Reactogenicity and Concomitant Administration of the COVID-19 Booster and Influenza Vaccine

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Concomitant administration of the COVID-19 vaccine booster and the seasonal influenza vaccine could support uptake of both vaccines, augmenting protection against these preventable infectious diseases with potential implications for racial and ethnic disparities in vaccination rates.1 Vaccine coadministration could also introduce efficiencies in currently overburdened health care settings. Despite these many benefits, little is known about reactogenicity from concomitant dosing of COVID-19 and seasonal influenza vaccines. This situation is largely because, to avoid misattribution and more accurately estimate adverse event incidence, participants who had recently received other vaccines were excluded from early COVID-19 vaccine trials. COVID-19 and influenza vaccines have several known adverse events which could increase in frequency with coadministration and in turn negatively affect vaccine uptake. Although a 2021 phase 4 trial2 of simultaneous administration of Pfizer BioNTech and influenza vaccines in the UK raised no safety concerns, to date, there are no studies combining COVID-19 mRNA boosters with the influenza vaccine in the US. Hause et al3 examine adverse events in the week following simultaneous receipt of a COVID-19 mRNA booster and influenza vaccine in the US population.

Using v-safe, the large vaccine surveillance self-report registry from the Centers for Disease Control and Prevention, Hause et al3 compared reactogenicity among respondents who received the Pfizer BioNTech or Moderna COVID-19 mRNA booster concomitant with a seasonal influenza vaccine with those who received the booster alone between September 22, 2021, and January 16, 2022. As was the case with COVID-19 vaccine booster trials,4 local and systemic adverse events with booster alone were reported to be mild to moderate and transient, occurring most often the day after vaccination. With coadministration of a booster with an influenza vaccine a small but significant increase in reactogenicity was observed: 8% among those who received the Pfizer mRNA booster and 11% among those who received the Moderna mRNA booster. The most frequently reported systemic reactions with vaccine coadministration were fatigue, headache, and myalgia. Local reactogenicity was dominated by pain at the injection site, and, as in the UK study, serious adverse events were infrequent. In addition, compared with those who received the Pfizer booster alone, those who simultaneously received the Pfizer booster and influenza vaccine were not more likely to report a health impact such as being unable to work, attend school, or perform normal activities. In contrast, those who received the Moderna booster and influenza vaccine were more likely to report a health impact in the following week than those who received the Moderna COVID-19 booster alone.

Reactogenicity to vaccination is not wholly attributable to vaccine contents or delivery. In both influenza and COVID-19 vaccine clinical trials, substantial adverse events or so-called nocebo effects have been reported by participants randomized to the placebo arms of these trials. Nocebo effects may be affected by anxiety and expectation of adverse events. A meta-analysis5 of 45 380 participants in randomized COVID-19 vaccine clinical trials found that 76% of systemic and 24% of local reactogenicity could be attributed to nocebo effects. Thus, although Hause et al3 observed a slight but significant increase in adverse event reporting with vaccine coadministration, without a clinical trial and the requisite placebo controls, this increase cannot be simply attributed to the active agents in these vaccines. Further, by virtue of their acceptance of three COVID-19 vaccinations and an influenza vaccination, the v-safe participants studied by Hause et al3 may have lower expectation...
of adverse events than the general population, and thus may be less likely than the general population to experience nocebo effects.

Another potential selection bias in the population included in Hause et al relates to who has the technology to report to v-safe. The v-safe platform includes less than 10% of people vaccinated and is only usable by individuals who have access to a smartphone with a touch screen, text messaging, and internet access. The racial and ethnic demographic characteristics of those included are not representative of the US population. Although no differences in effectiveness by race or ethnicity were noted in the clinical trials of primary COVID-19 vaccination, most White non-Hispanic respondents reporting to v-safe may bias results and limit the ability to assess differences in self-reported reactions by race or ethnicity.

During the COVID-19 pandemic low vaccination confidence emerged as a significant barrier to the uptake of vaccines and a threat to individual health, public health, and health equity. The reasons for low vaccine confidence are multiple and complex. In addition to mistrust of health systems, the pharmaceutical industry and the government, fear regarding adverse events and safety was a factor in low vaccine confidence and unwillingness to accept COVID-19 vaccination. Although adverse events, including local and systemic reactions, are often mild and transient, they may still significantly affect willingness to accept future vaccination. Informing patients about potential adverse events can substantially affect anxiety related to adverse events and in turn their experience of them.

Although emphasis on the benefits of vaccination and minimization of their adverse events might seem a reasonable approach to limiting nocebo effects, negative information about the COVID-19 vaccine is common, and from an ethics standpoint, individuals have the right to complete information so they can decide whether they want to receive the vaccine. Some argue that the best approach to gaining the public’s trust is to offer both the positive and negative scientific evidence, with refutational 2-sided risk and benefit messages. Thus, while messaging could include the fact that serious reactions are rare even when the vaccines are given concomitantly, in light of these data, clinicians can confidently inform patients that concurrent administration of the COVID-19 booster and seasonal influenza vaccine is both safe and associated with only a slight increase in adverse events compared with the COVID-19 booster alone.

Substantial efforts have been undertaken to increase rates of COVID-19 vaccination and boosting; however, less effort has focused on influenza vaccination. Nationally, during the 2020 to 2021 season, influenza vaccination coverage was only 50.2%. Significant disparities have also been noted by race and ethnicity. Influenza results in significant morbidity annually which could be averted by increased vaccination coverage. Despite the limitations detailed above, the data reported by Hause et al suggest that the development of public health campaigns to increase dual vaccination should be undertaken. Although logistical challenges may serve as barriers to the implementation of dual vaccination, organizing for provision of both influenza vaccination and COVID vaccination within clinical settings and at community-based nonclinical venues would be advantageous and may increase the likelihood of uptake. Given the small increase in rate of adverse events reported by Hause et al, health care systems should be encouraged to develop routine and streamlined processes for coadministration of these vaccinations.
Conflict of Interest Disclosures: None reported.

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