

SUPPLEMENT ARTICLE

One step closer to influenza vaccine inclusiveness

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Abstract

Flu virus infection is a common cause of acute respiratory illness, with the major incidence in pediatric age, high morbidity, and mortality. The flu vaccine is recommended for all people aged ≥ 6 months, unless specific contraindications are present. Younger and older age, pregnancy, chronic diseases like asthma, and immunodeficiency are risk factors for severe complications following flu infection. Thus, these categories represent the target for flu vaccine strategies in most countries. Inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV) or live-attenuated influenza virus (LAIV) are currently available, with specific precautions and contraindications. We aim to resume the current indications for vaccines in the vulnerable populations to support flu vaccination inclusiveness, in anticipation of a "universal vaccine" strategy.

KEYWORDS

asthma, children, immunodeficiency, influenza vaccine, pregnancy, universal vaccine

1 | INTRODUCTION

Seasonal influenza virus infection is one of the most relevant causes of acute respiratory illness in children,¹ with high morbidity and mortality rate. Although flu may have an uncomplicated clinical course, it could also present itself as a severe condition. Epidemiological data showed that severe complications of flu infection occurred in more than 3 million people every year, with hundreds of thousands of deaths.² The risk of complications, hospitalization, and poor outcome is higher in specific categories of patients (ie, younger children,

the elderly, pregnant women, immunocompromised patients, and people affected by chronic conditions eg, asthma).³ It goes without saying how influenza vaccination is essential in the vulnerable hosts.² In agreement with the Advisory Committee on Immunization Practices (ACIP), we, as the Italian Pediatric Immunology and Allergology Society (SIAIP) Vaccine Committee, recommend flu vaccination for all people aged ≥ 6 months, unless they have specific contraindications. Current influenza vaccines include inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), or live-attenuated influenza virus (LAIV), to match specific needs and

contraindications,^{3,4} although a "broadly reactive" and "universal" vaccine is desirable for higher effectiveness against circulating seasonal or pandemic strains.

2 | FLU VACCINE IN ALLERGIC CHILDREN

Among children with allergies, asthmatic patients are prone to a more severe clinical course in a flu infection. Flu, as with other respiratory viruses, can be responsible for acute asthma exacerbations (AAE) and a higher rate of hospitalization and admission to the intensive care unit (ICU).⁵ Specifically, the risk of hospitalization for children affected by asthma seems to be four-fold higher than for non-asthmatic children. Several studies have shown the effectiveness and safety of both IIV and LAIV in children with asthma,⁵ but LAIV is contraindicated in children between 2 and 4 years of age affected by asthma or with history of recurrent wheezing because of reported increase of acute asthma attacks after vaccine administration.⁴ In general, it has been reported that the flu vaccine allows a reduction of 59%-78% of AAE with fewer requests for emergency visits and hospitalizations.⁶ Among children, egg allergy is frequently reported in patients with asthma. Both IIV and LAIV may contain traces of egg proteins, mainly ovalbumin. Past concerns about the safety of egg-derived influenza vaccines in patients with egg allergy are now outdated.^{3,5} In fact, egg allergy is no longer considered a contraindication to the administration of the influenza vaccine. People with mild allergy reactions (ie, itching) or tolerance to cooked eggs can be regularly vaccinated in the outpatient environment. Only in the case of more severe allergic symptoms such as angioedema, vomiting, respiratory symptoms or anaphylaxis, flu vaccine administration is recommended in a protected environment and should be followed by 60 minutes monitoring.⁷ Of note, flu vaccines are contraindicated only in those with a previous severe allergic reaction to other components of flu vaccines (ie, gelatin alpha-gal) or a previous dose of any influenza vaccine.³

3 | FLU VACCINE DURING PREGNANCY AND BREASTFEEDING

In pregnant women, the incidence of severe flu-related illness and complications, in both mother and fetus, is significantly higher, particularly during the second and third trimester of gestation.³ Thus, pregnant women represent a relevant target group for influenza vaccination, as defined by World Health Organization (WHO), and together with ACIP and American College of Obstetrics and Gynecology (ACOG), we recommend the influenza vaccine for all pregnant women at any time of gestation. In particular, while IIV is safe during pregnancy, LAIV is contraindicated. No association with congenital malformations, spontaneous abortion, or preterm birth has ever been found. Studies on the use of RIV in pregnant women are limited.⁴ Another critical advantage of flu vaccination during pregnancy is that vaccinated pregnant women also protect against

Key Message

In children with asthma, the flu vaccine is recommended, except for live-attenuated influenza virus that is contraindicated in patients between 2 and 4 years of age. In patients with egg allergy, both inactivated influenza vaccine and live-attenuated influenza virus could be administered. Only in the case of previous severe reactions to eggs, the administration should be done in a protected environment, with 60 minutes of monitoring. In all pregnant women at any time of gestation, inactivated influenza vaccine is recommended to prevent severe flu-related complications in either mother or fetus. Instead, live-attenuated influenza virus is contraindicated. Notably, inactivated influenza vaccine should be administered in post-partum or during breastfeeding, if not done during pregnancy. In patients with immunodeficiency and their close contacts and household members, inactivated influenza vaccine is recommended. Instead, live-attenuated influenza virus is contraindicated in patients with confirmed or suspected immunodeficiency, as well as in close contacts and caregivers of patients with severe immunodeficiency. Patients with severe immunodeficiency should minimize contacts with live-attenuated influenza virus-vaccinated healthcare providers for 7 days after immunization.

flu to their infants during the first 6 months of life, through the transplacental transfer of influenza-specific maternal IgG.² A reduction of 72% of laboratory-confirmed influenza hospitalizations in the first months of life has been observed in infants born to women who have received the flu vaccine during gestation.⁸ In unvaccinated pregnant women, IIV administration is recommended at post-partum or during breastfeeding. Breastfeeding might also protect infants against influenza because of both activation of innate antiviral mechanisms (ie, type 1 interferon) and the presence of influenza-specific IgA in human milk of flu-vaccinated women.⁴

4 | FLU VACCINE IN IMMUNOCOMPROMISED CHILDREN

Children with primary and secondary immunodeficiency are particularly susceptible to infections and at higher risk of complications from vaccine-preventable diseases such as influenza. Due to influenza infection, immunocompromised patients can develop severe lower respiratory tract disease, unusual manifestations (ie, rhabdomyolysis and myocarditis), or bacterial super-infections.⁹ As previously reported,¹⁰ IIV may be administered in patients with immunodeficiency, even though specific antibody response may be suboptimal. Moreover, patients with primary antibody deficiencies (PADS) might mount a CD4-mediated antibody response to the

flu vaccine. Vaccine administration is also recommended during immunoglobulin replacement therapy since influenza-specific antibodies are not present in immunoglobulin products due to virus variability. Instead, LAIV is contraindicated in children and adults with confirmed or suspected immunodeficiency, as well as in close contacts and caregivers of patients with severe immunodeficiency in whom IIV is recommended. In these patients, contact with LAIV-vaccinated healthcare providers should be minimized for 7 days after immunization.^{4,10}

5 | FLU VACCINE DURING COVID-19 PANDEMIC

Clinical spectrum of recently emerged COVID-19 and influenza infections is very similar. They may both cause respiratory disease, with a variable range of severity from an asymptomatic or mild presentation to severe disease, with a higher risk in vulnerable populations. Also, the impact of co-infection is still unclear. In this scenario, to prevent this vaccine-preventable disease outbreak during COVID-19 pandemic, routine influenza vaccination is recommended for all children of 6 months of age and older, unless specific contraindications are reported by the Referral Center.^{11,12}

In conclusion, although current flu vaccines confer protective immunity only against selected matched circulating virus strains, health and economic burden of influenza urges to broaden the implementation of vaccination programs. Further efforts are needed to enhance flu vaccination coverage and inclusiveness for age, health status, and timing, in the expectation of a “universal vaccine”.¹³

CONFLICT OF INTEREST

All authors reported no conflicts of interest.

AUTHOR CONTRIBUTIONS

Mayla Sgrulletti: Conceptualization (equal); Methodology (equal); Writing-original draft (equal). **Giorgio Ottaviano:** Visualization (equal); Writing-review & editing (equal). **Maria Sangerardi:** Visualization (equal); Writing-review & editing (equal). **Loredana Chini:** Visualization (equal); Writing-review & editing (equal). **Rosa Maria Dellepiane:** Visualization (equal); Writing-review & editing (equal). **Baldassarre Martire:** Visualization (equal); Writing-review & editing (equal). **Davide Montin:** Visualization (equal); Writing-review & editing (equal). **Caterina Rizzo:** Visualization (equal); Writing-review & editing (equal). **Viviana Moschese:** Conceptualization (equal); Methodology (equal); Project administration (equal); Supervision (equal); Visualization (equal); Writing-review & editing (equal).

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