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EDITORIAL

Guillain-Barré Syndrome Following Influenza Vaccines Affords Opportunity to Improve Vaccine Confidence

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Influenza causes serious illness and death, especially in high-risk groups such as older adults [1]. The United States (US) Centers for Disease Control and Prevention estimated an average of 23 607 annual US influenza-associated deaths from 1976 to 2007, although these estimates ranged widely from year to year [2]. Studies have also estimated an average of 130 000 annual US influenza-associated hospitalizations [3, 4].

The US Advisory Committee on Immunization Practices recommends that all persons without contraindications >6 months old receive annual influenza vaccination [1]. However, coverage remains suboptimal; only 45% of US adults were vaccinated during the 2018–2019 season [5]. The effectiveness of influenza vaccines varies each year in relation to the match between vaccine strains and circulating strains, and depends on the age and health of each recipient [6]; however, even when the vaccine has a lower effectiveness relative to other years, vaccination still reduces risk of infection, severe illness, hospitalization, and death [7]. Adults >65 years old have the option to receive Fluzone High-Dose (IIV3-HD) vaccine [1], as it may have increased effectiveness among this age group compared with standard-dose vaccines [8].

A main reason for suboptimal coverage is vaccine hesitancy, or "concerns about the decision to vaccinate oneself or one's children" [9]. Many factors contribute to vaccine hesitancy [9]. One factor is confidence in vaccine safety, which impacts vaccination behaviors [10]. Influenza vaccines have been carefully studied and we likely understand their safety profile better than many other vaccines because of how long they have been used, as well as extensive postlicensure safety monitoring for the 2009–2010 H1N1 vaccination program [11]. Influenza vaccines are very safe; common adverse reactions including local (eg, soreness, swelling) and systemic (eg, fever, chills, malaise, myalgia) reactions are typically mild and transient, and hypersensitivity reactions are rare [12, 13].

Guillain-Barré syndrome (GBS) was first identified as a safety issue with the 1976 swine influenza vaccine, which was found to have a relative risk of approximately 7–8, with a corresponding attributable risk of about 1 excess case per 100 000 persons vaccinated [14–17]. Most of this increased risk was in the 6 weeks after vaccination, although in 1 study the risk extended as far as 10 weeks [14]. Epidemiological studies from 1977–2009 have had mixed results, with the majority of evidence suggesting that influenza vaccines have not been associated with GBS since 1976 [18–26]. However, these studies were underpowered to detect a small relative risk. The most recent Institute of Medicine report on this topic in 2011, which included studies with data through 2008–2009, concluded that "the evidence is inadequate to accept or reject a causal relationship between seasonal influenza vaccine and GBS" [27].

The 2009–2010 H1N1 US vaccination program had the most safety monitoring for any vaccine, with a particular focus on GBS. With 23 million vaccinated persons under active surveillance through 6 systems, an approximate doubling of risk in the 42 days after inactivated influenza vaccine was found using a self-controlled case series design [28]. This incidence rate ratio (IRR) of 2.35 translated into 1–3 excess cases of GBS per million persons vaccinated. An international study had almost identical findings (IRR, 2.42) [29].

We are aware of only 4 well-conducted epidemiological studies since the 2009–2010 pandemic that have examined GBS following seasonal influenza vaccine [30–33]. Findings are similar to those from 1977 to 2008 in that only 1 found a statistically significant association,

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but they were largely underpowered to detect an IRR of 2. Influenza itself is a known cause of GBS, so by preventing infection the influenza vaccine is also preventing GBS [12, 34]. Additionally, because 2009–2010 H1N1 vaccines were rolled out amid widely circulating H1N1 disease, there remains some scientific uncertainty if findings of an association between the 2009–2010 H1N1 vaccine and GBS were due to undetected H1N1 infection or perhaps similarities between the 2009–2010 H1N1 and the 1976 swine influenza viruses. These studies led to the National Vaccine Injury Compensation Program adding GBS to the table of compensable events, improving equitable and efficient compensation as GBS was often being compensated as an "off table" claim.

In a study by Perez-Vilar et al in this issue of *The Journal of Infectious Diseases*, the Vaccine Safety Datalink (VSD) identified a statistical signal for an increased risk of GBS in days 1–42 following 2018–2019 high-dose influenza vaccine, and this signal was explored among Medicare beneficiaries aged ≥65 years and VSD chart-confirmed analyses. The study found a small, nonsignificant risk (point estimates ranging from 1.12 to 1.85 depending on the analysis) among Medicare beneficiaries and a relative risk of 1.0 among chart-confirmed cases in the VSD. The authors appropriately conclude from these data that they could not exclude an association between high-dose influenza vaccine and GBS, but if such a risk existed, it was similar to previous seasons.

The benefits of influenza vaccine vastly outweigh the very small risks associated with vaccination, as exemplified in this study. Had a risk of GBS at the level seen in 1976 occurred, ongoing federal vaccine safety activities would have identified it quickly. However, studying extremely small risks on order of 1–3 per million is exceedingly difficult. Large linked administrative databases such as the VSD and Medicare greatly facilitate the efficiency and validity of such studies. Examining multiple years of data and combining databases globally affords the opportunity to increase power sufficiently to answer such questions [29].

Although such small levels of risk are difficult to study, doing so is extremely important for at least 2 reasons. First, a small risk such as 2 per million persons vaccinated can still impact substantial numbers of people. In the US, this level of risk translates into about 300 cases of GBS with current levels and about 600 cases with ideal levels of immunization coverage, every year. With a relative risk of 2, an equal number of cases would occur in this population as the background rate of GBS; thus, 600–1200 total with 50% and 100% vaccine coverage, respectively, will occur within 42 days of vaccination. Without understanding the biological mechanisms or risk factors for vaccine-induced GBS (such as adversomics), patients and clinicians will likely presume that all these cases were caused by the vaccine. The number of people impacted by a belief that the influenza vaccine caused GBS would further increase if patients or clinicians ascribe GBS cases >42 days after vaccination, which is likely to occur. Family members of these patients may have concerns that they are also at increased risk of GBS or other adverse reactions. Vaccine-hesitant and refusing persons often express such concerns because of family history [35].

This raises the second reason for the importance of such study: It is critical that the public be assured that scientists and public health authorities rigorously investigate and, whenever possible, prevent serious adverse reactions to vaccines. Fortunately, most serious vaccine reactions are very rare, and coincidental adverse events following immunization (AEFIs) can be ruled out. We can and should fully characterize the risk of GBS following influenza vaccination, including among subpopulations and by vaccine type/formulation/manufacturer. Additionally, when relationships are found between vaccine(s) and GBS, we should identify the biological mechanism by which the vaccine can induce GBS, including the possible role of genomics. Doing so will improve vaccine communication and compensation. Importantly, it will clearly demonstrate to clinicians and the public that we take AEFIs seriously, fully investigate even rare AEFIs, prevent serious adverse reactions whenever possible, and compensate for vaccine injuries based upon strong scientific evidence, all of which are essential for public confidence in vaccines.

Daniel Kahneman's work (Nobel Prize in Economic Sciences, 2002) regarding human behavior under uncertainty suggests that people will gamble more freely to win than to lose [36]. Vaccine-hesitant people see the gamble of vaccination as a losing proposition; they see AEFIs as a loss more than the gain of avoiding the disease. Adversomics modeling may be helpful in that it can show which patients are actually at elevated risk for AEFIs. Showing someone that based on their genetic traits they are not at higher risk of AEFIs will help them to feel comfortable that they will not lose this gamble. Conversely, if someone tests positive for a genetic trait that increases their risk of an AEFI, a discussion about relative risk of the AEFI vs disease can be better communicated in a patient-specific context.

The importance of influenza vaccine and vaccine confidence are more important than ever with the confluence of coronavirus disease 2019 (COVID-19) and seasonal influenza this fall and winter [37]. These dual epidemics are likely to lead to substantial morbidity and mortality and put tremendous stress on our healthcare system. While we do not currently have vaccines to prevent COVID-19, we have extremely safe and moderately effective influenza vaccines. Federal vaccine safety activities that have well established the safety profile of influenza vaccines, as exemplified in the article by Perez-Vilar et al, should reassure vaccine-hesitant clinicians and the public and thus improve vaccine confidence, vaccine coverage, and population health.

Notes

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