

# January 30 – February 17, 2021

This weekly science review is a snapshot of the new and emerging scientific evidence related to COVID-19 during the period specified. It is a review of important topics and articles, not a guide for policy or program implementation. **The findings captured are subject to change as new information is made available.** We welcome comments and feedback at [covid19-eiu@vitalstrategies.org](mailto:covid19-eiu@vitalstrategies.org).

## In depth: Should second doses of COVID-19 vaccines be delayed?

### Main message:

While the rollout of multiple vaccines has offered hope to control or end the COVID-19 pandemic, global vaccine demand will continue to outpace supply for the foreseeable future. To date, people in 130 countries have **not yet received a single dose of COVID-19 vaccine**. In countries where vaccination has begun, limited supplies of vaccine in combination with surges in cases and deaths have overwhelmed health care systems. Further, the emergence of more transmissible SARS-CoV-2 variants has led many to question existing vaccine rollout plans and propose alternative strategies. Some countries and experts have recommended

delaying second doses of vaccine to maximize the number of people who receive at least one dose. This raises a critical question: What do we know about vaccines, especially the vaccines for COVID-19, that may allow flexibility in vaccine schedules? This is a complex question and there may not be a straightforward answer. Our knowledge is evolving rapidly as vaccine trials progress and rollout continues, and we must keep in mind that different approaches to vaccine scheduling may be appropriate in different settings. Global inequity in access to COVID-19 vaccines means that these questions around adjusting vaccine intervals are being confronted primarily in wealthier countries as of now; however, these questions may become increasingly relevant around the world as the global vaccination effort continues. No matter how the doses are scheduled, increased manufacturing of safe, effective, quality-assured vaccines is urgently needed.

Vaccines **prevent millions of deaths worldwide each year**. Few public health interventions have had as great an impact on individual and population health. **Diseases that once caused a tremendous burden of illness and death are now controlled in many places** because of routine immunization programs. Vaccination led to the eradication of smallpox, which saved hundreds of millions of lives, and has led to the near eradication of polio, which previously affected more than 350,000 children each year. Vaccines have also played a **defining role in controlling epidemics**. During an influenza pandemic, the **objective for influenza vaccine distribution** is to reduce illness and death and minimize disruption to society and the economy; COVID-19 vaccination programs **have similar goals**. Although vaccine rollout in a pandemic scenario will always present challenges, in an influenza pandemic, we benefit from years of experience designing, producing and administering influenza vaccines (which typically require only a single dose) and in stockpiling influenza vaccines for a potential pandemic. In contrast, during the COVID-19 pandemic, we are confronting a new infectious disease with concurrent high rates of transmission around the world and rolling out new vaccines that were created, manufactured and authorized in record time, building on many years of research and unprecedented national and global investments. Most currently authorized COVID-19 vaccines, and **most COVID-19 vaccines in development**, use a two-dose regimen. Two doses may be necessary to provide sufficient strength and

duration of immunologic protection, but the need to administer two doses, at a specific time interval, presents additional resource and logistical challenges.

As efforts have intensified to rapidly distribute and facilitate uptake of COVID-19 vaccines, there is debate about whether there should be flexibility in the vaccine dosing schedule so that more people can get first doses. In many countries, including the United States, adherence to recommended schedules has been advised, while in others, including the United Kingdom and India, delaying second doses has been advised. It is useful to frame these decisions against a backdrop of how vaccine schedules are typically developed, how COVID-19 vaccine schedules have been developed, local epidemiology, vaccine type, and the evidence we may have to support flexibility within the recommended schedules.

### **How are vaccine regimens, including the number of doses and multidose schedules, typically determined?**

*Why are multiple doses of some vaccines needed?*

Similar to many COVID-19 vaccines, almost all routine immunizations recommended by the Advisory Committee on Immunization Practices (ACIP) and the World Health Organization (WHO) require multiple doses administered at predetermined intervals. There are different reasons why multiple doses may be needed. For many vaccines, such as hepatitis B vaccine, multiple doses are needed to produce long-lasting immune protection. In this case, the first dose “primes” the immune system by provoking an initial response to the antigens contained in the vaccine. Subsequent doses “boost” the immune response by activating immune cells created after the first dose to produce stronger, longer-lasting protection. For some vaccines, such as the measles, mumps and rubella (MMR) vaccine, just one dose can produce long-lasting protection, but multiple doses are recommended because a small proportion of people do not respond to the first dose or because protection is longer-lasting and more complete after a second dose. (Adding a second dose of the measles vaccine was critical in controlling the measles resurgence in the United States in the early 1990s, and continues to be an essential

strategy for the control of measles, which still kills 100,000 children or more each year, globally.) In contrast, for influenza, the genetic code of the circulating virus is different from year to year and vaccine-induced immunity may wane after just a few months. For these reasons, the U.S. Centers for Disease Control and Prevention (CDC) **recommends that people get an influenza vaccine annually.**

For some COVID-19 vaccines, an important reason for multiple doses is to increase the strength of antibody response. As shown in **Figure 1** below, **antibody titers reached levels of around  $10^4$  after the first dose of the Moderna COVID-19 vaccine. After the second dose administered on day 29, antibody titers increased to  $10^6$ .**

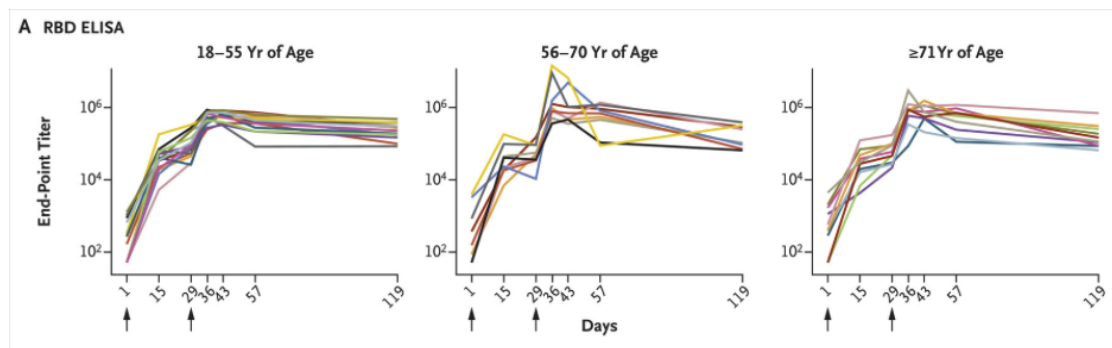


Figure 1. Shown are data from 34 participants who were stratified according to age: 18 to 55 years of age (15 participants), 56 to 70 years of age (9 participants), and 71 years of age or older (10 participants). All the participants received 100  $\mu\text{g}$  of Moderna COVID-19 vaccine on days 1 and 29, indicated by arrows. The titers shown are the binding to spike receptor-binding domain (RBD) protein (the end-point dilution titer) assessed on enzyme-linked immunosorbent assay (ELISA) on days 1, 15, 29, 36, 43, 57 and 119. **Source: New England Journal of Medicine**

How do scientists determine the recommended number and schedule of vaccine doses?

The number and schedule of vaccine doses are determined during vaccine trials. Traditionally, multiple vaccination schedules are investigated during pre-clinical studies in animals and early clinical trials in humans (Figure 2). **A primary objective of Phase II trials is to identify an optimal vaccination schedule.** To do this, scientists

compare the strength, type and duration of immune responses produced by multiple vaccine schedules and assess the safety of each schedule. According to **WHO guidance**, vaccine trials should evaluate the shortest proposed interval between doses. Testing for the minimum interval between doses is important because there should be time to allow the body to mount a response to the first dose before the second dose is administered.

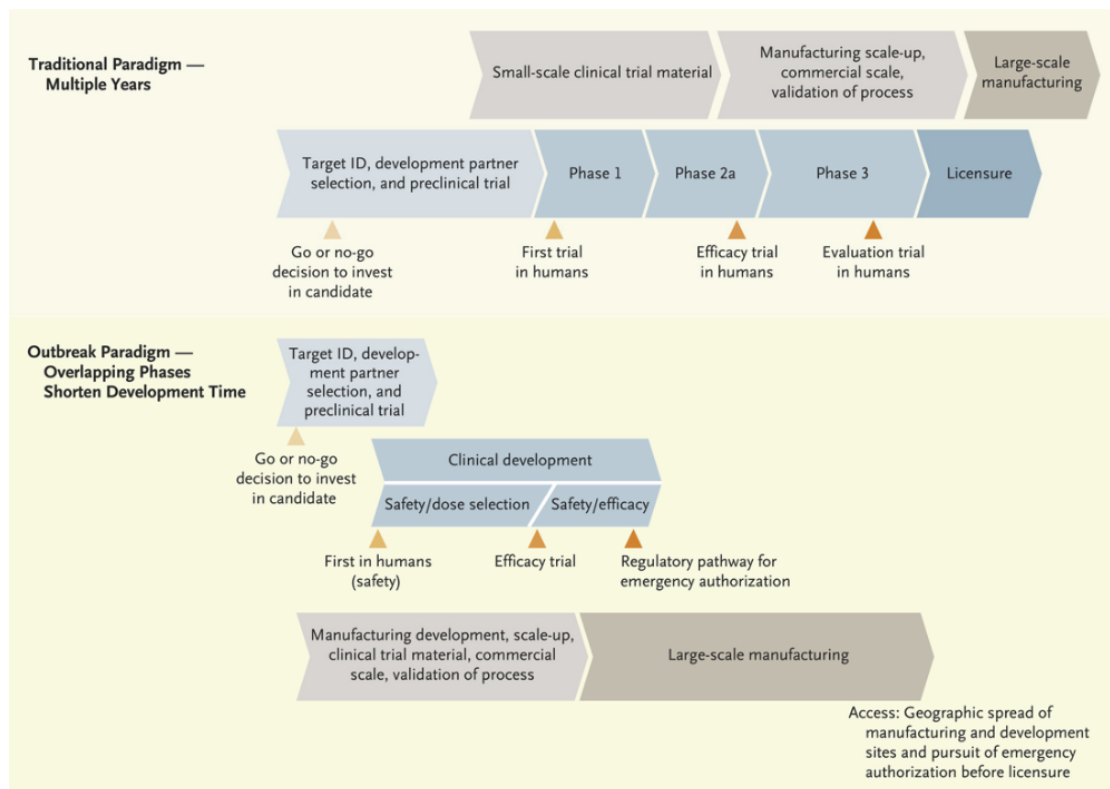


Figure 2. Difference between traditional vaccine development and development using a pandemic paradigm. The pandemic paradigm requires multiple activities to be conducted at financial risk to developers and manufacturers and without knowing whether the vaccine candidate will be safe and effective, including very early manufacturing scale-up to commercial scale before establishment of clinical proof of concept. ID denotes identification. **Source: New England Journal of Medicine**

Which vaccination schedules are tested during trials is often informed by findings from earlier studies of similar types of vaccines. For example, **in developing the Oxford University/AstraZeneca (Oxford) vaccine**, which uses an adenovirus-vectored platform to deliver SARS-CoV-2

proteins to the immune system, researchers built on previous experience developing a similar type of vaccine for Middle East Respiratory Syndrome coronavirus (MERS-CoV). This previous research showed that a single dose protected non-human primates against disease. Similarly, **testing of the Johnson & Johnson adenovirus-vectored COVID-19 vaccine** as both a single dose and two-dose regimen was informed by prior experience with candidate adenovirus-vectored vaccines for other diseases. A **Zika virus vaccine candidate** generated a durable antibody response after a single dose in non-human primates, whereas an **HIV vaccine candidate** resulted in a 10-fold higher antibody titer after two doses compared to a single dose.

*What is the potential impact of deviating from the recommended dose schedule?*

The effect of changing the interval between doses is likely to vary by vaccine, and not all dose schedules have been studied. **ACIP recommends a minimum interval** between doses of each vaccine but does not specify a maximum interval between doses for most vaccines. **Increasing the interval between doses has generally not been found to decrease vaccine effectiveness.** While recommending that providers administer vaccines as close to the recommended schedule as possible, ACIP acknowledges that a few days is unlikely to have a substantial impact and so allows for a “**grace period**” of **four days shorter** than the recommended spacing of most vaccines, including **COVID-19 vaccines.**

In some cases, a longer interval between doses has been associated with increased antibody response, including for **Ebola** and **human papillomavirus (HPV) vaccines.** Recently, a study suggested that the **efficacy of the Oxford adenovirus-vectored COVID-19 vaccine may be increased by waiting 12 or more weeks compared to less than six weeks between doses.** However, a disadvantage of a longer interval between doses of any type of vaccine is that full protection is unlikely until all doses have been administered. In addition, for mRNA vaccines such as the Pfizer and Moderna vaccines, it is not yet known whether the timing of the second dose is critical to producing a sustained immune response, because mRNA vaccines had not been used in late-stage trials or approved for use prior to the COVID-19 pandemic. **An animal study**



showed decreased antibody production four weeks after a first mRNA vaccine dose, suggesting limited durability of the immune response after just one dose. However, these findings cannot be extrapolated to humans; long-term research in humans is needed to understand how long the immune response to a dose of mRNA vaccine may persist.

#### *The development of COVID-19 vaccination schedules*

COVID-19 vaccines were developed at an accelerated pace, with multiple phases of clinical trials underway at the same time (**Figure 2**, above). Additional considerations that may have informed the selection of dosing schedules for COVID-19 vaccines include:

- **Achieving protective immunity as quickly as possible.** For vaccines requiring multiple doses, using the minimum interval between the first and second dose could help build maximum immunity in the shortest time.
- **Simplifying administration in the pandemic context.** Administering a single dose rather than a two-dose series is easier operationally and requires producing half as many doses to fully vaccinate the population. Amid an accelerating pandemic, scientists developing the Oxford vaccine initially pursued a single higher dose vaccine because it could quickly induce protective immunity.

Most currently approved COVID-19 vaccines use two-dose schedules, including the Pfizer/BioNTech (Pfizer), Moderna, Oxford, Gamalaya Sputnik V and Sinopharm vaccines. The CanSino adenovirus-vectored vaccine, which is being used in China and has recently been licensed for use in Mexico, has a single-dose regimen. A single-dose regimen of the Johnson & Johnson vaccine will be evaluated for Emergency Use Authorization by the U.S. Food and Drug Administration (FDA) in late February (clinical trials of a two-dose regimen are ongoing).

## *Contrasting the U.K. and U.S. approach to scheduling second doses of COVID-19 vaccines*

### United Kingdom

On Dec. 2, 2020, the U.K. became the first nation to authorize the use of the Pfizer vaccine as a two-dose regimen with three weeks between doses, as tested in clinical trials. In November 2020, a novel, more transmissible SARS-CoV-2 variant known as B.1.1.7 was first recognized in England and quickly became the predominant variant. Models predicted that **COVID-19 hospitalizations and deaths could reach higher levels in 2021 than were observed in 2020**, and that it might be necessary to accelerate vaccine rollout to suppress transmission. On Dec. 30, 2020, the U.K. authorized the use of the Oxford vaccine as a two-dose regimen with a recommended four weeks between doses. Also on Dec. 30, the **Joint Committee on Vaccination and Immunisation**, which advises on vaccination policy in the U.K., recommended that the second dose of the Pfizer vaccine be given three to 12 weeks after the first dose, and that the second dose of the Oxford vaccine be given four to 12 weeks after the first dose. It was advised that, to have the greatest impact on morbidity and mortality and to protect the health care system, **second doses of Pfizer and Oxford vaccines should be administered closer to the 12-week mark** in order to provide as many people as possible with at least a single dose. This 12-week maximum interval was based on schedules implemented for a subset of participants in Oxford vaccine trials.

### United States

In the U.S., where only the Pfizer and Moderna vaccines are authorized for use, the **CDC** recommends that the second vaccine dose should be administered as close to the minimum recommended interval as possible (i.e., three and four weeks, respectively). Guidelines state that if a delay in vaccination is unavoidable, the second dose of Pfizer and Moderna COVID-19 vaccines may be administered up to six weeks after the first dose (though if the six-week interval is exceeded, the series should not be restarted). The **FDA** states that because a small minority of participants in the Pfizer and Moderna trials received their second dose beyond the recommended interval, and those that deviated from the



schedule were generally only followed for a short period of time, conclusions cannot be drawn about the amount or duration of protection after a single dose of vaccine.

Theoretically, the greatest reductions in morbidity and mortality may occur if more people are provided with some protection than if greater levels of protection are provided for fewer people. In order to determine whether vaccinating more people with single doses and delaying second doses would be beneficial for the population overall, the amount of protection against COVID-19 between the first and the second dose should be known. If the first dose provides little protection, or if protection wanes between the first dose and a delayed second dose, then **the number of cases averted and deaths avoided may be less with a delayed second dose than if the schedule used in clinical trials is maintained.** Bearing this in mind, two key questions are: 1) What amount of protection does a single dose of a two-dose COVID-19 vaccine regimen offer, and 2) How does delaying the second dose affect protection?

*What amount of protection does a single dose of a two-dose COVID-19 vaccine regimen offer, and how does delaying the second dose affect protection?*

Data from **Pfizer vaccine clinical trials**, in which the efficacy of the vaccine to prevent symptomatic infection was assessed starting seven days after receipt of the second dose, showed that participants who received a completed two-dose regimen of the vaccine had 95% less COVID-19 (95% vaccine efficacy) than those who received a placebo. In contrast, vaccine efficacy was 52% during the 21 days between administration of the first and second dose. Immunologic protection takes time to develop after administration of a vaccine; between the day that the second dose was given through seven days after the second dose (theoretically before the protective effect of the second dose would be observed), vaccine efficacy was 91%. An independent **analysis of data from days 15 to 21 after the first dose**—theoretically after protective immune response to the first dose and before administration of the second dose—estimated that the efficacy of a single dose was 89%. Estimates of real-world effectiveness may be gleaned from data from Israel, where **vaccine coverage is currently the highest in the world** (as

of Feb 14, approximately 45% of the population of Israel had received at least one dose of a COVID-19 vaccine, compared with 11% of the U.S. population). A [preprint from Israel](#) that analyzed the data of approximately 350,000 people 13 to 24 days after a single dose of the Pfizer vaccine estimated 51% effectiveness to prevent both symptomatic and asymptomatic infections. Another research group [analyzed the same data](#) and concluded that efficacy rose to about 90% at day 21, suggesting that it can take several weeks for the protective effects of vaccination to be observed. Meanwhile, Pfizer has stated that extrapolations about protection after a single dose cannot be made because clinical trials did not evaluate the efficacy of a single dose beyond 21 days, when the second dose was given.

A [preprint analysis of data from the Oxford vaccine clinical trials](#) showed that, starting 14 days after the vaccine series was completed, participants who received two doses of the vaccine had 67% less symptomatic disease than those who received placebo. Two protocol changes during the Oxford trials provide additional data on how variations to the two-dose regimen may affect efficacy of the vaccine. First, due to a vaccine dosing error, a subset of participants received a lower dose than intended for their first vaccine and a standard-dose second vaccine; among those participants who received low-dose first vaccines, efficacy was 81%; among those participants who received standard-dose vaccines, efficacy was 63%. Notably, the low-dose group was limited to healthy individuals under age 55, and the two groups (low-dose recipients and standard-dose recipients) may not be comparable in other ways as well. Second, because of manufacturing delays, a subset of participants received their second doses 12 weeks (instead of four weeks) after their first doses. Thus, efficacy of a single dose could be assessed over a longer time period. From day 22 to 90 after the first vaccination, the efficacy of a standard single dose was 76%. From 90 to 120 days after first vaccination, the efficacy of a standard single dose was 32%, but that estimate was so imprecise (95% confidence interval -142%, 81%) that conclusions about protection during that period cannot be drawn.

In addition, 59% (1407 of 2377) of U.K. participants in the [Oxford vaccine study](#) who received two standard doses received their second dose between nine and 12 weeks after the first; at the Brazil site, 18.6% (384 of

2063) received their second dose between nine and 12 weeks after the first. **Analysis of combined Brazil and U.K. data** showed that the efficacy of the vaccine in the prevention of symptomatic disease 14 days after a second dose was higher in the group that had more than six weeks between the two doses (65%) than in the group that had less than six weeks between doses (53%).

These data suggest that a single dose of the Pfizer or Oxford vaccine may provide good protection against COVID-19. Data also suggest that for the Oxford vaccine, similar efficacy may be observed in the three months following vaccination (whether or not the second dose was delayed) and that protection may not be affected if the second dose is delayed to 12 weeks. However, there are important limitations and remaining unknowns. The efficacy of single doses of mRNA (Pfizer or Moderna) vaccines beyond originally authorized time points for second doses are not known. Data on protection past the 90-day mark offered by any schedule are limited, and the long-term effects of a delayed second dose remain to be determined. Data from the Oxford trial are subject to a variety of limitations including small sample sizes, which can lead to less precise estimates of vaccine efficacy. In addition, data on the efficacy of a delayed second dose were collected among participants aged 18 to 55 years; the effects of delaying a second dose among older people are not known.

*Can single-dose approaches keep us ahead of variants?*

Maximizing the number of people with some level of immunity may be especially important if a highly transmissible variant is spreading rapidly. Some **experts in the U.S. have suggested** renewed consideration of a policy to delay second doses in favor of administering a first dose to more people, because highly transmissible variant strains of SARS-CoV-2 are spreading in the United States. Researchers who analyzed samples collected in the U.S. from December 2020 to January 2021 concluded that **variant B.1.1.7 may become the predominant strain in the U.S. by March**, given a 30% to 40% higher transmission rate than non-B.1.1.7 lineages. This variant **may cause more severe disease** but, even if this is not the case, increased caseloads can overwhelm hospitals, leading to

increased fatality rates. On the other hand, some experts have expressed concern that the emergence of new variants may be facilitated if second doses are delayed and this results in less robust immunity. Indeed, selective pressure exerted by weakened immune systems incapable of completely killing SARS-CoV-2 may have been a factor in the emergence of new variants. Others argue that high transmission rates, resulting in widespread replication of the virus, is the most important driver in the emergence of variants and thus, reducing transmission as quickly as possible is the real key to getting ahead of variants. There is evidence from Novavax and Oxford clinical trials conducted in South Africa that those vaccines are less effective at preventing symptomatic COVID-19 caused by variant B.1.351, the predominant variant circulating in South Africa. In contrast, studies conducted in the U.K. suggest that efficacy of Oxford and Pfizer vaccines against variant B.1.1.7 is not reduced. It is not clear how well a single dose of any two-dose COVID-19 vaccine may prevent infection with emerging variants.

*What are other ways we might alter vaccine schedules to make them more flexible during the pandemic response?*

Being able to mix and match COVID-19 vaccine doses from different manufacturers in a series could increase flexibility and reduce the impact of manufacturing or supply disruptions on vaccination campaigns. Mixing and matching doses from different manufacturers could offer a way to maximize first-dose recipients without extending vaccine dosing intervals. However, authorization or licensure of multiple vaccines for the same disease does not indicate that the vaccine products are interchangeable. For COVID-19 vaccines, studies will be needed to understand the safety and efficacy of mixed-product vaccination series. Currently, CDC recommends that all doses of COVID-19 vaccination should be completed with the same product, except in exceptional situations.

There is precedent for combining multiple vaccine products in a series. Vaccine developers have used this strategy, called “heterologous prime-boost,” in candidate Ebola and HIV vaccines. The Sputnik COVID-19

vaccine applies this strategy by using two different adenovirus vectors for the first and second vaccine dose. Because the immune system may respond to both the vector and the antigen target in a priming dose, a vaccine that uses the same vector for all doses might produce a weaker immune response to subsequent doses. The heterologous prime-boost approach avoids this issue by using different vectors for subsequent doses. Studies to investigate the safety and immunogenicity of mixed-product COVID-19 vaccination series are underway, including combinations of the Sputnik and Oxford vaccines and of the Pfizer and Oxford vaccines. Whereas both the Sputnik and Oxford vaccines rely on adenovirus vector platforms, the Pfizer-Oxford study will help to show whether immune response is improved by combining two different vaccine technologies that are better at activating different aspects of the immune system.

In conclusion, the question of whether modifying dosing schedules may provide optimal pandemic control does not have an easy answer. There are strong arguments to complete vaccine regimens as studied in clinical trials. However, emerging evidence may support the decision to speed the rollout of single doses by delaying second doses, especially when an increasingly transmissible variant is spreading rapidly, as has occurred in the U.K. Preliminary data on authorized COVID-19 vaccines support the hypothesis that a single vaccine dose may offer substantial protection against COVID-19 and that delaying a second dose of the Oxford vaccine may not decrease protection in the months following vaccination. This is consistent with what we know about non-COVID-19 vaccines. It is possible that—as has been observed for other vaccines—long-term protection will not be affected, or may be enhanced, by delaying the second dose, but these data are not yet available. Additional uncertainty around emerging variants complicates decision-making, and the use of novel mRNA platforms calls for caution when extrapolating findings from other vaccines to the Pfizer and Moderna vaccines. Ultimately, COVID-19 pandemic control hinges on achieving widespread immunologic protection at the population level. To minimize the health and societal effects of the pandemic and stay ahead of highly transmissible variants, rollout of complete vaccine series should proceed as quickly and equitably as possible. While vaccine supplies are limited,

it is crucial to prioritize vaccination of people at highest risk for exposure and severe disease, and to work toward ensuring global access to safe and effective vaccines.

## Weekly Research Highlights

### Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021

(MMWR, February 2021)

**Main message:** Recent experiments by the Centers for Disease Control and Prevention found that double-masking (placing a three-layer cloth mask on top of a medical procedure mask) or adjusting a medical procedure mask so that it fits tightly (see figure below) is more effective than either cloth or medical procedure masks alone. However, it also found that there is little difference in protection between mask types as long as both source and receiver are wearing masks (all >90%). If only one person is wearing a mask, double-masking provides a high level of protection to the receiver (82%-83%), is more effective than adjusted medical procedure masks (63%-65%), and is almost twice as effective as standard medical procedure masks (42%-44%).

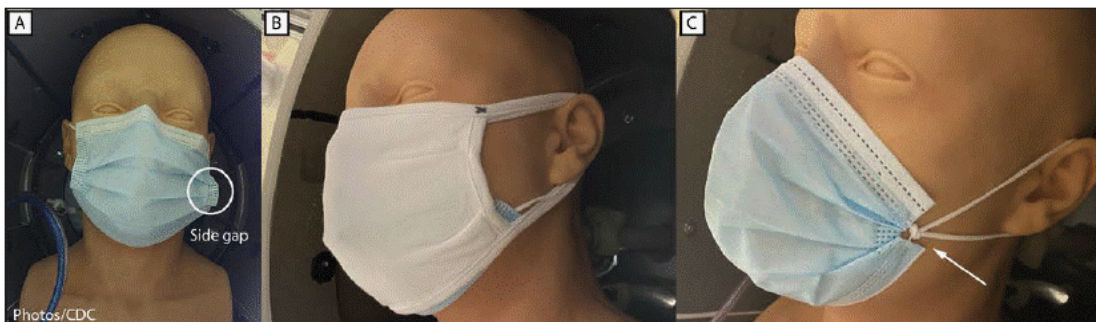
Despite concerns that mask-wearing only protects others, mask-wearing by either the source or the receiver appeared to be equally protective.

- The authors conducted two experiments. The first simulated a person coughing using a model of a head and compared the quantity of aerosols emitted when the model was wearing either a double mask, cloth mask alone or medical procedure mask alone. The second placed two head models in a small room and simulated the quantity of aerosols emitted from light breathing. It assessed which combination of masks best protected the receiver.



- Mask type: double masks, adjusted medical procedure masks, normal medical procedure masks
- Who is masked: no one, receiver only, source only, both
- The first experiment found that double-masking was superior to either cloth or medical procedure masks alone, blocking 93% of aerosols emitted during a simulated cough compared to 44% for cloth masks and 42% for medical procedure masks.
- The second experiment found that double-masking reduced exposure to aerosols by 82% when only the source was masked, by 83% when only the receiver was masked and by 96% when both were masked. Adjusting a medical procedure mask so it fit tightly reduced exposure by 63% when only the source was masked, 65% when only the receiver was masked and 96% when both were masked. Results for unadjusted medical procedure masks alone were 42%, 44% and 93%.

Limitations of the study include the fact that these were controlled simulations and do not cover the full range of real-world exposures. In addition, only one type of medical and cloth mask were tested, but many exist on the market. The masks may not fit well on children and people with facial hair, even with these methods.



Masks tested, including A, unknotted medical procedure mask; B, double mask (cloth mask covering medical procedure mask); and C, knotted/tucked medical procedure mask **Source: CDC**

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**Seasonal human coronavirus antibodies are boosted upon SARS-CoV-2 infection but not associated with protection**

(Cell, February 2021)

**Main message:** Previous exposure to other human coronaviruses does not appear to provide protection from either contracting SARS-CoV-2 or from more severe disease. Cross-protection between other coronaviruses and SARS-CoV-2 has been raised as one hypothesis for why severity of COVID-19 among children is reduced and why there have been fewer cases in some parts of the world. Researchers found that, before the COVID-19 pandemic, about 20% of people had antibodies that reacted to one or more proteins in the SARS-CoV-2 virus, likely due to a prior infection with a different coronavirus. However, a matched case-control study found that people who became infected with COVID-19 were equally likely to have cross-reactive antibodies as people who did not get infected. Further, among those who did get COVID-19, there was no relationship between cross-reactive antibodies and disease progression.

- The researchers conducted a number of different experiments including:
  - Analysis of 431 pre-pandemic human samples (263 children, 168 adults) from 2017 to determine if the samples had antibodies that reacted to SARS-CoV-2, the potential origin of those antibodies, and associations with age of the participant;
  - A case-control study matching a group of 251 people who had pre-pandemic specimens collected during the period from August 2013 to March 2020 and then received a positive PCR test for COVID-19, to a similar group who did not have a positive PCR test in their medical records; and
  - A longitudinal study assessing whether having cross-reactive antibodies was associated with disease severity among the 251 people with a positive PCR test.
- Researchers did not find any obvious age patterns in SARS-CoV-2 cross-reactivity, indicating that different age patterns of exposure to other human coronaviruses probably does not explain the difference in susceptibility to SARS-CoV-2 by age.
- Limitations: This was a small study and because antibody levels can wane quickly, antibody levels among cases at the time of exposure to SARS-CoV-2 may have differed from those detected in stored samples

collected as early as 2013. Further, people in the control group were chosen from medical records and it is possible that some of them had had COVID-19 but were not tested or were tested in a different health system. Lastly, all samples were from the U.S., and there may be different patterns of human exposure to coronaviruses in some populations that could result in different cross-reactivity patterns.

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