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# Hey, Doc: Could the 2023–2024 cold and flu season finally be the calm after the storm?

**T**HE 2023–2024 COLD AND FLU season is the first in history in which we're armed with vaccines against the 3 currently most common viral respiratory pathogens: influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the causative agent for coronavirus 2019 [COVID-19]), and respiratory syncytial virus (RSV). So, while the 2022–2023 season was viewed as a "triple-demic" or a "perfect storm,"<sup>1</sup> now, a year later, with these 3 vaccines, we are in a much better place.

In addition, home antigen testing kits for COVID-19 have been widely available for the last 2 years, and in February 2023 the US Food and Drug Administration (FDA) approved a combined influenza and COVID-19 home antigen detection test.<sup>2</sup> There are reasons for pursuing a specific laboratory diagnosis for viral upper respiratory tract infections: symptoms and signs have low diagnostic specificity, outcomes of antiviral treatment are better with early diagnosis, and, just as important, we need to be good stewards of antibacterial drugs. This is especially important with wider use of telemedicine and easy access to antibiotics on demand.<sup>3</sup> Recently, an FDA panel voted that although nasal decongestants decrease nasal airway resistance, they provide only temporary symptom relief.<sup>4</sup>

Despite cumulative data showing that RSV, influenza, and COVID-19 have similar disease severity among hospitalized adults age 60 and older,<sup>5</sup> and despite recent data showing long-term symptoms not only after COVID-19 but also after other acute respiratory viral infections,<sup>6</sup> vaccine coverage remains suboptimal, and vaccine hesitancy is widespread, including among pregnant women.<sup>7</sup>

Here, I will answer important "Hey, Doc" questions our patients have about the currently available influenza, COVID-19, and RSV vaccines.

## ***Hey, Doc: Why do I have to keep getting the flu shot every year?***

Shift happens. Pardon the pun: genetic shift is a sudden, relatively large change in the virus's genome, as opposed to genetic drift, which is the expected, gradual accumulation of small changes. This virus keeps drifting every year, but occasionally it shifts, precipitating pandemics and thus keeping us searching for the Holy Grail, a universal flu vaccine that would be good once and for all. Even though vaccinated people shed more virus than unvaccinated people, hospitalization and mortality rates are lower in vaccinated people.<sup>8</sup>

## ***Is there anything new about the flu shot this year (other than shifting)?***

Well, yes. I recall you were always trying to weasel out of getting your flu shot because you're allergic to eggs. For several years, the US Centers for Disease Control and Prevention (CDC) considered severe egg allergy a relative contraindication for receiving an egg-based influenza vaccine. This year, enough data have accumulated showing that people with egg allergies can receive any flu vaccine, egg-based or non-egg-based.<sup>9</sup>

## ***Why must the CDC keep guessing every year how good the flu shot is going to be?***

Guessing is not the right word. The CDC predicts influenza vaccine effectiveness based on circulating flu serotypes at the time the vaccine is manufactured.

Most influenza vaccines are produced using embryonated hen's eggs. Sialic acid receptors on the surface of human and avian cells are the binding sites for influenza virus. Differences between the human and avian sialic acid receptors may select for mutated viral variants that

doi:10.3949/cjfm.90a.23088

are better adapted for propagation in eggs. While this enhances affinity for avian cells, it unfortunately may reduce the vaccine's match to circulating viruses by 7% to 21%, and consequently reduce vaccine effectiveness by 4% to 16%.<sup>10</sup> In comparison, antigenic drift reduces vaccine match to circulating viruses by 8% to 24%, and reduces vaccine effectiveness by 5% to 20%.

Egg adaptation does not occur with the cell culture flu vaccine, making it about 10% more effective than egg-based vaccines.<sup>11</sup> While we cannot control viral antigenic drift or shift, we can avoid the reduction in vaccine match and effectiveness resulting from egg adaptation by avoiding egg-based vaccine production.

### ***Does the CDC really know how good this year's flu shot will be?***

Yes. The 2023 Southern Hemisphere seasonal influenza vaccine, which included influenza antigenic serotypes similar to those targeted by the 2023–2024 Northern Hemisphere influenza vaccine formulation, reduced the risk for influenza-associated hospitalizations by 52%.<sup>12</sup>

### ***Can you look at your crystal ball to tell me what to expect for next year's flu shot?***

No crystal ball is needed. The World Health Organization provided an update on September 29, 2023, indicating that the B/Yamagata lineage antigen (1 of the 2 influenza B serotypes in the current quadrivalent influenza vaccine) will no longer be needed.<sup>13</sup> So, we may be back to a trivalent vaccine next year, rather than the current quadrivalent one.

### ***Is COVID-19 still bad out there?***

Because many of us have had COVID-19 at least once by now, and most of us have received at least 1 dose of the COVID-19 vaccine, disease severity has fortunately decreased. However, COVID-19 continues to circulate year-round in the United States and Europe, with hospitalizations and deaths peaking in November through April.<sup>14</sup> Recent data from the United States showed that between January and August 2023, adults age 65 and older, particularly those with multiple underlying conditions, accounted for almost two-thirds of COVID-19-related hospitalizations, and fewer than a quarter of them had received the bivalent COVID-19 vaccine recommended during that period.<sup>15</sup>

COVID-19 vaccines prevented an estimated 1.5 million hospitalizations and 200,000 deaths during the first 10 months they were available.<sup>16</sup> Vaccine effectiveness of 3 doses of the first-generation COVID-19 messenger RNA (mRNA) vaccines dur-

ing the omicron BA.4/BA.5 sublineage-predominant periods was 68% for 4 months after vaccination but decreased to 36% after that.<sup>17</sup>

### ***Is there a way to detect COVID-19, perhaps in the air we breathe, before things get out of hand again?***

Funny you should ask. The concentration of SARS-CoV-2 in wastewater appeared to predict COVID-19 cases and hospitalizations in the United States, with the maximum sensitivity (93%) and specificity (82%) at a concentration of 51% relative to the peak in January 2022.<sup>18</sup>

### ***I've already had 5 COVID-19 shots and I have no clue what to call them anymore! Monovalent, bivalent, primary series, boosters? My head is spinning. What are you calling them this year?***

My head is spinning too!

SARS-CoV-2 is changing much more quickly than the influenza virus. Remember, we first had the wild type, then delta, then omicron. The current updated omicron XBB.1.5-adapted monovalent vaccine generates immune response against multiple XBB-related sublineage variants, including XBB.1.5, XBB.1.16, XBB.2.3, and EG.5.1 (Eris), which continue to dominate globally, and it is recommended for everyone 6 months of age and older.<sup>19</sup> This updated COVID-19 vaccine is not a booster, and it aims to further improve protection against severe illness and hospitalization.

The number of recommended doses depends on multiple factors, including receipt of prior COVID-19 vaccines, age, and underlying immunosuppressed states (Table 1).<sup>20</sup> The CDC recommends delaying receipt of the updated vaccine for 3 months after being diagnosed with COVID-19 infection.

### ***I read online that the mRNA COVID-19 vaccine can change my genetic makeup. What's up with that?***

Don't believe everything you read online. There are mRNA vaccines for other indications that have been studied for more than half a century, and they cannot change our genetic makeup (ie, our DNA, deoxyribonucleic acid) stored in the cell nucleus.<sup>21</sup> Human mRNA carries DNA-encoded information from the cell nucleus to the cytoplasmic ribosomes, which translate this information into amino acids, the building blocks of proteins. Once human mRNA completes its job, it rapidly degrades.

Similarly, synthetic mRNA vaccines expose human cells to COVID-19 spike protein, stimulating them to mount a protective immune response in the event of future exposure to SARS-CoV-2. This synthetic mRNA rapidly degrades after entering the human body.

**TABLE 1**  
**Guidance for the 2023–2024 COVID-19 vaccines for people age 12 and older**

Immune status	Vaccines received previously	What to give now
Not moderately or severely immunocompromised	None	1 dose of Moderna, or 2 doses of Novavax, or 1 dose of Pfizer
	1 or more doses of any messenger RNA vaccine, or 1 or more doses of Novavax or Janssen, including in combination with any original monovalent or bivalent COVID-19 vaccine doses	1 dose of Moderna, or 1 dose of Novavax, or 1 dose of Pfizer
Moderately or severely immunocompromised	None	3 doses of Moderna, or 2 doses of Novavax, or 3 doses of Pfizer
	1 dose of any Moderna	2 doses of Moderna
	2 doses of any Moderna	1 dose of Moderna
	1 dose of any Pfizer	2 doses of Pfizer
	2 doses of any Pfizer	1 dose of Pfizer
	3 or more doses of any messenger RNA vaccine, or 1 or more doses of Novavax or Janssen, including in combination with any original monovalent or bivalent COVID-19 vaccine doses	1 dose of Moderna, or 1 dose of Novavax, or 1 dose of Pfizer

Adapted from reference 20.

***Should even my 13-year-old grandson, who is healthy as a horse and is on his school's football team, take the COVID-19 shot? I heard it can affect his heart.***

Yes, he should, to protect himself as well as to protect you! More studies are showing that cardiac complications such as myocarditis are much more common after COVID-19 infection than after receiving COVID-19 vaccine.<sup>22</sup>

***What is the US government doing to tackle COVID-19 vaccine disparities among racial minorities, particularly after discontinuing the government-funded vaccination program?***

Thank you for bringing up the elephant in the room. COVID-19 vaccine disparities in the United States remain a problem, even in vulnerable populations such as residents of long-term care facilities<sup>23</sup> and pregnant women.<sup>24</sup> One thing is clear: not only do healthcare providers' recommendations to receive the COVID-19 vaccine positively impact patients' decisions, on-site administration of this and other indicated vaccines further increases vaccination rates.<sup>25</sup>

In September 2023, the US Department of Health and Human Services launched the Bridge Access Pro-

gram to safeguard free COVID-19 vaccination for 25 to 30 million uninsured and underinsured adults.<sup>26</sup>

***Is it true that a drug approved for treatment of COVID-19 is named after one of the Marvel Comics Avengers? Can it actually increase the spread of altered virus and thus further prolong the pandemic?***

You're partially right. Molnupiravir is named after Mjöltnir, the hammer of the Norse god Thor. Molnupiravir induces viral genomic mutations, impairing viral replication and reducing viral load. And patients in whom SARS-CoV-2 infection is not completely eradicated can—possibly unknowingly—transmit this mutated virus to other people.<sup>27</sup> The clinical impact of infection with a molnupiravir-associated mutated virus is yet to be determined.

***Please tell me we'll never go back to the 'lockdown' and universal masking days!***

I hate to disappoint you, but I'm afraid I cannot say that. So-called nonpharmaceutical interventions are what carried us through this pandemic: social-distancing measures (including stay-at-home orders, physical distancing, and restrictions on gathering size and room occupancy), masking (particularly with higher quality

masks [respirators] in healthcare settings), testing, contact tracing and isolating (of infected people as well as their contacts), travel restrictions and controls across international borders, and environmental controls (such as enhanced ventilation and air treatment to remove infectious virus<sup>28</sup>), together with widespread, effective vaccination.

### ***Is long COVID really the bogeyman? How scared should I be?***

We are learning more and more about long COVID. You should not be scared if you're protecting yourself by following the nonpharmaceutical interventions we talked about and by staying up to date on your COVID-19 vaccinations.

About 7% of US adults who had COVID-19 develop long COVID.<sup>29</sup> Women are about 1.5 times more likely than men to develop long COVID. The highest rate is in adults ages 35 to 49 compared with other age groups. Hispanic people are disproportionately affected, with a rate more than 3 times higher than in Asian people. Adults living in rural areas are more likely to develop long COVID than adults living in large central metropolitan areas. Adults with family incomes at 400% or more of the federal poverty level are less likely to develop long COVID.

Researchers from the University of Oxford in the United Kingdom performed serial brain magnetic resonance imaging and cognitive tests in 401 people with mild COVID-19 and 384 without COVID-19, ages 51 to 81.<sup>30</sup> Patients with COVID-19 had greater reduction in gray matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus, greater changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex, greater reduction in global brain size, and greater cognitive decline. These degenerative or neuroinflammatory changes involving the limbic cortex may have resulted from spread of the infection through olfactory pathways, or from the loss of sensory input due to anosmia. So it's unclear whether these changes are the chicken or the egg. Time will tell whether they are reversible.

### ***What about the new RSV vaccine? I thought only kids get this virus.***

Far from the truth. RSV sickens as many older adults as influenza does. Of the people that RSV infection

sends to the hospital, most are age 75 or older, reside in long-term care facilities, or have underlying obesity, chronic obstructive pulmonary disease, or congestive heart failure.<sup>31</sup> In 2023, after several decades of research, the FDA approved 2 RSV vaccines for adults age 60 and older.<sup>32</sup>

Adults ages 70 to 79, particularly those with underlying chronic lung and heart disease, benefit most from this vaccine, which decreases the incidence and severity of infection.<sup>33</sup> No data are available describing the effect of the RSV vaccine on infectivity. RSV vaccine development started in the 1960s. Real-world experience with RSV vaccines remains to be seen.

### ***My niece is pregnant. Should she get all these shots now or wait until she delivers the baby?***

Several studies over the last decade demonstrated the protective effect of influenza vaccination during pregnancy for newborns and infants 6 months and younger.<sup>34</sup> More recently, similar studies demonstrated similar protective effects of COVID-19 vaccination during pregnancy.<sup>35</sup> The good news is that the new RSV vaccine is also approved for pregnant persons at 32 to 36 weeks of gestation to prevent RSV-associated bronchiolitis in their newborns and infants up to 6 months after they are born.<sup>36</sup>

We can now nickname the influenza, COVID-19, and RSV vaccines the “mighty trio,” protecting those youngsters with yet-immature immune systems who would not mount protective responses to these vaccines.

### ***I'm 61 years old, so I'm not a kid, but I'm also not that old! Did I hear you correctly that you want me to take 3 shots today?***

Yes. While I understand that nobody is eager to take yet another shot for the cold and flu season, experts advise that these shots can be coadministered.<sup>37</sup> Unfortunately, combined vaccines against any of these viruses will not be available for the current season.<sup>38</sup> ■

## ■ DISCLOSURES

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

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