Health care professionals are bracing for new demands as the influenza season approaches, raising concerns about how a convergence of the annual illness with the coronavirus disease 2019 (COVID-19) pandemic might affect public health.

The MJH Life Sciences™ COVID-19 Coalition, a partnership with top health care thought leaders across a variety of medical disciplines, offers resources to help navigate these challenges, with an advisory panel of nationally recognized experts guiding live webinars, white papers, infographics, and more.

“Battling Dual Threats: Flu and COVID-19 Converge” was the first in a biweekly series of webinars hosted by the Coalition, which was established to keep health care professionals up-to-date and informed on the science and latest learnings on COVID-19.

Moderated by Angela Rasmussen, PhD, associate research scientist at Columbia University Mailman School of Public Health, “Battling Dual Threats: Flu and COVID-19 Converge” also featured Andreas Handel, PhD, associate professor in the department of epidemiology and biostatistics at the University of Georgia, and Juliet Morrison, PhD, assistant professor in the department of microbiology and plant pathology at University of California Riverside.

Register to watch the program on-demand.
“As we know, the convergence of COVID-19 and influenza this fall represents a pressing public health threat as hospital systems, clinicians, and the world’s population brace for the impact of dual epidemics,” Rasmussen said.

What follows are 5 key takeaways from the webinar.

1 **SARS-CoV-2 and influenza viruses are very different despite the fact that the diseases they cause share some common features.**

   “SARS-coronavirus-2 and influenza are taxonomically distinct,” Rasmussen said. “They are members of 2 distinct viral families. They are actually separated as far back as the level of phylum.”

   SARS-CoV-2 is a nonsegmented ssRNA virus, whereas the influenza A genome has 8 segments. Both are enveloped, but they have different surface glycoproteins that bind the cell receptors.

   Differences between the viruses include:

   • **Unique evolutionary origins and host adaptations.**
     SARS-CoV-2 is thought to have originally circulated in wild bats. Scientists are uncertain whether an intermediate species, such as a palm civet, passed the virus to humans. Cats and ferrets are known to contract SARS-CoV-2 from humans and may represent new reservoirs for the virus into the future.

     Influenza, on the other hand, typically circulates among wild, migratory birds, contributing to its seasonal occurrence. It also spreads among domestic birds and pigs, which serve as intermediate species.

     “And, flu viruses can do something that coronaviruses cannot do and that is re assort the segments of their genome,” Rasmussen said. “So, if a pig or a bird becomes infected with more than 1 strain of influenza, those segments can re assort, almost like a deck of cards shuffling, and create essentially a new virus. This can change that virus’ properties, including its properties of transmissibility from human to human.”

     As a result, SARS-CoV-2 has a much lower mutation rate than that of influenza.

     • **Different receptors and mechanisms of entry.**
     SARS-CoV-2 attaches to angiotensin-converting-enzyme 2 receptors\(^1\) on the surface of epithelial cells in the respiratory tract. The virus is processed by several proteases on the surface of the cell, such as TMPRSS2, as well as lyso somal proteases, such as cathepsins, and furin, in order to complete entry.

     By contrast, influenza virus binds sialic acid residues on the surface of proteins on the outside of the cells.\(^2\) It is thought that calcium influx then allows the virus to enter the cell.
“These are 2 very different receptors in the sense that SARS-coronavirus-2 binds a protein and has to be processed by proteases, whereas influenza binds a carbohydrate sialic acid and then the action of the protein that that sialic acid is attached to allows the virus to get into the cell,” Rasmussen said.

• **Variations in viral replication processes.**

The SARS-CoV-2 genome is 30 kilobases. It is translated as 2 large polyproteins and then transcribed into a series of subgenomic RNAs that are then translated into proteins, Rasmussen said. The assembly of these replication complexes, all viral transcription, and translation of the viral proteins occurs in the cytoplasm.

Replication of influenza virus is more complicated, with segments of the genome binding to nucleoproteins. These viral ribonucleoproteins are imported into the nucleus, where RNA is transcribed and “cap snatching” occurs before the capped messenger RNAs move back out of the nucleus to the cytoplasm for translation.

• **Differences in sequelae.**

“While we know that these viruses can infect common tissues such as the respiratory tract, and there is a common route of infection in that people are generally exposed to this through nasal or oral exposure to either droplets or inhaled aerosols, they really have distinct tropism as well, meaning they infect different types of cells and affect organ systems in the body,” Rasmussen said.

SARS-CoV-2 has been known to cause a broader range of symptoms than influenza. These can include neurological effects; inflammatory disease in cardiac tissue; thrombotic sequelae such as blood clots, stroke, and heart attack; and diarrhea or other gastrointestinal symptoms.

• **Host response differences.**

Patients infected with SARS-CoV-2 show profound repression of type 1 and type 3 interferon signaling, which are a key part of innate antiviral immune response.³

“It really rings the warning bell to let the host know that a virus has infected it,” Rasmussen said “So, SARS-coronavirus-2 suppresses those interferons and also induces the expression of a number of inflammatory cytokines and chemokines, which are thought to contribute to more severe COVID-19 disease.”

2 **More research is needed to understand the risk of coinfections.**

A study of diagnostic specimens at Stanford Health Care⁴ found a number of coinfections with respiratory pathogens, not specific to influenza.
Rasmussen also noted a number of case studies that have shown that SARS-CoV-2 and influenza coinfections have occurred all over the world, including the Middle East, Europe, and the United States.

“The big question here is whether or not coinfection increases disease severity, and we don’t know,” Rasmussen said. “So, these case reports are from hospitalized patients who are more severely ill anyway. We need more data from a broader range of patients to find out. We need to do these studies in a more rigorous way to determine if coinfection has any impact on disease severity.”

Different theories have arisen to predict the effects of the convergence of influenza and SARS-CoV-2.

One theory predicts that flu and COVID-19 together will create a perfect storm with a combined impact that is worse than the sum of the 2 alone, Handel said. Another theory predicts that the 2 viruses would compete with each other, resulting in an outcome that is ultimately less severe than that of either virus alone.

“What I think is the right way of thinking about it is the middle,” Handel said. “I think the 2 of them is definitely worse than if we had either only flu or only COVID, but also don’t think the 2 together are worse than the sum.”

3 Nonpharmaceutical interventions work.

Factors that will influence the severity of the influenza/COVID-19 convergence include:

- Nonpharmaceutical interventions (NPI). Measures taken to slow the spread of COVID-19, such as mask use, hand-washing, and social distancing, also slow the spread of influenza.

- Future vaccines.

- Competition for hosts. When a person is sick with one of the viruses, they may be at home and less likely to catch the other.

Early evidence suggests that incidences of influenza in the United States dropped below expectations after public health measures were established to address the COVID-19 pandemic. Similar trends have been noted in Japan, China, and Australia.

Handel noted that the studies reflect reduced positivity rates among those who were tested for influenza and fewer hospitalizations, indicating that there really was a drop in infections rather than just in reporting.

“These NPI work, and they work not only against COVID-19 but against pretty much all respiratory infections, and thus have led to strong reduction in flu cases,” Handel said.

4 The effects of competition for host and immunological interactions are uncertain.

Determining how competition for hosts and immunological interactions between the 2 viruses might affect public health outcomes is more difficult to determine. Lacking data on COVID-19, Handel turned to studies that looked at other human coronavirus infections, finding mixed results.

A study from the Netherlands found that seasons with low incidences of influenza also saw low incidences of human coronavirus and vice versa.
“There is some indication that there might be something going on, but we don’t know if it’s actually one affecting the other or if it’s just some general environmental factor,” Handel said.

A study from Scotland\textsuperscript{11} looked at influenza B and human coronavirus and did not find interactions between the 2 viruses. A study from Australia\textsuperscript{12} showed a possible interaction between human coronavirus and influenza A, with odds of coinfection being lower, indicating that if you have one you are less likely to be coinfected with the other. The same was not seen for influenza B. A study of military recruits in Singapore\textsuperscript{13} showed no interactions between influenza and human coronavirus.

A preliminary study in China\textsuperscript{14} that looked at COVID-19 found some evidence suggesting that those who had a previous influenza A infection may have a somewhat less severe COVID-19 infection. However, Handel cautioned that the study was preliminary and observational.

“I think there are probably host and immunity interactions, but I think the effect is much smaller, especially compared with the nonpharmaceutical interventions we’ve had in place so far,” Handel said.

Handel predicts that, given the NPI that are in place, this flu season will be mild, with few cases reported; most respiratory illness likely will be COVID-19, and he doesn’t expect to see many coinfections. Over the long term, he expects COVID-19 and influenza to cocirculate, and a future vaccine will be the greatest factor in determining how the 2 viruses interact.

\section*{5 Vaccination is a key to mitigating the convergence of influenza and COVID-19.}

While researchers around the world race to develop SARS-CoV-2 vaccine candidates, seasonal influenza vaccines are being administered. The fast pace of development along with the antivax movement pose challenges for health care professionals hoping to boost vaccination rates during the current health crisis.

- **Flu vaccines.**

  The US Centers for Disease Control and Prevention (CDC) recommends that everyone 6 months and older get a licensed, age-appropriate influenza vaccine annually. Several options are available, and the CDC hasn’t expressed a preference for any particular vaccine.

  “Several groups are developing universal influenza vaccines. The hope is that instead of having to have a vaccine formulation every year, we would be able to have our vaccines delivered on a less frequent basis because of this universal platform,” Morrison said.

  “We are expecting to see results of certain of those trials within the next few years, so it is possible that we might end up having influenza vaccine options that we do not have to take annually, and that would be a big breakthrough.”
All 3 panelists recommended getting a flu vaccine as soon as possible. There has been some evidence that immunity wanes over time, leading some to recommend waiting until October to stretch immunity further into the flu season. However, timing is a trade-off between risking becoming infected early in the season before getting the vaccine and being vulnerable later in the season.

Those with active infections should delay vaccination until their symptoms have resolved, Morrison recommended.

**SARS-CoV-2 vaccines.**

Nine SARS-CoV-2 vaccine candidates are currently in phase 3 trials, representing an unprecedented push for vaccine development. With Operation Warp Speed aiming to deliver a SARS-CoV-2 vaccine as soon as possible, some concerns have been raised that corners might be cut.

“I think that is unlikely to be the case,” Morrison said, noting that prominent pharmaceutical firms involved in vaccine development have signed a pledge to make the safety and well-being of vaccinated individuals their top priority and to adhere to high scientific and ethical standards.

She pointed to the recent decision by AstraZeneca and University of Oxford to pause their vaccine trial—after reports that a serious adverse event hospitalized a United Kingdom participant—as evidence that companies are holding to high standards. The trial resumed after independent committees and regulators deemed it safe to do so.

“It seems that these companies really are actually following the rules, and that makes me feel pretty confident moving forward that when a vaccine is developed that we can be assured of its safety,” Morrison said.

**Vaccine hesitancy.**

Vaccine hesitancy has been a challenge for health care professionals since the 1990s, when a since-retracted paper raised questions about the safety of vaccines, sparking the antivax movement that persists to this day.

“Now we’re contending with that plus the fact that we have not been seeing the level of transparency necessary for some of the COVID-19 vaccine trials,” Morrison said.

Countering vaccine hesitancy comes down to how much of a threat the disease presents.

“In the case of COVID-19, it’s actually a very high threat,” Morrison said. “And not only is it that it’s causing death, but we don’t know what the long-term repercussions are. For many people who have been infected you’re hearing of these cases where people have long-term lung damage and damage in other organs.”

It will be important for vaccine developers to publish peer-reviewed documents detailing the safety and efficacy of their vaccines.
“I’m hoping that these companies will actually tell us exactly what’s going on and share this with the public, because at the end of the day, that is the only way that we’re going to see a real uptake in the vaccine once one comes on the market,” Morrison said. “Education is the key to fighting vaccine hesitancy.”

REFERENCES


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For over 20 years, MJH Life Sciences™ has established a reputation for embracing agility and offering relevant, practical information that meets the needs of our diverse audience. As the largest privately held medical media company in North America, we provide integrated communication products, services, education, and research to professionals within health care, animal health, and industry sciences.

Now, as cases of COVID-19 continue to mount, our calling is more relevant and urgent than ever.

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