COVID-19 Update
From Dr. Sara Knutson
Mon Dec 13, 2021

Delta Health Medical Providers:

1) **Monoclonal AB infusions are now available on a self-referral basis**. This week, the mobile bus is in Grand Junction. The state website is comassvax.org (this is a multi purpose website for vaccines, testing, antibody infusions). MCAB appointments can be found under the 'screening' tab. OR patients can call to schedule, at 1.877.268.2926.

   Patients need to meet the referral criteria: (positive test/within 10 days of symptom onset/no increased oxygen needs vs usual baseline and high risk disease criteria OR post exposure prophylaxis in patient who is unvaccinated or has limited immune response to vaccine.) **This is a useful option for patients who can easily travel or those who want faster access to the treatment than our system can provide.

   **We are continuing local access to the infusions for now via the familiar referral process we've been using over the last year.

2) As the guidelines for **booster doses** have been rolling out, there are a lot of FAQs about timing of vaccination, high risk groups, contraindications etc. Skimming thru the attached document I found, for example, the following information:

   - Immunocompromised persons (those deemed unlikely to mount a good vaccine response) should receive an additional mRNA dose at 28 days, and then can receive an additional 'booster' dose 6 months later.

   - MCAB recipients for post exposure prophylaxis can get vaccinated at 30 days; MCAB recipients for COVID infection need to wait 90 days.

   - IVIG administration has no impact on vaccine timing.

- Special groups at increased risk for vaccine complications (this is a bit oversimplified, but easier to remember):

- Prior history of HIT or thrombotic thrombocytopenic syndrome (TTS), any female age 18-48 and especially those who are pregnant, any patient with previous hypercoagulable state or history of clots I'd choose a mRNA vaccine rather than J&J.

- Male patients age 5-18 choose Pfizer; Moderna seems to have a higher risk for myocarditis. This demographic should be informed about the risk for myocarditis (generally mild self-limited disease but nonetheless appropriate to discuss)

- Patients with prior history of Guillian Barre, especially males age 50-64yo should avoid J&J.

3) We probably have about 2-3 weeks until the **Omicron variant** becomes more widely prevalent in the United States. We know this variant is MORE transmissible than Delta, and, given the spike protein mutations, will likely be more immune evasive. This is a very good time to strongly encourage your patients, especially those at higher risk for disease progression and more than 6 months (2 months for J&J) out from vaccine series, to get their boosters. It has been my experience that some patients seem a bit reluctant to bother with the booster dose, but it's more important right now than ever to review the benefits of the booster dose and make sure your patients get it done.

**see recent NEJM article from Israel demonstrates 90% mortality reduction in COVID infection between those with booster dose vs those just completing 2 dose series.

4) We've had a recent notable incidence of **DVT/PE among patients recovering at home from COVID infection**. This seems to especially include those with more severe disease and/or the obese patients. It is important to continue to assess your recovering COVID patients and consider post COVID complications such as PE, bacterial pneumonia, COPD/RAD exacerbation, and/or post COVID organizing pneumonia among patients with new clinical decline in disease course such as persistent or increasing oxygen needs, swollen lower extremity, chest pain, increasing fever curve or productive cough.

5) There continues to be local embrace of unproven therapies for COVID infections that can have **significant toxicity** (see NEJM letter). More recently I have even

seen social media traffic supporting use of hydrogen peroxide nebs. This is of special concern given the materials for this treatment are readily available. It is critical to understand that H2O2 nebs are widely panned (especially in the pulmonary literature) as having significant potential for pulmonary toxicity such as obliterative fibrosis. It is important for providers to inform themselves about which therapies are felt consistent with prevailing medical opinion for COVID infection, and present a reliable source of data within the community. The NIH treatment guidelines is a useful tool for up to date information: https://www.covid19treatmentguidelines.nih.gov/

6) Last, but not least: it is time (actually past time) to buy stock in Pfizer! They've just announced an 89% reduction in hospitalization and death for their **new antiviral 'Paxlovid'**, when taken within 3 days of symptom onset. The drug is now going before FDA for EUA approval. Paxlovid (3 pills bid for 5 days) is performing much better than Merck's offering molnupiravir.

Dr. Sara Knutson

Prevaccination Checklist for COVID-19 Vaccination

For vaccine recipients:

The following questions will help us determine if there is any reason you should not get the COVID-19 vaccine today. **If you answer "yes" to any question, it does not necessarily mean you should not be vaccinated.** It just means additional questions may be asked. If a question is not clear, please ask your healthcare provider to explain it.

Name _____

Age _____

	Yes	No	Don't know
1. Are you feeling sick today?	☐	☐	☐
2. Have you ever received a dose of COVID-19 vaccine?	☐	☐	☐
• If yes, which vaccine product(s) did you receive? ☐ Pfizer-BioNTech ☐ Moderna ☐ Janssen *(Johnson & Johnson)* ☐ Another Product _____			
• How many doses of COVID-19 vaccine have you received? _____			
• Did you bring your vaccination record card or other documentation?	☐	☐	
3. Do you have a health condition or are you undergoing treatment that makes you moderately or severely immunocompromised? *(This would include treatment for cancer or HIV, receipt of organ transplant, immunosuppressive therapy or high-dose corticosteroids, CAR-T-cell therapy, hematopoietic cell transplant [HCT], DiGeorge syndrome or Wiskott-Aldrich syndrome)*	☐	☐	☐
4. Have you received hematopoietic cell transplant (HCT) or CAR-T-cell therapies since receiving COVID-19 vaccine?	☐	☐	☐
5. Have you ever had an allergic reaction to: *(This would include a severe allergic reaction [e.g., anaphylaxis] that required treatment with epinephrine or EpiPen® or that caused you to go to the hospital. It would also include an allergic reaction that caused hives, swelling, or respiratory distress, including wheezing.)*			
• A component of a COVID-19 vaccine, including either of the following:			
○ Polyethylene glycol *(PEG)*, which is found in some medications, such as laxatives and preparations for colonoscopy procedures	☐	☐	☐
○ Polysorbate, which is found in some vaccines, film coated tablets, and intravenous steroids	☐	☐	☐
• A previous dose of COVID-19 vaccine	☐	☐	☐
6. Have you ever had an allergic reaction to another vaccine *(other than COVID-19 vaccine)* or an injectable medication? *(This would include a severe allergic reaction [e.g., anaphylaxis] that required treatment with epinephrine or EpiPen® or that caused you to go to the hospital. It would also include an allergic reaction that caused hives, swelling, or respiratory distress, including wheezing.)*	☐	☐	☐

7. Check all that apply to you:

- ☐ Am a female between ages 18 and 49 years old
- ☐ Am a male between ages 12 and 29 years old
- ☐ Have a history of myocarditis or pericarditis
- ☐ Have been treated with monoclonal antibodies or convalescent serum to prevent or treat COVID-19
- ☐ Diagnosed with Multisystem Inflammatory Syndrome (MIS-C or MIS-A) after a COVID-19 infection
- ☐ Have a bleeding disorder
- ☐ Take a blood thinner
- ☐ Have a history of heparin-induced thrombocytopenia (HIT)
- ☐ Am currently pregnant or breastfeeding
- ☐ Have received dermal fillers
- ☐ Have a history of Guillain-Barré Syndrome (GBS)

Form reviewed by _____ **Date** _____

Adapted with appreciation from the Immunization Action Coalition (IAC) screening checklists

Prevaccination Checklist for COVID-19 Vaccines

Information for Healthcare Professionals

For additional information on COVID-19 vaccine clinical guidance, see https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html.

For additional information on Advisory Committee on Immunization Practices *General Best Practice Guidelines for Immunization*, see https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.

COVID-19 vaccines are authorized and approved for different age groups and are given intramuscularly.

VACCINE PRODUCT	AUTHORIZED AGE GROUPS	SERIES	INTERVAL
Pfizer-BioNTech COVID-19 Vaccine (Orange cap and orange border on the label)	5 through 11 years of age	**Primary:** 2 doses	21 days
		Additional primary dose: N/A*	N/A
		Booster dose: N/A*	N/A
Pfizer-BioNTech COVID-19 Vaccine (Purple cap and may have a purple border on the label)	12 years of age and older	**Primary series:** 2 doses	21 days
		Additional primary dose: 1 dose*	At least 28 days after last primary series dose
		Booster dose: 1 dose for persons 18 years of age and older*†	At least 6 months after last primary series dose or additional primary dose
Moderna COVID-19 Vaccine	18 years of age and older	**Primary series:** 2 doses	28 days
		Additional primary dose: 1 dose*	At least 28 days after primary series dose
		Booster dose: 1 dose*†	At least 6 months after last primary series dose or additional primary dose
Janssen COVID-19 Vaccine (Johnson & Johnson)	18 years of age and older	**Primary series:** 1 dose	N/A
		Additional primary dose: N/A*	N/A
		Booster dose: 1 dose*†	At least 2 months (8 weeks) after primary dose

* See question 2 below for additional information regarding recommendations for additional (3rd) primary dose or booster dose.

† Booster doses can be a different COVID-19 vaccine product.

Postvaccination Observation Times for People without Contraindications to COVID-19 Vaccination

30 minutes:

- People with a history of:
  - A contraindication to another type of COVID-19 vaccine product (i.e., mRNA or viral vector COVID-19 vaccines)
  - Immediate (within 4 hours of exposure) non-severe allergic reaction to a COVID-19 vaccine or injectable therapies
  - Anaphylaxis due to any cause
  - Immediate allergic reaction of any severity to a non-COVID-19 vaccine

15 minutes:

- All other people

Prevaccination Checklist for COVID-19 Vaccines

Information for Healthcare Professionals

Co-administration of COVID-19 vaccines and other vaccines

COVID-19 vaccines and other vaccines **may be administered without regard to timing.** This includes simultaneous administration of COVID-19 vaccines and other vaccines during the same visit. Other vaccines can also be administered anytime before or after COVID-19 vaccination.

1. Are you feeling sick today?

While there is no evidence acute illness reduces vaccine efficacy or increases adverse reactions, as a precaution, **delay vaccinating patients with moderate or severe illness** until the illness has improved.

Defer vaccination of people with current SARS-CoV-2 infection until the person has recovered from acute illness and has discontinued isolation. This recommendation applies regardless of whether the SARS-CoV-2 infection occurred before the recipient received an initial dose or between doses. Viral or serological testing to assess for current or prior infection solely for the purpose of vaccine-decision making is not recommended.

People with mild illnesses can be vaccinated. Do not withhold vaccination if a person is taking antibiotics.

2. Have you ever received a dose of COVID-19 vaccine?

VACCINE PRODUCT	Primary Series Dosage (Amount)	Booster Dosage (Amount)
Pfizer-BioNTech COVID-19 Vaccine *(Orange Cap)* 5 through 11 years of age	0.2 mL	N/A
Pfizer-BioNTech COVID-19 Vaccine *(Purple Cap)* 12 years of age and older	0.3 mL	0.3 mL
Moderna COVID-19 Vaccine	0.5 mL	0.25 mL
Janssen COVID-19 Vaccine (Johnson & Johnson)	0.5 mL	0.5 mL

People 5 years of age and older **should** receive a primary series of COVID-19 vaccine. All COVID-19 primary series doses and additional primary doses should be the same vaccine product. Booster doses, for eligible persons, may be a different product than the COVID-19 vaccine product used in the primary series (e.g., mix and match may be used for boosters).

To determine previously administered COVID-19 doses, check medical records, immunization information systems, and vaccination record cards to help determine the initial product received. If the vaccine product for a primary mRNA dose cannot be determined or is no longer available, any available mRNA vaccine may be administered (separate doses by at least 28 days). If a different mRNA COVID-19 vaccine is inadvertently administered for the primary series or additional primary dose, the dose is considered valid, and no additional doses of either product are recommended.

People who were vaccinated as part of a clinical trial should consult with the trial sponsors to determine if it is possible to receive additional doses.

Ages 5 through 11 years of age:

Pfizer-BioNTech (orange cap), 2-dose primary series

Ages 12 through 17 years of age:

Pfizer-BioNTech (purple cap), 2-dose primary series

Ages 18 and older:

Pfizer-BioNTech (purple cap), 2-dose primary series followed by 1 booster dose

Moderna, 2-dose primary series followed by 1 booster dose

Janssen (Johnson & Johnson), 1-dose primary series followed by 1 booster dose

Immunocompromised Persons

See answers to question 3 to determine if an additional primary dose is recommended.

For people who received a COVID-19 vaccine outside the United States:

- People who received all recommended doses of an FDA-authorized or -approved COVID-19 vaccine or a WHO-EUL‡ COVID-19 vaccine do not need any subsequent primary series doses.
- People who received the first dose of an FDA-authorized or -approved COVID-19 vaccine that requires two doses **do not need** to restart the vaccine series in the United States but should receive the second dose as close to the recommended time as possible.
- People who completed a mix-product regimen of FDA-authorized, FDA-approved, or WHO-EUL† COVID-19 vaccines are considered fully vaccinated and do not need to restart a COVID-19 primary series.
- People who received only the first dose of a 2-dose WHO-EUL† COVID-19 vaccine primary series or who received all or some of a COVID-19 vaccine primary series doses not on the WHO-EUL list may be offered a complete FDA-approved or -authorized COVID-19 primary series. Wait at least 28 days after the last dose of the previous product before administering vaccine.
- People who completed a primary vaccination series of an FDA- approved or -authorized vaccine mRNA vaccine (including a mixed mRNA product primary series) may receive an additional primary mRNA dose at least 28 days after the second mRNA vaccine if they are moderately or severely immunocompromised.
- People who have completed a primary vaccination series of an FDA-approved or -authorized COVID-19 vaccine may receive or a booster dose if they are eligible.
- People who completed a primary series of a COVID-19 vaccine that is not FDA-approved or -authorized but is listed for emergency use by the World Health Organization and people who completed a mix-product regimen of FDA-authorized, FDA-approved, or WHO-EUL COVID-19 vaccines are eligible for†
  - An additional primary dose of Pfizer-BioNTech COVID-19 Vaccine, if 12 years of age or older and moderately to severely immunocompromised
  - A single Pfizer-BioNTech booster dose, if 18 years of age or older

3. Do you have a health condition or are you undergoing treatment that makes you moderately or severely immunocompromised?

COVID-19 vaccines may be administered to people with underlying medical conditions, such as HIV infection or other immunocompromising conditions, or who take immunosuppressive medications or therapies, who have no contraindications to vaccination.

VACCINE PRODUCT	Additional Primary Series Dosage (Amount)
Pfizer-BioNTech COVID-19 Vaccine *(Orange Cap)* 5 through 11 years of age	N/A
Pfizer-BioNTech COVID-19 Vaccine *(Purple Cap)* 12 years of age and older	0.3 mL
Moderna COVID-19 Vaccine	0.5 mL
Janssen COVID-19 Vaccine (Johnson & Johnson)	0.5 mL

Moderately or severely immunocompromised persons 12 years of age and older (Pfizer-BioNTech recipients) or 18 years and older (Moderna recipients) should receive an additional primary dose of the same mRNA COVID-19 vaccine administered for the primary series at least 28 days after completion of the initial 2-dose series. An additional primary dose is NOT recommended for Janssen vaccine recipients (see #2 for additional information for people who received a primary dose of Janssen.)

‡ See Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States (https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html) for a list of WHO vaccines for emergency use and additional guidance for people who received COVID-19 vaccine outside the United States.

These conditions and treatments include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of CAR-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids (i.e., ≥20mg prednisone or equivalent per day), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory

Moderately and severely immunocompromised people 18 years and older should follow the booster recommendations for the general population (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#considerations-covid19-vax-booster)

A patient's clinical team is best positioned to determine the degree of immune compromise and appropriate timing of vaccination.

People who are immunocompromised should be counseled about the potential for a reduced immune response to COVID-19 vaccines and the need to continue to follow current prevention measures (https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html) to protect themselves against COVID-19 until advised otherwise by their healthcare professional.

Additional information can be found in the Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

4. Have you received a hematopoietic cell transplant (HCT) or CAR-T-cell therapy since receiving COVID-19 vaccine?

HCT and CAR-T-cell recipients who received doses of COVID-19 vaccine prior to receiving an HCT or CAR-T-cell therapy should be revaccinated with a primary vaccine series at least 3 months (12 weeks) after transplant or CAR-T-cell therapy.

5. Have you ever had an allergic reaction to:

- A component of a COVID-19 vaccine, including:
  - Polyethylene glycol (PEG)[§], which is found in some medications, such as laxatives and preparations for colonoscopy procedures
  - Polysorbate[‡], which is found in some vaccines, film-coated tablets, and intravenous steroids
- A previous dose of COVID-19 vaccine

People with a severe allergic reaction[¶] to a previous COVID-19 vaccine dose or a known (diagnosed) allergy to a component of the vaccine have a contraindication to vaccination. People who had an immediate (< 4 hours), but non-severe allergic reaction to a previous dose of COVID-19 vaccine, have a precaution to receiving the same type of COVID-19 vaccine product. Although they can receive the same product, a different COVID-19 vaccine product can also be administered.

People with a contraindication to one type of COVID-19 vaccine (e.g., mRNA) should not receive any doses of that type of vaccine and have a precaution to the other type of vaccine (e.g., Janssen viral vector). People with a history of immediate allergic reaction to a vaccine or injectable therapy that contains multiple components, one or more of which is a component of a COVID-19 vaccine, have a precaution to vaccination with that COVID-19 vaccine, even if it is unknown which component elicited the allergic reaction.

§ Polyethylene glycol (PEG) is an ingredient in both mRNA COVID-19 vaccines, and polysorbate 80 is an ingredient in Janssen COVID-19 Vaccine. Because PEG and polysorbate are structurally related, cross-reactive hypersensitivity between these compounds may occur.

¶ When vaccine recipients report a history of an immediate allergic reaction, providers should attempt to determine whether reactions reported following vaccination are consistent with immediate allergic reactions versus other types of reactions commonly observed following vaccination, such as vasovagal reaction or postvaccination side effects (which are not contraindications to receiving the second of an mRNA COVID-19 vaccine dose).

Prevaccination Checklist for COVID-19 Vaccines

Information for Healthcare Professionals

COVID-19 Vaccine Components**

Description	Pfizer-BioNTech mRNA COVID-19 Vaccine		Moderna mRNA COVID-19 Vaccine	Janssen COVID-19 Vaccine
	For 5-11 years formulation (Orange Cap)	For 12 years and older formulation (Purple Cap)		
Active ingredients	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2		Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	Recombinant, replication-incompetent Ad26 vector, encoding a stabilized variant of the SARS-CoV-2 Spike (S) protein
Inactive ingredients	2[(polyethylene glycol {PEG})-2000]-N, N-ditetradecylacetamide		PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol	Polysorbate-80
	1,2-distearoyl-sn-glycero-3-phosphocholine		1,2-distearoyl-sn-glycero-3-phosphocholine	2-hydroxypropyl-β-cyclodextrin
	Cholesterol		Cholesterol	Citric acid monohydrate
	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl) bis(2-hexyldecanoate)		SM-102: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate	Trisodium citrate dihydrate
	Tromethamine	Sodium chloride	Tromethamine	Sodium chloride
	Tromethamine hydrochloride	Monobasic potassium phosphate	Tromethamine hydrochloride	Ethanol
	Sucrose	Potassium chloride	Acetic acid	
		Dibasic sodium phosphate dihydrate	Sodium acetate	
		Sucrose	Sucrose	

** None of the vaccines contain eggs, gelatin, latex, or preservatives.

Potential characteristics of allergic reactions, vasovagal reactions, and vaccine side effects following COVID-19 vaccination

In patients who experience post-vaccination symptoms, determining the etiology (including allergic reaction, vasovagal reaction, or vaccine side effects) is important to determine whether a person can receive additional doses of the vaccine. The following table of signs and symptoms is meant to serve as a resource but may not be exhaustive, and patients may not have all signs or symptoms. Providers should use their clinical judgement when assessing patients to determine the diagnosis and appropriate management.

Characteristic	Immediate allergic reactions (including anaphylaxis)	Vasovagal reactions	Vaccine side effects (local and systemic)
Timing after vaccination	Most occur within 15-30 minutes of vaccination	Most occur within 15 minutes	Median of 1 to 3 days after vaccination (with most occurring the day after vaccination)
SIGNS AND SYMPTOMS			
Characteristic	**Immediate allergic reactions (including anaphylaxis)**	**Vasovagal reactions**	**Vaccine side effects (local and systemic)**
Constitutional	Feeling of impending doom	Feeling warm or cold	Fever, chills, fatigue
Cutaneous	Skin symptoms present in ~90% of people with anaphylaxis, including pruritus, urticaria, flushing, angioedema	Pallor, diaphoresis, clammy skin, sensation of facial warmth	Pain, erythema, or swelling at injection site, lymphadenopathy in same arm as vaccination

Characteristic	Immediate allergic reactions (including anaphylaxis)	Vasovagal reactions	Vaccine side effects (local and systemic)
Neurologic	Confusion, disorientation, dizziness, lightheadedness, weakness, loss of consciousness	Dizziness, lightheadedness, syncope (often after prodromal symptoms for a few seconds or minutes), weakness, changes in vision (such as spots of flickering lights, tunnel vision), changes in hearing	Headache
Respiratory	Shortness of breath, wheezing, bronchospasm, stridor, hypoxia	Variable; if accompanied by anxiety, may have an elevated respiratory rate	N/A
Cardiovascular	Hypotension, tachycardia	Variable; may have hypotension or bradycardia during syncopal event	N/A
Gastrointestinal	Nausea, vomiting, abdominal cramps, diarrhea	Nausea, vomiting	Vomiting or diarrhea might occur
Musculoskeletal	N/A	N/A	Myalgia, arthralgia

VACCINE RECOMMENDATIONS AND CLINICAL MANAGEMENT

Characteristic	Immediate allergic reactions (including anaphylaxis)	Vasovagal reactions	Vaccine side effects (local and systemic)
Can receive a subsequent dose of COVID-19 vaccine	No, contraindicated if: ▪ Severe allergic reaction (e.g., anaphylaxis) ▪ Known (diagnosed) allergy to a component of a COVID-19 vaccine Yes, with precaution if: ▪ Any immediate (onset <4 hours after exposure) allergic reaction to other vaccines (non-COVID-19) or injectable therapies ▪ Non-severe, immediate allergic reaction after a previous dose of COVID-19 vaccine. People with a contraindication to mRNA COVID-19 vaccines have a precaution to Janssen COVID-19 vaccine and vice versa.	Yes	Yes

Healthcare providers or health departments in the United States can request a consultation from the Clinical Immunization Safety Assessment COVIDvax project (https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html) for a complex COVID-19 vaccine safety question not readily addressed by CDC guidance about an individual patient residing in the United States.

Healthcare professionals should be familiar with identifying severe allergic reactions, including anaphylaxis, and be competent in treating these events at the time of vaccine administration. Appropriate medical treatment for severe allergic reactions must be immediately available in the event that an acute anaphylactic reaction occurs following administration of a COVID-19 vaccine. See Management of Anaphylaxis at COVID-19 Vaccination Sites for additional guidance.
https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/anaphylaxis-management.html

Syncope may occur in association with injectable vaccines, in particular among adolescents. Procedures should be in place to avoid falling injuries and manage syncopal reactions. All people are recommended to be observed following COVID-19 vaccination for at least 15 minutes. Patients should be seated or lying down for vaccination and during the observation period to decrease the risk for injury should they faint. If syncope develops, patients should be observed until symptoms resolve.

6. Have you ever had an allergic reaction to another vaccine (other than COVID-19 vaccine) or another injectable medication?

A history of any immediate allergic reaction (onset <4 hours of exposure) to any other vaccine or injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies not related to a component of COVID-19 vaccines) is a precaution to currently FDA-authorized or -approved COVID-19 vaccines. This also applies if the non-COVID-19 vaccine or therapy has multiple components, one or more of which is a component of a COVID-19 vaccine, and it is unknown which component elicited the allergic reaction. Vaccine may be given, but counsel patients about unknown risks of developing a severe allergic reaction and balance these risks against the benefits of vaccination. Deferral of vaccination and/or consultation with an allergist-immunologist should be considered. Considerations for vaccination include risk of exposure to SARS-CoV-2, risk of severe disease or death due to COVID-19, previous infection with COVID-19, unknown risk of anaphylaxis following COVID-19 vaccination, and ability of recipient to receive care immediately for anaphylaxis, if necessary. **These individuals should be observed for 30 minutes after vaccination.**

7. Clinical Considerations:

Response	Consideration
Female between 18 and 49 years of age	Women 18 through 49 years of age can receive any FDA-authorized or -approved COVID-19 vaccine. However, they should be informed of the rare but increased risk of thrombosis with thrombocytopenia syndrome (TTS) after receipt of the Janssen COVID-19 Vaccine and the availability of other FDA-authorized and -approved COVID-19 vaccines. People who had TTS after a first dose of Janssen vaccine should not receive a subsequent dose of Janssen product. (https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine) Additional recipient education materials can be found at www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/JJUpdate.html.
Male between 12 and 29 years of age	Males 5 through 17 years of age may receive the correct formulation of Pfizer-BioNTech COVID-19 vaccine. Males 18 and older can receive any FDA-authorized or -approved vaccine. However, people receiving an mRNA COVID-19 vaccine, especially males 12 through 29 years of age and their parents/legal representative (when relevant), should be informed of the risk of developing myocarditis (an inflammation of the heart muscle) or pericarditis (inflammation of the lining around the heart) after receipt of an mRNA vaccine. Accumulating evidence from multiple sources suggests a higher risk for myocarditis following Moderna compared to Pfizer-BioNTech vaccination; however, it is not possible to directly compare the risk in persons aged 12–17 years old because Pfizer-BioNTech is the only COVID-19 vaccine authorized in this age group. There are currently no data comparing the risk for myocarditis after a booster dose of Pfizer-BioNTech COVID-19 Vaccine versus a booster dose of Moderna COVID-19 Vaccine. The risk of myocarditis or pericarditis associated with SARS-CoV-2 infection is greater than the risk of myocarditis or pericarditis occurring after receipt of an mRNA COVID-19 vaccine in adolescents and adults. Vaccine recipients should be counseled about the need to seek care if symptoms of myocarditis or pericarditis develop after vaccination. Additional recipient education materials can be found at www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html.

Response	Consideration
History of myocarditis or pericarditis	***Myocarditis or pericarditis after receipt of the first dose of an mRNA COVID-19 vaccine series but before administration of the second dose*** Experts advise that people who develop myocarditis or pericarditis after a dose of an mRNA COVID-19 vaccine not receive a subsequent dose of any COVID-19 vaccine, until additional safety data are available. Administration of a subsequent dose of COVID-19 vaccine before safety data are available can be considered in certain circumstances after the episode of myocarditis or pericarditis has completely resolved. Until additional data are available, some experts recommend a Janssen COVID-19 vaccine be considered instead of an mRNA COVID-19 vaccine. Decisions about proceeding with a subsequent dose should include a conversation between the patient, their parent/legal representative (when relevant), and their clinical team, which may include a cardiologist. Considerations for vaccination can be found at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#underlying-conditions. Healthcare providers and health departments may also request a consultation from the Clinical Immunization Safety Assessment Project at www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html. ***History of myocarditis or pericarditis prior to COVID-19 vaccination*** People who have a history of myocarditis or pericarditis unrelated to mRNA COVID-19 vaccination may receive any FDA-authorized or -approved COVID-19 vaccine after the episode of myocarditis or pericarditis has completely resolved.
Had a severe allergic reaction to something other than a vaccine or injectable therapy such as food, pet, venom, environmental or oral medication allergies	Allergic reactions, including severe allergic reactions, **NOT** related to vaccines, injectable therapies, or components of COVID-19 vaccines, are **NOT** contraindications or precautions to vaccination with currently FDA-authorized or -approved COVID-19 vaccines. However, individuals who have had severe allergic reactions to anything, regardless of cause, **should be observed for 30 minutes after vaccination.**
Treated with monoclonal antibodies or convalescent serum	Vaccination should be offered to people regardless of history of prior symptomatic or asymptomatic SARS-CoV-2 infection. There is no recommended minimal interval between infection and vaccination. However, vaccination should be deferred if a patient received monoclonal antibodies or convalescent serum as treatment for COVID-19 or for post-exposure prophylaxis. This is a precautionary measure until additional information becomes available, to avoid interference of the antibody treatment with vaccine-induced immune responses. Defer COVID-19 vaccination for 30 days when a passive antibody product was used for post-exposure prophylaxis. Defer COVID-19 vaccination for 90 days when a passive antibody product was used to treat COVID-19.

Response	Consideration
Had multisystem inflammatory syndrome; either MIS-C (children) or MIS-A (adults)	It is unknown if people with a history of MIS-C or MIS-A are at risk for a dysregulated immune response to COVID-19 vaccination. People with a history of MIS-C or MIS-A may choose to be vaccinated. Considerations for vaccination may include: ■ Clinical recovery from MIS-C or MIS-A, including return to normal cardiac function ■ Personal risk of severe acute COVID-19 (e.g., age, underlying conditions) ■ High or substantial community transmission of SARS-CoV-2 and personal increased risk of reinfection. ■ Timing of any immunomodulatory therapies (general best practice guidelines for immunization can be consulted for more information https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html) ■ It has been 90 days or more since their diagnosis of MIS-C ■ Onset of MIS-C occurred before any COVID-19 vaccination A conversation between the patient, their guardian(s), and their clinical team or a specialist may assist with COVID-19 vaccination decisions. Healthcare providers and health departments may also request a consultation from the Clinical Immunization Safety Assessment Project at www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html.
Have a bleeding disorder **Take a blood thinner**	As with all vaccines, any COVID-19 vaccine product may be given to these patients, if a physician familiar with the patient's bleeding risk determines that the vaccine can be administered intramuscularly with reasonable safety. ACIP recommends the following technique for intramuscular vaccination in patients with bleeding disorders or taking blood thinners: a fine-gauge needle (23-gauge or smaller caliber) should be used for the vaccination, followed by firm pressure on the site, without rubbing, for at least 2 minutes. People who regularly take aspirin or anticoagulants as part of their routine medications do not need to stop these medications prior to receipt of any COVID-19 vaccine.

Response	Consideration
History of heparin-induced thrombocytopenia (HIT) or thrombosis with thrombocytopenia syndrome (TTS)	Although the etiology of TTS associated with the Janssen COVID-19 vaccine is unclear, it appears to be similar to another rare immune-mediated syndrome, heparin-induced thrombocytopenia (HIT). People with a history of an episode of an immune-mediated syndrome characterized by thrombosis and thrombocytopenia, such as HIT, should be offered a currently FDA-approved or FDA-authorized mRNA COVID-19 vaccine if it has been ≤90 days since their TTS resolved. After 90 days, patients may be vaccinated with any currently FDA-approved or FDA-authorized COVID-19 vaccine, including Janssen COVID-19 Vaccine. However, people who developed TTS after their initial Janssen vaccine should not receive a Janssen booster dose. Experts believe the following factors do not make people more susceptible to TTS after receipt of the Janssen COVID-19 Vaccine. People with these conditions can be vaccinated with any FDA-authorized or - approved COVID-19 vaccine, including the Janssen COVID-19 Vaccine: ■ A prior history of venous thromboembolism ■ Risk factors for venous thromboembolism (e.g., inherited or acquired thrombophilia including Factor V Leiden; prothrombin gene 20210A mutation; antiphospholipid syndrome; protein C, protein S or antithrombin deficiency ■ A prior history of other types of thromboses not associated with thrombocytopenia ■ Pregnancy, post-partum status, or receipt of hormonal contraceptives (e.g., combined oral contraceptives, patch, ring) Additional recipient education materials can be found at www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/JJUpdate.html.
Currently pregnant or breastfeeding	Vaccination is recommended for all people aged 12 years and older, including people that are: ■ Pregnant ■ Breastfeeding ■ Trying to get pregnant now or who might become pregnant in the future Pregnant, breastfeeding, and post-partum people 18 through 49 years of age should be aware of the rare risk of TTS after receipt of the Janssen COVID-19 Vaccine and the availability of other FDA-authorized or -approved COVID-19 vaccines (i.e., mRNA vaccines). For purposes of decisions around administering both primary series vaccination and a booster dose, (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html) pregnant and recently pregnant people (for at least 42 days following end of pregnancy) should be considered in the same group as people with underlying medical conditions (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html).

Response	Consideration
Have dermal fillers	FDA-authorized or -approved COVID-19 vaccines can be administered to people who have received injectable dermal fillers who have no contraindications for vaccination. Infrequently, these people might experience temporary swelling at or near the site of filler injection (usually the face or lips) following administration of a dose of an mRNA COVID-19 vaccine. These people should be advised to contact their healthcare provider if swelling develops at or near the site of dermal filler following vaccination.
History of Guillain-Barré Syndrome (GBS)	People with a history of GBS can receive any FDA-authorized or -approved COVID-19 vaccine. However, given the possible association between the Janssen COVID-19 Vaccine and an increased risk of GBS, a patient with a history of GBS and their clinical team should discuss the availability of mRNA vaccines to offer protection against COVID-19. The highest risk has been observed in men aged 50-64 years with symptoms of GBS beginning within 42 days after Janssen COVID-19 vaccination. People who had GBS after receiving Janssen vaccine should be made aware of the option to receive an mRNA COVID-19 vaccine booster at least 2 months (8 weeks) after the Janssen dose. However, Janssen vaccine may be used as a booster, particularly if GBS occurred more than 42 days after vaccination or was related to a non-vaccine factor. Prior to booster vaccination, a conversation between the patient and their clinical team may assist with decisions about use of a COVID-19 booster dose, including the timing of administration.

ORIGINAL ARTICLE

BNT162b2 Vaccine Booster and Mortality Due to Covid-19

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ABSTRACT

BACKGROUND

The emergence of the B.1.617.2 (delta) variant of severe acute respiratory syndrome coronavirus 2 and the reduced effectiveness over time of the BNT162b2 vaccine (Pfizer–BioNTech) led to a resurgence of coronavirus disease 2019 (Covid-19) cases in populations that had been vaccinated early. On July 30, 2021, the Israeli Ministry of Health approved the use of a third dose of BNT162b2 (booster) to cope with this resurgence. Evidence regarding the effectiveness of the booster in lowering mortality due to Covid-19 is still needed.

METHODS

We obtained data for all members of Clalit Health Services who were 50 years of age or older at the start of the study and had received two doses of BNT162b2 at least 5 months earlier. The mortality due to Covid-19 among participants who received the booster during the study period (booster group) was compared with that among participants who did not receive the booster (nonbooster group). A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association of booster status with death due to Covid-19, with adjustment for sociodemographic factors and coexisting conditions.

RESULTS

A total of 843,208 participants met the eligibility criteria, of whom 758,118 (90%) received the booster during the 54-day study period. Death due to Covid-19 occurred in 65 participants in the booster group (0.16 per 100,000 persons per day) and in 137 participants in the nonbooster group (2.98 per 100,000 persons per day). The adjusted hazard ratio for death due to Covid-19 in the booster group, as compared with the nonbooster group, was 0.10 (95% confidence interval, 0.07 to 0.14; P<0.001).

CONCLUSIONS

Participants who received a booster at least 5 months after a second dose of BNT162b2 had 90% lower mortality due to Covid-19 than participants who did not receive a booster.

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The deployment of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) and other vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in a significant decrease in mortality due to coronavirus disease 2019 (Covid-19).[1] Israel deployed the vaccines rapidly, and accordingly, the incidence of Covid-19 dropped from almost 1000 cases per 1 million persons per day in January 2021 to 1 to 2 cases per 1 million persons per day in June 2021.[2] However, the emergence of the B.1.617.2 (delta) variant[3] and the reduced efficacy of BNT162b2 over time[4] led to a resurgence of Covid-19 cases in Israel[5] and in other populations that had been vaccinated early, such as the U.S. health care workforce.[6] By August 2021, Israel had the highest incidence of Covid-19 worldwide.[2] On July 30, 2021, the Israeli Ministry of Health approved the use of a third dose of BNT162b2 (booster). The booster was initially indicated for use in persons 60 years of age or older who had received a second dose at least 5 months earlier. Two weeks later, the age of eligibility was lowered to 50 years. This local regulatory approval was made despite the lack of robust evidence of efficacy and the absence of regulatory approval by the Food and Drug Administration and by the European Medicines Agency.

A global debate regarding the approval of Covid-19 vaccine boosters is ongoing.[7] Data regarding the effectiveness of the BNT162b2 booster in lowering mortality due to Covid-19 are still unavailable in all age groups. Therefore, our objective was to assess for any decrease in mortality associated with the use of the BNT162b2 booster.

Methods

Study Design

The study period started on August 6, 2021, which was 7 days after the approval of the booster for use in persons 60 years of age or older in Israel. The study period ended on September 29, 2021, which was the last date for which data regarding confirmed deaths due to Covid-19 were available on the day the data were extracted (October 3, 2021). The study timeline is depicted in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The Clalit Health Services (CHS) Community Helsinki Committee and the CHS Data Utilization Committee approved the study. The study was exempt from the requirement to obtain informed consent.

Study Population

The study included all CHS members who were 50 years of age or older on the study start date and had received two doses of BNT162b2 at least 5 months earlier. CHS covers approximately 52% of the Israeli population and is the largest of four health care organizations in Israel that provide mandatory health care. Participants with missing data regarding date of birth or sex were excluded from the study. In addition, participants were excluded if they had been infected with SARS-CoV-2 or had received a booster before August 6, 2021; early administration of the booster was indicated in immunocompromised persons. Finally, participants who received the booster and had a confirmed case of Covid-19 within 3 days before the effective-booster date (defined as 7 days after the booster was administered) were excluded.

The study population was divided into two groups: those who had received a booster during the study period (booster group) and those who had not received a booster (nonbooster group). Participants were included in the booster group on the effective-booster date to allow time for antibodies to build effectively.[4,8] Up to 7 days after receiving the booster, participants were still included in the nonbooster group. A description of the transition of participants from the nonbooster group to the booster group is provided in Figure S2.

Data Sources and Organization

We analyzed patient-level data that were extracted from CHS electronic medical records. A specific database was created for this study that integrated patient-level data from two primary sources: the CHS operational database and the CHS Covid-19 database. The CHS operational database includes sociodemographic data and comprehensive clinical information, such as coexisting chronic conditions, community-care visits, hospitalizations, medications, and results of laboratory tests and imaging studies. The CHS Covid-19 database includes information that is collected centrally by the Israeli Ministry

of Health and transferred daily to CHS, such as vaccination dates, reverse-transcriptase–quantitative polymerase-chain-reaction (RT-qPCR) test dates and results, and hospitalizations and deaths related to Covid-19.

The CHS databases were used in the primary studies that evaluated the effectiveness[1] and safety[9] of the BNT162b2 vaccine in a real-world setting. In addition, the Israeli Ministry of Health Covid-19 database was used as the basis of the initial study that evaluated the effectiveness of the BNT162b2 booster among persons 60 years of age or older.[10] A description of the CHS data repositories that were used in this study is provided in the Supplementary Appendix.

For each participant in the study, the following sociodemographic data were extracted: age, sex, population sector (general Jewish population, Arab population, or ultra-Orthodox Jewish population), and score for socioeconomic status (scores range from 1 [lowest] to 10 [highest]; details are provided in the Supplementary Appendix). The following clinical data were extracted: vaccination dates (first, second, and booster doses), RT-qPCR test dates and results, death due to Covid-19, and any clinical risk factors for death due to Covid-19 that have been identified in the general population,[11] such as diabetes mellitus, chronic obstructive pulmonary disease, asthma, chronic kidney failure, hypertension, ischemic heart disease, chronic heart failure, obesity, lung cancer, or a history of cerebrovascular accident, transient ischemic attack, or smoking.

STUDY OUTCOMES

The primary outcome was death due to Covid-19. In the primary analysis of the effectiveness of the booster with respect to this outcome, we compared the mortality due to Covid-19 in the booster group with that in the nonbooster group.

Because the initial approval of the booster by the Food and Drug Administration was for use in persons 65 years of age or older, we performed a subgroup analysis according to age group. We performed an additional subgroup analysis according to sex.

In a secondary analysis of the effectiveness of the booster in preventing SARS-CoV-2 infection, we compared the frequency of positive RT-qPCR tests in the booster group with that in the nonbooster group.

STATISTICAL ANALYSIS

A chi-square test was used to compare categorical variables according to study group. Given that the independent variable (booster status) varied over time, univariate and multivariate survival analyses were performed with time-dependent covariates, in accordance with the study design.[12] A Kaplan–Meier analysis with a log-rank test was used for the univariate analysis. Comparison of the survival curves and Schoenfeld's global test were used to test the proportional-hazards assumption for each dependent variable. Variables that met the testing criteria served as inputs for multivariate regression analysis.

A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association of booster status with death due to Covid-19. The regression model was used to estimate the hazard ratio for death due to Covid-19 in the booster group, as compared with the nonbooster group, with the use of sociodemographic and baseline clinical characteristics as independent variables.

The assumption of a 7-day lag time between the administration of the booster and the effective-booster date, during which participants were included in the nonbooster group, was further tested to verify that this grouping did not create any bias. Validation of the lag time used to ensure booster effectiveness was performed through estimation of the hazard ratio for death due to Covid-19 in participants up to 7 days after the administration of the booster, as compared with the nonbooster group. Use of an alternative 14-day lag time was also tested with the same method.

R statistical software, version 3.5.0 (R Foundation for Statistical Computing), was used for the univariate and multivariate survival analyses with time-dependent covariates. SPSS software, version 26 (IBM), was used for all other statistical analyses. A P value of less than 0.05 was considered to indicate significance in all analyses.

RESULTS

PATIENT POPULATION

A total of 843,208 participants met the eligibility criteria (Fig. 1). The characteristics of the study population are shown in Table 1. The mean age was 68.5 years; 60% of the participants were 65 years of age or older. The most common coexist-

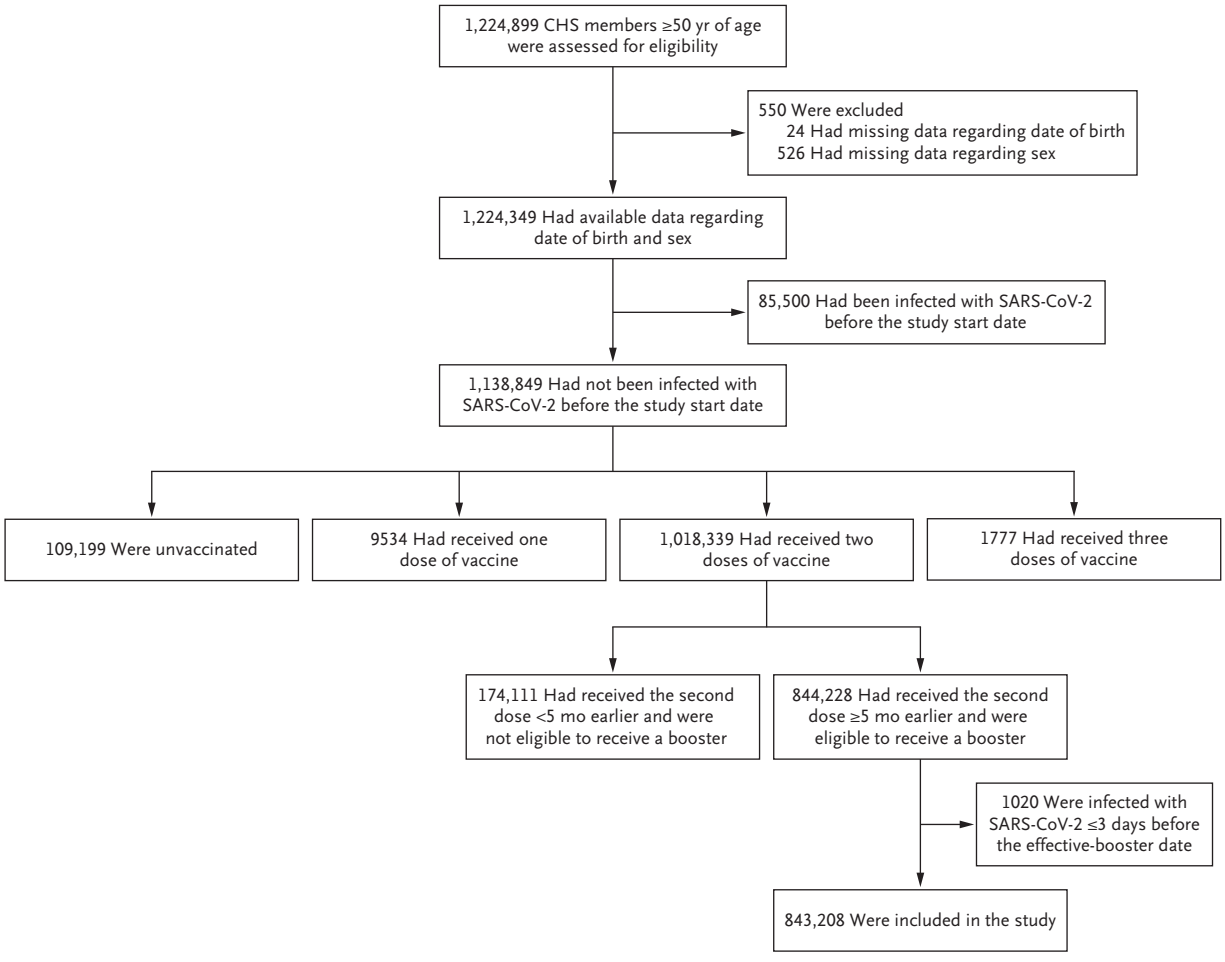


Figure 1. Assessment for Eligibility.
CHS denotes Clalit Health Services, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

ing conditions were hypertension (46%), obesity (33%), and diabetes (29%). For most sociodemographic and clinical characteristics, the difference between the booster group and the nonbooster group was significant.

PRIMARY OUTCOME

During the study period, death due to Covid-19 occurred in 65 participants in the booster group (0.16 per 100,000 persons per day) and in 137 participants in the nonbooster group (2.98 per 100,000 persons per day). The adjusted hazard ratio for death due to Covid-19 in the booster group, as compared with the nonbooster group, was 0.10 (95% confidence interval [CI], 0.07 to 0.14; P<0.001). Cumulative hazard-ratio curves are shown in Figure 2. At the end of the study period, 758,118 participants (90%) had received the booster.

The results of the Cox proportional-hazards regression model with time-dependent covariates are shown in Table 2. The model included only variables that met the criteria for the proportional-hazards assumption on the basis of the results of Schoenfeld's global test (Table S1). Therefore, population sector, asthma, and hypertension were not incorporated into the model. In the Cox regression model, age, male sex, chronic kidney failure, lung cancer, and history of cerebrovascular accident were confounding variables

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	All Participants (N=843,208)	Booster (N=758,118)	No Booster (N=85,090)	P Value
Age — yr	68.5±10.6	68.9±10.5	64.8±10.9	<0.001
Age group — no. (%)				
≥65 yr	506,016 (60)	470,808 (62)	35,208 (41)	<0.001
50–64 yr	337,192 (40)	287,310 (38)	49,882 (59)	<0.001
Female sex — no. (%)	448,272 (53)	400,300 (53)	47,972 (56)	<0.001
Population sector — no. (%)				
General Jewish population	732,493 (87)	674,266 (89)	58,227 (68)	<0.001
Arab population	86,162 (10)	62,042 (8)	24,120 (28)	<0.001
Ultra-Orthodox Jewish population	24,297 (3)	21,633 (3)	2,664 (3)	<0.001
Unknown	256 (<1)	—	—	—
Score for socioeconomic status — median (SD)†	5.9 (2.2)	6 (2.2)	4.8 (2.2)	<0.001
Clinical risk factors — no. (%)				
Diabetes	244,746 (29)	220,959 (29)	23,787 (28)	<0.001
Chronic obstructive pulmonary disease	41,449 (5)	37,291 (5)	4,158 (5)	0.68
Asthma	51,360 (6)	46,198 (6)	5,162 (6)	0.75
Chronic kidney failure	51,636 (6)	47,187 (6)	4,449 (5)	<0.001
Hypertension	391,654 (46)	358,517 (47)	33,137 (39)	<0.001
Ischemic heart disease	142,742 (17)	131,058 (17)	11,684 (14)	<0.001
Chronic heart failure	37,297 (4)	33,524 (4)	3,773 (4)	0.87
Obesity	278,097 (33)	249,152 (33)	28,945 (34)	<0.001
Lung cancer	5,661 (1)	5,132 (1)	529 (1)	0.06
History of cerebrovascular accident	60,343 (7)	54,328 (7)	6,015 (7)	0.30
History of transient ischemic attack	29,145 (3)	26,586 (4)	2,559 (3)	<0.001
History of smoking	348,654 (41)	314,226 (41)	34,428 (40)	<0.001

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Scores for socioeconomic status range from 1 (lowest) to 10 (highest).

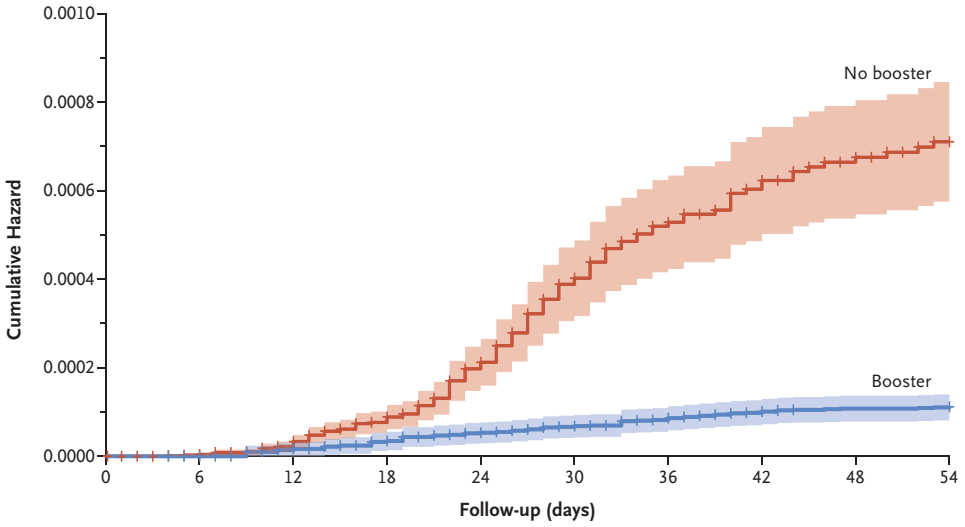
that had a significant association with death due to Covid-19. Socioeconomic status, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, chronic heart failure, obesity, history of transient ischemic attack, and history of smoking did not have a significant association with death due to Covid-19.

VALIDATION OF THE 7-DAY LAG TIME TO ENSURE BOOSTER EFFECTIVENESS

The hazard ratio for death due to Covid-19 in participants up to 7 days after the administration of the booster, as compared with the nonbooster group, was 0.95 (95% CI, 0.86 to 1.05; P=0.32). However, the hazard ratio for death due to Covid-19 in participants up to 14 days after the administration of the booster, as compared with the nonbooster group, was 0.67 (95% CI, 0.60 to 0.74; P<0.001). Therefore, our assumption of a 7-day lag time between the administration of the booster and booster effectiveness was confirmed. Details of the results of these analyses are provided in Tables S2 and S3.

SUBGROUP ANALYSIS

Among participants 65 years of age or older, death from Covid-19 occurred in 60 of 470,808 participants in the booster group and in 123 of 35,208 participants in the nonbooster group (adjusted hazard ratio, 0.09; 95% CI, 0.07 to 0.13; P<0.001) (Table S4). Among participants younger than 65 years of age, death from Covid-19 oc-



No. at Risk										
No booster	841,428	723,609	520,459	326,741	202,797	145,021	111,761	101,695	90,036	83,989
Booster	46,259	119,332	322,203	515,639	639,315	696,859	729,971	739,945	756,591	757,614
Cumulative No. of Events										
No booster	0	3	20	43	72	103	119	129	134	137
Booster	0	0	4	12	23	33	46	57	62	65

Figure 2. Cumulative Hazard Ratio for Death Due to Covid-19.
The shaded area indicates the 95% confidence interval. Covid-19 denotes coronavirus disease 2019.

Table 2. Association of Confounding Variables with Death Due to Covid-19.*

Variable	Hazard Ratio for Death Due to Covid-19 (95% CI)	P Value
Booster received	0.10 (0.07–0.14)	<0.001
Age	1.10 (1.09–1.12)	<0.001
Male sex	2.49 (1.82–3.41)	<0.001
Socioeconomic status	0.98 (0.92–1.04)	0.45
Diabetes	1.29 (0.96–1.72)	0.09
Chronic obstructive pulmonary disease	1.31 (0.86–1.99)	0.22
Chronic kidney failure	2.27 (1.63–3.15)	<0.001
Ischemic heart disease	0.96 (0.69–1.32)	0.79
Chronic heart failure	1.41 (0.95–2.09)	0.09
Obesity	1.17 (0.87–1.58)	0.30
Lung cancer	3.20 (1.49–6.87)	0.003
History of cerebrovascular accident	1.54 (1.08–2.17)	0.02
History of transient ischemic attack	0.87 (0.50–1.51)	0.63
History of smoking	1.10 (0.82–1.49)	0.52

* Age was a continuous variable, and socioeconomic status was an ordinal variable; all other variables were dichotomous (present vs. absent). Covid-19 denotes coronavirus disease 2019.

curred in 5 of 287,310 participants in the booster group and in 14 of 49,882 participants in the nonbooster group (adjusted hazard ratio, 0.13; 95% CI, 0.04 to 0.40; P<0.001) (Table S5).

Among female participants, death from Covid-19 occurred in 13 of 400,300 participants in the booster group and in 54 of 47,972 participants in the nonbooster group (adjusted hazard ratio, 0.06; 95% CI, 0.03 to 0.11; P<0.001) (Table S6). Among male participants, death from Covid-19 occurred in 52 of 357,818 participants in the booster group and in 83 of 37,118 participants in the nonbooster group (adjusted hazard ratio, 0.12; 95% CI, 0.08 to 0.18; P<0.001) (Table S7).

SECONDARY OUTCOME

During the study period, confirmed SARS-CoV-2 infection was observed in 2888 participants in the booster group and in 11,108 participants in the nonbooster group. The adjusted hazard ratio for SARS-CoV-2 infection in the booster group, as compared with the nonbooster group, was 0.17 (95% CI, 0.16 to 0.18; P<0.001) (Table S8).

Discussion

Our study showed that among participants who were 50 years of age or older and had received a second dose of the BNT162b2 vaccine at least 5 months earlier, those who received a booster had 90% lower mortality due to Covid-19 than those who did not receive a booster.

Israeli authorities approved the administration of a booster on July 30, 2021. In Israel, the decision to receive the booster is based entirely on personal preference. Delays in getting a booster may be related to logistic issues, including the ability to make an appointment at a convenient time and at a clinic close to home or at work. Delays in, or avoidance of, getting a booster may also be related to personal safety concerns. However, we found that by the end of our study period, most (90%) of the eligible persons 50 years of age or older had received the booster.

The waning vaccine effect that was observed in Israel and in other populations that had been vaccinated early[5,6,13,14] may occur in upcoming months in many other populations, in concordance with the timing of the first two doses of BNT162b2 in the mass vaccination campaign. Nevertheless, regulatory approval or recommendation of the booster, especially for participants younger than 65 years of age, is still under debate in many countries. The evidence generated in this study, which shows significant lifesaving potential from providing the booster, may help to resolve this issue.

The 90% lower mortality due to Covid-19 with the use of the booster is somewhat less substantial than the effect observed in a preliminary study based on data from the Israeli Ministry of Health,[15] which showed approximately 93% lower mortality due to Covid-19 with the booster. The difference could reflect the different study designs; the use of a 12-day lag time to ensure booster effectiveness in the Ministry of Health study, as compared with a 7-day lag time in our study; the 32-day follow-up period in the Ministry of Health study, which was considerably shorter than the 54-day follow-up period in our study; and our use of the CHS operational database to adjust for coexisting conditions.

The primary limitation of our study is the relatively short study period (54 days). However, during this time, the incidence of Covid-19 in Israel was one of the highest in the world.[2] Moreover, the social-distancing restrictions imposed on the public in Israel were limited. Therefore, exposure to SARS-CoV-2 was substantial, and accordingly, the number of deaths due to Covid-19 was sufficient to show a significant association between the use of the booster and lower mortality due to Covid-19.

Confounding sociodemographic and clinical characteristics may have led to bias in the analysis of effectiveness. We attempted to overcome such bias by adjusting for the variables known to affect mortality due to Covid-19. However, for some sources of bias, measurement or correction may not have been performed adequately.

Older participants (≥60 years of age) started to receive the booster earlier than younger participants (<60 years of age) and had higher mortality. This might have introduced bias in the estimation of survival, resulting in higher mortality in the booster group than would be expected in the overall study population. In addition, data from older participants were censored earlier in the survival analysis, as the participants were transitioned to the booster group. This may be a potential source of bias due to informative censoring. However, the inclusion of age as a covariate in the Cox regression model minimized such bias.

The main population sectors in Israel — the general Jewish population, Arab population, and ultra-Orthodox Jewish population — have different health-related behavioral patterns. Our analysis was adjusted for these subpopulations, but the adjustment did not significantly affect the study outcomes. This observation may be explained by the fact that all participants included in our study had chosen to receive the first two doses early in the vaccination campaign, and therefore, it is possible that they had similar health care–seeking behavior.

The incidence of Covid-19 and thus exposure to SARS-CoV-2 changed during the study period. However, we assume that after adjustment for all covariates, including socioeconomic status, these changes had a similar effect in the booster group and the nonbooster group.

Another major limitation of this study is the lack of data regarding serious adverse events. Future studies will be needed to assess the safety of the administration of the booster.

Finally, our findings are limited to the

BNT162b2 vaccine. Other vaccines have shown different patterns of waning immunity over time.[16] Ongoing research comparing the vaccines (e.g., a planned U.K. study[17]) may provide insight on this issue.

Despite these limitations, our study may provide meaningful answers to crucial questions regarding vaccination policy that remain partially unanswered by clinical trials.[18] Although this study is observational in nature, we believe that the significant findings and the observed potential for saving many lives could assist decision makers in assessing the benefit of providing the booster to broad populations, especially persons 50 years of age or older.

Our study showed that participants who received a booster at least 5 months after a second dose of BNT162b2 had 90% lower mortality due to Covid-19 in the short term than participants who did not receive a booster. However, studies with longer-term follow-up periods to assess the effectiveness and safety of the booster are still warranted.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Supplementary Appendix). Among adults who tested positive, those who were unvaccinated tended to be much younger, to have fewer coexisting conditions, and to have a lower socioeconomic status and were more likely to be men than those who were vaccinated; these differences tended to be especially pronounced in comparison with those who received the ChAdOx1 nCoV-19 vaccine (Table S2).

Overall, 201 deaths from Covid-19 were caused by SARS-CoV-2 that had been tested and found to be *S*-positive or *S*-negative (Table 1). Among persons 18 to 39 years of age who had infections for which data on *S* gene status were available, no deaths occurred among those who were fully vaccinated, as compared with 17 deaths among those who were unvaccinated. Among those who were 40 to 59 years of age, vaccine effectiveness against death from Covid-19 was 88% (95% confidence interval [CI], 76 to 93) for ChAdOx1 nCoV-19 and 95% (95% CI, 79 to 99) for BNT162b2; vaccine effectiveness was 90% (95% CI, 84 to 94) and 87% (95% CI, 77 to 93), respectively, among those 60 years of age or older. Overall, vaccine effectiveness against death from the delta variant 14 or more days after the second vaccine dose was 90% (95% CI, 83 to 94) for BNT162b2 and 91% (95% CI, 86 to 94) for ChAdOx1 nCoV-19 (Table S3).

A limitation of this study is the fact that it was based on an analysis of community samples. In addition, 1.8% of samples did not yield *S* gene categorization because of missing data in the Ct fields.

In summary, we found that the BNT162b2 and ChAdOx1 nCoV-19 vaccines offered substantial protection against death from Covid-19 caused by the delta variant.

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The data used to undertake this analysis are not publicly available because they are based on deidentified national clinical records. These data are available, subject to approval by the NHS Scotland Public Benefit and Privacy Panel, by application through the Scotland National Safe Haven. The R code used to perform this analysis is available from https://github.com/EAVE-II.

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Toxic Effects from Ivermectin Use Associated with Prevention and Treatment of Covid-19

TO THE EDITOR: Ivermectin is approved by the Food and Drug Administration as an oral treatment for intestinal strongyloidiasis and onchocerciasis and as a topical treatment for pediculosis and rosacea. It is also used as a treatment for parasites in pets and livestock. Ivermectin may decrease severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in vitro,[1,2] but randomized, controlled trials have shown no clinical benefit in the prevention or treatment of coronavirus disease 2019 (Covid-19).[3] Veterinary use of ivermectin has increased, and the number of prescriptions for use by humans in the United States is 24 times as high as the number before

the pandemic. Moreover, the number of such prescriptions in August 2021 was 4 times as high as the number in July 2021.[3,4]

The Oregon Poison Center is a telephone consultative center staffed by specialty-trained nurses, pharmacists, and physicians who provide treatment advice for the public and comprehensive treatment consultation for health care workers caring for patients in Oregon, Alaska, and Guam. The center has recently received an increasing number of calls regarding ivermectin exposure related to Covid-19. The rate of calls regarding ivermectin had been 0.25 calls per month in 2020 and had increased to 0.86 calls per month from January through July 2021; in August 2021, the center received 21 calls. Monthly total call volumes for all poison exposures were stable throughout 2020 and 2021.

Of the 21 persons who called in August, 11 were men, and most were older than 60 years of age (median age, 64; range, 20 to 81). Approximately half (11 persons) were reported to have used ivermectin to prevent Covid-19, and the remaining persons had been using the drug to treat Covid-19 symptoms. Three persons had received prescriptions from physicians or veterinarians, and 17 had purchased veterinary formulations; the source of ivermectin for the remaining person was not confirmed. Symptoms had developed in most persons within 2 hours after a large, single, first-time dose. In 6 persons, symptoms had developed gradually after several days to weeks of repeated doses taken every other day or twice weekly. One person had also been taking vitamin D to treat or prevent Covid-19. Reported doses ingested by the persons who had been using veterinary products ranged from 6.8 mg to 125 mg of 1.87% paste and 20 to 50 mg of the 1% solution. The dose of the human-use tablets was 21 mg per dose twice weekly for prevention.

Six of the 21 persons were hospitalized for toxic effects from ivermectin use; all 6 reported preventive use, including the 3 who had obtained the drug by prescription. Four received care in an intensive care unit, and none died. Symptoms were gastrointestinal distress in 4 persons, confusion in 3, ataxia and weakness in 2, hypotension in 2, and seizures in 1. Of the persons who were not admitted to a hospital, most had gastrointestinal distress, dizziness, confusion, vision symptoms, or rash.

These cases illustrate the potential toxic effects of ivermectin, including severe episodes of confusion, ataxia, seizures, and hypotension, and the increasing frequency of inappropriate use. There is insufficient evidence to support the use of ivermectin to treat or prevent Covid-19,[3] and improper use, as well as the possible occurrence of medication interactions,[5] may result in serious side effects requiring hospitalization.

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Benefits and Risks of Iron Interventions in Infants in Bangladesh

TO THE EDITOR: The randomized, placebo-controlled trial Benefits and Risks of Iron Interventions in Young Children (BRISC) (September 9 issue)[1] showed that 3 months of iron supplementation in infants reduced the prevalence of anemia but did not improve infant develop-