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Respiratory virus season: Strategies for successful navigation

“Everything should be made as simple as possible, but not simpler.” — Paraphrased from Albert Einstein

HELPING OUR PATIENTS stay healthy during respiratory virus season requires a comprehensive approach, with preventive measures, vaccination, efficient diagnostic tests, and targeted medications—and we need to communicate clearly with our patients what we want to do, and why.

Here, we review the burden, prevention, diagnosis, and treatment of 3 important respiratory viral illnesses: respiratory syncytial virus (RSV) infection, COVID-19, and influenza. Acknowledging the pressure that the respiratory virus season places on frontline clinicians and their practices, we offer an analogy-driven narrative for patient communication.

■ AN ANALOGY TO MOTOR-VEHICLE ACCIDENTS

When talking to patients about ways to avoid respiratory infections, we find it useful to use the analogy of avoiding motor-vehicle accidents:

First, avoid exposure to infections as much as possible. Use handwashing and mask-wearing as appropriate, and limit crowd contact. This is analogous to defensive driving.

Second, vaccinate against infectious diseases, especially when it is difficult to limit exposure. This is analogous to wearing seat belts.

Third, use symptom-triggered medication if a patient is allergic to vaccines, refuses to be vaccinated, or has a breakthrough infection. Analogy: air bags.

Influenza, COVID-19, and RSV infections can be compared to a car running through a stop sign—an event beyond our control. While seat belts (vaccines) and air bags (medications) cannot prevent accidents (illnesses), having them in place significantly reduces the severity of the outcomes. Vaccines prime our

immune system for a swift and effective response. Using all 3 elements together—avoidance, vaccination, and treatment—ensures an optimal outcome, embracing a “both/and” approach rather than an “either/or” mindset. This analogy helps some vaccine-hesitant patients to agree to vaccination by explaining its role in understandable terms.

■ BENEFITS OF DISTANCING AND VACCINATION

The early COVID-19 lockdown and the widespread adoption of physical distancing, mask-wearing, and enhanced hand hygiene helped limit the spread of not only COVID but other respiratory viruses as well. For example, only 1,899 (0.2%) of more than 1 million clinical samples tested positive for influenza A or B during the 2020 to 2021 period.¹

Vaccines also play a crucial role. Shattock et al² estimate that since 1974, childhood vaccination has prevented 150 million deaths, including 140 million among children under 5 and 100 million among children younger than 1 year. On average, for every life saved, 66 years of full health were gained, totaling approximately 10.2 billion years of health. The investigators estimate that vaccination contributed to 40% of the observed decline in global infant mortality, and 52% in Africa. Thanks to vaccination, in 2024, a child under 10 years old is 40% more likely to survive to their next birthday than they would be if vaccines had never been invented. This increased survival benefit extends into late adulthood as well.

The topic of vaccine hesitancy and how to deal with it has been recently covered in 2 excellent articles in this journal.^{3,4}

■ HIGH COST OF ILLNESS

Respiratory viruses cause significant morbidity and death. The Centers for Disease Control and Prevention

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TABLE 1
Some representative influenza vaccines

Brand name (vaccine form)	Approved ages	Dose
Fluzone (inactivated, egg-based)	6–35 months	0.25 mL
Fluzone (inactivated, egg-based)	≥ 3 years	0.5 mL
Fluzone High-Dose (inactivated, egg-based)	≥ 65 years	0.5 mL
FluBlok (recombinant, egg-free)	≥ 18 years	0.5 mL
FluMist (live attenuated, egg-based)	2–49 years	0.1 mL in each nostril (0.2-mL prefilled single-use intranasal sprayer)
Fluad (inactivated adjuvanted, egg-based)	> 65 years	0.5 mL

Information from reference 7.

estimates that, between 2010 and 2023, influenza caused 9.3 to 41 million illnesses, 100,000 to 710,000 hospitalizations, and 4,900 to 51,000 deaths each year.⁵

They also impose a significant economic burden on individuals and society. Molinari et al⁶ estimate that seasonal influenza costs the US economy nearly \$90 billion each year in the form of medical expenses, lost workdays due to illness, and deaths. They suggest that interventions targeting the elderly could offer the greatest economic benefit, as this group bears 64% of the total economic burden, including 36,000 deaths annually.

VACCINE FORMULATIONS AND RECOMMENDATIONS

Vaccination reduces illness severity and saves lives. Here are the current formulations and their indications.

Influenza vaccines are now trivalent

The 2024–2025 seasonal influenza vaccine in the United States is trivalent, containing hemagglutinin from 3 strains⁷:

- Influenza A/Victoria/4897/2022 (H1N1) or influenza A/Wisconsin/67/2022 (H1N1)
- Influenza A/Thailand/8/2022 (H3N2) or influenza A/Massachusetts/18/2022 (H3N2)
- Influenza B/Austria/1359417/2021 (Victoria lineage).

In past years, the US seasonal influenza vaccine was quadrivalent. However, this year, the vaccine no longer contains the B/Yamagata strain, which has not been detected globally since March 2020.

Three types of influenza vaccines are available: inactivated (which are egg-based), recombinant (which are not egg-based), and a live attenuated formulation (which, unlike the others, is inhaled rather than injected) (Table 1).⁷

Who should be vaccinated? Influenza vaccine is recommended for all persons age 6 months and older, but certain groups may be at higher risk of medical complications attributable to severe influenza and therefore should be prioritized for vaccination⁷:

- Children age 6 through 59 months
- Adults age 50 years or older
- Adults and children who have chronic disorders—pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic (including diabetes mellitus)
- Persons who are immunocompromised due to any cause
- Persons who are or will be pregnant during the influenza season
- Children and adolescents through 18 years who are receiving aspirin- or salicylate-containing medications and who might be at risk of Reye syndrome after influenza virus infection
- Residents of nursing homes and other long-term care facilities
- American Indian or Alaska Native persons
- Persons who are extremely obese (body mass index ≥ 40 kg/m² for adults).

Ideally, influenza vaccine should be offered in September or October, according to the Advisory Committee on Immunization Practices (ACIP). However, vaccination efforts should continue as long as the influenza virus is circulating.

All persons should receive a vaccine that is appropriate for their age. Adults age 65 and older should receive an enhanced influenza vaccine (ie, either a high-dose formulation of inactivated or recombinant influenza vaccine, or adjuvanted influenza vaccine), if these are available. Live attenuated influenza vaccine is not recommended in pregnancy or for immunocompromised persons.⁷

Persons with egg allergies may receive egg-based vaccines and are not at increased risk for adverse events in doing so.⁸ In most cases, no additional safety measures are needed when giving egg-based influenza vaccines to egg-allergic individuals.

COVID-19 vaccination is still needed

There are 2 types of COVID-19 vaccines: messenger RNA (mRNA)–based and protein subunit (spike)–based. The US Food and Drug Administration has approved the 2024–2025 COVID-19 mRNA vaccines by Moderna (Spikevax) and Pfizer-BioNTech (Comirnaty) for persons 12 years and older. These vaccines are also approved for children age 6 months to 11 years under emergency use authorization. The 2024–2025 COVID-19 adjuvanted protein subunit vaccine by Novavax (Nuvaxovid, Covovax) is also approved under emergency use authorization for persons 12 years and older.

The approved vaccines are monovalent and protect against the currently circulating JN.1 variant of COVID-19.^{9,10}

The ACIP recommends a US Food and Drug Administration–approved 2024–2025 COVID-19 vaccine for all persons age 6 months and older.

Why do we still need COVID-19 vaccinations?

Although hospitalization and death rates are much lower now than at the height of the pandemic, COVID-19 infection remains an ongoing public health concern. During the 2023–2024 season, by age group, the COVID-19–associated hospitalization rate was highest in those age 75 and older, in whom it peaked at 207 cases per 100,000 people in December 2023.¹¹ However, in the same month, hospitalization rates were also high in adults 65 through 74 years old (63 cases per 100,000 people) and infants younger than 6 months (75 cases per 100,000 people).¹¹ COVID-19–associated death rates were also highest in those 75 and older (peak of 46 deaths per 100,000 people in January 2024).¹¹

Data from the 2023–2024 bivalent COVID-19 vaccine were reviewed in the approval process for the updated vaccines.¹² Vaccine effectiveness, a comparison of the frequency of disease in vaccinated and unvaccinated people in real-world conditions, was evaluated for various end points in adults and adolescents: medically attended emergency department and urgent care visits due to COVID-19 (pooled vaccine effectiveness 43%), hospitalization due to COVID-19 (pooled vaccine effectiveness 44%), and prevention of death due to COVID-19 (pooled vaccine effectiveness 23%).

A vaccine effectiveness of 23% means that vaccination reduces the risk of death by 23%. This might seem like a modest reduction, but remember that the most vulnerable individuals have already been affected by the disease, and over time population immunity—due to vaccination and previous infections—continues to increase. In infants and children, the vaccine effectiveness in terms of medically attended emergency department and urgent care visits was 80%.¹²

Regarding safety, investigations are ongoing regarding possible associations between Guillain-Barré syndrome and Pfizer-BioNTech COVID-19 vaccine among people 65 years and older, ischemic stroke and Moderna COVID-19 vaccine in the same age group, and ischemic stroke and the Pfizer-BioNTech vaccine among adults age 50 to 64 years. However, at this time, no direct link to vaccination has been established.¹²

In August 2021, 69% of adults reported being up to date on COVID-19 vaccines. This had dropped to 28% in February 2024.¹² The 2024–2025 COVID-19 vaccines can provide protection against currently circulating variants and reduce rates of COVID-19–associated hospitalization and death.¹²

Respiratory syncytial virus vaccination

Three RSV vaccines are available from GSK, Moderna, and Pfizer. The GSK and Pfizer RSV vaccines are protein subunit products, while the Moderna RSV vaccine is an unadjuvanted mRNA-based product (Table 2).^{13–16} Overall, the Pfizer RSV vaccine demonstrated strong efficacy that was maintained over 2 seasons, and it was well tolerated by patients.¹⁵

Revised recommendation. In June 2024, the ACIP¹³ revised its recommendation on RSV vaccination. Previously, it said that adults age 60 years and older *may* receive a single dose of RSV vaccine; now, it says that all adults age 75 years and older *should* receive it, as should those age 60 through 74 years who are at higher risk for severe RSV disease, including, for example, those with any of the following:

- Chronic cardiovascular disease
- Chronic lung or respiratory disease
- End-stage renal disease
- Diabetes mellitus with complications or taking insulin, a sodium-glucose cotransporter 2 inhibitor, or both
- Neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness
- Chronic liver disease
- Chronic hematologic conditions
- Severe obesity (body mass index ≥ 40 kg/m²)
- Moderate or severe immune compromise
- Residence in a nursing home
- Other high-risk factors at the discretion of the clinician.

Pregnant women should also be vaccinated, which is beneficial both for their own protection and for passing on immunity to their babies. Only the Pfizer RSV vaccine is approved to be given in pregnancy.^{14,15}

TABLE 2
Respiratory syncytial virus vaccines

Brand name (vaccine form)	Approved ages ^a	Dose	Efficacy, % ^b	Side-effect rates, %
Arexvy (inactivated protein subunit, adjuvanted) ¹⁵	≥ 75 years 60–74 years with high-risk factor	0.5 mL	Season 1: 94.1 Season 2: 84.6	Severe reactogenicity events 3.8 (vs 0.9 with placebo) Pain 60.9 Fatigue 33.6 Myalgia 28.9 Headache 27.2
Abrysvo (inactivated protein subunit, nonadjuvanted) ^{14,15}	≥ 75 years 60–74 years with high-risk factor Pregnant at 32–36 weeks' gestation	0.5 mL	Season 1: 88.9 Season 2: 78.6	Severe reactogenicity events 1.0% (vs 0.7% with placebo) Pain 10.5 Fatigue 15.5 Myalgia 10.1 Headache 12.8
mResvia (inactivated messenger RNA encoding the respiratory syncytial virus F glycoprotein) ^{13,16}	≥ 75 years 60–74 years with high-risk factor	0.5 mL	Season 1: 80.9 Season 2: 61.1	Severe reactogenicity events 6.1 (vs 4.0 with placebo) Pain 55.9 Fatigue 30.8 Myalgia 25.6 Headache 26.7

^aThis table does not include maternal indication data.

^bEfficacy in preventing symptomatic, laboratory-confirmed respiratory syncytial virus–associated lower respiratory tract disease with at least 3 lower respiratory signs.

VIRAL TESTING WITH REVERSE-TRANSCRIPTION POLYMERASE CHAIN REACTION TESTS

It can be hard to tell which virus a patient has solely on the basis of signs and symptoms. Multiple respiratory viruses are often circulating simultaneously and producing similar clinical signs. Perhaps the distinction did not matter so much in the past, when we could just say “the patient has a virus.” But now we have specific drugs for some viruses, and moreover, the drugs need to be started as soon as possible after the onset of symptoms. Thus, the need for laboratory tests to identify the pathogen—and quickly! Delays in obtaining precise and timely results can compromise patient care.¹⁷

Triple reverse-transcription polymerase chain reaction (RT-PCR) tests can simultaneously detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, which causes COVID-19), influenza, and RSV from a nasopharyngeal swab, and their use can accelerate the process from sampling to diagnosis to treatment. As COVID-19 and influenza have specific antiviral treatments, testing for them conserves resources, especially when timely treatment prevents severe illness or hospitalization. Multiplex assays such as these also have the potential to enhance and expand surveillance

systems, leveraging the capabilities developed during the COVID-19 pandemic to improve epidemic and pandemic preparedness, prevention, and response.¹⁷

Using RT-PCR rather than rapid antigen tests may seem counterintuitive, since the latter are, well, rapid, and patients can do them themselves in the comfort and privacy of their own homes. However, PCR is more sensitive than rapid antigen testing and thus gives fewer false-negative results. Also, testing for 3 viruses at once is an advantage, and if we get organized and set up our practices to obtain and process RT-PCR tests quickly, the time and convenience factors can be overcome.

In a study in 263 children, the sensitivity of a triple RT-PCR test was 88.9% (95% confidence interval [CI] 51.8%–99.7%) for SARS-CoV-2, 91.6% (95% CI 84.1%–96.3%) for influenza, and 79.1% (95% CI 64.0%–90.0%) for RSV.¹⁸ Specificity was 100% for each virus.

We encourage both patients and clinicians to prioritize early testing, ideally using nasopharyngeal swab PCR platforms rather than home antigen tests. In a study in Florida, state organizations provided PCR testing for individuals who tested positive on the home antigen tests, showed symptoms, or requested PCR testing.¹⁹ Of 18,457 individuals tested, 3,153 (17.1%)

TABLE 3
COVID-19 outpatient treatments

Treatments	Who ^a	When	How	Clinical considerations
Molnupiravir	Adults	Start as soon as possible; must begin within 5 days of symptom onset	Taken at home orally	Not recommended in pregnant or lactating women No renal or hepatic adjustment
Nirmatrelvir-ritonavir	Adults; children ages 12 years and older	Start as soon as possible; must begin within 5 days of symptom onset	Taken at home orally	Renal dosing if estimated glomerular filtration rate is 30–59 mL/min, and not recommended if < 30 mL/min Review drug-drug interactions
Remdesivir	Adults and children	Start as soon as possible; must begin within 7 days of symptom onset	Intravenous infusions at a healthcare facility for 3 consecutive days	Consider stopping if patient develops alanine aminotransferase (ALT) elevation ≥ 10 times the upper limit of normal during treatment Discontinue if ALT elevation is accompanied by signs or symptoms of liver inflammation

^aAge ≥ 65 years and those with certain underlying medical conditions including: asthma, cancer (hematologic malignancy), cerebrovascular disease, chronic kidney disease (people receiving dialysis), chronic lung diseases (bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension), chronic liver diseases (cirrhosis, nonalcoholic fatty liver disease, alcoholic fatty liver disease, autoimmune hepatitis), cystic fibrosis, diabetes mellitus type 1 and 2, disabilities including Down syndrome, heart disease (heart failure, coronary artery disease, cardiomyopathies), human immunodeficiency virus, mental health conditions (mood disorders, schizophrenia), neurologic conditions (dementia), obesity, physical inactivity, recent or current pregnancy, primary immunodeficiencies, current or former smoking, transplantation, tuberculosis, and use of corticosteroids or immunosuppressive medications.

Information from references 20 and 21.

TABLE 4
Anti-influenza outpatient treatments

Treatments	Who	When	How	Clinical considerations
Influenza treatment: oseltamivir	Adults and children from birth	As soon as possible; ideally begin within 2 days of symptom onset	Taken at home orally	For persons at high risk of complications, ^a initiate as soon as possible, even if > 2 days since symptom onset Renal dosing if creatinine clearance is < 60 mL/min
Influenza prevention after exposure ^b : oseltamivir	Adults and children from 3 months of age at very high risk for influenza complications ^a	Start as soon as possible after exposure	Taken at home orally	Prophylaxis and treatment dosing differ—refer to your institutional guideline Renal dosing if creatinine clearance is < 60 mL/min

^aAdults ≥ 65 years, people who are pregnant or post partum (within 2 weeks after delivery), residents of long-term care facilities, non-Hispanic Black persons, Hispanic or Latino persons, American Indians and Alaska natives, persons with body mass index ≥ 40 kg/m², and individuals with certain chronic medical conditions (eg, pulmonary, cardiovascular, endocrine [eg, diabetes mellitus], renal, hepatic, hematologic, metabolic, neurologic, human immunodeficiency virus, malignancy), or those receiving immunosuppressive medications.

^bContact within the past 48 hours with a confirmed or suspected case.

Information from reference 22.





Caregiver Instructions

Nasopharyngeal Swab Collection for Respiratory Virus Testing

These instructions illustrate how to correctly use a swab to collect a specimen for respiratory virus testing.

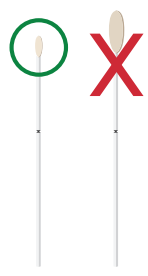
1. Don the appropriate PPE. Refer to the Standard Precautions Policy.



2. Document the collection in Epic, print the label, and place the label on the UTM tube. Verify patient identifiers on the label with the patient before collecting the specimen.

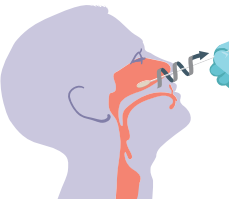


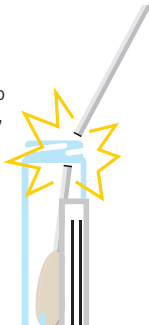
UTM
(Universal Transport Media)
3. Obtain a UTM, Nasopharyngeal Swab with a flexible shaft for specimen collection.

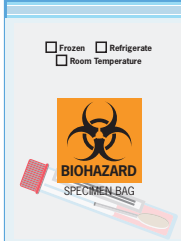
Small swab, flexible shaft = Nasopharynx
Large swab, rigid shaft = Nasal/Nares


4. Tilt the patient's head back 70 degrees. Gently and slowly insert the mini-tip swab through the nostril parallel to the palate (not upward) until you encounter resistance or the distance is equivalent to that from the patient's ear to the nostril, indicating contact with the nasopharynx. Gently rub and roll the swab. Leave the swab in place for several seconds to absorb secretions.


5. Slowly remove the swab while rotating it. If the swab is saturated or a nostril is blocked, collection from one nostril is adequate."


6. Place the swab, tip first, into the transport tube provided. Break the swab shaft at the score line, discard the top portion of the stem, and close the cap.


7. Place the UTM into a biohazard bag and walk or send it via the tube system to the lab.



Specimens will be rejected if there is more than one swab in transport media, no swabs in the transport media, dry swabs without transport media, or if they are inappropriately labeled.

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Figure 1. Nasopharyngeal swab collection for respiratory virus testing.

PPE = personal protective equipment

were PCR-positive. The positive percent agreement of the antigen test compared with PCR was 49.2% overall and 51.9% for people with symptoms. The study found that the antigen test's performance was lower than previously reported. Without amplification and with the potential for incomplete sample collection when conducted at home rather than by healthcare professionals, real-world antigen testing is expected to be less accurate than PCR testing. Additionally, a negative result from a home antigen test—especially early in the course of illness—should be repeated in 2 to 3 days, when viral load is typically higher, often leading to a positive result at that time.¹⁹

Starting antiviral medications early is important—within 2 days for oseltamivir and 5 days for nirmatrelvir-ritonavir, molnupiravir, and remdesivir for patients with intact immune systems—emphasizing the importance of prompt testing. Patients on steroids, other immunosuppressant medications, or periodic infusions (eg, adalimumab, ocrelizumab) should start oseltamivir with a confirmed influenza diagnosis regardless of duration of symptoms (Table 3,^{20,21} Table 4²²).

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GETTING READY

Every year, the respiratory viral season puts a strain on the entire medical system, from clinician offices to diagnostic laboratories to hospitals. Before the onset of the season, it is helpful to establish clear and straightforward procedures in the office for ordering PCR nasopharyngeal swabs when symptoms arise (Figure 1). Training office staff, and possibly yourself, in the correct technique for specimen collection is essential, as accurate results depend on obtaining cells from the swab. Viruses are obligate intracellular pathogens and, therefore, you must get cells on the swab. Don't be too gentle, as this can affect test accuracy.

Additionally, practices need to develop treatment protocols and possibly template prescriptions to facilitate timely issuance of medications (Table 3,^{20,21} Table 4²²). Pay particular attention to nirmatrelvir-ritonavir due to its potential for drug-drug interactions.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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