DEPARTMENT OF THE NAVY
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MEMORANDUM

From: Director, Military Personnel Plans and Policy (N13)
To: Deputy Chief of Naval Operations (Manpower, Personnel, Training and Education) (N1)

Subj: RELIGIOUS ACCOMMODATION (RA) REQUESTS FROM SAILORS SEEKING IMMUNIZATION WAIVERS

Ref: (a) 42 U.S.C. §2000bb-1
(b) DoD Instruction 1300.17 of 1 Sep 20
(c) SECNAVINST 1730.8B Ch-1
(d) BUPERSINST 1730.11A
(e) MILPERSMAN 1730-020
(f) ASN (M&RA) memo of 6 Jun 13
(g) BUMEDINST 6230.15B
(h) OPNAVINST 1300.20

Encl: (1) CHBUMED ltr 6320 Ser M44/21UM401 of 22 Sep 21
(2) CDC Information of 15 Sep 21

1. Purpose. This memorandum provides analysis of the least restrictive means for achieving the Navy's compelling government interest in preventing the spread of diseases to support mission accomplishment, including military readiness, unit cohesion, good order and discipline, or health and safety, at the individual, unit, and organizational levels. This includes reducing vaccine preventable diseases in individual Sailors and preventing the spread of vaccine-preventable communicable diseases among Sailors. The compelling government interest is not in dispute and is addressed here only briefly. Navy leaders have determined that requiring all Navy Service Members ("Sailors") to be vaccinated against certain diseases is the least restrictive means of achieving that compelling government interest. This memorandum explains the analysis behind that determination and addresses the risk to mission accomplishment inherent in deviating from requiring vaccination of all Sailors.

2. References. Reference (a), the Religious Freedom Restoration Act (RFRA), prohibits the U.S. Government from substantially burdening a person's exercise of a sincerely held religious belief unless the restriction, as applied to the specific person, is in furtherance of a compelling government interest and is the least restrictive means of furthering that compelling government interest. References (b) through (d) establish procedures for Sailors seeking religious accommodations (RAs). Reference (e) provides amplifying details on RA requests for

immunization waivers.[1] Reference (f) designates the Deputy Chief of Naval Operations (Manpower, Personnel, Training, and Education) (DCNO N1) as the U.S. Navy adjudication authority for RAs, including requests for immunization waivers. In cases where DCNO N1 has disapproved a request, and the member submits an appeal, the adjudication authority rests with the Chief of Naval Operations (CNO), in line with references (c) and (d).

Compelling Government Interest

3. The Navy's compelling government interest in preventing spread of diseases to support mission accomplishment, including military readiness, unit cohesion, good order and discipline, or health and safety, at the individual, unit, and organizational levels is addressed in enclosures (1) and (2), along with the Bureau of Medicine and Surgery (BUMED) endorsement on each RA request seeking an immunization waiver. Vaccine-preventable diseases cause severe illness, long-term health effects, and death, interfere with the ability of Sailors to accomplish the Navy's mission at the individual, unit, and organizational levels, decrease the overall health of the force, and place additional strain on medical resources. Spread of communicable diseases among Sailors who live and work in tight quarters aboard ships or in communal environments while deployed, or who live or work in close proximity to others in the shore establishment, have the potential to cause mission failure when one or more personnel become too sick to effectively do their jobs. Logistical challenges inherent in moving personnel to and from deployed ships and other deployed environments make it difficult to quickly evacuate sick personnel and replace them with healthy personnel who are adequately trained and ready at a moment's notice. The Navy's lean manning methodology to operate successfully during prolonged budget constraints further limits the quick replacement of personnel in deployed environments. In the case of personnel operating in foreign locations, the spread of communicable diseases from U.S. Navy personnel to host-nation personnel would have a detrimental impact on U.S. foreign relations, especially if the illness was viewed as preventable. Additionally, Navy ships have limited medical and long-term placement capabilities. If even one Sailor infected with a communicable disease requires treatment beyond the capabilities of a ship's medical department, or if multiple Sailors must be placed in critical care, a decision will have to be made whether the ship may have to abandon its mission and transit to a location that offers more adequate treatment. Foreign medical facilities may also refuse to accept a U.S. Navy patient infected with a communicable disease, requiring the ship to transit farther—potentially thousands of miles, exacerbating an already difficult situation. Foreign ports may refuse entry to a Navy ship with a communicable disease onboard. The ship may be denied free pratique and not allowed to enter

[1] As of the date of this memorandum, reference (e) is out of conformity with reference (b), rendering many provisions of reference (e) invalid. For example, a commanding officer (CO) cannot order a Sailor with an RA approved by DCNO N1 to receive a vaccine waived by the RA because reference (b) allows rescission of an RA only by an official at the level in the chain of command that granted the RA. In other words, if DCNO N1 grants an RA, then only DCNO N1 (or someone senior to DCNO N1) may rescind the RA. The only exception is for exigent circumstances amounting to a life-threatening or mission critical emergency. (For example, a CO could order a Sailor to shave a religious beard approved by DCNO N1 to get an effective seal on a gasmask in response to credible intelligence of an imminent chemical weapons attack.) Because immunizations do not provide immediate immunity, it is unlikely a CO would have bona fide exigent circumstances to order a Sailor to receive an immunization where a RA waived the requirement for a Sailor to receive that immunization. *See, e.g.,* CDC guidance on the COVID-19 Delta variant, available online at: https://www.cdc.gov/coronavirus/2019-ncov/variants/delta-variant.html?s_cid=11617:delta%20variant%20covid:sem.ga:p:RG:GM:gen:PTN.Grants:FY22.

port or allow personnel to embark or disembark. While the consequences of disease are most severe in deployed ships, they are nevertheless compelling in Navy billets ashore. A significant portion of the shore establishment is collocated with the operating forces and supports those forces with readiness activities such as maintenance, technical support, training, and medical care. Many shore duty billets require in-person work in enclosed office spaces where spread of disease is possible. Even Sailors who might be able to work in isolation a large portion of the time have certain military duties, such as medical exams, physical fitness tests, urinalysis, and ad hoc meetings. Finally, because the Navy prioritizes manning on deployable units first, many shore units are manned only at or *below* the planned manning levels, magnifying the impact of preventable sickness on mission accomplishment.

4. There are specific compelling government interest concerns for each required vaccination.

a. COVID-19 can cause severe illness and death in young, otherwise healthy individuals, including the eight active duty Sailors and two active duty Marines killed by the disease as of 26 October 2021. All ten of these personnel were not fully vaccinated. No deaths caused by COVID-19 have been reported in fully vaccinated service members, active or reserve. The highly transmissible Delta variant is of particular concern and is more transmissible than other variants.[2] As reported in enclosure (1), studies of available mRNA vaccines, including the FDA-approved Comirnaty vaccine manufactured by Pfizer, have shown an 88% efficacy rate against the Delta variant. Further, enclosure (1) discusses a recent study showing over 71% of recent COVID infections occurring in unvaccinated individuals and more than 85% of hospitalizations in unvaccinated individuals. For people evaluated in the study, the hospitalization rate of unvaccinated individuals was more than 29 times that of fully vaccinated individuals. While anyone can spread COVID-19, fully-vaccinated people will likely spread the virus for less time and to fewer people than unvaccinated people.

b. In the case of Sailors, including those in the accession pipeline, who are requesting waiver of all future immunizations, the following considerations apply to vaccinations required by reference (g) for all Sailors, regardless of location:

(1) Every year, the influenza vaccine is required for all Sailors who do not have a medical or administrative exemption. As explained in enclosure (1), the spread of influenza will deprive the Navy of medical resources and commands of personnel needed to accomplish the mission while those personnel recover and place additional strain on those who must augment to fill the sick Sailors' positions. In severe cases, personnel infected with influenza require hospitalization. Influenza outbreaks can be explosive, with the potential to incapacitate many Sailors assigned to one command.

(2) Every 10 years, the Tdap (tetanus, diphtheria, pertussis) or Td (tetanus, diphtheria) vaccine is required for all Sailors who do not have a medical or administrative exemption. Enclosure (1) explains the specific, debilitating consequences of infection with each of the diseases prevented by the highly effective Tdap vaccine. For example, the Tdap vaccine is almost 100% effective at preventing tetanus, a disease with an 11% mortality rate. Infection

[2] Centers for Disease Control and Prevention. "Delta Variant: What We Know About the Science" 26 Aug 2021.

with tetanus would prevent a Sailor from performing their individual mission and affect mission accomplishment at the unit level, and recovery takes months. Tdap is 97% effective at preventing diphtheria, which is common in some areas outside of the United States. Before the development of a vaccine, diphtheria was a leading cause of death among children in the United States. Diphtheria has a 5 to 10% mortality rate. Tdap is 80 to 85% effective at preventing pertussis, a disease that causes bacterial pneumonia in more than 13% of cases. A Sailor infected with any of the diseases that Tdap successfully prevents could be inhibited from accomplishing their mission for months, and death is possible.

c. A number of vaccines are required by reference (g) for deployment and/or overseas assignment. These location-specific vaccinations protect Sailors against local threats, including anthrax, Japanese encephalitis, yellow fever, typhoid fever, and smallpox. The Geographic Combatant Command (GCC) establishes these requirements, and the GCC Command Surgeon serves as the approval authority for waivers of the GCC requirements. The following information is from the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov) and other public sources:

(1) The CDC website reports the anthrax vaccine is 93% effective. Anthrax inhalation[3] is almost always fatal in unvaccinated individuals who do not receive immediate treatment, and even with aggressive treatment, anthrax inhalation kills 45% of unvaccinated patients.

(2) The World Health Organization website (www.who.int) indicates the Japanese encephalitis vaccine is more than 99% effective. The CDC website indicates that, although Japanese encephalitis is rare, one in four cases is fatal.

(3) According to the CDC, typhoid fever is common in developing nations, with as many as 21 million cases occurring each year, mostly in South Asian and Southeast Asian nations frequented by deployed Sailors. Because antibiotic treatments are effective against the disease, only about 200,000 of these patients die each year. However, the CDC reports a growing incidence of typhoid fever resistant to antimicrobial drugs. The disease can be spread both by contaminated food and water and by contact with infected persons.

(4) The CDC website reports that, although yellow fever infection is rare, 30 to 60% of those who develop severe yellow fever disease die.

(5) The smallpox vaccination is so effective that it eradicated a disease the World Health Organization characterizes on its website as "one of the most devastating diseases known to humanity." Before mass vaccination, millions of people were killed or disfigured by the disease. It is believed that smallpox no longer exists in nature. However, the CDC reports, "There is a credible concern that in the past some countries made the virus into weapons, which may have fallen into the hands of terrorists or other people with criminal intentions."

[3] The anthrax immunization requirement in reference (g) is designed to protect personnel against weaponized anthrax. Research into the harm of anthrax has been possible because of exposure to naturally occurring anthrax.

d. Requiring new accessions to the Navy to have completed or receive traditionally childhood immunizations is also critical to mission accomplishment. Although an individual breakdown of these required immunizations is beyond the scope of this memorandum, it is addressed in Appendix D to reference (g). Examples of diseases for which new accessions must receive immunizations, if not previously immunized, include adenovirus, polio, measles, mumps, rubella, hepatitis A and B, and varicella.

Non-Pharmaceutical Interventions (NPIs)

5. BUMED reports that the CDC recommends use of NPIs in conjunction with vaccination to stem the spread of diseases transmitted by respiratory droplets, including COVID-19, influenza, and pertussis. Specifically, the CDC recommends respiratory hygiene (covering mouth and nose while coughing or sneezing), avoiding touching the face, frequent hand washing with soap for at least 20 seconds, cleaning and disinfecting objects and surfaces that are frequently touched, avoiding sick people, and self-quarantine when a person feels unwell. BUMED reports that masking is appropriate in some circumstances, as well as social distancing of six feet or more to stem the spread of certain respiratory illnesses. Unfortunately, BUMED reports that there is very limited data available on the effectiveness of NPIs. This makes it difficult to compare scientifically proven efficacy rates of NPIs not accompanied by vaccination to the efficacy rates of vaccination or vaccination with NPI usage. BUMED states that NPIs are known to be more effective at preventing spread of disease when implemented as community-wide mandates than when implemented by one individual. This factor is key in the determination that NPIs are not sufficient alone to protect Sailors from the risks imposed by COVID-19 and other communicable diseases, and ultimately to ensure the Navy's ability to achieve mission accomplishment, including readiness, unit cohesion, good order and discipline, or health and safety, at the individual, unit, and organizational levels.

Least Restrictive Means

6. COVID-19. As discussed below, mandatory immunization of all Sailors against COVID-19 is the least restrictive means of achieving the Navy's compelling government interest in reducing to zero any preventable impairment to mission accomplishment, including readiness, health, and safety, at the individual, unit, and organizational levels in the operating forces and shore establishment.

a. Health and Safety. The Navy has not identified any means equally or more effective than mandatory immunization against COVID-19 to ensure the health and safety of Sailors, including a Sailor who seeks a religious accommodation from the mandatory COVID-19 vaccination requirement. As discussed in paragraph 4 and enclosure (1), the scientific data shows that a fully vaccinated Sailor is at far less risk of serious illness or death in the event of a "breakthrough COVID-19 case." To date, not one fully vaccinated Sailor has died from COVID-19. Among those Sailors who are fully vaccinated, only 1.7 percent contracted a "breakthrough case" between 17 December 2020 and 26 October 2021. In the same timeframe, 23.3% of unvaccinated active duty Sailors experienced COVID-19 infections. Regardless of whether a Sailor is assigned to the operating forces or the shore establishment, mandatory COVID-19

immunization is the least restrictive means to ensure readiness and health and safety at the individual, unit, and organizational levels of the Navy.

b. Restriction of Movement (ROM). For more than a year during the COVID-19 pandemic, the Navy imposed stringent restrictions across the force in every location to limit the activities and behaviors of Sailors assigned to both shore and operational units to keep them and the force healthy. Almost all quality-of-life port visits were cancelled, and Sailors were ordered to quarantine within the bubbles of their ships for two weeks before getting underway. (This quarantine is referred to as restriction of moment (ROM).) Ashore, Sailors were ordered to forego haircuts, prohibited from dining in restaurants, and restricted from recreation to a far greater degree than the general public. COVID-19 vaccinations have allowed the lives of many Sailors to start getting back to normal. ROM periods have been relaxed for fully vaccinated Sailors and for crews of ships with very high vaccination rates.

(1) In the best of times, Navy life is hard on Sailors' family and social lives. There are many challenges that our Sailors face that are unique to naval service. In the case of an operational unit preparing to deploy, additional stress is expected as the Sailors must balance the demands of work and home. Long periods of time underway are known to strain the emotional and psychological wellbeing of Sailors. Adding additional periods of time isolated from family, friends, and society at large due to ROM requirements has exacerbated these concerns and negatively impacted readiness. This concern is equally as important on shore duty, which the Navy relies on as a periodic respite from the stress of sea duty. However, the ROM periods were justified as a necessary mitigation technique to avoid COVID-19 infections that could interfere with mission accomplishment, and were largely effective.

(2) It is not safe for a vessel to deploy with even one unvaccinated Sailor unless the entire crew goes through a ROM period and port visits continue to be cancelled. As explained in enclosure (2), "Vaccinated people can still become infected and have the potential to spread the virus to others, although at much lower rates than unvaccinated people." Further, unvaccinated personnel are significantly more likely to require hospitalization than vaccinated individuals with breakthrough infections. Taken together, these two facts make clear that imposing ROM measures only on unvaccinated Sailors would be insufficient to protect against risk of mission failure inherent in allowing unvaccinated Sailors to go to sea because an unvaccinated Sailor can be exposed to COVID-19 via a breakthrough case in a vaccinated shipmate who was not required to ROM. There is an appreciable risk that acquiring treatment for one unvaccinated Sailor would require a ship to abandon its mission and transit to a location with a shore-based medical facility able and willing to care for the COVID-19 patient. Some countries may deny a Navy ship free pratique, that is entry into port and disembarkation or embarkation of personal, if there is a communicable disease onboard, or host-nation medical facilities may be unwilling or unable to accept unvaccinated U.S. COVID-19 patients, which could lead to a ship abandoning its mission and transiting thousands of miles in an effort to save a life, with negative impact on unit and organizational mission accomplishment.

(3) Continuing to require 14-day ROM periods for all Sailors and canceling future port visits is not a sustainable approach. Port visits serve as a much-needed venue to acquire parts, mail, fresh food, and a quality of life respite for Sailors. This approach would involve a very

high cost to the emotional and psychological wellbeing of other Sailors, decreasing the readiness of the entire crew. Further, a deployment with no port visits that locks Sailors to their ships weeks before getting underway will likely lead to diminished job satisfaction and discourage Sailor recruitment and retention. While this tradeoff was temporarily acceptable during the COVID-19 pandemic before vaccinations were available, use of ROM as permanent means of accomplishing the Navy's compelling governmental interest in mission accomplishment is untenable.

c. Other available NPIs, both those identified by BUMED and others discussed by recent news articles, are insufficient to protect unvaccinated Sailors aboard U.S. Navy ships for the following reasons:

(1) Masking. The Navy can require all Sailors to wear masks, but full-time tight quarters on a ship severely limits its effectiveness, as does communal living in barracks or working in close quarters ashore. Aboard ship, unvaccinated Sailors will have to eat, sleep, shower, and brush their teeth in the same spaces as vaccinated Sailors who have gone on liberty among the general public and been excused from ROM requirements.

(2) Ventilation. U.S. Navy ships have almost no windows, and fresh air circulation is limited by steel construction that includes collective protection systems (CPS) in place to seal off areas of ships for protection against chemical, biological, or radiological weapons attacks. During training drills, the ship will secure ventilation to demonstrate the required actions in the case of a damage-control emergency.

(3) Social distancing. Maintaining a social distance for Sailors on U.S. Navy ships is impossible. Narrow passageways do not allow for Sailors to maintain social distances when transiting a ship. Almost all enlisted berthing compartments feature three-foot by six-foot bunks, referred to as "racks," that are stacked three high and have only narrow passages between rows. Enlisted berthing compartments have as few as 12 and as many 210 personnel sleeping in the same space, where there are generally racks for six Sailors in every thousand cubic yards. Sailors in larger berthing compartments are never alone in the head when they shower or brush their teeth while underway because a head the size of a studio apartment can be shared among 200 or more personnel. In the case of fast-attack submarines, populations are smaller, but some Sailors have to take turns sleeping in shared racks. Most officers share small staterooms with between one and five of their peers, and tiny heads are often shared between many officers. In addition to sleeping and engaging in personal hygiene, meals are also unconducive to use of NPIs. Sailors are fortunate if they can keep their elbows and knees six inches from those around them while eating on mess decks. The wardrooms where officers dine are only slightly more spacious. Extending meal hours to allow fewer people to dine at a time would unfairly burden Culinary Specialists and Food Service Attendants, who are already known in the Navy for having some of the longest and most arduous working hours, and would not be sustainable. There are few alternative locations for Sailors to eat on ships, and allowing Sailors to take meals out of areas designated for eating has the potential to invite rodent and insect infestations. Even if the recommended 6-foot spacing were possible, it may not be adequate aboard ships due to the ventilation characteristics of the vessel. Social distancing may be more tenable ashore, but is highly dependent on the type of work a Sailor does and the configuration of their workspace(s).

(4) Cleanliness. As hard as Sailors work to keep their ships clean, safe transit up and down ladders and through watertight doors requires everyone to touch all of the same handrails and handles frequently. Further, although Sailors can be reminded to use hand sanitizer, frequent handwashing is not generally possible because Sailors have to transit up and down ladders, with those shared handrails, to get between their workspaces and the heads in which they can wash their hands.

(5) Self Quarantine. It is very difficult to quarantine individual Sailors onboard an underway U.S. Navy ship because there are limited extra spaces. On smaller ships, medical divisions operate out of one space. Even on larger ships, medical departments have limited space to quarantine or isolate personnel. Further, vaccinated or unvaccinated Sailors with COVID-19 infections may be asymptomatic or may suffer such mild symptoms that they do not realize they are contagious until after an unvaccinated shipmate has become infected.

d. Because shipboard environments significantly limit the effectiveness of all NPIs, and because even one serious COVID-19 infection can pull a ship off station resulting in mission failure at the unit and possibly organizational levels, immunization of all Sailors against COVID-19 is absolutely necessary and is the least restrictive means of achieving the Navy's compelling government interest in preventing spread of communicable disease to ensure mission accomplishment.

e. Although the drawbacks of NPIs are most acute shipboard, the NPIs still do not meet the compelling government interest ashore. Ashore, a Sailor is in more frequent contact with the public, and has significant interaction outside the Navy workplace. Therefore, the opportunity to be in close contact with an infected person is actually greater. Additionally, none of the NPI, individually or together, is sufficiently effective to meet the Navy's compelling government interest.

7. Other Respiratory Illnesses. NPIs are ineffective at stemming the spread of other respiratory illnesses aboard ships for the same reasons NPIs are ineffective against COVID-19. For many years, U.S. Navy units have been spared serious outbreaks of influenza, diphtheria, and pertussis by widespread vaccination among the U.S. population and among Sailors in particular. Unfortunately, vaccine hesitancy in recent years has allowed for an uptick in communicable disease in the American public. Due to the tight quarters aboard ships discussed above, infection with one of these respiratory illnesses by an unvaccinated Sailor is likely to spread quickly and incapacitate other unvaccinated Sailors. Because of lean shipboard manning and the possible need to abandon a mission to seek higher-level medical care for an infected Sailor, one of these diseases could lead to mission ineffectiveness or mission failure. Therefore, immunization is the least restrictive means available to achieve the Navy's compelling government interest in reducing to zero any preventable impairment to mission accomplishment because it helps to prevent the spread of these diseases through individual infections or community spread of these diseases.

8. Mosquito-Borne Illnesses. Japanese encephalitis and yellow fever are transmitted by mosquitos. Sailors traveling to or stationed in parts of the world where one of these diseases is

endemic can protect themselves through very careful use of mosquito repellents. Unfortunately, there is risk in forgetting to apply repellent or getting bitten immediately after showering but before having an opportunity to apply repellent. Also, the potential harm from these diseases is great, including risk of death. Because NPIs are significantly less reliable than immunization, NPIs alone are not sufficient to prevent spread of mosquito-borne illnesses, and immunization is the least restrictive means available for preventing the spread of these diseases to allow for mission accomplishment. These vaccines are required only of Sailors who are likely to be deployed to areas of the world where the diseases are common.

9. Contamination-Related Illnesses. Typhoid fever is usually caused by consumption of contaminated food or water or by close contact with an infected person, and is common in certain parts of the world. Tetanus is caused by bacterium spores entering the body through broken skin. Ships, piers, and shipyards are industrial environments in which any scrape or scratch could cause a tetanus infection for an unvaccinated Sailor. There are no NPIs to prevent the spread of these illnesses, and risk of harm is great. Therefore, immunization is the least restrictive means available for preventing harm from these diseases to allow for mission accomplishment. The Typhoid vaccine is required only of Sailors who are likely to be deployed to areas of the world where the disease is common.

10. Weaponized Disease. Anthrax and smallpox present a threat to Sailors only if weaponized by an enemy or terrorist organization. Immunization is the only measure to prevent either of these diseases. Therefore, immunization is the least restrictive means for preventing harm from these diseases to allow for mission accomplishment.

11. Sailors on Shore. The U.S. Navy budget, end-strength limits, and personnel strategy dictate that every Sailor must be deployable and do not allow for keeping Sailors on the payroll who are unable to deploy. This policy is documented by reference (h), OPNAVINST 1300.20, "Deployability Assessment and Assignment Program," which requires administrative separation processing or referral to the Disability Evaluation System for any Sailor who is undeployable for 12 months or longer. It is very rare for a Sailor to be retained in a permanent limited duty status because the Navy needs Sailors who can go to sea or otherwise deploy.

a. Authorizing Sailors assigned to shore duty or the Navy Reserve to forego required immunizations is untenable because of the need for Sailors to be ready to deploy at a moment's notice. Even a Sailor on shore duty pending retirement can be called up to deploy when necessary to achieve mission requirements. Presidential recall under Title 10, U.S. Code, authorizes the Reserve Component to mobilize in a variety of geographic locations, including overseas.

b. Immunity is not instantaneous. Every vaccination requires time to confer immunity. In the case of the now-mandatory COVID-19 Pfizer vaccination, immunity is achieved five weeks after the first dose (two weeks after the second dose). For a short-notice mission, whether in response to tasking or to relieve other Sailors impacted by injury or illness, mission failure could result if Navy leaders are required to wait five weeks to safely deploy Sailors waived from vaccination requirements because of assignment to shore duty.

c. Even one unvaccinated Sailor, after contracting COVID-19, affects mission accomplishment at the individual level, and can infect dozens of other Sailors, exacerbating the problem of shore and Reserve deployability. Vaccines for worldwide-deployable Sailors throughout the force (shore and sea) constitute the least restrictive means of ensuring a ready, agile fighting force.

d. In addition, individual Sailors and units ashore perform important duties in support of the Navy mission. As an "optimally" manned organization, the Navy relies on each Sailor and unit to be fully ready to accomplish their mission because there is often no backup person with the same skillset. Therefore, even a Sailor who is not subject to imminent deployment must be ready, healthy, and safe to perform their shore-based mission.

12. To achieve its mission, the Navy relies on all Sailors receiving required immunizations, except where the health risk of vaccination exceeds the benefits of vaccination, such as in the case of life-threatening allergies to vaccine components. The small group of Sailors who have temporary medical exemptions and the very small group with permanent medical exemptions are at higher risk for infection, hospitalization, and death, making it even more important that those who work with and around them to be vaccinated. Deviating from this standard will put the mission, our medical capabilities, our Sailors, and their families at risk.

(b) (6)

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IN REPLY REFER TO
6320
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From: Chief, Bureau of Medicine and Surgery
To: Deputy Chief of Naval Operations, Manpower, Personnel, Training, and Education (N1)

Subj: DISEASES TARGETED WITH MANDATORY VACCINATIONS FOR UNITED STATES NAVY ACTIVE DUTY AND RESERVE PERSONNEL

1. Subject matter experts at the Bureau of Medicine and Surgery have compiled the below facts on certain mandatory vaccines for United States (U.S.) Navy Active Duty and Reserve personnel. The information below provides some of the scientific and medical rationale for the vaccine requirements for vaccine-preventable diseases that would otherwise create risk to the readiness of the Force.

2. Coronavirus Disease 2019 (COVID-19)

a. Means of infection and infectivity. Person-to-person transmission via respiratory fluids, composed mainly of respiratory droplets and aerosol particles. Basic reproduction numbers (i.e., the number of people who become ill due to exposure to a single case) are estimated to be 2.8 for the original strain, 4-5 for the Alpha variant, and 5-8 for the Delta variant. In other words, every case of Delta variant COVID-19 can infect 5-8 people if effective countermeasures are not employed.

b. Disease's specific harm to health. COVID-19 symptoms are extremely unpredictable, and range from non-existent (asymptomatic) to death. The most common symptoms are: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion, nausea or vomiting, and diarrhea. These more minor symptoms result in clinic visits, time off work, reduced productivity, possible temporary incapacitation (requiring bed rest). Most serious cases may require hospitalization, the need for oxygen support, and mechanical ventilation. Between 17 December 2020 and 31 August 2021, six Sailors and one Marine have died due to COVID-19; none of them were fully immunized.

(1) The risk of complications from COVID-19 illness is significant. A recent Center for Disease Control and Prevention (CDC) report showed COVID-19 patients had nearly 16 times the risk for myocarditis compared with patients who did not have COVID-19, and this risk was higher in younger age groups.

(2) In addition, there is a significant risk of persistent COVID symptoms after recovery from acute illness, or "long COVID." A recent study found that in patients who had recovered from COVID-19, 87.4% reported persistence of at least one symptom, particularly fatigue and

dyspnea at an average of 60 days after symptoms onset. Another found that nearly 2/3 of people hospitalized with COVID-19 still had symptoms 6 months later.

c. Treatment required and level of medical treatment facility capable of delivering that treatment. While mild cases may only require isolation and routine symptomatic care, severe cases may rapidly require intensive resources (Role 3 hospital with Intensive Care Unit (ICU) level care and mechanical ventilation) that are not routinely available in a deployed setting. A recent study of over 43,000 COVID-positive patients in England showed the rate of hospitalization within 14 days of testing was 2.2% for the Alpha variant and 2.3% for the Delta variant (74% were unvaccinated).

d. Efficacy/effectiveness of available vaccine(s). In large phase III trials, the Food and Drug Administration (FDA) approved COVID-19 vaccine was shown to have over 94% efficacy at preventing symptomatic COVID-19. For the same vaccine, against the Delta variant in a real world setting, studies show 88% effectiveness against symptomatic disease, to include hospitalization and death. Nationally in the United States, per the CDC, from January through August 2021, the unvaccinated comprised over 99% of all hospitalized COVID patients (over 1.6 million) as well as over 99% of all COVID-19 deaths (over 264,000). There have been zero COVID-19 deaths of Sailors or Marines among those fully immunized, and zero deaths of Sailors or Marines due to vaccination administration.

e. Likelihood of infection if unvaccinated. In a recent (24 Aug 2021) CDC report of over 43,000 SARS-CoV-2 infections in Los Angeles County, California (population approx. 9.6M), over 71% of the infections were unvaccinated and over 85% of hospitalizations were unvaccinated. The same study reported infection and hospitalization rates among unvaccinated persons were 4.9 times and 29.2 times the rates of those for fully vaccinated people, respectively. According to current surveillance data, nearly 87% of hospitalized Department of the Navy (DON) Active Duty COVID-19 cases since 17 December 2020 are among unvaccinated service members. For DON Service members who had COVID-19 since December 2020, surveillance data indicates that hospitalization rates are approximately 500 per 100,000 cases, which is substantially higher than for influenza (see paragraph 2b).

f. Other methods of prevention. For diseases transmitted by respiratory droplets and aerosol particles such as COVID-19, the CDC recommends non-pharmaceutical interventions (NPI) in addition to vaccination. NPIs recommended by the CDC to avoid contracting or spreading COVID-19 have been categorized as either personal or community based. Personal interventions comprise respiratory hygiene (covering the mouth and nose during coughing and sneezing), avoiding touching the face, frequent hand washing, cleaning and disinfecting objects and surfaces that are frequently touched, avoiding sick people, and self-quarantine when a person feels unwell. Community-based actions include public education through a variety of communication strategies, social distancing (6 feet), wearing facemasks, ensuring adequate ventilation of indoor spaces, and restrictions on public gatherings.

g. Efficacy of non-pharmaceutical interventions. Despite the ability of NPIs to prevent respiratory virus transmission, there are very limited data available on their effectiveness at the individual level. Data on the effectiveness of NPIs implemented as community-wide mandates

(where NPI impacts both source control and personal protection) would not be applicable at the individual level.

(1) Recent studies have shown efficacy of mask wearing to prevent COVID-19. During a COVID-19 outbreak on the *USS THEODORE ROOSEVELT*, persons who wore masks experienced a 70% lower risk of testing positive for SARS-CoV-2 infection. Similar reductions have been reported in case contact investigations when contacts were masked and in household clusters in which household members were masked.

(2) However, in order to be effective, NPI must be implemented rigorously and continuously, and breaches in implementation are common. This is particularly true in communal environments such as aboard ships, in barracks, or in field situations; high rates of transmission have been documented in schools and household settings. One study during a recent mask mandate found that 90% of 5,893 individuals were observed not wearing a mask or not wearing it correctly, despite 75.9% of those individuals self-reporting always wearing a mask in public.

(3) Similarly, NPI such as masks provide measures of community protection, as described above, only while they are in use. Because the scientific and medical communities predict that SARS-CoV-2 will remain in global circulation as an endemic virus, the risk to the Force associated with COVID-19 in unvaccinated personnel may exist in perpetuity.

h. Scientific and Medical opinion on whether non-pharmaceutical interventions, alone or in concert, will be successful in meeting the compelling government interest. Any combination of NPI, in the absence of vaccination, are not likely to be effective at preventing COVID-19 outbreaks and their resulting impacts on the Navy's mission, especially in the setting of the highly contagious Delta variant. Unlike NPI, vaccination provides its full measure of protection in an enduring capacity, subject to potential boosters as recommended by the FDA. Vaccination is not subject to reductions in efficacy due to incomplete implementation as with NPI. For this reason, vaccination is significantly superior to NPI, and mask wearing, for preventing respiratory infections such as COVID-19, especially when only implemented at the individual level and not by the entire community.

3. Influenza

a. Means of infection. Person-to-person transmission via respiratory droplets. Basic reproduction numbers are estimated to be 0.9-2.1, which means, on average, a person infected with influenza will spread the virus to 1-2 other people, if no additional protective measures are in place.

b. Disease's specific harm to health. Typical symptoms include: fever, cough, sore throat, runny nose, muscle aches, headaches, fatigue, and vomiting / diarrhea (more common in children than adults). This results in clinic visits, time off work, reduced productivity, possible temporary incapacitation (requiring bed rest), and viral shedding, potentially infecting those who come in contact with the person. Hospitalization is rare among young adults with influenza, 3-7 per 100,000 age 18-49. The most common complications of influenza include secondary bacterial

pneumonia, exacerbations of underlying respiratory conditions, otitis media, laryngotracheobronchitis, and bronchitis. Other complications may include primary pneumonia, encephalitis, aseptic meningitis, transverse myelitis, myocarditis, pericarditis, and Guillain-Barré syndrome.

c. Treatment required and level of medical treatment facility capable of delivering that treatment. For mild cases, rest at home /in quarters (in isolation), oral rehydration, antipyretics, and medications to target symptoms. For severe cases or those with complications, hospitalization (role 3 hospital, minimum) and ICU-level care with mechanical ventilation may be required.

d. Efficacy of available vaccine(s). Although influenza vaccine effectiveness is variable from season to season, since 2003, on average it has been 40% (range 10-60%). In addition, influenza vaccination has been shown in several studies to reduce severity of illness in people who get vaccinated but still get influenza illness. Influenza vaccination can also reduce transmission of the virus, thus protecting family members, co-workers, and other contacts from getting sick. Some of these contacts may be more vulnerable to serious influenza illness, like babies and young children, the elderly, and those with certain chronic health conditions.

e. Periodicity of vaccine boosters. Annual vaccination is required due to changes in the circulating viruses.

f. Likelihood of infection if unvaccinated. If unvaccinated for influenza, a Sailor will have a higher risk of contracting the disease and transmitting it to co-workers. According to the Centers for Disease Control and Prevention, the estimated annual incidence of influenza infection is approximately 8% (varying from 3% to 11%); approximately half of these cases would be symptomatic. However, outbreaks can be explosive, with attack rates exceeding 60% over periods as short as 10 days.

g. Other methods of prevention. For diseases transmitted by respiratory droplets such as influenza, the CDC recommends NPI in addition to vaccination. NPIs recommended by the CDC to avoid contracting or spreading respiratory infections have been categorized as either personal or community based. Personal interventions comprise respiratory hygiene (covering the mouth and nose during coughing and sneezing), avoiding touching the face, frequent hand washing, cleaning and disinfecting objects and surfaces that are frequently touched, avoiding sick people, and self-quarantine when a person feels unwell. Community-based actions include public education through a variety of communication strategies, social distancing (6 feet), ensuring adequate ventilation of indoor spaces, and restrictions on public gatherings. The use of masks may be appropriate in certain situations such as during periods of high community transmission and when an individual or contact is immunocompromised.

h. Efficacy of other methods of prevention. Despite the potential for NPIs to prevent respiratory virus transmission, there are very limited data available on their effectiveness at the individual level. Data on the effectiveness of NPIs implemented as community-wide mandates (where NPI impacts both source control and personal protection) would not be applicable at the individual level.

(1) One published observational study out of Japan regarding influenza transmission showed the overall effectiveness of mask wearing was 8.6%, while handwashing showed a negative association (i.e., not protective). A meta-analysis of NPIs to prevent 2009 pandemic influenza infection showed a statistically significant protective effect for regular hand hygiene (38%) and a statistically non-significant protective effect for facemask use.

(2) In order to be effective, NPI must be implemented rigorously and continuously, and breaches in implementation are common. This is particularly true in communal environments such as aboard ships, in barracks, or in field situations; high rates of transmission have been documented in schools and household settings. One study during a recent mask mandate found that 90% of 5,893 individuals were observed not wearing a mask or not wearing it correctly, despite 75.9% of those individuals self-reporting always wearing a mask in public.

i. Medical opinion on whether other methods of prevention, alone or in concert, will be successful in meeting the compelling government interest. Any combination of NPI in the absence of vaccination are not likely to be effective at preventing influenza outbreaks and their resulting impact on the Navy's mission. Vaccination is not subject to reductions in efficacy due to incomplete implementation as with NPI. For this reason, and given the limited data available, it appears vaccination is significantly superior to NPI and mask wearing in particular, for preventing respiratory infections such as influenza, especially when only implemented at the individual level and not by the entire community.

4. Tetanus

a. Means of infection. The bacteria that causes tetanus, *C. tetani*, usually enters the body through a wound. In the presence of anaerobic conditions, the spores germinate. Toxins are produced and disseminated via blood and lymphatics.

b. Disease's specific harm to health. On the basis of clinical findings, three different forms of tetanus have been described.

(1) The most common type (more than 80% of reported cases) is generalized tetanus. The disease usually presents with a descending pattern. The first sign is trismus, or lockjaw, followed by stiffness of the neck, difficulty in swallowing, and rigidity of abdominal muscles. Other symptoms include elevated temperature, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes. Spasms continue for 3 to 4 weeks. Complete recovery may take months.

(2) Localized tetanus is an uncommon form of the disease in which patients have persistent contraction of muscles in the same anatomic area as the injury. These contractions may persist for many weeks before gradually subsiding. Localized tetanus may precede the onset of generalized tetanus, but is generally milder.

(3) Cephalic tetanus is a rare form of the disease, occasionally occurring with otitis media in which clostridium tetani is present in the flora of the middle ear or following injuries to the head. There is involvement of the cranial nerves, especially in the facial area.

(4) Complications of tetanus are common. Laryngospasm or spasm of the muscles of respiration leads to interference with breathing. Fractures of the spine or long bones may result from sustained contractions and convulsions. Hyperactivity of the autonomic nervous system may lead to hypertension or an abnormal heart rhythm. Nosocomial infections are common because of prolonged hospitalization. Secondary infections may include sepsis from indwelling catheters, hospital-acquired pneumonias, and decubitus ulcers. Pulmonary embolism is particularly a problem in persons who use drugs and elderly patients. Aspiration pneumonia is a common late complication of tetanus, found in 50% to 70% of autopsied cases. In recent years, tetanus has been fatal in approximately 11% of reported cases.

c. Treatment required and level of medical treatment facility capable of delivering that treatment. Tetanus cases must be treated in a tertiary care facility with capability to provide long term ICU care and mechanical ventilation. Tetanus immune globulin (TIG) is recommended for persons with tetanus. Intravenous immune globulin (IVIG) contains tetanus antitoxin and may be used if TIG is not available. Because of the extreme potency of the toxin, tetanus disease does not result in tetanus immunity. Active immunization with tetanus toxoid should begin or continue as soon as the person's condition has stabilized.

d. Efficacy of available vaccine(s). Efficacy of the tetanus toxoid has never been studied in a vaccine trial. It can be inferred from protective antitoxin levels that a complete tetanus toxoid series has an efficacy of almost 100%. In the series of 233 cases from 2001–2008, only 7 cases (3%) had received a complete tetanus toxoid series with the last dose within the last 10 years.

e. Periodicity of vaccine boosters. Every 10 years.

f. Likelihood of infection if unvaccinated. While tetanus is rare in the US (averaging 31 cases per year for 2000-2007), nearly all of those cases were in unvaccinated or under-vaccinated individuals. Tetanus is much more common outside the US; in 2015 there were approximately 209,000 infections and about 59,000 deaths globally. As noted above, vaccine efficacy is high, with over 32 times the risk for unvaccinated persons compared to vaccinated.

g. Other methods of prevention. Usual safety measures can help prevent injuries resulting in cuts or puncture wounds from contaminated objects.

h. Efficacy of non-pharmaceutical interventions. At the individual level, such accidents are common and have proven difficult to prevent.

i. Medical opinion on whether other methods of prevention, alone or in concert, will be successful in meeting the compelling government interest. Safety measures alone will not likely be successful in preventing tetanus-prone wounds.

5. Diphtheria

a. Means of infection. Transmission of diphtheria is most often person-to-person through respiratory droplets. Transmission may also occur from exposure to infected skin lesions or articles soiled with discharges from these lesions. The basic reproduction number is about 2.6.

b. Disease's specific harm to health. This may be a spectrum, but should include worst case scenarios and likelihood of worst case scenarios. Understand that co-morbidities play a significant role in these calculations, and our population tends to lack co-morbidities. The most common form of diphtheria results in a membranous pharyngitis and tonsillitis, with symptoms of fever, sore throat, malaise, and anorexia. While some patients may recover at this point without treatment, others may develop severe disease. The patient may appear quite toxic, but the fever is usually not high. Patients with severe disease may develop marked edema of the submandibular areas and the anterior neck along with lymphadenopathy, giving a characteristic "bull neck" appearance. If enough toxin is absorbed, the patient can develop severe prostration, pallor, rapid pulse, stupor, and coma. Death can occur within 6 to 10 days. Death occurs in 5-10% of diphtheria cases.

c. Treatment required and level of medical treatment facility capable of delivering that treatment. In addition to supportive care, as described for influenza and COVID-19, specific treatments include antitoxin and antibiotics. Diphtheria antitoxin, produced in horses, has been used for treatment of respiratory diphtheria in the United States since the 1890s. Diphtheria antitoxin is available only from CDC, through an Investigational New Drug (IND) protocol. Diphtheria antitoxin does not neutralize toxin that is already fixed to tissues, but it will neutralize circulating toxin and prevent progression of disease.

(1) After a provisional clinical diagnosis of respiratory diphtheria is made, appropriate specimens should be obtained for culture and the patient placed in isolation. Persons with suspected diphtheria should be promptly given diphtheria antitoxin and antibiotics in adequate dosage, without waiting for laboratory confirmation. Respiratory support and airway maintenance should also be provided as needed. Consultation on the use of and access to diphtheria antitoxin is available through the duty officer at CDC's Emergency Operations Center at 770-488-7100.

(2) In addition to diphtheria antitoxin, patients with respiratory diphtheria should also be treated with antibiotics. The disease is usually no longer contagious 48 hours after antibiotics have been given. Elimination of the organism should be documented by two consecutive negative cultures taken 24 hours apart, with the first specimen collected 24 hours after therapy is completed.

d. Efficacy of available vaccine(s). Diphtheria toxoid-containing vaccine has been estimated to have an efficacy of 97%.

e. Periodicity of vaccine boosters. Every 10 years in adults.

f. Likelihood of infection if unvaccinated. Diphtheria is rare in the U.S. (14 cases were reported between 1996 and 2018), but it is much more common outside the U.S. where vaccination coverage is suboptimal (4,500 cases worldwide in 2015).

g. Other methods of prevention. For diseases transmitted by respiratory droplets such as diphtheria, the CDC recommends non-pharmaceutical interventions (NPI) in addition to vaccination, although widespread vaccination has all but eliminated disease incidence in the U.S. (ex. no cases in 2017 and 2018 according to World Health Organization, which largely eliminated the subsequent need for diphtheria-related NPI in practice). NPIs recommended by the CDC to avoid contracting or spreading respiratory infections have been categorized as either personal or community based. Personal interventions comprise respiratory hygiene (covering the mouth and nose during coughing and sneezing), avoiding touching the face, frequent hand washing, cleaning and disinfecting objects and surfaces that are frequently touched, avoiding sick people, and self-quarantine when a person feels unwell. Community-based actions include public education through a variety of communication strategies, social distancing (6 feet), ensuring adequate ventilation of indoor spaces, and restrictions on public gatherings. The use of masks may be appropriate in certain situations such as during periods of high community transmission and when an individual or contact is immunocompromised.

h. Efficacy of non-pharmaceutical interventions. While we are not aware of any studies evaluating the efficacy of NPI specifically for diphtheria, it is likely the effectiveness of most NPI would be similar to that for other infections transmitted by respiratory droplets.

(1) Despite the potential for NPIs to prevent respiratory disease transmission, there are very limited data available on their effectiveness at the individual level. Data on the effectiveness of NPIs implemented as community-wide mandates (where NPI impacts both source control and personal protection) would not be applicable at the individual level.

(2) In order to be effective, NPI must be implemented rigorously and continuously, and breaches in implementation are common. This particularly true in communal environments such as aboard ships, in barracks, or in field situations; high rates of transmission have been documented in schools and household settings. One study during a recent mask mandate found that 90% of 5,893 individuals were observed not wearing a mask or not wearing it correctly, despite 75.9% of those individuals self-reporting always wearing a mask in public.

i. Medical opinion on whether non-pharmaceutical interventions, alone or in concert, will be successful in meeting the compelling government interest. Any combination of NPI in the absence of vaccination are not likely to be effective at preventing diphtheria outbreaks and their resulting impact on the Navy's mission. Vaccination is not subject to reductions in efficacy due to incomplete implementation as with NPI. For this reason, and given the limited data available, it appears vaccination is significantly superior to NPI and mask wearing in particular, for preventing respiratory infections such as diphtheria, especially when only implemented at the individual level and not by the entire community.

6. Pertussis. Note: there is no pertussis vaccine preparation that does not contain tetanus and diphtheria toxoids.

a. Means of infection. Transmission most commonly occurs person-to-person through contact with respiratory droplets, or by contact with airborne droplets of respiratory secretions. Transmission occurs less frequently by contact with an infected person's freshly contaminated articles. The basic reproduction number is about 5.5.

b. Disease's specific harm to health. The clinical course of pertussis is divided into three stages: catarrhal (with symptoms similar to the common cold lasting 1-2 weeks), paroxysmal (with more severe cough and paroxysms of numerous rapid coughs lasting 1-6 weeks), and convalescent (with gradual recovery over weeks to months). The most common complication and cause of death is secondary bacterial pneumonia, occurring in 13.2% of cases. Between 2000 and 2017, 307 deaths from pertussis were reported to CDC, mostly in children. Adults may also develop complications of pertussis, such as difficulty sleeping, urinary incontinence, pneumonia, rib fracture, syncope, and weight loss

c. Treatment required and level of medical treatment facility capable of delivering that treatment. Varying levels of supportive management are required, depending on severity of disease, as with influenza and COVID-19. Antibiotics are of some value if administered early (i.e., during the first 1 to 2 weeks of cough before coughing paroxysms begin).

d. Efficacy of available vaccine(s). Diphtheria, Tetanus, and Pertussis (DTaP) vaccine efficacy ranged from 80% to 85%, with overlapping confidence intervals.

e. Periodicity of vaccine boosters. Every 10 years.

f. Likelihood of infection if unvaccinated. Reported pertussis incidence has been gradually increasing in the U.S. since the late 1980s and early 1990s, and large epidemic peaks in disease have been observed since the mid-2000s. A total of 48,277 pertussis cases were reported in 2012, the largest number reported since the mid-1950s. Recent outbreaks of pertussis in the U.S. were due to low vaccination rates with large numbers of vaccine refusals (over 75% in one cluster) based on nonmedical reasons. The disease is more common outside the U.S.; an estimated 16.3 million people worldwide were infected in 2015, with 58,700 deaths.

g. Other methods of prevention, such as non-pharmaceutical interventions. For diseases transmitted by respiratory droplets such as pertussis, the CDC recommends non-pharmaceutical interventions (NPI) in addition to vaccination. NPIs recommended by the CDC to avoid contracting or spreading respiratory infections have been categorized as either personal or community based. Personal interventions comprise respiratory hygiene (covering the mouth and nose during coughing and sneezing), avoiding touching the face, frequent hand washing, cleaning and disinfecting objects and surfaces that are frequently touched, avoiding sick people, and self-quarantine when a person feels unwell. Community-based actions include public education through a variety of communication strategies, social distancing (6 feet), ensuring adequate ventilation of indoor spaces, and restrictions on public gatherings. The use of masks may be appropriate in certain situations such as during periods of high community transmission and when an individual or contact is immunocompromised.

h. Efficacy of non-pharmaceutical interventions. While we are not aware of any studies evaluating the efficacy of NPI specifically for pertussis, it is likely the effectiveness of most NPI would be similar to that for other infections transmitted by respiratory droplets.

(1) Despite the potential for NPIs to prevent respiratory disease transmission, there are very limited data available on their effectiveness at the individual level. Data on the effectiveness of NPIs implemented as community-wide mandates (where NPI impacts both source control and personal protection) would not be applicable at the individual level.

(2) In order to be effective, NPI must be implemented rigorously and continuously, and breaches in implementation are common. This is particularly true in communal environments such as aboard ships, in barracks, or in field situations; high rates of transmission have been documented in schools and household settings. One study during a recent mask mandate found that 90% of 5,893 individuals were observed not wearing a mask or not wearing it correctly, despite 75.9% of those individuals self-reporting always wearing a mask in public.

i. Medical opinion on whether non-pharmaceutical interventions, alone or in concert, will be successful in meeting the compelling government interest. Any combination of NPI in the absence of vaccination are not likely to be effective at preventing pertussis outbreaks and their resulting impact on the Navy's mission. Vaccination is not subject to reductions in efficacy due to incomplete implementation as with NPI. For this reason, and given the limited data available, it appears vaccination is significantly superior to NPI and mask wearing in particular, for preventing respiratory infections such as pertussis, especially when only implemented at the individual level and not by the entire community.

7. My point of contact is CDR (b) (6), MC, USN, Preventive Medicine, who can be reached at (b) (6) or (b) (6) @mail.mil.

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Centers for Disease Control and Prevention

COVID-19

Science Brief: COVID-19 Vaccines and Vaccination

Updated Sept. 15, 2021

Summary of Recent Changes

Last updated September 15, 2021

- Data were added indicating that COVID-19 vaccination remains highly effective against COVID-19 hospitalization and death caused by the Delta variant of SARS-CoV-2.
- Data were added from studies published since the last update that further characterize reduced COVID-19 vaccine effectiveness against asymptomatic and mild symptomatic infections with the Delta variant of SARS-CoV-2.
- Data were added from studies published since the last update that suggest decreased vaccine effectiveness against SARS-CoV-2 infection, symptomatic disease, and hospitalization in several groups of immunocompromised persons and potential benefit of a third dose of COVID-19 vaccine in immunocompromised populations.
- Data were added summarizing several small studies of heterologous COVID-19 vaccination series (i.e., mixed schedules), which found that a dose of adenovirus vector vaccine followed by a dose of mRNA vaccine elicits antibody responses at least as high as two doses of mRNA vaccine.
- Data were added from recent studies examining the duration of protection conferred by COVID-19 vaccination.
- Data were added from recent studies describing clinical outcomes and transmissibility of SARS-CoV-2 infections in fully vaccinated persons.

View Previous Updates

Key Points

- All COVID-19 vaccines currently approved or authorized in the United States (Pfizer-BioNTech/Comirnaty, Moderna, and Janssen [Johnson & Johnson]) are effective against COVID-19, including against severe disease, hospitalization, and death.
- Available evidence suggests the currently approved or authorized COVID-19 vaccines are highly effective against hospitalization and death for a variety of strains, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2); data suggest lower effectiveness against confirmed infection and symptomatic disease caused by the Beta, Gamma, and Delta variants compared with the ancestral strain and Alpha variant. Ongoing monitoring of vaccine effectiveness against variants is needed.
- Limited available data suggest lower vaccine effectiveness against COVID-19 illness and hospitalization among immunocompromised people. In addition, numerous studies have shown reduced immunologic response to COVID-19 vaccination among people with various immunocompromising conditions.
- The risk for SARS-CoV-2 infection in fully vaccinated people cannot be completely eliminated as long as there is continued community transmission of the virus. Early data suggest infections in fully vaccinated persons are more commonly observed with the Delta variant than with other SARS-CoV-2 variants. However, data show fully vaccinated persons are less likely than unvaccinated persons to acquire SARS-CoV-2, and infections with the Delta variant in fully

vaccinated persons are associated with less severe clinical outcomes. Infections with the Delta variant in vaccinated persons potentially have reduced transmissibility than infections in unvaccinated persons, although additional studies are needed.

- This updated science brief synthesizes the scientific evidence supporting CDC's guidance for fully vaccinated people and will continue to be updated as more information becomes available.

Background

COVID-19 vaccination is a critical prevention measure to help end the COVID-19 pandemic. COVID-19 vaccines are now widely available in the United States, and CDC recommends all people 12 years and older be vaccinated against COVID-19.

On August 23, 2021, the U.S. Food and Drug Administration (FDA) approved an mRNA vaccine (Pfizer-BioNTech/Comirnaty) as a 2-dose series for prevention of symptomatic COVID-19 in persons aged ≥16 years. This vaccine is also authorized under an Emergency Use Authorization (EUA) to be administered to prevent COVID-19 in persons aged 12-15 years. A second mRNA vaccine (Moderna), as well as a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector vaccine (Janssen vaccine [Johnson & Johnson]) are authorized under an EUA for use in persons aged ≥18 years. Both mRNA vaccines are also authorized for administration of an additional dose to certain immunocompromised persons.

People are considered fully vaccinated if they are ≥2 weeks following receipt of the second dose in a 2-dose series (mRNA vaccines), or ≥2 weeks following receipt of a single-dose vaccine (Janssen vaccine).*

Public health recommendations for people fully vaccinated with FDA-approved or FDA-authorized COVID-19 vaccines consider evidence of vaccine effectiveness against symptomatic COVID-19 with and without severe outcomes, as well as vaccine impact on SARS-CoV-2 transmission. Other individual and societal factors are also important when evaluating the benefits and potential harms of additional prevention measures (e.g., masking, physical distancing) among vaccinated individuals. The Advisory Committee on Immunization Practices and CDC routinely consider individual health benefits and risks along with factors such as population values, acceptability, and feasibility of implementation when making vaccine recommendations.(1) These factors were also considered when developing CDC's interim public health recommendations for fully vaccinated people.

In this scientific brief, we summarize evidence available through August 24, 2021, for the currently approved or authorized COVID-19 vaccines (administered according to the recommended schedules) and additional considerations used to inform public health recommendations for fully vaccinated people, including:

- Vaccine efficacy and effectiveness against SARS-CoV-2 infection in the general population as well as among immunocompromised persons
- Vaccine effectiveness of heterologous (mixed) vaccination series
- Vaccine performance (i.e., immunogenicity and effectiveness) against emerging SARS-CoV-2 variant viruses, with a particular focus on the Delta (B.1.617.2) variant

Current evidence indicates that fully vaccinated people without immunocompromising conditions are able to engage in most activities with low risk of acquiring or transmitting SARS-CoV-2, with additional prevention measures (e.g. masking) where transmission is substantial or high.

Emerging SARS-CoV-2 viral variants

As of August 28, 2021, the Delta variant of concern (B.1.617.2) is the predominant variant in the United States, with 99% of sequenced specimens being identified as Delta; current data on variant prevalence can be found on CDC's website. The Delta variant, first detected in India, has been shown to have increased transmissibility, potential reduction in neutralization by some monoclonal antibody treatments, and reduction in neutralization by post-vaccination sera.(2)

Other variants that are either no longer detected or are circulating at very low levels in the United States include: Alpha (B.1.1.7), first detected in the United Kingdom; Beta (B.1.351), first detected in South Africa; Gamma (P.1), first detected in Japan/Brazil; Iota (B.1.526), first detected in the United States-New York; Eta (B.1.525), first detected in the United Kingdom/Nigeria; Kappa (B.1.617.1) and B.1.617.3, first detected in India. These variants have mutations that alter the

receptor binding domain of the spike protein and have variable impact on vaccine effectiveness (notably the E484K/Q mutation in Beta, Gamma, Eta, Iota, Kappa, and B.1.617.3; the N501Y mutation occurring in Alpha, Beta, and Gamma; the E417T/N mutations in Beta and Gamma; and the L452R mutation in Delta, Kappa and B.1.617.3).(2) Vaccine performance against emerging SARS-CoV-2 variants is an important consideration when evaluating the need for prevention measures in vaccinated people and will require continued monitoring.

COVID-19 vaccine efficacy, effectiveness, and immunogenicity

Immunogenicity is the generation of effective protective immunity against a vaccine antigen as measured by laboratory tests. Vaccine efficacy refers to how well a vaccine performs in a carefully controlled clinical trial, and effectiveness describes its performance in real-world observational studies. Evidence demonstrates that the approved or authorized COVID-19 vaccines are both efficacious and effective against symptomatic, laboratory-confirmed COVID-19, including severe forms of the disease. In addition, as shown below, a growing body of evidence suggests that COVID-19 vaccines also reduce asymptomatic infection and transmission. Substantial reductions in SARS-CoV-2 infections (both symptomatic and asymptomatic) will reduce overall levels of disease, and therefore, SARS-CoV-2 virus transmission in the United States. Investigations are ongoing to further assess the risk of transmission from fully vaccinated persons with SARS-CoV-2 infections to other vaccinated and unvaccinated people. Early evidence suggests infections in fully vaccinated persons caused by the Delta variant of SARS-CoV-2 may be transmissible to others; however, SARS-CoV-2 transmission between unvaccinated persons is the primary cause of continued spread.

Animal challenge studies

Rhesus macaque challenge studies provided the first evidence of the potential protective effects of Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines against SARS-CoV-2 infection, including both symptomatic and asymptomatic infection. Vaccinated macaques developed neutralizing antibodies that exceeded those in human convalescent sera and showed no or minimal signs of clinical disease after SARS-CoV-2 challenge.(3-5) In addition, COVID-19 vaccination prevented or limited viral replication in the upper and lower respiratory tracts, which may have implications for transmission of the virus among humans.(3-5)

Vaccine efficacy from human clinical trials

Clinical trials subsequently demonstrated the FDA-approved or authorized COVID-19 vaccines to be efficacious against laboratory-confirmed, symptomatic COVID-19 in adults, including severe forms of the disease, with evidence for protection against both symptomatic and asymptomatic SARS-CoV-2 infection (6-12) (**Box**). Trial data demonstrated 100% efficacy of the Pfizer-BioNTech vaccine against laboratory-confirmed, symptomatic COVID-19 in adolescents 12–15 years old; this estimate was based on small numbers of cases and prior to emergence of the Delta variant.(13)

Clinical trial data suggest that the Janssen COVID-19 vaccine may have reduced overall efficacy against disease caused by the Beta variant, compared to the other COVID-19 vaccines. Although sero-response rates were similar between U.S. clinical trial participants and those from Brazil and South Africa, vaccine efficacy against moderate to severe-critical COVID-19 after ≥14 days was 74% in the United States (where ~96% of infections were due to the ancestral strain with the D614G mutation), 66% in Brazil (where ~69% of infections were due to Zeta [P.2]), and 52% in South Africa (where ~95% of infections were due to Beta).(14) Notably, Janssen vaccine showed good efficacy against severe or critical disease (73%–82%) across all sites.

Box. Summary of vaccine efficacy estimates for approved or authorized COVID-19 vaccines

All approved or authorized COVID-19 vaccines demonstrated efficacy (range 65% to 95%) against symptomatic, laboratory-confirmed COVID-19 in adults ≥18 years.

- For each approved or authorized COVID-19 vaccine, efficacy was demonstrated across different populations, including elderly and younger adults, in people with and without underlying health conditions, and in people representing different races and ethnicities.
- The Pfizer-BioNTech COVID-19 vaccine also demonstrated high efficacy against symptomatic, laboratory-confirmed COVID-19 in adolescents aged 12-17 years.

All approved or authorized COVID-19 vaccines demonstrated high efficacy (≥89%) against COVID-19 severe enough to require hospitalization.

All approved or authorized COVID-19 vaccines demonstrated high efficacy against COVID-19-associated death.

- In the clinical trials, no participants who received a COVID-19 vaccine died from COVID-19; the Moderna and Janssen vaccine trials among adults ≥18 years each had COVID-19 deaths in the unvaccinated placebo arm.

Data from the clinical trials among adults ≥18 years old suggest COVID-19 vaccination protects against symptomatic infection and may also protect against asymptomatic infection.

- In the Moderna trial, among people who had received a first dose, the number of asymptomatic people who tested positive for SARS-CoV-2 at their second-dose appointment was approximately 67% lower among vaccines than among placebo recipients (0.1% [n=15] and 0.3% [n=39], respectively)
- Efficacy of Janssen COVID-19 vaccine against asymptomatic infection was 74% in a subset of trial participants.

No trials have compared efficacy between any of the approved or authorized vaccines in the same study population at the same time, making comparisons of efficacy difficult.

- All Phase 3 trials differed by calendar time and geography.
- Vaccines were tested in settings with different background COVID-19 incidence and circulating variants.

Vaccine effectiveness from real-world studies

Multiple studies from the United States and other countries have demonstrated that a two-dose COVID-19 mRNA vaccination series is effective against SARS-CoV-2 infection (including both symptomatic and asymptomatic infections) caused by ancestral and variant strains and sequelae including severe disease, hospitalization, and death. Early evidence for the Janssen vaccine also demonstrates effectiveness against COVID-19 in real-world conditions. There is now a substantial volume of scientific literature examining the effectiveness of COVID-19 vaccination against SARS-CoV-2 infection, symptomatic disease, and other clinical outcomes; detailed summaries of these studies are available in the International Vaccine Access Center's VIEW-Hub resource library .

Several systematic reviews and meta-analyses of vaccine effectiveness have recently been published (15-17); meta-analyses indicate an average effectiveness of full vaccination against SARS-CoV-2 infection of 85%–95% shortly after completion of vaccination. (16, 17) However, many of the studies in these reviews were conducted prior to the emergence of the variants of concern. Studies in Israel, Europe, and the United Kingdom have demonstrated high real-world effectiveness (>85%) of two doses of Pfizer-BioNTech COVID-19 vaccine while the Alpha variant was prevalent.(18-26) Studies from Qatar have demonstrated high effectiveness against documented infection with Alpha and Beta ≥14 days after receiving the Pfizer-BioNTech vaccine (90% and 75%, respectively) and the Moderna vaccine (100% and 96%, respectively); importantly, both vaccines were 96%–100% effective against severe, critical, or fatal disease, regardless of strain.(27, 28) In three studies from Canada, one demonstrated 79% effectiveness for mRNA vaccines against confirmed infection during a time when Alpha and Gamma represented most infections, while another two demonstrated 84% and 88% effectiveness, respectively, against symptomatic infection caused by Gamma/Beta.(29-31)

Individual studies specifically examining vaccine effectiveness against the Delta variant or conducted in the context of substantial circulation of Delta are summarized in Table 1a and as follows. Studies from the United Kingdom have noted effectiveness of the Pfizer-BioNTech vaccine against confirmed infection (79%) and symptomatic infection (88%), compared with the Alpha variant (92% and 93%, respectively).(23, 25) A study from Canada demonstrated 87% effectiveness against symptomatic illness caused by the Delta variant ≥7 days after receipt of the second dose of Pfizer-BioNTech vaccine, compared with 89% for the Alpha variant.(32)Data from Qatar demonstrated 54% effectiveness against symptomatic illness for the Pfizer-BioNTech vaccine compared with 85% for the Moderna vaccine.(33). Preliminary data from South Africa on the effectiveness of the Janssen vaccine showed 71% effectiveness against hospitalization when Delta variant was predominant, compared to 67% when Beta was predominant. Data from Israel also suggest decreased effectiveness of vaccines against infection and illness caused by Delta. The variability in vaccine effectiveness estimates between countries may in part reflect differences in study methodology, intervals used between vaccine doses, and timing of vaccine effectiveness assessments. Of note, the United Kingdom and Canada used prolonged intervals of 12–16 weeks between vaccine doses, which have been observed to induce higher immunogenicity and effectiveness (including in ages ≥80 years) (34-37). The most recent estimates from Israel and Qatar represent time points >6 months after initiating respective national vaccination campaigns and 2–5 months after prior assessments of vaccine effectiveness against the Alpha variant, with

potential for waning immunity. Notably, in the United Kingdom, Canada, Qatar, South Africa, and Israel, vaccine effectiveness against hospitalization related to Delta was >90% and comparable to that observed with Alpha for all vaccines currently approved or authorized in the United States.(26, 32, 33)

Table 1a. *Effectiveness of COVID-19 Vaccination Against SARS-CoV-2 Infection and Symptomatic Disease (Including Severe Disease and Hospitalization) Caused by the Delta Variant*

Country	Population	Vaccine	Outcome	Vaccine Effectiveness*
UK[38]	General population ≥16 years	Pfizer-BioNTech	Symptomatic disease	88%[1](85-90)
Canada[32]	General population ≥16 years	Pfizer-BioNTech	Symptomatic disease	85%[1](59-94)
UK (Scotland)[25]	General population	Pfizer-BioNTech	SARS-CoV-2 infection	79%[1](75-82)
UK[23]	General population	Pfizer-BioNTech	SARS-CoV-2 infection	80%[1](77-83)
United States[39]	Healthcare workers, first responders, and other essential and frontline workers	Pfizer-BioNTech, Moderna, or Janssen	SARS-CoV-2 infection	66%[1](26-84)
United States[40]	Health system members ≥12 years	Pfizer-BioNTech	SARS-CoV-2 infection	75%[2](71-78)
			Hospitalization	93%[2](84-96)
Qatar[33]	General population ≥12 years	Moderna	SARS-CoV-2 infection	85%[1](76-91)
		Pfizer-BioNTech	SARS-CoV-2 infection	54%[1](44-61)
		Moderna	Symptomatic disease	86%[1](71-94)
		Pfizer-BioNTech	Symptomatic disease	56%[1](41-67)
		Moderna	Severe, critical, or fatal disease	100%[1](41-100)
		Pfizer-BioNTech	Severe, critical, or fatal disease	90%[1](61-98)
UK[26]	Patients hospitalized following ED visit	Pfizer-BioNTech	Hospitalization	96%[1](86-99)

*Only studies including estimates of vaccine effectiveness ≥7 days following a completed vaccination series of a COVID-19 vaccine currently approved or authorized for use in the United States are included here. For studies that examined variant-specific vaccine effectiveness against multiple variants of SARS-CoV-2, only estimates for effectiveness against the Delta variant are shown. The 95% confidence interval for each estimate of vaccine effectiveness is displayed in parentheses following the estimate.

[1]≥14 days after second dose

[2]≥7 days after second dose

In addition to preventing morbidity and mortality associated with COVID-19, currently approved or authorized vaccines also demonstrate effectiveness against asymptomatic SARS-CoV-2 infection. However, most studies of asymptomatic infection prevention were conducted in the context of circulation of different variants and the effectiveness of COVID-19 vaccines in preventing asymptomatic infection differs by variant and vaccine. In addition, infections identified in such studies as asymptomatic may simply have been identified prior to the infected person developing symptoms, i.e., these infections are presymptomatic rather than asymptomatic. Asymptomatic people are also less likely to be tested for SARS-CoV-2 infection in most settings and thus less likely to be captured in "real world" effectiveness studies.

Table 1b. *Effectiveness of COVID-19 Vaccination Against Asymptomatic SARS-CoV-2 Infection When Different Variants Predominated*

Country	Population	Vaccine	Dominant Variant(s)	Vaccine Effectiveness*
Israel [24]	Healthcare workers	Pfizer-BioNTech	Alpha	65%[1](45-79)
United States (California) [41]	General population ≥18 years	Pfizer-BioNTech or Moderna	Epsilon, Alpha	68%[2](29-86)
United States[42]	Preprocedural adult patients	Pfizer-BioNTech or Moderna	Ancestral strain	80%[3](56-91)
Qatar[33]	General population ≥12 years	Moderna	Delta	80%[4](54-93)
		Pfizer-BioNTech	Delta	36%[4](11-54)
Israel[43]	Healthcare workers	Pfizer-BioNTech	Alpha	86%[5](69-93)
Israel[21]	General population ≥16 years	Pfizer-BioNTech	Alpha	92%[5](91-92)
Israel[19]	General population ≥16 years	Pfizer-BioNTech	Ancestral strain, Alpha	90%[5](83-94)

*The 95% confidence interval for each estimate of vaccine effectiveness is displayed in parentheses following the estimate.

[1]≥11 days after second dose
[2]≥15 days after second dose
[3]≥0 days after second dose
[4]≥14 days after second dose
[5]≥7 days after second dose

Vaccine immunogenicity and effectiveness in immunocompromised people

Vaccination is particularly important for people with immunocompromising conditions, who are at increased risk of severe COVID-19 illness. However, current evidence suggests reduced protection from COVID-19 vaccines for many immunocompromised persons. Recent studies in several countries found significantly lower vaccine effectiveness among immunocompromised adults compared to those without immunocompromising conditions (44-46) (Table 2), although each study defined the immunocompromised population differently. Studies in the United States and Israel have also found that immunocompromised persons account for a high proportion (≥40%) of infections among fully vaccinated hospitalized persons. (46, 47)

Compared with those who are not immunocompromised, reduced antibody response to a two-dose primary series of mRNA COVID-19 vaccines has also been observed in specific groups of immunocompromised adults, including people receiving solid organ transplants (48-54); some people with cancer, particularly hematologic cancers (55, 56); some people receiving

hemodialysis for kidney disease (57, 58); and people taking certain immunosuppressive medications (51, 53, 54, 59). While antibody measurement and threshold levels varied by study, a large proportion of immunocompromised persons overall had a measurable immune response after a two-dose series of mRNA vaccine, although some remained seronegative. The distribution of antibody response by immunocompromising condition in several recent studies is summarized in Figure 1.

Emerging data suggest an additional COVID-19 vaccine dose in immunocompromised people, typically administered at least 28 days after completion of the primary series, increases antibody response: in small observational studies of solid organ transplant recipients (60-63) or hemodialysis patients (64-66), 33%-54% of persons who had no detectable antibody response to an initial two-dose mRNA vaccine series developed an antibody response to an additional dose of a COVID-19 vaccine. A recently published randomized controlled trial demonstrated substantial increases in serologic immune response to a third dose of Moderna's mRNA vaccine compared with placebo among solid organ transplant recipients who previously received a two-dose series of that vaccine.(67) While these studies evaluated serologic immune response to an additional vaccine dose, the clinical impact of an additional dose on acquisition, severity, and infectiousness of infections in fully vaccinated immunocompromised persons is not yet known.

Table 2. *Effectiveness of COVID-19 Primary Series Vaccination Against SARS-CoV-2 Infection and Symptomatic Disease among Immunocompromised Persons*

Country	Population	Vaccine	Outcome	Dominant Variant(s)	Vaccine Effectiveness in IC Population	Vaccine Effectiveness in Comparison Population*
United States[45]	Veterans ≥18 years taking immunosuppressive medications for inflammatory bowel disease	Pfizer-BioNTech or Moderna	SARS-CoV-2 infection	Unknown	69%[1](44-83)	No comparison
United States[68]	Solid organ transplant recipients	Pfizer-BioNTech, Moderna, or Janssen	SARS-CoV-2 infection	Ancestral strain, Alpha	81%[2](50-95)	No comparison
Israel[44]	General population ≥16 years	Pfizer-BioNTech	SARS-CoV-2 infection	Ancestral strain, Alpha	71%[1](37-87)	90%(79-95)
			Symptomatic disease		75%[1](44-88)	94%(88-97)
Qatar[69]	Kidney transplant recipients	Pfizer-BioNTech or Moderna	SARS CoV-2 infection	Alpha, Beta	47%[2](0-74)	No comparison
			Severe, critical, or fatal COVID-19 disease		72%[2](0-91)	
United States[46]	Hospitalized patients ≥18 years	Pfizer-BioNTech or Moderna	Hospitalization	Ancestral strain, Alpha	59%[2](12-81)	91%(86-95)

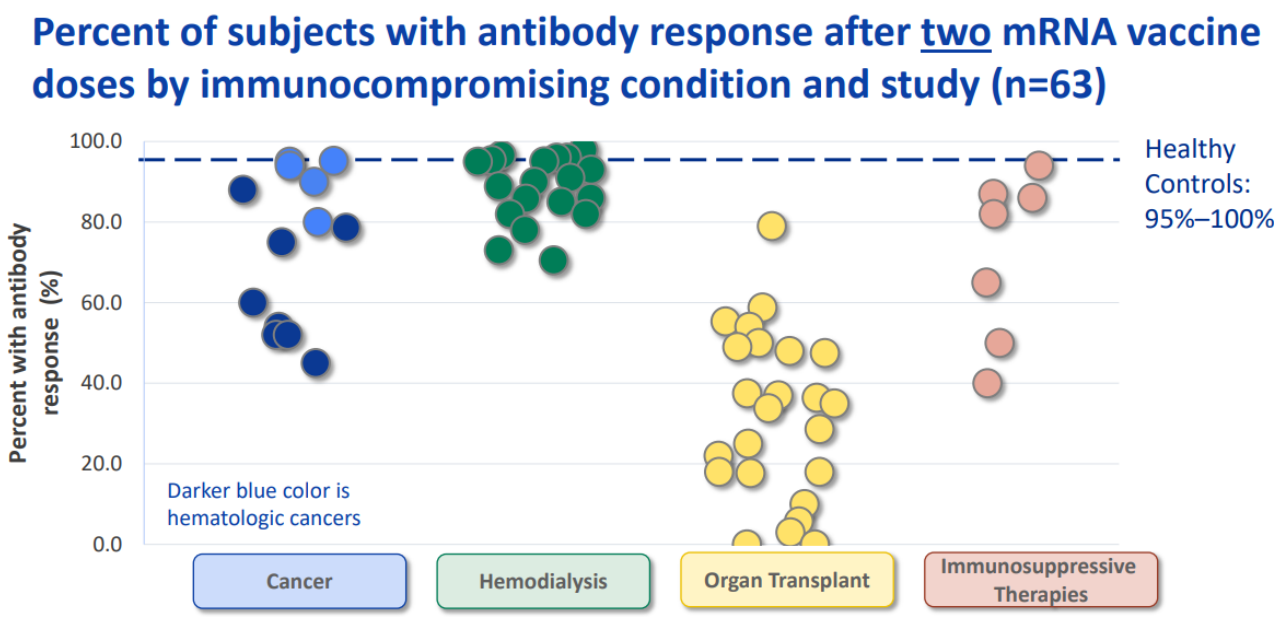
IC: Immunocompromised

* In the Israeli study, the comparison is with overall vaccine effectiveness (i.e., vaccine effectiveness in the entire study population, including those with immunocompromising conditions). In the U.S. study, the comparison is with vaccine effectiveness among members of the study population without immunocompromising conditions.

The 95% confidence interval for each estimate of vaccine effectiveness is displayed in parentheses following the estimate.

[1]≥7 days after second dose
[2]≥14 days after second dose

Figure 1:



*The studies displayed in Figure 1 represent the results of a literature review conducted by the Advisory Committee on Immunization Practices' COVID-19 Vaccines Work Group and are current as of July 21, 2021. Numerous additional studies of antibody response to COVID-19 vaccination in various immunocompromised populations have been published since that date and are not captured here.

Vaccine immunogenicity and effectiveness of heterologous (mixed) dosing regimens

Multiple small studies from Europe have examined the immunogenicity of a heterologous or 'mixed' series of COVID-19 vaccines. These studies found that receipt of a dose of AstraZeneca's adenovirus vector vaccine followed by a dose of an mRNA vaccine (most frequently Pfizer-BioNTech) induced a robust immune response (70-72) and was at least as immunogenic as two doses of mRNA vaccines by most measures of immune response.(73-79) One study examined vaccine effectiveness of this heterologous series and estimated an effectiveness of 88% against any SARS-CoV-2 infection two weeks following the mRNA (second) dose.(80) Only one study examined a heterologous series in which the mRNA vaccine was the priming (first) dose; this study found that a dose of Pfizer-BioNTech vaccine followed by a dose of AstraZeneca vaccine did not achieve non-inferiority of immune response when compared with two doses of Pfizer-BioNTech.(81) A single study to date examined heterologous dosing with a primary mRNA vaccine series followed by a dose of the Janssen adenovirus vector COVID-19 vaccine in four subjects and noted substantially increased immune response against SARS-CoV-2 after the third dose.(82)

Vaccine-induced neutralizing antibody activity

Sera from mRNA COVID-19 vaccine (both Pfizer-BioNTech and Moderna) recipients have demonstrated minimal to large reductions in antibody neutralization activity against a variety of mutations, as reviewed in VIEW-Hub. Two related systematic reviews and meta-analyses have also been published (83, 84); however, these reviews do not include all available neutralization studies of the Delta variant with sera from people who received mRNA vaccines or the Janssen vaccine.(85-96) Across studies of VOCs, the greatest reductions were observed for Beta, followed by Gamma and Delta; reductions for Alpha were minimal. The E484K/Q and L452R mutations alone or in combination with other mutations in the receptor binding domain have been shown to account for the majority of the reduction in vaccine-induced neutralizing antibody activity for the Beta, Gamma, and Delta variants.(97-103) Alpha and Iota variants with E484K mutations, which have been detected in the United Kingdom, United States, and other countries, have shown further reductions in neutralization above Alpha and Iota alone, respectively.(87, 97, 104-109) For two-dose COVID-19 vaccines, multiple studies have shown greater neutralization against variants after the second dose (i.e. among fully vaccinated people) compared with after the first dose alone.(88, 91, 97, 98, 110-118)

98, 110-118)

Robust correlation has been demonstrated between vaccine efficacy and neutralizing antibody levels induced by different vaccines.(119, 120) Based on evidence from clinical trials, the correlate of protection, or antibody threshold providing protection against severe disease, has been estimated to be much lower than that required for protection against confirmed infection.(120) However, in the absence of an accepted antibody threshold that correlates with protection, it is difficult to fully predict how reduced neutralizing activity may affect COVID-19 vaccine effectiveness. Some variants may reduce neutralizing antibody levels to near or below the protective threshold, resulting in lowered vaccine efficacy, increased infections in vaccinated persons, and shortened duration of immunity, and others may not be significant.

Vaccine-induced cellular immunity

Several studies have assessed CD4+ and CD8+ T cell responses from Moderna or Pfizer-BioNTech vaccine recipients to the ancestral SARS-CoV-2 strain compared with the Alpha, Beta, Gamma, and Epsilon variants; these studies observed modest or no defects in cellular immune recognition of the variants.(112, 116, 121-126) Thus, cellular immunity may help limit disease severity in infections caused by variants that partially escape neutralizing antibodies. Variations in the genes encoding human leukocyte antigens have been observed to result in variation of the T cell response to specific SARS-CoV-2 variants, which may impact different subpopulations differently based on genetic prevalence of these variations.(127-132) There are currently no studies of vaccine-induced cellular immunity against the Delta variant.

Older adults and long-term care facility residents

Multiple studies have noted reduced vaccine effectiveness in older adults (≥60 years) (38, 133-135) or residents of long-term care facilities, compared with general population estimates.(136-138) Compared with younger individuals, persons aged >80 years have been noted to have reduced T-cell responses, lower neutralizing antibody levels, and less potential antibody diversity (somatic hypermutation), potentially giving this group increased risk for susceptibility to SARS-CoV-2 infection in vaccinated people. (139) Two studies have observed poor antibody response to the Pfizer-BioNTech vaccine among nursing home residents compared with staff (140, 141); one study noted 38% of nursing home residents had undetectable antibodies to the Beta variant at 2–4 weeks after the second dose of Pfizer-BioNTech vaccine, compared with 12% with Moderna vaccine. (140) Another study showed declining antibody levels among nursing home residents, with 72% of residents having undetectable neutralizing antibody levels at 6 months post-vaccination with Pfizer-BioNTech.(142)

Duration of protection

Immunogenicity of COVID-19 vaccines has been demonstrated out to 6–8 months after vaccination.(86, 143) At 2–3 months post vaccination, two studies have shown lower neutralizing titers, including against the Beta and Delta variants, for Janssen (an adenovirus vector vaccine) compared with the mRNA vaccines.(144, 145) Two studies have shown a combined impact of waning antibody levels and reduced neutralization of variants; six months after receiving the Moderna vaccine, neutralizing antibody levels were reduced but sufficient to protect against the ancestral strain, while about 50% of people had undetectable neutralization activity against Beta and Gamma compared with the ancestral strain.(146, 147) However, a small study of people 8 months after receiving the Janssen vaccine had minimal decline in neutralizing titers against Beta, Gamma, and Delta and there was evidence of expanded breadth of neutralizing antibody response against variants over this time period, likely through B cell maturation.(86) More evidence is still needed in this area, including understanding potential differences in the kinetics of immune response related to different vaccine platforms. One recent modeling study based on immunogenicity data predicted that vaccine effectiveness against symptomatic infection caused by the Delta variant may drop below 50% within the first year after vaccination for most current vaccines in use globally, while the majority are protected from severe illness.(148)

Six-month clinical efficacy for the Pfizer-BioNTech vaccine shows an overall efficacy against infection of 91% and 97% efficacy against severe illness.(149) However, a non-significant decrease of six percentage points was observed for every two months ≥7 days post-vaccination, from 96% at ≥7 days to <2 months, 90% at 2 to <4 months, and 84% at 4 to <6 months. Similar results for the Moderna vaccine have not yet been published, but data from the manufacturer cite 93% overall efficacy up to 6 months.

Several recent studies have noted decreases over time in the effectiveness of COVID-19 vaccines against SARS-CoV-2 infection. A study of U.S. long-term care residents, who were among the first groups in the United States to be vaccinated, found effectiveness of mRNA vaccination against infection declined from 75% in March–May 2021 to 53% in June–July 2021. (150) A study of adults in one U.S. state found a decline in vaccine effectiveness against SARS-CoV-2 infection from 92% the week of May 3, 2021 to 80% the week of July 19, 2021.(151) Two studies in large U.S. health systems examined mRNA vaccine effectiveness longitudinally from December 2020 and January 2021 through July 2021 and August 2021 and noted marked declines over this period (40, 152); similarly, a large population-based study in the UK identified decreases in effectiveness of

Pfizer-BioNTech vaccination over 4-5 months following the second dose.(153) Observed changes in vaccine effectiveness against infection with SARS-CoV-2 may reflect reduced vaccine performance against the Delta variant, waning immunity from primary vaccination, or other unmeasured confounders. In addition, as people at the highest risk of SARS-CoV-2 infection were generally vaccinated first, observational studies of duration of immunity may be subject to confounding by risk status. Importantly, data as of July 2021 confirm sustained high effectiveness of full mRNA vaccination against COVID-19 hospitalization, even up to 6 months post-vaccination.(151, 154)

A retrospective cohort study in a large healthcare system in Israel noted a 2.3-fold increased risk for infection among fully vaccinated persons who were vaccinated with Pfizer-BioNTech in January vs. April 2021.(155) A similar study observed a higher rate (2.4% v. 1.1%, OR=2.2) of infection in fully vaccinated persons who received the second Pfizer-BioNTech dose ≥5 months ago compared with those who received it <5 months ago, with higher magnitude of difference with increasing age.(156)

Infections in fully vaccinated persons: clinical implications and transmission

As expected, because no vaccines is 100% effective, infections in fully vaccinated persons (e.g. breakthrough infections) have been observed, albeit at much lower rates than infections among unvaccinated persons; vaccine effectiveness against severe disease remains high. From January through June 2021, COVID-NET data from laboratory-confirmed COVID-19-associated hospitalizations in adults ≥18 years of age for whom vaccination status is known showed 3% of hospitalizations occurred in fully vaccinated persons. In general, symptoms and duration of illness in infections among fully vaccinated persons have been attenuated compared with cases among unvaccinated people.(157) CDC conducts nationwide monitoring of infections in fully vaccinated persons resulting in hospitalization or death. Among hospitalized or fatal cases reported to CDC as of August 30, 2021, 70% of hospitalized cases and 87% of fatal cases of COVID-19 in fully vaccinated persons were in persons aged 65 years or older. Infections in fully vaccinated persons may be associated with lower antibody levels compared with those who maintain protection, as shown in a study of fully vaccinated healthcare workers in Israel with infections caused by the Delta variant.(158) However, infection in a fully vaccinated person may boost immunity; four weeks after an outbreak in a long-term care facility, fully vaccinated residents who experienced SARS-CoV-2 infections were found to have significantly higher antibody levels than vaccinated individuals who did not experience SARS-CoV-2 infections.(159)

The proportions of VOCs observed among cases in fully vaccinated persons has been similar to that observed in CDC's national genomic surveillance,(160) but interpretation of these data are challenging because of local variation and changes in variant proportions over time. An Israeli study of VOC infections in adults fully vaccinated with Pfizer-BioNTech vaccine compared with unvaccinated matched controls, during a time when Alpha was the dominant strain and Beta was detected in <1% of all specimens, found a higher proportion of Beta in fully vaccinated cases (matched odds ratio = 8.0) and a higher proportion of Alpha in partially vaccinated cases (matched odds ratio = 2.6), though small sample sizes, especially for Beta, were noted as a limitation.(161) Results of a study from Maryland showed that variants with E484K substitutions (e.g., Beta, Gamma) were associated with increased odds of SARS-CoV-2 infection (OR=2.0) in fully vaccinated persons and infection in fully vaccinated persons associated with hospitalization (OR=2.6), while L452R substitutions (e.g., Delta) were not.(162) However, a study from Houston, Texas observed that Delta caused a significantly higher rate of infections in fully vaccinated people compared with infections from other variants, but noted that only 6.5% of all COVID-19 cases occurred in fully vaccinated individuals(163); similar findings were noted in India.(96)

In studies conducted before the emergence of the Delta variant, data from multiple studies in different countries suggested that people vaccinated with mRNA COVID-19 vaccines who develop COVID-19 generally have a lower viral load than unvaccinated people.(157, 165-169) This observation may indicate reduced transmissibility, as viral load has been identified as a key driver of transmission.(170) Studies from multiple countries found significantly reduced likelihood of transmission to household contacts from people infected with SARS-CoV-2 who were previously vaccinated for COVID-19.(171-176) For the Delta variant, early data indicate vaccinated and unvaccinated persons infected with Delta have similar levels of viral RNA and culturable virus detected, indicating that some vaccinated people infected with the Delta variant of SARS-CoV-2 may be able to transmit the virus to others.(163, 164, 177-180) However, other studies have shown a more rapid decline in viral RNA and culturable virus in fully vaccinated people (96, 177, 180-182). One study observed that Delta infection in fully vaccinated persons was associated with significantly less transmission to contacts than persons who were unvaccinated or partially vaccinated.(181)

Together, these studies suggest that vaccinated people who become infected with Delta have potential to be less infectious than infected unvaccinated people. However, more data are needed to understand how viral shedding and transmission from fully vaccinated persons are affected by SARS-CoV-2 variants, time since vaccination, and other factors, particularly as

transmission dynamics may vary based on the extent of exposure to the infected vaccinated person and the setting in which the exposure occurs. Additional data collection and studies are underway to understand the extent and duration of transmissibility of Delta variant SARS-CoV-2 in the United States and other countries.

Conclusions

COVID-19 vaccines currently approved or authorized in the United States have been shown to provide considerable protection against severe disease and death caused by COVID-19. These findings, along with the early evidence for reduced levels of viral mRNA and culturable virus in vaccinated people who acquire SARS-CoV-2 infection, suggest that any associated transmission risk is substantially reduced in vaccinated people: even for Delta, evidence suggests fully vaccinated people who become infected are infectious for shorter periods of time than unvaccinated people infected with Delta. While vaccine effectiveness against emerging and other SARS-CoV-2 variants will continue to be assessed, available evidence suggests that the COVID-19 vaccines approved or authorized in the United States offer substantial protection against hospitalization and death from emerging variants, including the Delta variant. Data suggest lower vaccine effectiveness against laboratory-confirmed illness and symptomatic disease caused by the Beta, Gamma, and Delta variants compared with the ancestral strain and Alpha variant. Early data also find some decline in vaccine effectiveness against SARS-CoV-2 infection over time, although in fall 2021, 9 months after the start of the U.S. COVID-19 vaccination program, vaccination remains highly protective against hospitalization with COVID-19.

Evidence suggests the U.S. COVID-19 vaccination program has substantially reduced the burden of disease in the United States by preventing serious illness in fully vaccinated people and interrupting chains of transmission. Vaccinated people can still become infected and have the potential to spread the virus to others, although at much lower rates than unvaccinated people. The risks of SARS-CoV-2 infection in fully vaccinated people are higher where community transmission of the virus is widespread. Current efforts to maximize the proportion of the U.S. population that is fully vaccinated against COVID-19 remain critical to ending the COVID-19 pandemic.

*Note: This brief summarizes evidence related to vaccines approved or authorized for emergency use in the United States. In specific circumstances, CDC guidance for fully vaccinated people can also be applied to COVID-19 vaccines that have been listed for emergency use by the World Health Organization (e.g. AstraZeneca/Oxford) and to some vaccines used for U.S. participants in COVID-19 vaccine trials.

Previous Updates

Updates from Previous Content

As of July 27, 2021

- Data were added from studies published since the last update that demonstrate currently authorized mRNA vaccines provide protection against variants of concern, including the Delta strain that is now predominant in the United States. Vaccine effectiveness against hospitalization and death is high for all current SARS-CoV-2 variants; emerging data suggest lower effectiveness against confirmed infection and symptomatic disease caused by the Beta, Gamma, and Delta variants compared with the ancestral strain and the Alpha variant.

References

Note: Preprints have not been peer-reviewed. They should not be regarded as conclusive, guide clinical practice/health-related behavior, or be reported in news media as established information.

1. Lee G, Carr W, ACIP Evidence Based Recommendations Work Group. Updated Framework for Development of Evidence-Based Recommendations by the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2018;67(45):1271-2.
2. Centers for Disease Control and Prevention. SARS-CoV-2 Variant Classifications and Definitions [Available from:

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

3. Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. N Engl J Med. 2020;383(16):1544-55.
4. Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature. 2020;586(7830):583-8.
5. Vogel AB, Kanevsky I, Che Y, Swanson KA, Muik A, Vormehr M, et al. BNT162b vaccines protect rhesus macaques from SARS-CoV-2. Nature. 2021.
6. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.
7. Food and Drug Administration. Pfizer-BioNTech COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee Briefing Document – Sponsor. https://www.fda.gov/media/144246/download .
8. Food and Drug Administration. Moderna COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Briefing Document- Sponsor. https://www.fda.gov/media/144452/download .
9. Food and Drug Administration. Moderna COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Briefing Document Addendum- Sponsor. https://www.fda.gov/media/144453/download .
10. Food and Drug Administration. Janssen COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee February 26, 2021 Meeting Briefing Document – Sponsor. https://www.fda.gov/media/146219/download .
11. Food and Drug Administration. Janssen COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee February 26, 2021 Meeting Briefing Document Addendum – Sponsor. https://www.fda.gov/media/146218/download .
12. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
13. Food and Drug Administration. Emergency Use Authorization (EUA) Amendment for an Unapproved Product Review Memorandum. https://www.fda.gov/media/148542/download .
14. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-201.
15. Harder T, Koch J, Vygen-Bonnet S, Kulper-Schiek W, Pilic A, Reda S, et al. Efficacy and effectiveness of COVID-19 vaccines against SARS-CoV-2 infection: interim results of a living systematic review, 1 January to 14 May 2021. Euro Surveill. 2021;26(28).
16. Kow CS, Hasan SS. Real-world effectiveness of BNT162b2 mRNA vaccine: a meta-analysis of large observational studies. Inflammopharmacology. 2021;29(4):1075-90.
17. Shapiro J, Dean NE, Madewell ZJ, Yang Y, Halloran ME, Longini I. Efficacy Estimates for Various COVID-19 Vaccines: What we Know from the Literature and Reports. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.05.20.21257461v2 .
18. Björk J, Inghammar M, Moghaddassi M, et al. Effectiveness of the BNT162b2 vaccine in preventing COVID-19 in the working age population – first results from a cohort study in Southern Sweden. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.04.20.21254636v1 .
19. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021.
20. Goldberg Y, Mandel M, Woodbridge Y, et al. Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.04.20.21255670v1 .
21. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021.
22. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397(10286):1725-35.
23. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021.

against the B.1.617.2 (Delta) variant. N Engl J Med. 2021.

24. Regev-Yochay G, Amit S, Bergwerk M, et al. Decreased Infectivity Following BNT162b2 Vaccination: A prospective cohort study in Israel. The Lancet Regional Health – Europe. 2021;7(100150).
25. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health S, the EIIC. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2461-2.
26. Stowe J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. khubnet. 2021;https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZlEig/view/479607266 .
27. Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med. 2021.
28. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021.
29. Chung H, He S, Nasreen S, et al. Effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe COVID-19 outcomes in Ontario, Canada. BMJ. 2021;Aug 20; 374:n1943.
30. Nasreen S, Chung H, He S, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.06.28.21259420v2 .
31. Yassi A, Grant JM, Lockhart K, et al. Infection control, occupational and public health measures including mRNA-based vaccination against SARS-CoV-2 infections to protect healthcare workers from variants of concern: a 14-month observational study using surveillance data. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.05.21.21257600v1 .
32. Nasreen S CH, He S, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada. medRxiv. 2021;https://doi.org/10.1101/2021.06.28.21259420 .
33. Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.11.21261885v1 .
34. Amirthalingam G, Lopez Bernal J, Andrews NJ, et al. Higher serological responses and increased vaccine effectiveness demonstrate the value of extended vaccine schedules in combatting COVID-19 in England. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.26.21261140v1 .
35. Carazo S, Talbot D, Boulianne N, et al. Single-dose mRNA vaccine effectiveness against SARS-CoV-2 in healthcare workers extending 16 weeks post-vaccination: a test-negative design from Quebec, Canada. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.19.21260445v1 .
36. Flaxman A, Marchevsky N, Jenkin D, et al. Tolerability and Immunogenicity After a Late Second Dose or a Third Dose of ChAdOx1 nCoV-19 (AZD1222). Preprints with The Lancet. 2021;https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3873839 .
37. Parry H, Bruton R, Stephens C, Amirthalingam G, Hallis B, Otter A, et al. Extended interval BNT162b2 vaccination enhances peak antibody generation in older people. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.05.15.21257017v1 .
38. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373:n1088.
39. Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep. 2021;ePub: 24 August 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7034e4http://dx.doi.org/10.15585/mmwr.mm7034e4 .
40. Tartof SY, Slezak JM, Fischer H, et al. Six-Month Effectiveness of BNT162B2 mRNA COVID-19 Vaccine in a Large US Integrated Health System: A Retrospective Cohort Study. Preprints with The Lancet. 2021;https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3909743 .
41. Andrejko K, Pry J, Myers JF, et al. Early evidence of COVID-19 vaccine effectiveness within the general population of California. MedRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.04.08.21255135v2 .
42. Tande AJ, Pollock BD, Shah ND, Farrugia G, Virk A, Swift M, et al. Impact of the COVID-19 Vaccine on Asymptomatic Infection Among Patients Undergoing Pre-Procedural COVID-19 Molecular Screening. Clin Infect Dis. 2021.
43. Angel Y, Spitzer A, Henig O, et al. Association Between Vaccination With BNT162b2 and Incidence of Symptomatic

and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. JAMA. 2021;325(24):2457-2465.

44. Chodick G, Tene L, Rotem RS, Patalon T, Gazit S, Ben-Tov A, et al. The effectiveness of the two-dose BNT162b2 vaccine: analysis of real-world data. Clin Infect Dis. 2021.
45. Khan N, Mahmud N. Effectiveness of SARS-CoV-2 Vaccination in a Veterans Affairs Cohort of Patients With Inflammatory Bowel Disease With Diverse Exposure to Immunosuppressive Medications. Gastroenterology. 2021;161(3):827-36.
46. Tenforde MW, Patel MM, Ginde AA, et al. Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States. medRxiv. 2021;https://doi.org/10.1101/2021.07.08.21259776
47. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Nesher L, Stein M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect. 2021.
48. Boyarsky BJ, Chiang TP, Ou MT, Werbel WA, Massie AB, Segev DL, et al. Antibody Response to the Janssen COVID-19 Vaccine in Solid Organ Transplant Recipients. Transplantation. 2021;105(8):e82-e3.
49. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA. 2021.
50. Chavarot N, Ouedrani A, Olivier M, et al. Poor Anti-SARS-CoV-2 Humoral and T-cell Responses After 2 Injections of mRNA Vaccine in Kidney Transplant Recipients Treated with Belatacept. Transplantation. 2021;105(9):e94-e5.
51. Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M, et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. Am J Transplant. 2021.
52. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients – a prospective cohort study. Eur J Heart Fail. 2021.
53. Rabinowich L, Grupper A, Baruch R, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol. 2021;75:435-8.
54. Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, et al. Antibody response to mRNA SARS-CoV-2 vaccine among kidney transplant recipients – Prospective cohort study. Clin Microbiol Infect. 2021.
55. Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with Chronic Lymphocytic Leukemia. Blood. 2021.
56. Monin L, Laing AG, Munoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol. 2021.
57. Broseta JJ, Rodriguez-Espinosa D, Rodriguez N, Mosquera MDM, Marcos MA, Egri N, et al. Humoral and Cellular Responses to mRNA-1273 and BNT162b2 SARS-CoV-2 Vaccines Administered to Hemodialysis Patients. Am J Kidney Dis. 2021.
58. Simon B, Rubey H, Treipl A, et al. Hemodialysis Patients Show a Highly Diminished Antibody Response after COVID-19 mRNA Vaccination Compared to Healthy Controls. Nephrol Dial Transplant. 2021:1-8.
59. Boyarsky BJ, Ruddy JA, Connolly CM, Ou MT, Werbel WA, Garonzik-Wang JM, et al. Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis. 2021.
60. Charmetant X, Espi M, Benotmane I, et al. Comparison of infected and vaccinated transplant recipients highlights the role of Tfh and neutralizing IgG in COVID-19 protection. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.22.21260852v1 .
61. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021;385(7):661-2.
62. Schrezenmeier E, Rincon-Arevalo H, Stefanski AL, et al. B and T cell responses after a third dose of SARS-CoV-2 vaccine in Kidney Transplant Recipients. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.12.21261966v2.full .
63. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Ann Intern Med. 2021.
64. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. Kidney Int. 2021;100(3):702-4.
65. Espi M, Charmetant X, Barba T, et al. Justification, safety, and efficacy of a third dose of mRNA vaccine in

maintenance hemodialysis patients: a prospective observational study. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.02.21259913v1 .

66. Longlune N, Nogier MB, Miedouge M, Gabilan C, Cartou C, Seigneuric B, et al. High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrol Dial Transplant. 2021.
67. Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med. 2021.
68. Aslam S, Adler E, Mekeel K, Little SJ. Clinical effectiveness of COVID-19 vaccination in solid organ transplant recipients. Transpl Infect Dis. 2021:e13705.
69. Chemaitelly H, AlMukdad S, Joy JP, et al. SARS-CoV-2 vaccine effectiveness in immunosuppressed kidney transplant recipients. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.07.21261578v1.full .
70. Behrens GM, Cossmann A, Stankov MV, Nehlmeier I, Kempf A, Hoffmann M, et al. SARS-CoV-2 delta variant neutralisation after heterologous ChAdOx1-S/BNT162b2 vaccination. Lancet. 2021.
71. Borobia AM, Carcas AJ, Perez-Olmeda M, Castano L, Bertran MJ, Garcia-Perez J, et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet. 2021;398(10295):121-30.
72. Normark J, Vikstrom L, Gwon YD, Persson IL, Edin A, Bjorsell T, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination. N Engl J Med. 2021.
73. Rose R, Neumann, F., Grobe, O., et al. Heterologous immunisation with vector vaccine as prime followed by mRNA vaccine as boost leads to humoral immune response against SARS-CoV-2, which is comparable to that according to a homologous mRNA vaccination scheme. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.09.21260251v1 .
74. Groß R, Zanoni M, Seidel A, et al. Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.05.30.21257971v2 .
75. Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med. 2021.
76. Hillus D, Schwarz T, Tober-Lau P, Vanshylla K, Hastor H, Thibeault C, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. Lancet Respir Med. 2021.
77. Tenbusch M, Schumacher S, Vogel E, Priller A, Held J, Steininger P, et al. Heterologous prime-boost vaccination with ChAdOx1 nCoV-19 and BNT162b2. Lancet Infect Dis. 2021.
78. Barros-Martins J, Hammerschmidt SI, Cossmann A, Odak I, Stankov MV, Morillas Ramos G, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Nat Med. 2021.
79. Brehm TT, Thompson M, Ullrich F, et al. Low SARS-CoV-2 infection rate and high vaccine-induced immunity among German healthcare workers at the end of the third wave of the COVID-19 pandemic. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.02.21260667v1 .
80. Gram MA, Nielsen J, Schelde AB, et al. Vaccine effectiveness when combining the ChAdOx1 vaccine as the first dose with an mRNA COVID-19 vaccine as the second dose. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.26.21261130v1 .
81. Liu X, Shaw RH, Stuart ASV, Greenland M, Aley PK, Andrews NJ, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. Lancet. 2021.
82. Iketani S, Liu L, Nair MS, et al. A third COVID-19 vaccine shot markedly boosts neutralizing antibody potency and breadth. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.11.21261670v1 .
83. Chen X, Chen Z, Azman AS, et al. Comprehensive mapping of neutralizing antibodies against SARS-CoV-2 variants induced by natural infection or vaccination. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.05.03.21256506v1 .
84. Noori M, Nejadghaderi SA, Arshi S, Carson-Chahhoud K, Ansarin K, Kolahi AA, et al. Potency of BNT162b2 and mRNA-1273 vaccine-induced neutralizing antibodies against severe acute respiratory syndrome-CoV-2 variants of concern: A systematic review of in vitro studies. Rev Med Virol. 2021:e2277.
85. Arora P, Kempf A, Nehlmier I, et al. Increased lung cell entry of B.1.617.2 and evasion of antibodies induced by infection and BNT162b2 vaccination. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.06.23.449568v1 .

86. Barouch DH, Stephenson KE, Sadoff J, et al. Durable Humoral and Cellular Immune Responses Following Ad26.COV2.S Vaccination for COVID-19. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.05.21259918v1 .
87. Choi A, Koch M, Wu K, et al. Serum Neutralizing Activity of mRNA-1273 against SARS-CoV-2 Variants. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.06.28.449914v1 .
88. Davis C, Logan N, Tyson G, et al. Reduced neutralisation of the Delta (B.1.617.2) SARS-CoV-2 variant of concern following vaccination. MedRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.06.23.21259327v1 .
89. Edara VV, Pinsky BA, Suthar MS, Lai L, Davis-Gardner ME, Floyd K, et al. Infection and Vaccine-Induced Neutralizing-Antibody Responses to the SARS-CoV-2 B.1.617 Variants. N Engl J Med. 2021.
90. Jongeneelen M, Kaszas K, Veldman D, et al. Ad26.COV2.S elicited neutralizing activity against Delta and other SARS-CoV-2 variants of concern. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.07.01.450707v1 .
91. Liu C, Ginn HM, Dejnirattisai W, Supasa P, Wang B, Tuekprakhon A, et al. Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. Cell. 2021.
92. Liu J, Liu Y, Xia H, Zou J, Weaver SC, Swanson KA, et al. BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants. Nature. 2021.
93. Lustig Y, Zuckerman N, Nemet I, Atari N, Kliker L, Regev-Yochay G, et al. Neutralising capacity against Delta (B.1.617.2) and other variants of concern following Comirnaty (BNT162b2, BioNTech/Pfizer) vaccination in health care workers, Israel. Euro Surveill. 2021;26(26).
94. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-80.
95. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. Lancet. 2021;397(10292):2331-3.
96. Mlcochova P KS, Dhar MS, et al. . SARS-CoV-2 B.1.617.2 Delta variant emergence and vaccine breakthrough. Research Square. 2021 https://www.researchsquare.com/article/rs-637724/v1 .
97. Collier DA, De Marco A, Ferreira I, Meng B, Datir R, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021.
98. Garcia-Beltran WF, Lam EC, St Denis K, Nitido AD, Garcia ZH, Hauser BM, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell. 2021.
99. Jangra S, Ye C, Rathnasinghe R, Stadlbauer D, Personalized Virology Initiative study g, Krammer F, et al. SARS-CoV-2 spike E484K mutation reduces antibody neutralisation. Lancet Microbe. 2021.
100. Lucas C, Vogels CBF, Yildirim I, et al. Impact of circulating SARS-CoV-2 variants on mRNA vaccine-induced immunity in uninfected and previously infected individuals. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.14.21260307v1 .
101. Tada T, Dcosta BM, Samanovic MI, Herati RS, Cornelius A, Zhou H, et al. Convalescent-Phase Sera and Vaccine-Elicited Antibodies Largely Maintain Neutralizing Titer against Global SARS-CoV-2 Variant Spikes. mBio. 2021;12(3):e0069621.
102. Tada T, Zhou H, Dcosta BM, et al. SARS-CoV-2 Lambda Variant Remains Susceptible to Neutralization by mRNA Vaccine-elicited Antibodies and Convalescent Serum. BioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.07.02.450959v1 .
103. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. Nature. 2021.
104. Annavajhala MK, Mohri H, Zucker JE, Sheng Z, Wang P, Gomez-Simmonds A, et al. A Novel SARS-CoV-2 Variant of Concern, B.1.526, Identified in New York. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.02.23.21252259v4 .
105. Carreno JM, Alshammary H, Singh G, et al. Reduced neutralizing activity of post-SARS-CoV-2 vaccination serum against variants B.1.617.2, B.1.351, B.1.1.7+E484K and a sub-variant of C.37. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.21.21260961v1 .
106. Liu Y, Liu J, Xia H, Zhang X, Zou J, Fontes-Garfias CR, et al. BNT162b2-Elicited Neutralization against New SARS-CoV-2 Spike Variants. N Engl J Med. 2021.
107. West AP WJ, Wang JC, et al. Detection and characterization of the SARS-CoV-2 lineage B.1.526 in New York. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.02.14.431043v3 .
108. Wu K, Werner AP, Koch M, Choi A, Narayanan E, Stewart-Jones GBE, et al. Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine. N Engl J Med. 2021.

109. Zhou H, Dcosta B, Samanovic M, et al. B.1.526 SARS-CoV-2 variants identified in New York City are neutralized by vaccine-elicited and therapeutic monoclonal antibodies. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.03.24.436620v1.full.pdf .
110. Alenquer M, Ferreira F, Lousa D, et al. Amino acids 484 and 494 of SARS-CoV-2 spike are hotspots of immune evasion affecting antibody but not ACE2 binding. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.04.22.441007v2 .
111. Becker M, Dulovic A, Junker D, Ruetalo N, Kaiser PD, Pinilla YT, et al. Immune response to SARS-CoV-2 variants of concern in vaccinated individuals. Nat Commun. 2021;12(1):3109.
112. Geers D, Shamier MC, Bogers S, den Hartog G, Gommers L, Nieuwkoop NN, et al. SARS-CoV-2 variants of concern partially escape humoral but not T-cell responses in COVID-19 convalescent donors and vaccinees. Sci Immunol. 2021;6(59).
113. Marot S, Malet I, Leducq V, Abdi B, Teyssou E, Soulie C, et al. Neutralization heterogeneity of United Kingdom and South-African SARS-CoV-2 variants in BNT162b2-vaccinated or convalescent COVID-19 healthcare workers. Clin Infect Dis. 2021.
114. Planas D, Bruel T, Grzelak L, Guivel-Benhassine F, Staropoli I, Porrot F, et al. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. Nat Med. 2021;27(5):917-24.
115. Shen X, Tang H, McDanal C, Wagh K, Fischer W, Theiler J, et al. SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral spike vaccines. Cell Host Microbe. 2021.
116. Skelly D, Harding A, Gilbert-Jaramillo J, et al. Two doses of SARS-CoV-2 vaccination induce robust immune responses to emerging SARS-CoV-2 variants of concern. Nature Communications. 2021;12(5061):1-12.
117. Stamatatos L, Czartoski J, Wan YH, Homad LJ, Rubin V, Glantz H, et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Science. 2021.
118. Supasa P, Zhou D, Dejnirattisai W, Liu C, Mentzer AJ, Ginn HM, et al. Reduced neutralization of SARS-CoV-2 B.1.1.7 variant by convalescent and vaccine sera. Cell. 2021.
119. Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. Vaccine. 2021;39(32):4423-8.
120. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021;27(7):1205-11.
121. Gallagher KME, Leick MB, Larson RC, Berger TR, Katsis K, Yam JY, et al. SARS -CoV-2 T-cell immunity to variants of concern following vaccination. bioRxiv. 2021.
122. Lilleri D, Vassaniti I, Bergami F, et al. SARS-CoV-2 mRNA vaccine BNT162b2 elicited a robust humoral and cellular response against SARS-CoV-2 variants. Research Square. 2021;https://www.researchsquare.com/article/rs-396284/v1 .
123. Neidleman J, Luo X, McGregor M, et al. mRNA vaccine-induced SARS-CoV-2-specific T cells recognize B.1.1.7 and B.1.351 variants but differ in longevity and homing properties depending on prior infection status. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.05.12.443888v2 .
124. Stankov MV, Cossmann A, Bonifacius A, Dopfer-Jablonka A, Ramos GM, Godecke N, et al. Humoral and cellular immune responses against SARS-CoV-2 variants and human coronaviruses after single BNT162b2 vaccination. Clin Infect Dis. 2021:1-9.
125. Tarke A, Sidney J, Methot N, et al. Impact of SARS-CoV-2 variants on the total CD4+ and CD8+ T cell reactivity in infected or vaccinated individuals. Cell Reports Medicine. 2021;2(7):1-12.
126. Woldemeskel BA, Garliss CC, Blankson JN. SARS-CoV-2 mRNA vaccines induce broad CD4+ T cell responses that recognize SARS-CoV-2 variants and HCoV-NL63. J Clin Invest. 2021;131(10).
127. Motozono C, Toyoda M, Zahradnik J, et al. An emerging SARS-CoV-2 mutant evading cellular immunity and increasing viral infectivity. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.04.02.438288v1 .
128. Pretti MAM, Galvani RG, Farias AS, et al. New SARS-CoV-2 lineages could evade CD8+ T-cells response. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.03.09.434584v2 .
129. Reynolds CJ, Pade C, Gibbons JM, Butler DK, Otter AD, Menacho K, et al. Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose. Science. 2021.
130. Dolton G, Rius C, Hasan MS, et al. Emergence of immune escape at dominant SARS-CoV-2 killer T-cell epitope. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.06.21.21259010v2 .
131. Agerer B, Koblischke M, Gudipati V, Montano-Gutierrez LF, Smyth M, Popa A, et al. SARS-CoV-2 mutations in MHC-I-restricted epitopes evade CD8(+) T cell responses. Sci Immunol. 2021;6(57).

132. Buckley PR, Lee CH, Pinho MP, et al. HLA-dependent variation in SARS-CoV-2 CD8+ T cell cross-reactivity with human coronaviruses. bioRxiv. 2021;https://www.biorxiv.org/content/10.1101/2021.07.17.452778v1 .

133. Aran D. Estimating real-world COVID-19 vaccine effectiveness in Israel using aggregated counts. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.02.05.21251139v3 .

134. Gomes D, Beyerlein A, Katz K, et al. Is the BioNTech-Pfizer COVID-19 vaccination effective in elderly populations? Results from population data from Bavaria, Germany. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.19.21262266v1 .

135. Mason T, Whitston M, Hodgson J, et al. Effects of BNT162b2 mRNA vaccine on Covid-19 infection and hospitalisation among older people: matched case control study for England. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.04.19.21255461v1 .

136. Cavanaugh AM, Fortier S, Lewis P, Arora V, Johnson M, George K, et al. COVID-19 Outbreak Associated with a SARS-CoV-2 R.1 Lineage Variant in a Skilled Nursing Facility After Vaccination Program – Kentucky, March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(17):639-43.

137. Emborg H, Valentiner-Branth P, Schelde AB, et al. Vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine against RT-PCR confirmed SARS-CoV-2 infections, hospitalisations and mortality in prioritised risk groups. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.05.27.21257583v1 .

138. Moustsen-Helms I, Emborg HD, Nielsen J, et al. Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 Vaccine in long-term care facility residents and healthcare workers – a Danish cohort study medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.03.08.21252200v1(March 24, 2021).

139. Collier DA, Ferreira I, Kotagiri P, Datir RP, Lim EY, Touizer E, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature. 2021;596(7872):417-22.

140. Abe KT, Hu Q, Mozafarihashjin M, et al. Neutralizing antibody responses to SARS-CoV-2 variants in vaccinated Ontario long-term care home residents and workers. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.06.21261721v1.full.pdf .

141. Pannus P, Neven, K.Y., De Craeye, S., et al. Poor antibody response to BioNTech/Pfizer COVID-19 vaccination in SARS-CoV-2 naïve residents of nursing homes. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.06.08.21258366v1 .

142. Canaday DH, Oyebanji OA, Keresztesy D, et al. Significant reduction in humoral immunity among healthcare workers and nursing home residents 6 months after COVID-19 BNT162b2 mRNA vaccination. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.15.21262067v1.full.pdf .

143. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, et al. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. N Engl J Med. 2021;384(23):2259-61.

144. Tada T, Zhou H, Samanovic M, et al. Comparison of Neutralizing Antibody Titers Elicited by mRNA and Adenoviral Vector Vaccine against SARS-CoV-2 Variants. bioRxiv. 2021;https://doi.org/10.1101/2021.07.19.452771

145. Naranbhai V, Garcia-Beltran, W.F., Berrios Mairena, C., et al. . Immunogenicity of mRNA-1273, BNT162b2 and Ad26.COV2.S COVID-19 vaccines. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.18.21260732v1 .

146. Pegu A, O'Connell S, Schmidt SD, O'Dell S, Talana CA, Lai L, et al. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. Science. 2021.

147. Wu K, Choi A, Koch M, et al. Preliminary Analysis of Safety and Immunogenicity of a SARS-CoV-2 Variant Vaccine Booster. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.05.05.21256716v1 .

148. Cromer D, Steain M, Reynaldi A, et al. SARS-CoV-2 variants: levels of neutralisation required for protective immunity. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.11.21261876v1 .

149. Thomas SJ, Moreira ED, Kitchin N, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.28.21261159v1 .

150. Nanduri S, Pilishvili T, Derado G, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morb Mortal Wkly Rep. 2021;ePub: 18 August 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7034e3 .

151. Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep. 2021;ePub: 18 August 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7034e1 .

152. Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv.

2021;https://www.medrxiv.org/content/10.1101/2021.08.06.21261707v3 .

153. Pouwels KB, Pritchard E, Matthews PC, et al. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. 2021;https://www.ndm.ox.ac.uk/files/coronavirus/covid-19-infection-survey/finalfinalcombinedve20210816.pdf .
154. Tendforde MW, Self WH, Naioti EA, et al. Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults — United States, March–July 2021. MMWR Morb Mortal Wkly Rep. 2021;ePub: 18 August 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7034e2 .
155. Mizrahi B, Lotan R, Kalkstein N, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.29.21261317v1.full .
156. Israel A, Merzon E, Schäffer AA, et al. Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.03.21261496v1 .
157. Thompson MG, Burgess JL, Naleway AL, Tyner H, Yoon SK, Meece J, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. N Engl J Med. 2021;385(4):320-9.
158. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. N Engl J Med. 2021.
159. Muller L, Andree M, Ostermann PN, et al. SARS-CoV-2 infection in fully vaccinated individuals of old age strongly boosters the humoral immune response. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.19.21260563v1 .
160. Centers for Disease Control and Prevention. COVID-19 Vaccine Breakthrough Infections Reported to CDC — United States, January 1–April 30, 2021 [Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7021e3.htm?s_cid=mm7021e3_w.
161. Kustin T, Harel N, Finkel U, Perchik S, Harari S, Tahor M, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. Nat Med. 2021.
162. Feder KA, Patel A, Vepachedu VR, et al. Association of E484K and L452R spike protein mutations with SARS-CoV-2 infection in vaccinated persons—Maryland, January – May 2021. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.29.21261006v2 .
163. Musser JM, Christensen PA, Olsen RJ, et al. Delta variants of SARS-CoV-2 cause significantly increased vaccine breakthrough COVID-19 cases in Houston, Texas. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.19.21260808v2 .
164. Brown CM, Vostok J, Johnson H, Burns M, Gharpure R, Sami S, et al. Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings – Barnstable County, Massachusetts, July 2021. MMWR Morb Mortal Wkly Rep. 2021;70(31):1059-62.
165. Jones NK, Rivett L, Seaman S, Samworth RJ, Warne B, Workman C, et al. Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. Elife. 2021;10.
166. Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, et al. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. Nat Med. 2021;27(5):790-2.
167. McEllistrem MC, Clancy CJ, Buehrle DJ, Lucas A, Decker BK. Single dose of a mRNA SARS-CoV-2 vaccine is associated with lower nasopharyngeal viral load among nursing home residents with asymptomatic COVID-19. Clin Infect Dis. 2021.
168. Petter E, Mor O, Zuckerman N, et al. Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.02.08.21251329v1 .
169. Abu-Raddad LJ, Chemaitelly H., Ayoub H.H., et al. Effect of vaccination and of prior infection on infectiousness of vaccine breakthrough infections and reinfections. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.28.21261086v1 .
170. Marks M, Millat-Martinez P, Ouchi D, Roberts CH, Alemany A, Corbacho-Monne M, et al. Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study. Lancet Infect Dis. 2021.
171. de Gier B, Andeweg S, Joosten R, Ter Schegget R, Smorenburg N, van de Kassteele J, et al. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Euro Surveill. 2021;26(31).
172. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. N Engl J Med. 2021;385(8):759-60.
173. Layan M, Gilboa M, Gonen T. Impact of BNT162b2 vaccination and isolation on SARS-CoV-2 transmission in Israeli households: an observational study. medRxiv.

households: an observational study. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.12.21260377v1 .

174. Prunas O, Warren JL, Crawford FW, et al. Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.13.21260393v1 .
175. Salo J, Hagg M, Kortelainen M, et al. The indirect effect of mRNA-based Covid-19 vaccination on unvaccinated household members. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.05.27.21257896v2 .
176. Shah A, Gribben C, Bishop J, et al. Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.03.11.21253275v1 .
177. Chia PY, Ong SWX, Chiew C, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1 .
178. Griffin JB, Haddix M, Danza P, et al. SARS-CoV-2 Infections and Hospitalizations Among Persons Aged ≥16 Years, by Vaccination Status — Los Angeles County, California, May 1–July 25, 2021. MMWR Morb Mortal Wkly Rep. 2021;ePub: 24 August 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7034e5 .
179. Riemersma KK, Grogan BE, Kita-Yarbro A, et al. Shedding of Infectious SARS-CoV-2 Despite Vaccination when the Delta Variant is Prevalent – Wisconsin, July 2021. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v4 .
180. Shamier MC, Tostmann A, Bogers S. Virological characteristics of SARS-CoV-2 vaccine breakthrough infections in health care workers. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.20.21262158v1 .
181. Kang M, Xin H, Yuan J. Transmission dynamics and epidemiological characteristics of Delta variant infections in China. medRxiv. 2021;https://www.medrxiv.org/content/10.1101/2021.08.12.21261991v1 .
182. Ong SWX, Chiew CJ, Ang LW, et al. Clinical and Virological Features of SARS-CoV-2 Variants of Concern: A Retrospective Cohort Study Comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta). Preprints with The Lancet. 2021;https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3861566 .

Previous Updates

As of May 27, 2021

- Data were added from studies published since the last update that further demonstrate currently authorized COVID-19 vaccines are effective against SARS-CoV-2 infection, symptomatic and severe disease, and hospitalization with COVID-19.
- Data were added suggesting that currently authorized mRNA vaccines provide protection against variants of concern, including the B.1.1.7 strain that is predominant in the United States.
- Data were added from studies published since the last update that further demonstrate people who are fully vaccinated with a currently authorized mRNA vaccine are protected against asymptomatic infection and, if infected, have a lower viral load than unvaccinated people.

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