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# How to respond to flu vaccine doubters

**T**HE BENEFITS OF INFLUENZA VACCINATION are clear to those in the medical community. Yet misinformation and unfounded fears continue to discourage some people from getting a flu shot. During the 2018–2019 influenza season, only 45% of US adults and 63% of children were vaccinated.<sup>1</sup>

What should we tell patients who say no to the flu shot? Here are 12 reasons people give for not wanting to receive the inactivated influenza vaccine, along with some potential responses and comments about the nasal live-attenuated vaccine (Table 1).

## ■ 'IT DOESN'T WORK FOR MANY PEOPLE'

Multiple studies have shown that the flu vaccine prevents millions of flu cases and flu-related doctor's visits each year. During the 2016–2017 flu season, flu vaccine prevented an estimated 5.3 million influenza cases, 2.6 million influenza-associated medical visits, and 85,000 influenza-associated hospitalizations.<sup>2</sup>

Several viral and host factors affect vaccine effectiveness. In seasons when the vaccine viruses have matched circulating strains, flu vaccine has been shown to reduce the following:

- The risk of having to go to the doctor with flu by 40% to 60%
- Children's risk of flu-related death and intensive care unit (ICU) admission by 74%
- The risk in adults of flu-associated hospitalizations by 40% and ICU admission by 82%
- The rate of cardiac events in people with heart disease
- Hospitalizations in people with diabetes or underlying chronic lung disease.<sup>3</sup>

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In people hospitalized with influenza despite receiving the flu vaccine for the season, studies have shown that receiving the flu vaccine shortens the average duration of hospitalization, reduces the chance of ICU admission by 59%, shortens the duration of ICU stay by 4 days, and reduces deaths.<sup>3</sup>

Since 2010, the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) has recommended routine annual influenza vaccination for all persons 6 months of age and older who do not have a contraindication to it.<sup>4</sup> Table 2 summarizes the current contraindications to and cautions regarding influenza vaccination.

## ■ 'IT TARGETS THE WRONG VIRUS'

Selecting an effective influenza vaccine is a challenge. Every year, the World Health Organization and the CDC decide on the influenza strains expected to circulate in the upcoming flu season in the Northern Hemisphere, based on data for circulating strains in the Southern Hemisphere. This decision takes place about 7 months before the expected onset of the flu season. Flu viruses may mutate between the time the decision is made and the time the vaccine is administered (as well as after the flu season starts). Also, vaccine production in eggs needs time, which is why this decision must be made several months ahead of the flu season.

Vaccine effectiveness varies by virus serotype. Vaccines are typically less effective against influenza A H3N2 viruses than against influenza A H1N1 and influenza B viruses. Effectiveness also varies from season to season depending on how close the vaccine serotypes match the circulating serotypes, but some effectiveness is

**Misinformation and unfounded fears persist. What should we tell patients who say no to the flu shot?**

TABLE 1

**Reasons people give for not wanting the influenza vaccine, and potential responses**

Reason	Potential responses
<b>'It doesn't work for many people'</b>	While the vaccine may not work for some people, it does work for most. Even when it does not prevent influenza, it makes influenza-related illness less severe.
<b>'It has been made to target the wrong virus'</b>	Even when vaccine serotypes don't match circulating virus serotypes, some effectiveness is retained. Some protection is better than none. A universal flu vaccine that does not need to be updated annually is likely several years away.
<b>'It makes people sick'</b>	The inactivated vaccine cannot biologically "make people" get influenza, as the virus in the vaccine is inactivated. The nasal live-attenuated vaccine can result in acute upper respiratory tract symptoms, but because it is cold-adapted, it multiplies in the nose, eliciting immunity—but not in the lungs, and thus cannot cause influenza pneumonia.
<b>'It causes Guillain-Barré syndrome (GBS)'</b>	The increased risk of GBS in the 6 weeks after vaccination reported in 1976 has not been seen in more than 40 influenza seasons since then. The risk is 15 times higher after influenza <i>illness</i> than after influenza <i>vaccination</i> .
<b>'I got the flu shot, and I still got sick'</b>	The vaccine is intended to prevent influenza. It does not prevent other viral or bacterial illness that may mimic influenza.
<b>'I'm allergic to eggs'</b>	Persons with a history of urticaria (hives) after exposure to eggs can receive any influenza vaccine.  Persons with a history of angioedema, respiratory distress, lightheadedness, or recurrent vomiting, or who required epinephrine or other emergency intervention after exposure to eggs, should receive the vaccine only in an inpatient or outpatient setting, monitored for severe allergic reactions.  History of a severe allergic reaction such as anaphylaxis to a previous dose of any influenza vaccine, regardless of the suspected component (eg, eggs), is a contraindication to influenza vaccination.
<b>'I don't want to put poisonous mercury in my body'</b>	Ethylmercury preservative in influenza vaccine is safe, but methylmercury in fish, if ingested in large quantities, can be toxic to the central nervous system.
<b>'I don't like needles'</b>	Take the nasal flu vaccine.
<b>'I don't want to take anything that can mess with my other medications'</b>	Immunosuppressive drugs may reduce influenza vaccine immunogenicity, but the vaccine does not alter the efficacy of these drugs, other medications, or vaccines.
<b>'I'm afraid it will trigger an immune response that will make my asthma worse'</b>	The inactivated influenza vaccine does not precipitate asthma exacerbations. Rather, it prevents 59%–78% of attacks leading to emergency visits or hospitalization. The live-attenuated influenza vaccine is contraindicated in children 2 to 4 years old with asthma.
<b>'I had an organ transplant, and I'm afraid the flu shot will cause organ rejection'</b>	Influenza infection—not the vaccine—can precipitate organ rejection.
<b>'I'm pregnant, and I don't want to expose my unborn baby to anything potentially harmful'</b>	The flu vaccine during pregnancy protects you and your infant, since protective antibodies are transmitted through the placenta and can last up to 6 months. After the age of 6 months, the child should get annual influenza vaccination.

**TABLE 2**

**Contraindications and precautions to the use of influenza vaccines**

Contraindications	Precautions
History of a severe allergic reaction such as anaphylaxis to a previous dose of any influenza vaccine, regardless of the component suspected (including eggs)	Moderate or severe acute illness with or without fever
<b>For the live-attenuated quadrivalent influenza vaccine only:</b>	
Concomitant aspirin- or salicylate-containing therapy in children and adolescents	Asthma in persons age 5 and older
Children 2 to 4 years old who have diagnosed asthma or whose parents or caregivers report that a healthcare provider has told them during the past 12 months that their child had wheezing or asthma, or whose medical record indicates a wheezing episode in the past 12 months	Other underlying medical conditions that may predispose to complications after wild-type influenza infection:
Children and adults who are immunocompromised due to any cause including immunosuppressive medications and human immunodeficiency virus infection	Chronic pulmonary disease
Close contacts and caregivers of severely immunosuppressed persons who require care in a protected environment	Cardiovascular disease, excluding isolated hypertension
Pregnancy	Renal, hepatic, neurologic, hematologic, or metabolic disorders including diabetes mellitus
Receipt of influenza antiviral medication within the past 48 hours	

Adapted from reference 4.

retained even in seasons when some of the serotypes don't match circulating viruses. For example, in the 2017–2018 season, when the influenza A H3N2 vaccine serotype did not match the circulating serotype, the overall effectiveness in preventing medically attended, laboratory-confirmed influenza virus infection was 36%.<sup>5</sup>

A universal flu vaccine that does not need to be updated annually is the ultimate solution, but according to the National Institute of Allergy and Infectious Diseases, such a vaccine is likely several years away.<sup>6</sup>

**■ 'IT MAKES PEOPLE SICK'**

Pain at the injection site of a flu shot occurs in 10% to 65% of people, lasts less than 2 days, and does not usually interfere with daily activities.<sup>7</sup>

Systemic symptoms such as fever, malaise, and myalgia may occur in people who have had no previous exposure to the influenza virus antigens in the vaccine, particularly in children. In adults, the frequency of systemic symptoms after the flu shot is similar to that with placebo.

The Vaccine Adverse Event Reporting System, which has been capturing data since 1990, shows that the influenza vaccine accounted for 5.7% of people who developed malaise after receiving any vaccine.<sup>8</sup>

The injectable inactivated influenza vaccine cannot biologically cause an influenza virus-related illness, since the inactivated vaccine viruses can elicit a protective immune response but cannot replicate. The nasal live-attenuated flu vaccine can in theory cause acute illness in the person receiving it, but because it is cold-adapted, it multiplies only in the colder environment of the nasal epithelium, not in the lower airways where the temperature is higher. Consequently, the vaccine virus triggers immunity by multiplying in the nose, but doesn't infect the lungs.

From 10% to 50% of people who receive the nasal live-attenuated vaccine develop runny nose, wheezing, headache, vomiting, muscle aches, fever, sore throat, or cough shortly after receiving the vaccine, but these symptoms are usually mild and short-lived.

The most common reactions people have to flu vaccines are considerably less severe than the symptoms caused by actual flu illness.

While influenza illness results in natural immunity to the specific viral serotype causing it, this illness results in hospitalization in 2% and is fatal in 0.16% of people. Influenza vaccine results in immunity to the serotypes included in the vaccine, and multiple studies have not found a causal relationship between vaccination and death.<sup>9</sup>

### ■ 'IT CAUSES GUILLAIN-BARRÉ SYNDROME'

In the United States, 3,000 to 6,000 people per year develop Guillain-Barré syndrome, or 1 to 2 of every 100,000, which translates to 80 to 160 cases per week.<sup>10</sup> While the exact cause of Guillain-Barré syndrome is unknown, about two-thirds of people have an acute diarrheal or respiratory illness within 3 months before the onset of symptoms. In 1976, the estimated attributable risk of influenza vaccine-related Guillain-Barré syndrome in the US adult population was 1 case per 100,000 in the 6 weeks after vaccination.<sup>11</sup> Studies in subsequent influenza seasons have not shown similar findings.<sup>12</sup> In fact, one study showed that the risk of developing Guillain-Barré syndrome was 15 times higher after influenza illness than after influenza vaccination.<sup>13</sup>

Since 5% to 15% of the US population develop symptomatic influenza annually,<sup>14</sup> the decision to vaccinate with respect to the risk of Guillain-Barré syndrome should be obvious: vaccinate. The correct question to ask before influenza vaccination should be, "Have you previously developed Guillain-Barré syndrome within 6 weeks after receiving the flu vaccine?" If the answer is yes, the CDC considers this a caution, not a contraindication against receiving the influenza vaccine, since the benefit may still outweigh the risk.

### ■ 'I GOT THE FLU SHOT AND STILL GOT SICK'

The flu vaccine does not prevent illnesses caused by other viruses or bacteria that can make people sick during flu season. Influenza, the common cold, and streptococcal pharyngitis can have similar symptoms that make it difficult for patients—and, frequently, even healthcare providers—to distinguish between these illnesses with certainty.

One study suggested that influenza vaccine recipients had an increased risk of virologically confirmed noninfluenza respiratory viral infections,<sup>15</sup> citing the phenomenon of virus interference that was described in the 1940s<sup>16</sup> as a potential explanation. In essence, people protected against influenza by the vaccine may lack temporary nonspecific immunity against other respiratory viruses. However, these findings have not been replicated in subsequent studies.<sup>17</sup>

Viral gastroenteritis, mistakenly called "stomach flu," is also not prevented by influenza vaccination.

### ■ 'I'M ALLERGIC TO EGGS'

The prevalence of egg allergy in US children is 0.5% to 2.5%.<sup>18</sup> Most outgrow it by school age, but in one-third, the allergy persists into adulthood.

In general, people who can eat lightly cooked eggs (eg, scrambled eggs) without a reaction are unlikely to be allergic. On the other hand, the fact that egg-allergic people may tolerate egg included in baked products does not exclude the possibility of egg allergy. Egg allergy can be confirmed by a consistent medical history of adverse reaction to eggs and egg-containing foods, in addition to skin or blood testing for immunoglobulin E directed against egg proteins.<sup>19</sup>

Most currently available influenza vaccines are prepared by propagation of virus in embryonated eggs and so may contain trace amounts of egg proteins such as ovalbumin, with the exception of the inactivated quadrivalent recombinant influenza vaccine (Flublok) and the inactivated quadrivalent cell culture-based vaccine (Flucelvax).

The ACIP recommends that persons with a history of urticaria (hives) after exposure to eggs should receive any licensed, recommended influenza vaccine that is otherwise appropriate for their age and health status. Persons who report having angioedema, respiratory distress, lightheadedness, or recurrent vomiting, or who required epinephrine or another emergency medical intervention after exposure to eggs, should receive the influenza vaccine in an inpatient or outpatient medical setting under the supervision of a healthcare

**The best way to protect infants from influenza is for all household members to be vaccinated**

TABLE 3

Two different forms of mercury

	Ethylmercury	Methylmercury
Sources	Used as a preservative in vaccines and medicines	Foods, particularly fish, and dental amalgam
Mercury concentration	≤ 25 µg per 0.5 mL in some influenza vaccine products	Higher in larger fish: eg, 0.003 parts per million (PPM) in scallops vs 1.23 PPM in tilefish from Gulf of Mexico
Clearance from the human body	Rapid	Slow, since it is not soluble and cannot be excreted
Toxicity	Redness at injection site; no increased risk of autism	Central nervous system effects: eg, tremor, weakness, and behavioral changes

provider who is able to recognize and manage severe allergic reactions.

A history of severe allergic reaction such as anaphylaxis to a previous dose of any influenza vaccine, regardless of the vaccine component (including eggs) suspected of being responsible for the reaction, is a contraindication to influenza vaccination. The ACIP recommends that vaccine providers consider observing patients for 15 minutes after administration of any vaccine (regardless of history of egg allergy) to decrease the risk of injury should syncope occur.<sup>20</sup>

■ 'I DON'T WANT TO PUT POISONOUS MERCURY IN MY BODY'

Thimerosal is a preservative that has been used to prevent the growth of bacteria and fungi in multidose vials of vaccines and medicines in the United States for several decades.<sup>21</sup> It is important to understand the difference between ethylmercury in thimerosal and methylmercury found in certain foods (Table 3), as ethylmercury is safe, but methylmercury may not be safe, particularly when ingested in large quantities.

A process of biomagnification of methylmercury occurs when humans eat large fish that have eaten smaller fish. Thus, larger fish such as shark can be hazardous for women who are or may become pregnant, for nursing mothers, and for young children, while smaller fish such as herring are relatively safe.

As a precautionary measure, thimerosal was taken out of childhood vaccines in the United States in 2001. Thimerosal-free influ-

enza vaccine formulations include the nasal live-attenuated flu vaccine, the inactivated quadrivalent recombinant influenza vaccine, and the inactivated quadrivalent cell culture-based vaccine.

■ 'I DON'T LIKE NEEDLES'

At least 10% of US adults have aichmophobia, the fear of sharp objects including needles.<sup>22</sup> Vasovagal syncope is the most common manifestation. Behavioral therapy, topical anesthetics, and systemic anxiolytics have variable efficacy in treating needle phobia. For those who are absolutely averse to needles, the nasal flu vaccine is an appropriate alternative.

■ 'I DON'T WANT TO TAKE ANYTHING THAT CAN MESS WITH MY OTHER MEDICATIONS'

Some immunosuppressive medications may decrease influenza vaccine immunogenicity. Concomitant administration of the inactivated influenza vaccine with other vaccines is safe and does not alter immunogenicity of other vaccines.<sup>1</sup> The live-attenuated influenza vaccine is contraindicated in children and adolescents taking aspirin or other salicylates due to the risk of Reye syndrome.

■ 'I'M AFRAID IT WILL TRIGGER AN IMMUNE RESPONSE THAT WILL MAKE MY ASTHMA WORSE'

A recent systematic review and meta-analysis showed that the inactivated influenza vaccine is not associated with asthma exacerbation.<sup>23</sup>

Try to understand the public's misconceptions about influenza and influenza vaccines to best address them

However, the nasal live-attenuated influenza vaccine is contraindicated in children 2 to 4 years old who have asthma and should be used with caution in persons with asthma 5 years old and older. In the systematic review, influenza vaccine prevented 59% to 78% of asthma attacks leading to emergency visits or hospitalization.<sup>23</sup> In other immune-mediated diseases such as rheumatoid arthritis, influenza vaccine does not precipitate exacerbations.<sup>24</sup>

### ■ 'I HAD AN ORGAN TRANSPLANT, AND I'M AFRAID THE FLU SHOT WILL CAUSE ORGAN REJECTION'

A study of 51,730 kidney transplant recipients found that receipt of the inactivated influenza vaccine in the first year after transplant was associated with a lower risk of subsequent allograft loss (adjusted hazard ratio 0.77; 95% confidence interval 0.69–0.85;  $P < .001$ ) and death (adjusted hazard ratio 0.82; 95% confidence interval 0.76–0.89;  $P < .001$ ).<sup>25</sup> In the same study, although acute rejection in the first year was not associated with influenza vaccination, influenza infection in the first year was associated with rejection (odds ratio 1.58; 95% confidence interval 1.10–2.26;  $P < 0.001$ ), but not with graft loss or death. Solid organ transplant recipients should receive the inactivated influenza vaccine starting 3 months after transplant.<sup>26</sup>

Influenza vaccination has not been shown to precipitate graft-vs-host disease in hematopoietic stem cell transplant recipients. These patients should also receive the inactivated influenza vaccine starting 3 to 6 months after transplant.<sup>27</sup>

The nasal live-attenuated influenza vaccine is contraindicated in these immunocompromised patients.

### ■ 'I'M PREGNANT, AND I DON'T WANT TO EXPOSE MY UNBORN BABY TO ANYTHING POTENTIALLY HARMFUL'

The morbidity and mortality risk from influenza is high in children under 2 years old because of low immunogenicity to flu vaccine. This is particularly true in children younger than 6 months, but the vaccine is not recommended in this population. The best way to protect infants is for all household members to be vaccinated against the flu.

Equally important, morbidity and mortality risk from influenza is much higher in pregnant women than in the general population. Many studies have shown the value of influenza vaccination during pregnancy for both mothers and their infants. A recently published study showed that 18% of infants who developed influenza required hospitalization.<sup>28</sup> In that study, prenatal and postpartum maternal influenza vaccination decreased the odds of influenza in infants by 61% and 53%, respectively. Another study showed that vaccine effectiveness did not vary by gestational age at vaccination.<sup>29</sup> A post hoc analysis of an influenza vaccination study in pregnant women suggested that the vaccine was also associated with decreased rates of pertussis in these women.<sup>30</sup>

Healthcare providers should try to understand the public's misconceptions<sup>31</sup> about seasonal influenza and influenza vaccines in order to best address them.

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