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Update on Adult Vaccinations in the ED with a Focus on SARS-CoV-2/COVID-19

In the late 1700s, Edward Jenner heard that milkmaids who frequently were exposed to cowpox seemed to be immune to smallpox (variola) infection. Many think that this is the first time patients were "vaccinated" against disease; however, there is evidence that inoculation with a needle dipped in the sores of a patient with smallpox may have started as early as 1000 AD.[1] Jenner did prove that immunity could be developed by injecting cowpox into subjects whom he later challenged with smallpox.[2] The Latin word for cow is vacca — thus, the medical term for vaccines.

Over recent decades, new advances in vaccination have altered the epidemiology of common infectious diseases. For instance, childhood meningitis caused by *Haemophilus influenzae* type B has been nearly eradicated in the United States since universal childhood vaccination against this pathogen began in 1991.[3] Likewise, chickenpox has been reduced 90% with the widespread uptake of varicella vaccination.[4] The last case of smallpox in the world was in 1980, and there are fewer than 100 cases of polio worldwide per year.[5]

Vaccinations in the Emergency Department

There are some emergency care providers who hold fast to the belief that emergency departments (EDs) are for emergencies only. Despite years of trying to dissuade patients from coming to the ED for "primary care," patients continue to seek care in the ED for perceived emergencies and for convenience. Studies have shown that, in addition to perceived urgency, patients come to the ED because of lack of access to healthcare and because of confidence in the emergency system. Despite all attempts, a portion of individuals in the United States will receive all or nearly all of their care in the ED.[6]

It is well-documented that rates of adult vaccination in the United States are lower than desired. For example, 2017-2018 Centers for Disease Control and Prevention (CDC) data show that only 49.2% of adults older than 6 months of age received the influenza vaccine.[7] This compares to goal rates of 70% vaccination under the Healthy People 2030 program.[7] This problem is not new, and a variety of methods have been studied to increase vaccine coverage rates in adults in both outpatient and inpatient settings.

Providing vaccines in the ED may be good public health; it meets patients where they are. Many, perhaps most, of the individuals (including children) who use the ED for primary care simply will not get immunized. Pediatric EDs have long screened for childhood immunizations and, in some cases, provided those immunizations to children during their ED visit. EDs routinely

EXECUTIVE SUMMARY

- Emergency departments have a unique role in public health. They care for a disproportionate number of patients who lack access to care in other venues. Emergency departments currently provide tetanus vaccines to millions of patients per year. Many emergency departments are expanding their role to provide COVID-19 vaccine to patients who might not receive it otherwise. Such programs can be carried out without interfering with emergency care for that patient or others in the department.
- Emergency departments also can play a role in decreasing vaccine hesitancy, providing information to patients on the vaccine, answering their questions, and correcting misinformation when it is present.
- Most of the side effects associated with the COVID-19 vaccines are mild — one to two days of fever, headache, or fatigue. These are most common on the second shot of those vaccines that require two injections. A very rare but serious side effect has been described four to 30 days following the Johnson & Johnson or AstraZeneca vaccines. Vaccine-induced thrombotic thrombocytopenia is similar in many ways to heparin-induced thrombocytopenia. It presents with signs of significant thrombosis, such as central venous sinus thrombosis. Heparin should be avoided. Platelet transfusion may increase clotting, and the physician should consider the risk/benefit to the patient. Patients can receive treatment with intravenous immune globulin and a non-heparin anticoagulant.
- Emergency departments should consider vaccine programs for other immunizations depending on their patient population and the local access to other sites. Many emergency departments provide influenza vaccine and some hepatitis A vaccine to specific high-risk populations.

provide tetanus immunizations to injured individuals whose tetanus status indicates or is unknown. Using the National Hospital Ambulatory Medical Care Surveys from 1992-2000, Palin et al estimated that EDs gave more than 27 million vaccinations, 93% against tetanus.[8]

One of the arguments against vaccination in the ED is loss of continuity. There is concern that patients may get vaccinated repeatedly because they have forgotten or are uncertain about a prior vaccination. In the ideal world, a patient's medical record would reside in a single source. Some states have created registries for childhood immunizations, but widespread use of such registries is not common for adults. In the past, patients would receive their immunizations at their primary care medical home. However, medical care is fragmented in today's world, with pharmacies giving up to 25% of influenza vaccines.[9] A generation of Americans has grown up using urgent care, pharmacies, and even EDs for their care.

There are several ways that EDs can play a role. A toolkit produced by the American College of Emergency Physicians (ACEP) outlines the process involved in greater detail.[10] First, emergency physicians, nurses, and other personnel should address vaccine hesitancy. There are some patients who are eager to get vaccinated and others who have determined they will never get vaccinated. Between those two groups are a large number of individuals who are hesitant, who have questions. Those questions can be addressed by healthcare providers. Patients who are vaccine hesitant often receive the vaccine after a conversation with a trusted healthcare provider or when their questions have been addressed. As already stated, the emergency department may be the only contact some patients have with the healthcare system. Tips for addressing vaccine hesitancy can be found on the CDC website (https://www.cdc.gov/vaccines/covid-19/vaccinate-with-confidence.html). In addition, ACEP has developed "smart phrases," which can be added to the a physician's electronic medical record repository and printed on a patient's discharge instruction sheet.[11] Because many of our patients are not native English speakers, smart phrases have been created in other languages by physician's fluent in those languages.

Some emergency departments have gone beyond just addressing vaccine hesitancy. There have been several successful ED-based vaccination programs in the United States.[12,13] These programs show that it is possible to screen patients and administer vaccine to appropriate patients without interrupting the care to the patient or to others in the department. With the current pandemic, there is a greater need for EDs to play a role in protecting the public health of our country. In most cases, EDs use the single-dose Johnson & Johnson vaccine, providing it to patients who are going to be discharged and who are seen for a non-acute-respiratory condition.

In neighborhoods where access to care is limited, some EDs have extended their vaccine program into the waiting room, offering vaccines to appropriate family and friends who accompany the patient. This often is done using non-emergency personnel and does not interfere with emergency treatment of patients.

Finally, because the public knows and trusts emergency care, there is the potential to use the ED entrance to welcome patients and direct them to adjacent vaccine administration sites. In addition, community paramedics can administer vaccines in the home to high-risk house-bound patients.[14]

Coronavirus Disease 2019 (COVID-19) Vaccines

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, first identified in Wuhan, China, in December 2019. Like other beta coronaviruses, such as Middle Eastern respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), these viruses originate from an animal reservoir. The main animal reservoir for SARS-CoV-2 likely is in bats; however, the exact intermediate host not been identified (the pangolin is a prime suspect). Reported

manifestations range from asymptomatic infection to severe illness and death. The most common symptoms include fevers/chills, cough, shortness of breath, fatigue, headache, new loss of taste or smell, sore throat, nausea or vomiting, and diarrhea.[15] Death rates from COVID-19 are variable but average about 1.7% in the United States, with half of all deaths occurring in those older than 80 years of age. At the time of this writing, it is estimated that more than 580,000 individuals have died from COVID-19 in the United States, and more than 3.2 million have died worldwide. The COVID-19 pandemic has been fueled in large part by the fact that asymptomatic persons are able to transmit the virus to contacts.

Controlling the pandemic will require a lowering of the number of cases as well as herd immunity. SARS-CoV-2, the virus that causes COVID-19, is a ribonucleic acid (RNA) virus. Like other RNA viruses, it is prone to mutate. The more virus present in a population, the more mutations that will occur and the greater the potential for increased virulence or resistance to natural or vaccine-induced antibodies. Natural immunity is protective for at least eight months in 95% of patients.[16]

At the time of this writing, there currently are three vaccines available and given emergency use authorizations (EUAs) by the Food and Drug Administration (FDA) in the United States: one manufactured by Pfizer-BioNTech named BNT162b2 (authorized Dec. 11, 2020), one manufactured by Moderna named mRNA-1273 (authorized Dec. 18, 2020), and one manufactured by Johnson & Johnson's Janssen named JNJ-78436735 (authorized Feb. 27, 2021).[17] (*See Table 1.*) Antibody levels after vaccination are higher than with natural immunity, leading to the recommendation that all individuals, including those with a history of COVID-19 infection, should be immunized.[18]

The Pfizer-BioNTech COVID-19 vaccine is indicated in individuals 16 years of age and older and must be administered as a two-dose series separated by 21 days. A two-dose regimen of BNT162b2 was noted to confer 95% protection against COVID-19 in persons 16 years of age or older with safety over a median of two months, similar to that of other viral vaccines.[19] This vaccine was recently approved for use in children 12-15 years of age.[20] Trials are ongoing to assess the safety in younger children.

Table 1. Comparison of COVID-19 Vaccines Given Emergency Use Authorization in the United States

	Pfizer-BioNTech	Moderna	Johnson & Johnson
Type	mRNA	mRNA	Modified adenovirus
Doses and administration (days apart)	2 doses; 0, 21 days apart	2 doses; 0, 28 days apart	1 dose
Emergency use authorization	Dec. 11, 2020	Dec. 18, 2020	Feb. 27, 2021
Efficacy	~95%	~94.1%	~85%
Age recommendations	16+ years	18+ years	18+ years

mRNA: messenger ribonucleic acid

The Moderna vaccine is indicated in individuals 18 years of age and older and must be administered in a two-dose series separated by 28 days. A two-dose mRNA-1273 vaccine showed 94.1% efficacy at preventing COVID-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified.[21] Currently, the series of COVID-19 vaccine is recommended to be completed with the same manufacturer and product.

The Advisory Committee on Immunization Practices (ACIP) convened on Dec. 1, 2020, and recommended that both healthcare personnel and residents of long-term care facilities be offered vaccination in the initial phase of the COVID-19 vaccination program.[22]

Unlike the vaccines manufactured by Pfizer-BioNTech and Moderna, the vaccine manufactured by Johnson & Johnson is a single-dose vaccine.[23] In a Phase III trial, Johnson & Johnson's vaccine candidate was found to be 85% effective overall in preventing moderate to severe COVID-19 by 28 days after vaccination.[24] Unlike the Pfizer-BioNTech and Moderna vaccines, which leverage messenger RNA (mRNA) technology, Johnson & Johnson's vaccine makes use of a modified adenovirus as a vector to express the antigen's genetic code.[25] The two authorized mRNA vaccines by Pfizer-BioNTech and Moderna are the first-of-a-kind vaccines that have strands of mRNA inside a special coating, enabling genetic material to directly enter dendritic cells and macrophages near the site of vaccination. Once inside the cell, the mRNA provides the blueprint for host cells to manufacture a "spike protein" unique to SARS-CoV-2.[26] It should be noted that only part of a protein is created, allowing it to be antigenic for the immune system without causing infection or direct harm. These proteins then are taken up by immune cells and displayed upon cell surfaces to trigger the immune system to produce antibodies.

The rollout of vaccines was done in phases, with healthcare workers receiving the vaccine first. With the increase in production, it appears there is now enough vaccine for the U.S. population, so all individuals now, or shortly, will be able to get the vaccine free at mass vaccine sites, health departments, physician offices, and pharmacies. While the United States has done well to vaccinate more than 151 million individuals,[27] other countries, such as Israel, have done better.

The need and timing for booster doses for any of the COVID-19 vaccines have not yet been established.

Side Effects of COVID-19 Vaccination

The most commonly reported side effects, which can last a few days, are pain at the injection site, headache, chills, joint pain, fatigue, and fever. There appear to be higher rates of side effects after the second dose compared to the first dose.[28] There have been a few cases of anaphylaxis (rate 2-11 per 1 million).[29,30] Many of these patients have a history of allergic reactions to vaccines in the past.

As far as contraindications, the Centers for Disease Control and Prevention (CDC) recommends that anyone with a severe allergic reaction after a previous dose of either mRNA COVID-19 vaccine should not receive another dose.[28] This also extends to individuals with immediate allergic reactions to components of these vaccines, such as polyethylene glycol or polysorbate. Although no trials in pregnant or breastfeeding women have been completed, there currently is no contraindication to receipt of either vaccine. It is recommended that pregnant or breastfeeding women should discuss their options with their healthcare providers. There are reports of anti-SARS-CoV-2-specific antibodies in the breast milk of vaccinated women.[31]

In March, vaccination with AstraZeneca's vaccine was halted due to a few cases of unusual clotting. In April, rare but serious clotting was reported with the Johnson & Johnson vaccine, which had recently received an EUA in the United States. The reports indicated a very rare side effect, seen four to 30 days after vaccination, with venous or arterial thrombosis (often cerebral or abdominal) associated with thrombocytopenia.[32] Cerebral sinus vein thrombosis (CVST) normally affects about two to five people in 1 million. However, the risk of CVST is about three to 15 times higher in women who receive the Johnson & Johnson vaccine. Blood clotting events are known to be associated adenoviral vectors.[33] Both the Johnson & Johnson and AstraZeneca vaccines are built on an adenoviral vector.

Table 2. Vaccine-Induced Thrombotic Thrombocytopenia

Symptoms
- Headache, severe
- Visual changes
- Severe abdominal pain
- Severe back pain
- Shortness of breath (signs of a pulmonary embolism)
- Swelling/pain in the leg (signs of deep vein thrombosis)
- Petechiae, ecchymosis

Diagnosis
- COVID-19 vaccine (Johnson & Johnson or AstraZeneca) four to 30 days previously
- Evidence of venous or arterial thrombosis
- Thrombocytopenia
- Platelet factor 4 heparin-induced thrombocytopenia enzyme-linked immunosorbent assay (PF4 HIT ELISA)

If suspected (signs/symptoms of serious thrombosis AND either positive imaging or low platelet, or both), seek consultation with a hematologist if possible. Avoid the use of heparin, avoid platelet transfusion if possible. Consider administration of intravenous immune globulin and nonheparin anticoagulation pending results of PF4 ELISA.

In many ways, vaccine-induced thrombotic thrombocytopenia resembles heparin-induced thrombotic thrombocytopenia (HIT). In HIT, antibodies form to platelet factor 4 (PF4). Activated platelets form a clot, leading to thrombocytopenia through consumption of platelets. Heparin is contraindicated. Platelet transfusion may increase clotting, and the risk/benefit of its use in a bleeding patient must be considered. (*See Table 2.*)

The syndrome vaccine-induced thrombotic thrombocytopenia is rare. Patients present with severe acute headache, severe diffuse abdominal pain, or signs of peripheral thrombosis (venous or arterial). Patients may have back pain, nausea, vomiting, vision changes, a change in mental status, shortness of breath, and/or evidence of bleeding or petechiae. Nearly all patients will have thrombocytopenia. A rare patient may present as their platelet count is falling but has not crossed into the thrombocytopenia range. Most patients also will have an elevated D-dimer and low fibrinogen. Antibodies to PF4 are seen in nearly 100% of cases (PF-4-heparin enzyme-linked immunosorbent assay [ELISA]); however, this test is not commonly available in the ED.

Imaging is performed to confirm clotting. Computed tomography angiography/computed tomography venography (CTA/CTV) is most useful for CVST and for abdominal clots; ultrasound may be more useful for peripheral clotting.

Heparin is contraindicated, but direct oral anticoagulants that do not require heparin lead-in, or fondaparinux can be used. Other low molecular-weight heparins are best avoided. Intravenous immune globulin (IVIG) has been recommended.[34] Early consultation with a hematologist is advised. Because this condition can be fatal, emergency physicians may consider starting treatment in the ED.

Variants

All RNA viruses mutate over time. The more virus in the area, the more likely a variant will emerge that is resistant to the vaccine. Current variants of concern include the B.1.351 (South Africa), the B.1.1.7 (UK), and the most recent B.1.1617 (India) variants, although it is likely that there are many more variants circulating at this time. (*See Table 3.*) Variants can be of concern because they are more contagious (B.1.1.7), more deadly (potentially B.1.617), or more resistant

Table 3. Selected Characteristics of SARS-CoV-2 Variants of Concern+

Name (Pango lineage)[a]	Spike Protein Substitutions	Name (Nextstrain)[b]	First Detected	BEI Reference Isolate[c]	Attributes[d]
B.1.1.7	Δ69/70, Δ144, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*)	20I/501Y.V1	United Kingdom	NR-54000	• ~50% increased transmission[1] • Potential increased severity based on hospitalizations and case fatality rates[2] • No impact on susceptibility to EUA monoclonal antibody treatments[3,4] • Minimal impact on neutralization by convalescent and post-vaccination sera[5,6,7,8,9,10,11]
P.1	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	20J/501Y.V3	Japan/ Brazil	NR-54982	• Significant decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment,[3] but other EUA monoclonal antibody treatments are available[4] • Reduced neutralization by convalescent and post-vaccination sera[12]
B.1.351	D80A, D215G, Δ241/242/243, K417N, E484K, N501Y, D614G, A701V	20H/501.V2	South Africa	NR-54009	• ~50% increased transmission[13] • Significant decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment,[3] but other EUA monoclonal antibody treatments are available[4] • Reduced neutralization by convalescent and post-vaccination sera[5,9,11,14,15]
B.1.427	L452R, D614G	20C/S:452R	United States-(California)		• ~20% increased transmissibility[16] • Modest decrease in susceptibility to the combination of bamlanivimab and etesevimab; however, the clinical implications of this decrease are not known.[3] Alternative monoclonal antibody treatments are available.[4] • Reduced neutralization by convalescent and post-vaccination sera[16]
B.1.429	S13I, W152C, L452R, D614G	20C/S:452R	United States-(California)		• ~20% increased transmissibility[16] • Modest decrease in susceptibility to the combination of bamlanivimab and etesevimab; however, the clinical implications of this decrease are not known.[3] Alternative monoclonal antibody treatments are available.[4] • Reduced neutralization by convalescent and post-vaccination sera[16]

(*Continued*)

Table 3. Selected Characteristics of SARS-CoV-2 Variants of Concern+ (*continued*)

(*) = detected in some sequences but not all

+These variants share one specific mutation called D614G. This mutation was one of the first documented in the US in the initial stages of the pandemic, after having initially circulated in Europe[10]. There is evidence that variants with this mutation spread more quickly than viruses without this mutation [9].

a – Phylogenetic Assignment of Named Global Outbreak (PANGO) Lineages is software tool developed by members of the Rambaut Lab. The associated web application was developed by the Centre for Genomic Pathogen Surveillance in South Cambridgeshire and is intended to implement the dynamic nomenclature of SARS-CoV-2 lineages, known as the PANGO nomenclature.

b – Nextstrain, a collaboration between researchers in Seattle, USA and Basel, Switzerland, provides open-source tools for visualizing the genetics of outbreaks. The goal is to support public health surveillance by facilitating understanding of the spread and evolution of pathogens.

c – The Biodefense and Emerging Infections Research Resources (BEI Resources) is a NIAID-funded repository to provide reagents, tools, and information to the research community. The reference viruses proposed here facilitate the harmonization of information among all stakeholders in the COVID-19 pandemic research community. Please note that the reference viruses provided in the tables below are based on what is currently available through the BEI resources.

d – Attributes listed are based on data available from pseudoviruses or recombinant viruses containing combinations of substitutions characteristic of specific lineages or from reference virus isolates.

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*Non-peer-reviewed

Source: Centers for Disease Control and Prevention.

to current vaccines. The Moderna and Pfizer vaccines create antibodies to the "spike" protein used by the virus to gain entry into the cell. Mutations around the spike protein area may lead to decreased recognition of the protein and, therefore, less effectiveness of the vaccine. However, in studies done in vitro, all current vaccines produce neutralizing antibodies to these variants.[35] However, as discussed in the reference, it is not clear how much antibody is enough to prevent illness. For now, the news is good from countries with a high percentage of the population

immunized. Decreases in hospitalization have occurred in Israel, the United Kingdom, and the United States since January.

Yet even with this good news, it is probably too early to say the pandemic is over. Much of the world has yet to receive the vaccines, particularly the entire continent of Africa. As of this writing, cases have soared in India. Given the population density there, emergence of additional variants is very likely. It is likely that a booster will be necessary in the future.

There is also concern that the United States will never attain herd immunity.[36] Epidemiologists now warn that COVID likely will become a chronic infection and continue to circulate in the United States for years to come. It is likely that yearly vaccines will be needed, and these may be bundled with the influenza vaccine.

Other Vaccines for the ED Population

Influenza Vaccine

Influenza A and B cause annual epidemics worldwide, with severity determined by the degree of change in the hemagglutinin and, to a lesser degree, the neuraminidase antigens on the viral surface. Since 1968, the predominant strains have been H3N2, but a pandemic occurred in 2009, with an antigenic shift to the H1N1 (swine flu) strain.[37] During interpandemic years, there is antigenic drift such that the prior year's vaccine is unlikely to remain effective. Thus, influenza vaccination is recommended annually for all adults in the United States who lack a contraindication. The currently available vaccines include trivalent and quadrivalent intramuscular and intradermal preparations, as well as a high-dose form and a newer recombinant form that has no ovalbumin and, therefore, is safe for use in patients with severe egg allergies.[38] The ACIP does not state a preference of which vaccine should be given, although some experts favor high-dose influenza vaccination for those ≥ 65 years of age,[39] since the efficacy may be better in this group. A live attenuated influenza vaccine that has been approved for use in those ages 2-49 years no longer is recommended, since preliminary data show only 3% protective efficacy vs. 63% efficacy of the standard inactivated vaccines in children ages 2-17 years.[40] In adults, the efficacy of influenza vaccination depends on the status of the host as well as how well-matched the vaccine is with circulating strains. A recent meta-analysis determined the vaccine efficacy to be 60% in healthy adults,[41] whereas studies in human immunodeficiency virus (HIV)-infected patients suggest efficacy to prevent laboratory-confirmed influenza may be as high as 71% to 85%.[42] The currently marketed influenza vaccines are extremely safe, with the most common side effect being pain at the injection site. Prior anaphylaxis to an influenza vaccine (which is a rare event) is the only absolute contraindication. As noted earlier, those with severe egg allergy can receive the recombinant influenza vaccine. The swine flu vaccine given in 1976 led to an increase in cases of Guillain-Barré syndrome (GBS), but a recent study suggests the current vaccine leads to very small increased rates of GBS that are lower than the rate of GBS seen after naturally occurring influenza infection.[43]

Tetanus, Diphtheria, and Pertussis

For several decades, the recommendation for diphtheria/tetanus (Td) vaccination in adults simply was for booster shots every 10 years. Although rare in the United States, tetanus is most common in older adults whose immunity has waned as a result of lack of receipt of the Td booster. Although diphtheria also remains rare in the United States, epidemics have occurred overseas in recent years. Vaccine refusal is one of the factors leading to a resurgence of pertussis in children and adults.[44] This resurgence has led to a revision of the recommendations, since the Td booster does not protect against pertussis.

The ACIP now recommends one tetanus/diphtheria/acellular pertussis (Tdap) booster for all adults in the United States, followed by Td boosters every 10 years. Special consideration regarding Td boosters applies for tetanus-prone wounds. All patients who have received fewer than three doses of tetanus-containing vaccine should receive a booster. Those in this category with major tetanus-prone wounds also should receive tetanus immune globulin administered at a different site. Fully vaccinated patients with minor wounds only require a booster if the most recent tetanus-containing vaccine was given more than 10 years previously, while those with major wounds should receive a booster if their last dose was given more than five years previously. Neither of these groups requires tetanus immune globulin.[45]

As per the general ACIP recommendations, if adult patients with wounds in need of a booster have not had the Tdap, then this preparation should be given. Pain at the injection site is the most common side effect of Tdap vaccine in adults. Low-grade fever is relatively common, while a higher grade fever of > 102˚F is more common among children. The acellular pertussis vaccine has fewer side effects than the older whole-cell pertussis vaccines. The use of Tdap vaccines in pregnant women is discussed later in this article.

Vaccinations for Special Adult Populations

Hepatitis A Vaccine

Hepatitis A virus does not cause chronic disease, but acute infection produces a miserable illness characterized by nausea, malaise, and, occasionally, severe liver dysfunction. Although less common in the United States than in developing countries, the virus is transmitted via the fecal-oral route, so everyone is at risk. Most infections are transmitted by food handlers, so common source outbreaks occur. The vaccine is recommended for patients with chronic liver disease, including hepatitis B or C infections; men who have sex with men; intravenous (IV) drug users; and travelers. For the latter group, the first injection provides protection for a trip, but a second shot six months after the first completes the series and provides prolonged protection.[46] If more than six months has elapsed between doses, the series does not need to be restarted; the second shot is sufficient. Soreness at the injection site is the most common side effect of this vaccine. Severe reactions are extremely uncommon.

Outbreaks of hepatitis A in homeless populations have been described throughout the United States. The CDC has advised vaccination for high-risk groups, and some EDs have provided vaccination during an ED visit.[47] Like other ED-based vaccination programs, pharmacists can be used to provide the vaccination, reducing interference with emergency care.

Hepatitis B Vaccine

Hepatitis B vaccine is generally not given in the ED because it requires follow-up visits, which may be difficult to schedule for the homeless and others at risk. However, where there is the potential for follow-up, patients can start their immunization in the ED. The hepatitis B vaccine is highly effective at preventing infection, as evidenced by the epidemiology of hepatitis B infection in healthcare workers, all of whom are vaccinated. Hepatitis B is much more transmissible than hepatitis C or HIV, but there has been an approximate 30-fold reduction in hepatitis B infections among healthcare workers since universal vaccination began.[48] However, rates of vaccination in other adults are low, and those who were not vaccinated in childhood remain at risk via sexual exposure or the sharing of needles used for IV drug injection.[49] Although a large proportion of patients with acute hepatitis B clear the infection spontaneously, those who develop chronic infection are at risk of progressing to cirrhosis or developing hepatocellular carcinoma. Given the safety of this vaccine, the high burden of disease, and the ease of transmission, the hepatitis B vaccine now is a routine childhood vaccine. Adults who should be vaccinated are described in Table 4.

The hepatitis B vaccine is given as a series of three injections over six months, alone or in combination with the hepatitis A vaccine. Response rates are high, although not universal, and titers should be drawn after vaccination of healthcare workers or others with ongoing risk, such as IV drug users or hemodialysis patients. In general, nonresponders require an additional three-dose series. Severe adverse reactions to hepatitis B vaccination are rare.[50]

Table 4. Persons Who Should Be Vaccinated Against Hepatitis B

- Healthcare workers
- Patients with end-stage renal disease or liver disease who are not immune, people with diabetes (depending on risk)
- Intravenous drug users and their sexual partners who are not immune
- Public safety workers at risk for blood and body fluid exposure
- Men who have sex with men
- Patients in a sexually transmitted disease treatment center
- Household contacts of patients with hepatitis B surface antigen positivity
- Adults with multiple sexual partners

COVID-19 Vaccinations for Immunosuppressed Patients

While the current COVID-19 vaccines are highly effective, there is only preliminary evidence of their effectiveness in immunosuppressed patients. Although up to 3% of individuals may have impaired immune systems, patients who are labeled "immunosuppressed" may be very different.

To date, it appears that patients with immunosuppression can safely receive vaccines. However, the effectiveness of those vaccines still is being determined. Patients with significant immunosuppression were excluded from vaccine trials. Chemotherapy, radiation, anti-rejection drugs, and others suppress the immune response from other vaccines, such as influenza. Other illnesses, such as Waldenstrom's macroglobulinemia, may produce ineffective immunoglobulins, leaving the patient susceptible to infection. It is likely this will be the case with COVID-19 vaccines as well. An early study suggests patients with solid tumors on immunosuppressive medications may have an antibody response that is less than that seen in normal patients. Nonetheless, vaccines should be administered to these patients.[51]

Vaccinations for Patients with Chronic Diseases

Patients with end-stage renal disease,[52] chronic liver disease, and diabetes all should be vaccinated against hepatitis B if not already immune, whereas this is not universally needed for those patients with chronic cardiopulmonary diseases and alcoholism. Non-immune patients with chronic liver disease also should receive the hepatitis A vaccine series.

Vaccinations for Pregnant Women

Pregnancy is a relatively immunocompromising state and, as such, live vaccines, such as the measles, mumps, rubella (MMR) and varicella vaccines, are contraindicated. Despite this recommendation, fetal infection in women who inadvertently were given a dose of MMR has never been documented.[53]

Influenza vaccine should be given to all pregnant women lacking a contraindication during the season when the vaccine is available. In addition, protection against diphtheria, pertussis, and tetanus is essential in pregnant women. Although diphtheria has re-emerged mainly outside of the United States, pertussis (whooping cough) has had a significant resurgence here this decade, affecting both young children and adults.[54] Guidelines now recommend that all pregnant women be vaccinated against these pathogens. Those women who have not completed the vaccine series previously should have a full three-shot series, including one dose of the Tdap. All previously vaccinated pregnant women should have a Tdap booster with each pregnancy, even when there is a short time interval between pregnancies, since young infants need maternal antibody for protection during the first six months of life.[55]

The COVID-19 vaccine appears to be safe for pregnant women, although large studies are not yet completed. The CDC guidance can be found at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html. On the other hand, women who

contract COVID-19 during pregnancy are at greater risk.[56]

Vaccinations for Healthcare Workers

Well-established guidelines have been published for the vaccinations recommended (and often required) for healthcare personnel.[57] All healthcare workers should be vaccinated against hepatitis B, since this is the most transmissible virus in healthcare settings. Annual influenza vaccination also is critical for healthcare workers.

At this point in time, vaccination against SARS-CoV-2 also is strongly recommended to contain the current COVID-19 pandemic. It remains to be seen when and if booster vaccinations may be necessary.

Measles can be transmitted via an airborne route, and outbreaks have occurred in hospital settings in the United States. Since immunity from childhood vaccines often wanes, the MMR is recommended for nonimmune healthcare workers.[53]

All healthcare personnel also should be updated with the Tdap if they have not had this formulation previously. Immunity against varicella is important for healthcare workers, since this is an airborne virus and also because severe disease can ensue in adults.

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CME/CE Questions

1. A female patient presents with a mild headache for the past 24 hours. She received her first shot of the Moderna COVID-19 vaccine 36 hours ago. She heard on the news that people can get blood clots after vaccination and is worried. Of the following, which is the best course of action?
   a. Obtain a platelet count and, if normal, discharge the patient.
   b. Order a computed tomography angiography/computed tomography venography of the head.
   c. Order a D-dimer.
   d. Reassure the patient.
2. Which of the following vaccines is associated with vaccine-induced thrombotic thrombocytopenia?
   a. Moderna COVID
   b. Pfizer COVID
   c. Johnson & Johnson COVID
   d. Influenza
3. Which of the following is true regarding anaphylactic reactions to the Moderna and Pfizer COVID-19 vaccines?
   a. Anaphylactic reactions are seen most commonly in patients with a history of vaccine allergies.
   b. Anaphylactic reactions are seen most commonly in patients with egg allergy.
   c. Anaphylactic reactions are seen most commonly in patients older than the age of 65 years.
   d. Anaphylactic reactions are resistant to treatment with epinephrine.
4. Which of the following increases the risk of mutation by SARS-CoV-2?
   a. Humid conditions
   b. Increased number of cases
   c. Sunlight
   d. Hydroxychloroquine
5. Tetanus/diphtheria/acellular pertussis (Tdap) is now recommended at least one time in adulthood because:
   a. Tetanus is becoming more prevalent in the United States.
   b. Diphtheria immunity wanes over time.
   c. The bacteria that causes diphtheria has mutated.
   d. Tdap is cheaper than other vaccines for tetanus.
6. Which of the following would best indicate the presence of vaccine-induced thrombotic thrombocytopenia?
   a. A low D-dimer
   b. A low red cell count
   c. A low platelet count
   d. An elevated fibrinogen
7. Treatment for vaccine-induced thrombotic thrombocytopenia should be started in the emergency department. Which of the following is the best "cocktail" for this disorder?
   a. Intravenous immune globulin (IVIG) and a direct-acting anticoagulant
   b. IVIG and platelet transfusion
   c. Platelet transfusion and heparin
   d. Heparin and high-dose aspirin

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- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

Correction

In the May 15, 2021, issue, the executive summary included an incorrect definition of the shock index. The shock index is defined as heart rate ÷ systolic blood pressure. The issue has been updated online.

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Update on Adult Vaccinations in the ED with a Focus on SARS-CoV-2/COVID-19

Comparison of COVID-19 Vaccines Given Emergency Use Authorization in the United States

	Pfizer-BioNTech	Moderna	Johnson & Johnson
Type	mRNA	mRNA	Modified adenovirus
Doses and administration (days apart)	2 doses; 0, 21 days apart	2 doses; 0, 28 days apart	1 dose
Emergency use authorization	Dec. 11, 2020	Dec. 18, 2020	Feb. 27, 2021
Efficacy	~95%	~94.1%	~85%
Age recommendations	16+ years	18+ years	18+ years

mRNA: messenger ribonucleic acid

Vaccine-Induced Thrombotic Thrombocytopenia

Symptoms
- Headache, severe
- Visual changes
- Severe abdominal pain
- Severe back pain
- Shortness of breath (signs of a pulmonary embolism)
- Swelling/pain in the leg (signs of deep vein thrombosis)
- Petechiae, ecchymosis

Diagnosis
- COVID-19 vaccine (Johnson & Johnson or AstraZeneca) four to 30 days previously
- Evidence of venous or arterial thrombosis
- Thrombocytopenia
- Platelet factor 4 heparin-induced thrombocytopenia enzyme-linked immunosorbent assay (PF4 HIT ELISA)

If suspected (signs/symptoms of serious thrombosis AND either positive imaging or low platelet, or both), seek consultation with a hematologist if possible. Avoid the use of heparin, avoid platelet transfusion if possible. Consider administration of intravenous immune globulin and nonheparin anticoagulation pending results of PF4 ELISA.

Persons Who Should Be Vaccinated Against Hepatitis B

- Healthcare workers
- Patients with end-stage renal disease or liver disease who are not immune, people with diabetes (depending on risk)
- Intravenous drug users and their sexual partners who are not immune
- Public safety workers at risk for blood and body fluid exposure
- Men who have sex with men
- Patients in a sexually transmitted disease treatment center
- Household contacts of patients with hepatitis B surface antigen positivity
- Adults with multiple sexual partners

Selected Characteristics of SARS-CoV-2 Variants of Concern+

Name (Pango lineage)[a]	Spike Protein Substitutions	Name (Nextstrain)[b]	First Detected	BEI Reference Isolate[c]	Attributes[d]
B.1.1.7	Δ69/70, Δ144, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*)	20I/501Y.V1	United Kingdom	NR-54000	• ~50% increased transmission[1] • Potential increased severity based on hospitalizations and case fatality rates[2] • No impact on susceptibility to EUA monoclonal antibody treatments[3,4] • Minimal impact on neutralization by convalescent and post-vaccination sera[5,6,7,8,9,10,11]
P.1	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	20J/501Y.V3	Japan/ Brazil	NR-54982	• Significant decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment,[3] but other EUA monoclonal antibody treatments are available[4] • Reduced neutralization by convalescent and post-vaccination sera[12]
B.1.351	D80A, D215G, Δ241/242/243, K417N, E484K, N501Y, D614G, A701V	20H/501.V2	South Africa	NR-54009	• ~50% increased transmission[13] • Significant decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment,[3] but other EUA monoclonal antibody treatments are available[4] • Reduced neutralization by convalescent and post-vaccination sera[5,9,11,14,15]
B.1.427	L452R, D614G	20C/S:452R	United States- (California)		• ~20% increased transmissibility[16] • Modest decrease in susceptibility to the combination of bamlanivimab and etesevimab; however, the clinical implications of this decrease are not known.[3] Alternative monoclonal antibody treatments are available.[4] • Reduced neutralization by convalescent and post-vaccination sera[16]
B.1.429	S13I, W152C, L452R, D614G	20C/S:452R	United States- (California)		• ~20% increased transmissibility[16] • Modest decrease in susceptibility to the combination of bamlanivimab and etesevimab; however, the clinical implications of this decrease are not known.[3] Alternative monoclonal antibody treatments are available.[4] • Reduced neutralization by convalescent and post-vaccination sera[16]

(*) = detected in some sequences but not all

+These variants share one specific mutation called D614G. This mutation was one of the first documented in the US in the initial stages of the pandemic, after having initially circulated in Europe[10]. There is evidence that variants with this mutation spread more quickly than viruses without this mutation [9].

a – Phylogenetic Assignment of Named Global Outbreak (PANGO) Lineages is software tool developed by members of the Rambaut Lab. The associated web application was developed by the Centre for Genomic Pathogen Surveillance in South Cambridgeshire and is intended to implement the dynamic nomenclature of SARS-CoV-2 lineages, known as the PANGO nomenclature.

b – Nextstrain, a collaboration between researchers in Seattle, USA and Basel, Switzerland, provides open-source tools for visualizing the genetics of outbreaks. The goal is to support public health surveillance by facilitating understanding of the spread and evolution of pathogens.

c – The Biodefense and Emerging Infections Research Resources (BEI Resources) is a NIAID-funded repository to provide reagents, tools, and information to the research community. The reference viruses proposed here facilitate the harmonization of information among all stakeholders in the COVID-19 pandemic research community. Please note that the reference viruses provided in the tables below are based on what is currently available through the BEI resources.

d – Attributes listed are based on data available from pseudoviruses or recombinant viruses containing combinations of substitutions characteristic of specific lineages or from reference virus isolates.

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