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EDITORIAL COMMENT

Influenza Vaccination in Adult Patients With Congenital Heart Disease*

Doreen DeFaria Yeh, MD,[a] Charmaine S. Lam, MD[b]

Influenza has been associated with a spectrum of cardiovascular (CV) complications.[1] Patients with underlying CV conditions are predisposed to infection and more severe or fatal disease courses.[1,2] Adults with congenital heart disease (CHD) represent a unique population within this sector. A retrospective cohort study evaluating cases of viral pneumonia among patients with CHD, the majority of which were secondary to influenza viruses, demonstrated increased mortality among CHD patients compared to their age-matched non-CHD peers.[2] As such, adults with CHD should be considered high risk for morbidity and mortality. With advances in medical, surgical, and catheter-based interventions, adults with CHD are also now living longer lives.[3] Consequently, they face significant CV morbidities like arrhythmias, heart failure, and pulmonary hypertension further complicating their clinical course and increasing risk for mortality.[3] Preventative strategies such as influenza vaccination become critical public health measures to decrease morbidity and mortality. In addition to immunization, vaccine formulation is also an important consideration. It has been demonstrated that a high-dose, trivalent inactivated influenza vaccine induces higher antibody responses and provides better protection against laboratory-confirmed influenza illness than a standard-dose vaccine in adults age 65 years of age or older in the setting of immunosenescence.[4] It is well known that CHD is associated with immune alterations[5]; however, implications on the response to different influenza vaccine formulations remain unclear.

In this issue of *JACC: Advances*, Dehghani et al[6] reported findings from a prespecified subgroup analysis of the previously published INVESTED trial. The INVESTED (INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated heart failure) trial, published in 2020, compared the efficacy of 2 influenza vaccines on all-cause mortality and cardiopulmonary hospitalization in a high CV risk population.[7] It was a randomized, double-blinded trial evaluating standard dose quadrivalent inactivated influenza vaccine containing 4 virus antigens vs a high-dose trivalent inactivated influenza vaccine containing 4 times the hemagglutinin content of each of the 3 virus antigens.[7,8] The study was conducted across 157 sites in North America and spanned 3 influenza seasons. There were 5,260 participants with inclusion criteria restricted to patients with acute myocardial infarction in the preceding 12 months or hospitalization for heart failure in the preceding 24 months and at least 1 additional high-risk condition.[7] The authors concluded that there was no difference in the rates of the composite of all-cause mortality or cardiopulmonary hospitalization, within-season or across the 3-year study period, between the 2 vaccine formulations.[7]

The current prespecified subgroup analysis described the clinical and adverse events in adult patients with or without CHD comparing those receiving high-dose vs standard-dose vaccine. Within the 5,260-patient cohort in the INVESTED trial, 272 adult patients self-identified with CHD.[6] The adult CHD cohort was younger (mean age 59.3 years), more likely to be female (40.1%), to be smokers, to have a qualifying event of HF, and to have atrial fibrillation (44.1%) compared to those without CHD.[6]

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From the [a]Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA; and the [b]Division of Cardiology, Children's Hospital Boston, Boston, Massachusetts, USA.

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The rates of the primary outcome (death from all-causes and cardiopulmonary hospitalization) were similar in those with compared to those without CHD: 49.8 vs 42.8 per 100 years.[6] In addition, among adult patients with CHD, there was no difference in the primary endpoint comparing those who received the high-dose vaccination vs the standard-dose group.[6] Both vaccines were well tolerated in CHD patients with low rates of adverse events, and no differences between the high-dose group vs the low-dose group were reported.[6]

When interpreting the results of this subgroup analysis of the INVESTED trial, there are several considerations. First, the adult CHD population represents a unique and heterogeneous group immunologically. Due to the size and location of the thymus, infant CHD surgery often involves the removal of this organ, altering T-cell populations mirroring immunological aging.[9] In addition, many genetic syndromes associated with immunodeficiency like 22q11.2 deletion, Down syndrome, and Noonan syndrome are also linked to CHD.[5] Despite these immune alterations, it has been shown that adult CHD patients with or without early thymectomy had comparable T-cell activation and increase in hemagglutination titers in response to influenza vaccine compared to healthy controls.[9] However, the mechanism behind the lack of additional immunological response and resultant improved clinical outcome in patients who received high-dose vs standard-dose vaccine as demonstrated in this subgroup analysis is not entirely clear and requires further investigation. Secondly, adult CHD patients in this study were self-identified which can result in incorrect classification. Details including the participants' underlying anatomic complexity and physiological staging were also not provided. Recent studies has shown that more advanced baseline CHD physiological stage (as defined by American Heart Association/American College of Cardiology Adult Congenital Heart Disease guidelines) or a decline in CHD physiological stage was associated with increased mortality.[10-12] Patients with more advanced physiological stage have also been shown to have a lower antibody response to COVID-19 vaccination as measured by anti-spike IgG titers.[13] Given that antibody titers were not measured in the INVEST trial, it is unclear whether the same conclusions can be made for the influenza vaccine and patients with more advanced disease may derive a bigger benefit from high-dose influenza vaccination. Finally, although this subgroup analysis did not demonstrate any differences in the primary endpoint between CHD patients receiving the high-dose vs standard-dose influenza vaccine, it is important that the results are not interpreted as the influenza vaccines being ineffective.[8] It has been well demonstrated that influenza vaccination is associated with lower risk of major CV events, particularly among those with who are high risk with more active coronary artery disease.[14,15] Therefore, health care providers should encourage adults with CHD to receive their annual influenza vaccination. Studies have shown a wide range of 20% to 70% influenza vaccine uptake among adults with CHD and thus efforts to improve vaccination rates should be amplified.[16,17] Older age, anatomical complexity of CHD, female gender, perceived susceptibility and severity to influenza illness, perceived benefits and side effects from influenza vaccination as well as physician recommendation have been identified as predictors of receipt of influenza vaccination in adults with CHD.[16,17] Both patient- and provider-level education could be targeted to improve vaccination rates among individuals with and without these predictors.

Adults with CHD are susceptible to influenza infection with higher rates of CV complications, and it has been established that vaccination can reduce CV events in this population. The anatomic and physiologic heterogeneity of the adult CHD population, however, complicates our understanding of who may derive greatest benefit and who may potentially benefit from higher dose vaccination formulations. While we await answers to these uncertainties, cardiologists should see it as their responsibility to encourage annual influenza vaccination for patients with underlying CV disease, particularly those with CHD.

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ADDRESS FOR CORRESPONDENCE: Dr Doreen DeFaria Yeh, Division of Cardiology, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114, USA. E-mail: ddefariayeh@mgh.harvard.edu.

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