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The Flu Doesn't Stand a Chance

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Along with COVID-19, seasonal influenza is among us in the United States as it typically peaks between the months of December and February. The Centers for Disease Control and Prevention (CDC) recommends that all individuals greater than 6 months of age receive an annual flu vaccine for protection against the flu.[1] However, even after taking the recommended precautions, some individuals can still contract this contagious, respiratory virus. The CDC recommends people who are hospitalized; have severe, complicated or progressive illness; or are at a higher risk of flu complications receive antiviral therapy as soon as possible, ideally within 48 hours of symptom onset.[1] The CDC does not recommend routine post exposure antiviral to all outpatients. Antiviral medications can shorten the duration of the flu and reduce the risk of severe outcomes. There are several antiviral therapies available. Which one may be appropriate to prescribe for your patient?

Currently there are four antiviral therapies in the United States approved for treatment or prophylaxis of influenza during the 2020–2021 flu season: oral oseltamivir (Tamiflu®), inhaled zanamivir (Relenza®), intravenous peramivir (Rapivab®), and oral baloxavir (Xofluza®).[1] People who are not hospitalized can be prescribed oseltamivir, zanamivir, or baloxavir. The prodrug of oseltamivir, oseltamivir carboxylate, and zanamivir have the same mechanism of action in which they inhibit the influenza enzyme, neuraminidase, which cleaves the budding viral progeny from its cellular envelope attachment point prior to releasing.[2] Baloxavir marboxil is a prodrug of baloxavir which inhibits influenza replication by inhibiting the endonuclease activity of a selective polymerase acidic (PA) protein, which is needed in viral gene transcription.[2] The main difference between the neuraminidase inhibitors and baloxavir is the point of viral replication inhibition. Neuraminidase inhibitors block the last step in viral replication, while baloxavir inhibits a step early on in the replication process. Based on the step baloxavir inhibits, there is a smaller viral load and less viral shedding which explains why only one dose is needed.[2] It is hypothesized that due to the decrease in viral replication there is also a decrease in the transmission of the virus, however more studies are needed to confirm this association.[3]

People who have a high risk of flu complications include:[1]

- Children under the age of 2 years old
- Pregnant women and women up to 2 weeks postpartum
- Adults 65 years and older
- American Indians and Alaska Natives
- People living in long-term-care or nursing homes
- Individuals with chronic lung disease (COPD, asthma, cystic fibrosis)
- Obese individuals with BMI ≥40
- Heart disease
- Endocrine disorders such as diabetes
- Kidney or liver disorders
- Metabolic disorders
- Neurological and neurodevelopmental conditions
- People younger than 19 years old on chronic aspirin/salicylate containing medications
- People with weakened immune systems due to disease or medications (HIV, AIDS, cancer, chemotherapy, radiation, corticosteroids)

The CDC recommends the use of oral oseltamivir as soon as possible, or within 48 hours of symptom onset, for outpatients with complications or progressive disease, such as pneumonia or exacerbation of an underlying health condition, who are suspected to have or have a confirmed case of influenza. However, for otherwise healthy outpatients with suspected or confirmed cases of acute, uncomplicated influenza, the CDC does not recommend one antiviral therapy over the other, though treatment options depend on approved age groups.[1]

According to the CDC, neuraminidase inhibitor antivirals are approximately 70% to 90% effective in preventing against susceptible influenza viruses after an individual has been exposed to the virus.[1] Over the years, influenza viruses have developed resistance to neuraminidase inhibitors making this antiviral treatment less effective in certain circumstances.[3] Conversely, resistance has not developed to baloxavir due to the different mechanism of action.[2] In the CAPSTONE-2 study, it was found that the median time to improvement of influenza symptoms (TTIIS) is shorter with baloxavir than with placebo (73.2 h [95% CI 67.2-85.1] vs 102.3h [92.7-113.1]; p<0.0001). The study also revealed that the median TTIIS with oseltamivir was similar to baloxavir (81.0 h [95% CI 69.4 – 91.5] vs 73.2 h [95% CI 67.2-85.1]), however the TTIIS was significantly shorter in the baloxavir group than the oseltamivir group in individuals with the influenza B virus (27.1 h [6.9-42.3]; p = 0.025). Therefore, if patients are found to have an influenza B virus that is resistant to neuraminidase inhibitors, baloxavir would be a safe and effective alternative.

In conclusion, the CDC recommends that all outpatients with complications or progressive disease with a suspected or confirmed case of influenza receive treatment or post exposure chemoprophylaxis within 48 hours of symptom onset with oral oseltamivir. All outpatients with uncomplicated influenza can receive treatment or post exposure chemoprophylaxis within 48 hours of symptom onset with any of the three antivirals. Though it should be noted that baloxavir should be avoided in certain patient populations including pregnant women or breastfeeding mothers, and immunocompromised patients due to lack of safety data.

Antiviral Agent	Activity Against	Use	Recommended for	Not Recommended for	Dosage and Duration	Adverse Events
Tamiflu® (oseltamivir phosphate)	Influenza A and B	Treatment	Any age	N/A	Adults: 75 mg BID x 5 days If younger than 1 year old: 3mg/kg/dose BID x 5 days If 1 year or older, dose varies on child's weight: ≤15 kg: 30mg BID x 5 days >15 – 23 kg: 45mg BID x 5 days >23 – 40 kg: 60mg BID x 5 days >40 kg: 75mg BID x 5 days	Nausea, vomiting, headache, skin reactions, and sporadic, transient neuro-psychiatric events
		Chemo-prophylaxis	3 months and older	N/A	3 months up to 1 year of age: 3mg/kg/dose once daily x 7 days If 1 year or older, the dose depends on child's weight: > 15 – 23kg: 45 mg once daily x 7 days >23-40 kg: 60 mg once daily x 7 days >40kg: 75 mg once daily x 7 days	
Relenza® (zanamivir)	Influenza A and B	Treatment	7 years and older	People with underlying respiratory disease (asthma, COPD)	Adults: 10 mg BID x 5 days Children 7 years and older: 10 mg BID x 5 days	Diarrhea, serious skin reactions, and sporadic, transient neuro-psychiatric events
		Chemo-prophylaxis	5 years and older	People with underlying respiratory disease (asthma, COPD)	Adults: 10 mg once daily x 7 days Children 5 years and older: 10 mg once daily x 7 days	
Xofluza® (baloxavir marboxil)	Influenza A and B	Treatment	12 years and older	N/A	12 years or older: <80 kg: One 40 mg x 1 dose ≥80kg: one 80 mg x 1 dose	None that are more common than placebo in clinical trials
		Chemo-prophylaxis	12 years and older (post-exposure prophylaxis)	N/A		

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Racing Towards a Vaccine for COVID-19 –What Do We Know So Far?

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The COVID-19 pandemic has been a world-changing event, claiming an estimated 1.8 million lives globally as of January, 2021.[1] Coronavirus disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ranges in severity from asymptomatic cases to symptoms of fever, cough, fatigue, loss of smell and taste, and respiratory failure in the most severe cases. Although strides have been made in antiviral and supportive pharmacological care, there remains no cure for COVID-19. However, several candidates have been approved for use or have entered phase III trials with promising outcomes.[2,3]

COVID-19 has ignited a growing field of next-generation vaccines which use mRNA to facilitate immunity. These mRNA vaccines work by encoding for the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2, which allows the virus to attach to cells and propagate in the body. After inoculation with CoV-2 mRNA, the genetic material is translated into the protein, whereupon it elicits an immune response. This immune response creates the desired immunity for SARS-CoV-2, preventing the virus from attaching and replicating after the inoculation of the host.[3] The fragility of mRNA within the vaccine candidates requires an uninterrupted cold chain to be maintained, complicating the logistics of the vaccine's distribution. However, mRNA vaccines have the advantage of a production process in a cell-free system, using only a DNA template, which precludes growing large amounts of SARS-CoV-2 in a laboratory setting and/or using egg cultures which may introduce allergens into the vaccine manufacturing process.

There is an inherent difficulty in conducting vaccine trials during a global pandemic. A criticism of each of the following trials is the lack of diversity in patient groups. For instance, both the Moderna and AstraZeneca COVID-19 vaccines excluded children and adolescents, immunocompromised patients, pregnant women, and other patient groups which may otherwise be at increased risk for coronavirus infection, while the Pfizer vaccine enrolled patients 12 years and older.[2-4] Given the considerable spread of COVID-19 among vulnerable populations and the severity of COVID-19 cases in patients 65 years and older, significant research and post-marketing surveillance (phase IV) trials are necessary to determine safety and efficacy in these cohorts. Until then, clinical judgment analyzing the risks and benefits of COIVD-19 vaccination will be essential in selecting which patients with preexisting conditions should be vaccinated.

Furthermore, minority populations are historically underrepresented in vaccine trials, the SARS-CoV-2 vaccine trials notwithstanding. The Moderna vaccine trials were slowed to improve enrollment from "diverse communities" in the United States, thereupon accruing over one third (37%) of participants from communities of color, while the Pfizer and AstraZeneca vaccines sought to mitigate demographic bias by enrolling patients from multiple countries across Europe, Argentina, Brazil, and South Africa.[5] Regardless of this push for diversity in investigation, the need for further study in minority communities and high risk populations remains. People identifying as Black or African American in the United States are almost three times more likely to be infected with COVID-19 than their Caucasian American neighbors.[6] Phase IV trials may provide a clearer picture of the safety and efficacy of the vaccines in populations which are disproportionately affected by the coronavirus pandemic. That being said, all three vaccines developed by Pfizer, Moderna, and AstraZeneca show promise and efficacy in disease mitigation efforts.

The first vaccine candidate approved by the FDA for emergency use authorization is the BNT162b2 vaccine, an mRNA vaccine developed by Pfizer and BioNTech.[4] Phase I and II trials concluded that the two dose vaccine series 21 days apart in men and non-pregnant women ages 18-55 produced a favorable tolerability and safety profile.[7] The most common side effects exhibited in the seven days after vaccination were mild to moderate injection site pain, fatigue, and headache. Fever and chills, in addition to muscle and joint pain, were reported in ~8% of patients, generally resolving one day post-vaccination. The ongoing Phase III trial for the BNT162b2 vaccine has an estimated enrollment of just under 44,000 participants, examining low dose, mid dose, and high dose vaccine versus placebo.[4] Of the 170 confirmed cases of COVID-19 observed, 162 cases were in the placebo group vs. 8 cases in the vaccinated group; Pfizer's data suggests the vaccine is 95% effective 28 days after the second dose of BNT162b2.[8]

Of the three vaccines, Pfizer and BioNTech have the most people aged 56-85 years enrolled in trial proportionately (41% globally and 45% in the United States), making it perhaps the most extensively tested mRNA vaccine in geriatric populations. Given a wide-ranging distribution strategy, possible logistical challenges include the distribution of the vaccine, which must be stored and transported with dry ice at -70°C (-94°F) ±10°C (±18°F).[5,8,9] Once delivered, the vaccine will have a refrigeration shelf life of only five days at 2° to 8°C (36° to 46°F).[9] The temperature storage requirements will require the vaccine to be distributed via mass immunization clinics at specialized facilities in lieu of a vaccination effort organized in individual communities without access to long-term cold storage facilities. As of January, 2021, the United States has ordered 200 million doses of this vaccine, enough to vaccinate a maximum population of 100 million Americans.[10]

The next vaccine approved for use in the United States is the mRNA-1273 vaccine, developed by Moderna and United States National Institutes of Health (NIH). This eponymous mRNA vaccine has a similar mechanism of action to its Pfizer alternative and boasts a 94.5% efficacy rate in preliminary phase III trial data.[2,11-13] Over 30,000 participants were enrolled in the phase III trial after preliminary trials indicating safety and efficacy in patients receiving a two dose COVID vaccine series 28 days apart.[13] Of those 30,000 participants, 7,000 were over the age of 65 and 5,000 were under the age of 65 but deemed "high risk" for COVID-19 due to chronic diseases. The interim analysis released by Moderna and the NIH reports that of the 95 COVID-19 cases in the study, 90 were reported in the placebo group.[12,14] In all patients receiving the vaccine, adverse events were most commonly reported after the second dose. These side effects included fatigue in 9.7% of participants, myalgia (8.9%), arthralgia (5.2%), headache (4.5%), pain (4.1%), and erythema at the injection site (2.0%), all of which typically resolved in a matter of hours to a few days.[14]

The promising results of the Moderna vaccine, coupled with its development in coordination with the NIH as part of Operation Warp Speed, has secured 200 million doses for manufacture and distribution within the United States in 2021.[15] Its shelf life of six months at -20°C (-4°F) and 30 days at standard refrigerator temperatures of between 2° and 8°C (36° to 46°F) also make it less logistically challenging to distribute and store than its Pfizer mRNA vaccine counterpart.[14] It is likely that the Moderna vaccine will be the most widely available of the two approved vaccines in the United States, at least initially, although its relatively high price tag of between $25-$37 raises questions about the vaccine's obtainability without government subsidization beyond the 200 million doses promised to a population of more than 328 million Americans.[10,14,17]

The last of the major late-stage vaccine candidates has been developed by the University of Oxford and AstraZeneca.[18] Unlike the Pfizer and Moderna mRNA vaccines, the ChAdOx1 nCoV-19 vaccine (also known as AZD1222) is a replication-deficient simian adenovirus vector. A chimpanzee adenovirus has been genetically engineered to carry the DNA of SARS-CoV-2 into the cytoplasm without replicating within the cell. Once the coronavirus DNA is present within the cytoplasm, it is taken up into the nucleus without being incorporated into the host's genome. The DNA is then transcribed into RNA, exits the nucleus as mRNA, and is translated into the coronavirus spike protein, whereupon it triggers an immune response in the same manner as the mRNA vaccines. Essentially, the AstraZeneca/Oxford vaccine is analogous to a prodrug, allowing the natural processes of the body to convert its contents into a protein which elicits an immune response rather than more directly inoculating the body with mRNA.[18,19]

Phase I and II trials in the United Kingdom administered the AZD1222 or "placebo" (the MenACWY Meningitis B vaccine) in 1,090 volunteers, followed by an ongoing phase III trial with 12,390 participants, the majority of whom live in Brazil.[19-21] All phases have exhibited similar immune responses in older and younger patients, with phase III interim results suggesting 70% average efficacy, with individual cohort efficacy rates ranging from 62% to 90% prevention of infection. Due to a manufacturing error, 2,741 participants received a two dose series of a ½ dose and one whole dose 28 days apart. This arm of the trial exhibited a 90% efficacy rate, leading some scientists to postulate that the ½ dose inoculation may better mimic the body's typical response to coronavirus infection. However, the less efficacious arm of the trial (n = 8,895) received two full doses 28 days apart, resulting in only 62% efficacy. It is possible that the more effective arm was underpowered, leading researchers to pursue further study of the ½ and 1 dose series.[21,22] The vaccine was approved for use in the United Kingdom on December 30, 2020, which suggests that an emergency use authorization for AZD1222 in the USA is imminent.[23]

Nevertheless, the methods employed by the AstraZeneca/Oxford study should not be discounted, despite what might be seen as a haphazard manufacturing mistake. Of the "big three" approved vaccines and vaccine candidates, the Oxford vaccine study is the only one to actively check its participants for infection with nasal swab testing, whereas the Pfizer and Moderna vaccines only catalogued symptomatic infection.[7,12,20] This suggests that the AstraZeneca/Oxford vaccine may not only prevent symptomatic infection, but also asymptomatic infection and transmission of coronavirus. Moreover, AstraZeneca has repeatedly indicated that they will manufacture and deliver their vaccine at no profit, with each dose costing $3-$5.00.[17] This low pricing coupled with six months stability at refrigerator temperatures (2° to 8°C or 36° to 46°F) makes AZD1222 an excellent candidate for use in the developing world or rural areas which may not have the infrastructure to store mRNA vaccines.

As of January 2021, there are over one hundred SARS-CoV-2 vaccine candidates at varying stages of study around the world. The race to find a vaccine for COVID-19 is rapidly evolving, so much so that this article may be viewed months from now as an outdated snapshot of three vaccine candidates which did not become a standard of care for coronavirus disease immunization. However, healthcare providers everywhere wait with anticipation and hope that all of these promising vaccine candidates will be the key to ending the greatest public health crisis in a century.

COVID-19 Vaccine Statistics[2-4,8,10,11,16,20]							
Developers	**Vaccine**	**Type**	**Proposed Dosing (IM)**	**Interim Efficacy**	**Shelf Life (36 - 46°F)**	**Estimated Cost per Dose**	**US Distribution Agreements**
Pfizer BioNTech	BNT162b2	RNA	2 doses, 21 days apart	95%	5 days	$19.50	200 million doses
Moderna NIH	mRNA-1273	RNA	2 doses, 28 days apart	94.5%	30 days	$25.00 to $37.00	200 million doses
Oxford AstraZeneca	AZD1222	DNA	2 doses or ½ dose followed by 1 dose, 28 days apart	62% up to 90%	6 months	$3.00 to $5.00	500 million doses

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Role of Steroids in the Management of the Coronavirus Disease of 2019 (COVID-19)

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Therapeutic options for patients infected with COVID-19 are limited and potential therapies continue to arise. From oral medications to intravenous formulations and antiviral medications to monoclonal antibodies authorized via Emergency Use Authorizations[1,2,] therapy recommendations continue to change as information is gathered. To date, corticosteroids (more specifically, dexamethasone) remain the most evidence-based option for the management of select hospitalized patients with COVID-19.[3,4]

It was initially hypothesized that hydroxychloroquine may be of use in the management of patients with COVID-19 based on its in vitro activity against previous severe acute respiratory syndrome coronavirus (SARS-CoV) outbreaks in combination with its antiviral and immunomodulatory effects.[5] However, studies showed that the risks of its use can outweigh the benefits[6,7] and accordingly, neither the NIH nor the IDSA recommend its use for hospitalized patients with COVID-19.[3,4] As evidence continued to develop, it was discovered that the use of corticosteroids can provide the greatest benefits for certain hospitalized patients.

The role of corticosteroids in the management of COVID-19 infections comes in suppressing the inflammatory response, particularly in the lungs, that the disease can elicit. Their benefit was primarily observed in the RECOVERY trial.[8] This controlled, open-label trial included patients who were hospitalized with COVID-19. Patients were randomized to either receive standard of care or standard of care plus dexamethasone 6 mg PO/IV once daily for up to 10 days. The primary outcome of the study was all-cause mortality within 28 days after randomization.

The study observed a significantly lower 28-day mortality in the dexamethasone group than in the standard of care group, with deaths reported in 482 of 2,104 patients (22.9%) and in 1,110 of 4321 patients (25.7%), respectively. Furthermore, in the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation and among those receiving oxygen without invasive mechanical ventilation. A benefit was not observed among patients not receiving respiratory support at randomization. Data are available in Table 1. The study suggested that for patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization. However, among those not receiving respiratory support, there was no benefit observed and in fact, findings were suggestive of possible harm in this patient population.[8]

On the basis of the data from the RECOVERY trial, both the NIH and the IDSA recommend the use of dexamethasone in the appropriate patient populations.[3,4] Even though the study investigated dexamethasone, other corticosteroids can theoretically be used at equivalent doses in place of dexamethasone in situations where dexamethasone is not available. Dose equivalences are presented in Table 2.

As potential COVID-19 therapies continue to emerge, it is important to recognize which therapies are supported by evidence. Not only that, but providers must also recognize which therapies can provide the greatest benefits (or even harms) to patients based on disease severity as seen in the case of dexamethasone. We must adapt to the ever-changing information to provide the best patient care possible.

Table 1. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization[8]

Respiratory Support at Randomization	Dexamethasone (%)	Usual Care (%)	Rate Ratio (95% CI)
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51-0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72-0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91-1.55)
All patients	***482/2104 (22.9)***	***1110/4321 (25.7)***	***0.83 (0.75-0.93) P < 0.001***

Table 2. Corticosteroid Dose Equivalents

Medication	Dose
Dexamethasone*	6 mg
Methylprednisolone*	32 mg
Prednisolone	40 mg
Prednisone	40 mg
Hydrocortisone*	160 mg

* May be administered PO or IV

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