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**Influenza Vaccination Effectiveness, Unmeasured Confounding, and Immunomodulatory Treatment**

To the Editor—Inactivated influenza vaccines have been the foundation for public health strategies for the control of influenza for almost 50 years. Despite increasingly broad vaccination recommendations and expanded programs for vaccine delivery in many countries, there is still widespread public discussion and often partisan debate among experts about the effectiveness of annual vaccination in reducing influenza-related acute respiratory illness, hospitalization, and mortality. The recently introduced case test-negative method provides another way of evaluating influenza vaccination effectiveness [1]. With this method, patients with influenza-like illness are tested for influenza virus infection by reverse-transcription polymerase chain reaction; cases are those who are test-positive and controls are those who are test-negative. Several studies, including that by Bate-man et al [2], have used this method to estimate vaccination effectiveness in preventing acute respiratory illness and hospitalization with influenza-like illness in older adults [2–4]. While the case test-negative method offers greater sensitivity, it has several potential shortcomings, including delayed or incomplete virological testing and inadequate ascertainment of vaccination status. In addition, like case-control and other observational study designs, it too depends on statistical adjustment for confounding factors, such as chronic medical conditions, functional status, and patterns of healthcare-seeking behavior. Whether investigators examine groups of individual patients or large administrative databases, accurate adjustment for confounding variables remains an essential requirement for any valid observational study. All would agree that unmeasured confounding potentially affects the validity of any attempt to estimate influenza vaccination effectiveness.

Observational studies of influenza vaccination effectiveness in older adults report that a high proportion of study subjects have chronic medical conditions, and investigators routinely adjust for these conditions in their analyses. These patients also take a large number of medications for these conditions. In the Canadian study cited above, the average number of prescriptions received by each study subject during the preceding year was >15 [4]. In the United States, the National Center for Health Statistics has reported on current use of selected prescription drug classes for persons ≥65 years of age for the period 2007–2010 [5]. Among those with hyperlipidemia, 46.7% were receiving treatment, with most probably taking statins. For those with heart disease and high blood pressure, 21.9% were taking angiotensin-converting enzyme (ACE) inhibitors, and 12.2% were taking angiotensin receptor blockers (ARBs). For those with diabetes, 18.4% were being treated, with metformin probably used in most cases. These drugs have broad antiinflammatory and immunomodulatory (pleiotropic) effects and might be useful in treating influenza and other forms of acute critical illnesses [6]. Over the past decade, numerous observational studies have suggested that outpatient statin treatment reduces the risk of hospitalization and death due to pneumonia and sepsis [6]. A recent propensity-matched case-control study of 23,000 adults ≥65 years of age hospitalized with community-acquired pneumonia showed that inpatient statins, ACE inhibitors, and ARBs were associated with 32%–53% reductions in 30-day all-cause mortality [7]. In this study, 30% of subjects were receiving statins, 30% were receiving ACE inhibitors, and 4% were receiving ARBs. In another study, which examined 3043 patients hospitalized with laboratory-confirmed seasonal influenza, statins reduced 30-day mortality by 41% [8]. This reduction was in addition to any that might have been attributed to previous influenza vaccination or antiviral treatment. Moreover, a randomized controlled trial involving only 100 statin-naive patients hospitalized with sepsis showed that inpatient atorvastatin treatment began on the first hospital day reduced progression to severe sepsis by 83% [9]. These and many other studies suggest the possibility that statins, ACE inhibitors, ARBs, and other immunomodulatory agents might reduce mortality due to seasonal and pandemic influenza [6]. They also suggest that these agents might be important confounders in observational studies of influenza vaccination effectiveness [6].

None of the case test-negative studies mentioned above, nor earlier case-control and cohort studies of influenza vaccination effectiveness, have considered statins, ACE inhibitors, ARBs, or other immunomodulatory agents as potential confounding variables. We do not yet know whether it is essential to consider these agents in adjustment strategies, independent of the underlying medical conditions for which they have been prescribed. However, long-term adherence to treatment with statins and these other agents is often poor, and nonadherence can increase risks of hospital readmission and death [10]. Because these agents are often used to treat older adults, and because such treatment could affect rates of influenza-related hospitalization and mortality, estimates of influenza vaccination effectiveness based on studies that have not considered them as potential confounders should probably be regarded as imprecise.
Reply to Fedson

TO THE EDITOR—In response to our recent study on influenza vaccine effectiveness [1], Fedson points out that the validity of the test-negative design (TND) depends on appropriate statistical adjustment for confounding variables [2]. The TND is commonly used to estimate influenza vaccine effectiveness by determining the odds of vaccination in patients with laboratory-confirmed influenza and in patients with a negative result of an influenza test (test-negative controls). Fedson is concerned that such studies have seemingly ignored potentially important confounders in the use of common medications such as statins, angiotensin-converting enzyme inhibitors, and metformin (particularly in older adults). He cites evidence that statin use may modify the severity of pneumonia and sepsis in older adults and, on the basis of this, suggests that our study of influenza vaccine effectiveness, along with similar studies using the TND, may yield biased estimates of vaccine effectiveness because they did not adjust for medication use.

We agree with Fedson that adjustment for confounding factors is important in studies of vaccine effectiveness. However, we disagree with his assertion that the TND is limited by delayed or incomplete virologic testing and by inadequate ascertainment of vaccination status. We further note that it is associated with susceptibility to influenza as the outcome. This may be true for studies that use nonspecific end points such as pneumonia or mortality, which have many causes and are not specific to influenza. In contrast, vaccine effectiveness studies using the TND have a highly specific end point (ie, RT-PCR–confirmed influenza), which reduces the potential for confounding. By definition, a confounding variable is associated with both the primary exposure (ie, influenza vaccination) and the outcome (ie, RT-PCR–confirmed influenza vs noninfluenza respiratory illness). We are not aware of any evidence supporting a selective effect of statins on the infectiousness, replication, or human immune response to influenza viruses but not on other respiratory pathogens (including noninfluenza viruses) that cause illness in the control group. Two large observational studies have previously shown no association between statin use and subsequent development of (seasonally incident) influenza-like illness [7] and other respiratory tract infections [8]. Although statin use may be associated with seasonal influenza vaccination, there is no evidence that it is associated with susceptibility to influenza virus infection.

The validity and accuracy of the TND for measuring influenza vaccine effectiveness have been examined in 3 recent studies, and all concluded that it is a valid and robust method for estimating...