



The New Normal

Influenza Persists

Uday Jain, BSEE, MD, PhD, FASA

Daniel J. Cole, MD, FASA

There are four influenza viruses, A through D. Influenza A causes severe illness and is responsible for influenza pandemics. Influenza B is associated with less severe illness and has not caused any pandemics.

Every year, influenza A is associated with nine to 45 million cases in the United States, leading to 12,000 to 61,000 deaths (*JAMA* 2020;324:1362). The World Health Organization estimates influenza A is responsible for about 1 billion infections, 3-5 million severe illnesses, and 300,000-500,000 deaths every year (*Nat Rev Dis Primers* 2018;4:3).

As shown in Figure 1, the outer surface of the influenza virus has two proteins: hemagglutinin and neuraminidase. Hemagglutinin is responsible for binding to the target cells, much like the spike protein on SARS-CoV-2 targets the ACE2 receptor. Hemagglutinin attaches to sialic acid found on the surface of many proteins, including those of the respiratory tract. Sialic acid is also a prominent component of respiratory mucus.

For influenza to infect cells, the hemagglutinin receptor has to identify exactly the right surface protein on respiratory cells to initiate fusion. Most of the sialic acid residues on surface proteins or floating about in mucus are false targets. To keep the virus infectious, neuraminidase on the viral surface breaks the bond between hemagglutinin and sialic acid on false targets, allowing the virus to continue “shopping” for the right target permitting fusion.

Influenza A comprises 18 distinct hemagglutinin subtypes and 11 different neuraminidase subtypes. The virus is named after the specific subtypes on the surface. For example, H1N1, the virus responsible for the 1918 pandemic, is the strain with hemagglutinin 1 and neuraminidase 1 on the cell surface.

Influenza A recurs every year and is responsible for tens of thousands of deaths. Current influenza vaccines are safe but only 40%-60% efficacious (asamonitor.pub/3n2ocDF). Last year, influenza infection was unusually low, as transmission was mitigated by the public health measures designed to mitigate the spread of SARS-CoV-2 (*Cureus* 2021;13:e18007). Abandonment of non-pharmaceutical interventions (e.g., masks, social distancing, limiting indoor gatherings) will cause

influenza to return as a part of “the New Normal.”

Coinfection: Overlapping spread of COVID-19 and influenza could be a major strain on the health care system (asamonitor.pub/3qplzhj; asamonitor.pub/3kp11R6). Coinfection can also occur and has a nearly 10% mortality rate (*Emerg Infect Dis* 2021;27:2923-6). Animal models demonstrate that lethality of co-infection is reduced by prior vaccination against influenza, but not by prior vaccination against SARS-CoV-2 (*Nat Commun* 2021;12:5819). This emphasizes the importance of influenza vaccination this year. As always, vaccinations are particularly critical for persons at increased risk.

Incubation: Influenza’s median incubation period is two days. Patients are infectious for a day before and five to seven days after symptoms. Influenza symptoms peak in three to seven days. COVID-19 has an incubation period of four to 12 days, a median of about five days. Patients with COVID-19 are highly infectious from two days before symptom onset. COVID-19 symptoms peak in the second or third week. The spread of both viruses is facilitated by transmission by asymptomatic patients.

Transmission: About one-half of influenza A cases are due to aerosol transmission; adequate ventilation can reduce it (*Sci Rep* 2019;9:2185; *Environ Health Prev Med* 2020;25:66). Used appropriately, surgical masks reduce the concentration of aerosolized influenza virus by about 10-fold and are adequate for prophylaxis

against influenza. Transmission by respiratory droplets can also be reduced by masking. Transmission by direct contact can be reduced by hand and general hygiene. COVID-19 is transmitted in a similar manner. Social distancing reduces transmission by all the mechanisms. According to the Centers for Disease Control and Prevention (CDC), the precautions utilized for COVID-19 reduced the positivity rate for influenza tests from 16.8% in 2019-2020 to 0.15% in 2020-2021.

Influenza is less contagious and causes less severe disease than COVID-19. Quarantine recommended for COVID-19 patients is not necessary for those with influenza. As children play an important role in transmitting influenza, opening of schools is likely to increase transmission. Health care providers should take precautions to avoid infecting themselves and others.

Influenza-like illness: The CDC defines influenza-like illness as fever 100°F (38°C) or greater and cough or sore throat that is not due to another known cause such as streptococcal pharyngitis (strep throat). Influenza-like illness may be caused by something as benign as the common cold, i.e., nasopharyngitis caused by rhinovirus or other viruses. Influenza-like illness can also be caused by severe illnesses, including sepsis, meningitis, and COVID-19. The onset is often abrupt. Influenza-like illness can cause immunosuppression, leading to bacterial pneumonia and necessitating antibiotic treatment (*Curr Opin Infect Dis* 2017;30:201-7).

Influenza and COVID-19 generally cause mild disease (*Lancet Infect Dis*



Uday Jain, BSEE, MD, PhD, FASA

Staff Anesthesiologist, Anesthesia Care Consultants, San Francisco.



Daniel J. Cole, MD, FASA

Professor of Clinical Anesthesiology, Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, University of California, Los Angeles.

2020;20:e238-44). Severe disease, and most mortality, following COVID-19 occurs primarily in the elderly. In contrast, influenza is more evenly distributed across age groups.

After general anesthesia, children with influenza have a longer hospital length of stay and increased risk of requiring intensive care. Routine surgery should be postponed for about four weeks in a patient with influenza-like illness. Unvaccinated patients should be offered influenza vaccination after the acute phase of influenza-like illness has passed and before the surgery. Only the most urgent surgery should proceed in patients with severe cases of influenza-like illness (*BMC Anesthesiol* 2011;11:16).

Upper-respiratory tract infection: Upper-respiratory infections are common in the winter, likely caused by the low water content of cold air. Often an upper-respiratory tract infection will either be the common cold (rhinovirus) or noninfectious allergic or vasomotor rhinitis. Less commonly, an upper respiratory infection will be the initial presentation of more serious illness, including influenza-like illness, COVID-19, strep throat, or even herpes simplex. Early in the infection it is difficult to distinguish between different etiologies of upper-respiratory infections.

Upper-respiratory infections may cause sneezing, coughing, headache, malaise, rhinorrhea, sore throat, sinusitis, and bronchitis. Subsequently, bronchi may be hyperreactive for about six weeks.

Pulmonary complications associated with surgery in a patient with an upper-respiratory infection include bronchospasm, laryngospasm, coughing, breath holding, postintubation croup, episodes of desaturation, atelectasis, and pneumonia.

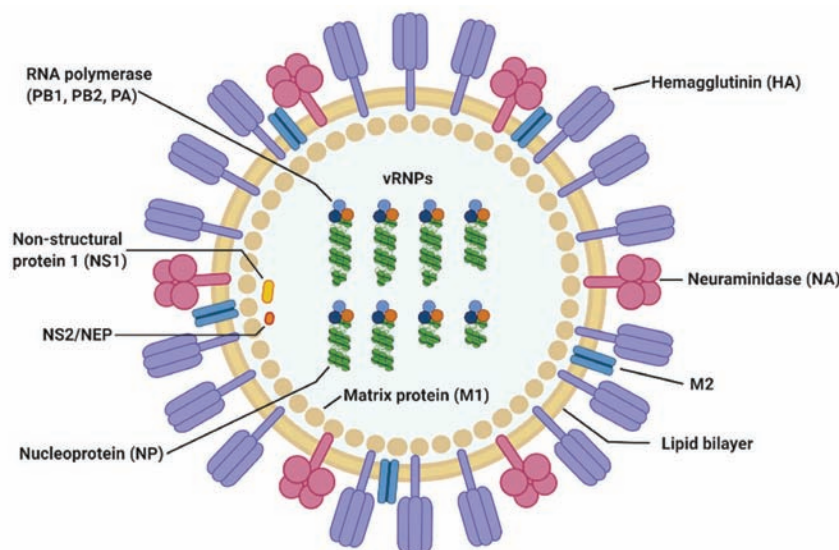


Figure 1: A schematic diagram of equine influenza virus, representative of influenza A.

Anticholinergics and bronchodilators may not be beneficial. If influenza-like illness and other serious illnesses are unlikely, routine surgery can be performed with caution. Perioperatively, adequate hydration and humidification should be maintained. There are no pediatric or adult anesthesia closed claims that implicate upper-respiratory infections, including influenza with serious adverse events (*Anesthesiology* 1991;75:932-9).

Cardiac effects: There is a very small incidence of viral myocarditis in patients with severe influenza, upper-respiratory illness, and influenza-like illness. Viral myocarditis may lead to serious arrhythmias and refractory heart failure (*J Crit Care* 2018;47:61-4). Cardiac abnormality should be excluded before performing non-emergent surgery in any patient with a recent viral illness who describes symptoms suggesting cardiac failure.

Diagnostics tests: Common tests for influenza include nucleic acid amplification via polymerase chain reaction (PCR) and antigen-based immunological assays. A PCR test can be performed even at the point of care, with results available within an hour (*Lancet Respir Med* 2021;9:419-29). This can facilitate infection control and utilization of antiviral therapeutics. It is especially useful for patients who have severe symptoms or are hospitalized. Test for COVID-19 may also be performed if indicated.

Influenza vaccine: As always, vaccination is the best preventive measure. Despite moderate efficacy, influenza vaccination substantially reduces morbidity and mortality because of the high prevalence of influenza. It is recommended for anyone over 6 months of age. It is especially beneficial for those less than 2 years old or older than 65 (*JAMA* 2020;324:1362). Vaccination is highly recommended for individuals with



Walter Reed Hospital flu ward during the Spanish Flu epidemic of 1918-19, in Washington, DC.

pre-existing conditions. Vaccination is important in pregnancy not only because influenza increases the risk to the mother but also increases risk of preterm birth, fetal death, infant respiratory infections, and hospital admission.

The T cell response to influenza vaccines is substantially weaker than the antibody response. Children may need two doses of the vaccine at least four weeks apart. The vaccine should be administered at least one week before surgery. It takes two weeks to develop full effect. As the protection wanes over time, mid-September to mid-October is preferred for vaccination. Influenza and COVID-19 vaccines may be administered together.

Influenza vaccines can be safely administered to surgical inpatients (*Ann Intern Med* 2016;164:593-9).

Available vaccines: The influenza virus mutates frequently. Quadrivalent vaccines protect against four of the currently most prevalent strains of influenza. The vaccines are altered every year for the predicted prevalent strains. All vaccines for the 2021-2022 influenza season are quadrivalent (asamonitor.pub/3CaulCg).

Most influenza vaccines are based on inactivated influenza virus. These are approved for persons above 6 months of age. As older individuals have a reduced response, higher vaccine doses are recommended for persons above 65 years of age.

The vaccine is usually administered intramuscularly, but a lower dose intradermal vaccine may be non-inferior (*JAMA Netw Open* 2021;4:e2035693).

Live attenuated influenza vaccine is administered via nasal spray (asamonitor.pub/3wHcvpi). The attenuated virus is approved for ages 2-49 years. It may be preferable in some situations, such as vaccinating many persons in a community. However, the CDC website notes numerous settings where the live attenuated vaccine should not be used (asamonitor.pub/3wHcvpi).

Recombinant vaccines and cell culture vaccines do not contain egg products (asamonitor.pub/3kpHLE8; asamonitor.pub/3HkoKNs). They are especially suitable for persons who need to avoid eggs because of allergy or dietary preferences.

Future vaccines: Universal vaccines that provide durable response against all influenza strains are in human trials (*Nat Med* 2021;27:106-14). These vaccines generate antibodies against the viral hemagglutinin protein stem (stalk) domain (HA2). Current vaccines generate antibodies against the immunodominant globular head domain (HA1), which is variable and mutates much more frequently.

Vaccines utilizing mRNA are also in human trials (*JAMA* 2021;326:1365). They are likely to have greater efficacy but more side effects than current vaccines. A major advantage of the mRNA vaccines is that they can be readily modified to match mutations in the virus.

Benefits of vaccination for adults: Influenza vaccine reduces the risk of respiratory and cardiovascular adverse outcomes and mortality among adults, especially in the presence of pre-existing conditions and advanced age. This was confirmed in a meta-analysis of studies on all adults (*Ageing Res Rev* 2020;62:101124). Another meta-analysis found that vaccination reduced the risk of adverse cardiac outcomes, especially in patients with more severe cardiac disease (*JAMA* 2013;310:1711-20).

Preoperative vaccination is beneficial. A large study of elderly patients who had major surgery found preoperative vaccination reduced by about one-half the risk of pneumonia, intensive care admission, and death (*J Infect Dis* 2018;217:816-26). Patients also had

shorter hospital stays and reduced resource utilization.

Influenza therapeutics: Specific therapeutic modalities include neuraminidase inhibitors (oseltamivir, zanamivir, peramivir, and laninamivir), the endonuclease inhibitor baloxavir (which inhibits a process called “cap-snatching” essential for influenza viral replication), and matrix protein M2 ion channel blockers (asamonitor.pub/3oavTa4; *JAMA Netw Open* 2021;4:e2119151). All attenuate viral replication, providing postexposure prophylaxis. Started within two days of symptom onset, these treatments can reduce duration and severity of the disease and decrease the incidence of complications. They also reduce transmission of influenza virus. Unfortunately, efficacy is limited, especially in patients with serious illness. As a result, they are not widely used.

Although influenza and COVID-19 have similar initial symptoms, their therapeutics are different. For example, dexamethasone reduces mortality for hospitalized COVID-19 patients on respiratory support but may increase mortality for hospitalized influenza patients (*JAMA* 2020;324:923-5).

Influenza pandemics: Influenza pandemics are usually caused by zoonotic influenza A virus strains migrating to humans. The 1918 “Spanish flu” pandemic caused by influenza A H1N1 virus led to more than 50 million deaths worldwide (asamonitor.pub/2YzXJnv). The pandemics of 1957, 1968, and 2009 were caused by influenza A H2N2, H3N2, and H1N1 viruses, respectively. The 2009 “swine flu” influenza A H1N1 virus that originated from pigs was antigenically different from previously dominant influenza A H1N1 viruses. It caused 150,000-600,000 deaths worldwide.

Figure 2 compares the time course of the 1918 influenza pandemic and the current COVID-19 pandemic. Even during the 1918 pandemic, influenza demonstrated strong seasonal variation. The 1918 pandemic lasted less than one year. As seen in Figure 2, SARS-CoV-2 is substantially less seasonal than influenza. Additionally, unlike the 1918 influenza pandemic, we are now almost two years into the current pandemic, and there is no suggestion in Figure 2 that it will be ending soon.

Conclusion: Influenza is a prevalent respiratory disease that will continue to affect anesthesia practice in the foreseeable future. Concurrent influenza and COVID-19 surges could be devastating to health care resources. The primary method of reducing the risks of both influenza and COVID-19 is vaccination. When illness occurs, new therapeutics offer the promise of attenuating morbidity and mortality for both illnesses. ■

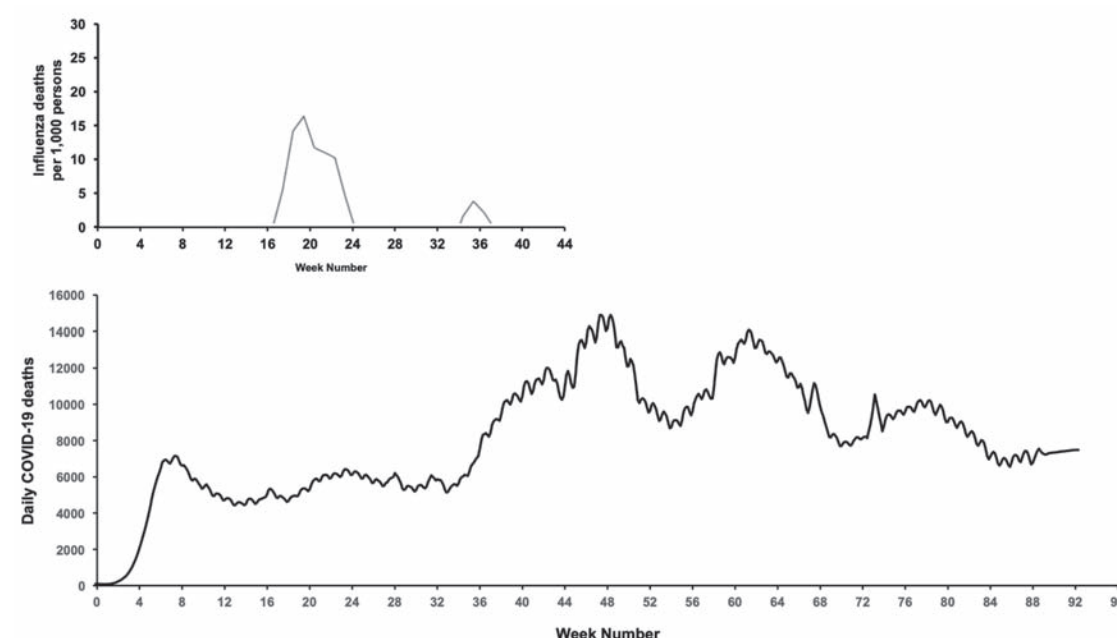


Figure 2: Comparison of the 1918 influenza pandemic with daily deaths from the COVID-19 pandemic (data from asamonitor.pub/3C2ukQt).