41 days post booster (range 14-72 days).

In individuals dually vaccinated with Oxford-AstraZeneca, there was no detectable efficacy against symptomatic infection with Omicron. In individuals dually vaccinated with Pfizer-BioNTech, efficacy against symptomatic infection was significantly degraded compared to the Delta variant.

However, 14 days following a Pfizer-BioNTech booster, efficacy against symptomatic infection increased to 71% (95% CI 41.8-86.0) among those previously dually vaccinated with Oxford-AstraZeneca and 75.5% (95% CI 56.1-86.3) among those previously dually vaccinated with Pfizer-BioNTech.

These results are based on extremely small samples of Omicron cases. There were only 183 Omicron cases in the study among those dually vaccinated with Pfizer-BioNTech and 190 among those dually vaccinated with Oxford-AstraZeneca. The number of Omicron cases among boosted individuals was even smaller, with 10 cases among individuals originally vaccinated with Oxford-AstraZeneca and 16 cases among individuals originally vaccinated with Pfizer-
BioNTech. Given this small sample size, extreme caution is warranted in interpreting these results.

However, these preliminary clinical data are broadly in line with the in vitro and immunological data discussed above. Even with large confidence intervals, the difference between the 2x and 3x dose regime in mRNA vaccines is statistically significant. Furthermore, all mRNA vaccine protocols are significantly better than the adenoviral Oxford-AstraZeneca vaccine, which loses its efficacy entirely with Omicron, an immune evasive variant.

*Figure 7 “Vaccine effectiveness against symptomatic diseases by period after dose 1 and dose 2 for Delta (black squares) and Omicron (grey circles) for (A) recipients of 2 doses of AstraZeneca vaccine as the primary course and a Pfizer as a booster and (B) recipients of 2 doses of Pfizer vaccine as the primary course and a Pfizer as a booster” (UK Health Security Agency, 2021)*