Regarding Primary Care Patients Who Received Influenza Vaccine at Veteran Health Administration Medical Centers

To the Editor—We read with interest Richardson and colleagues’ study among primary care patients who received influenza vaccine at Veteran Health Administration (VHA) medical centers from 2010 through 2011 [1]. The authors reported that the high-dose vaccine was not more effective in protecting against hospitalization for influenza or pneumonia, except in the subgroup aged ≥ 85 years.

Three effectiveness studies of Fluzone high-dose vaccine have been published. The prospective, randomized, controlled trial by DiazGranados et al [2] found high-dose vaccine was 24.2% more efficacious than standard-dose vaccine in preventing laboratory-confirmed influenza (19.7% and 32.5%, respectively, for participants aged 65–74 years and ≥ 75 years [3]). Izurieta et al [4] identified Medicare beneficiaries vaccinated in community pharmacies offering both vaccines who then experienced influenza infection or hospital admission and found high-dose vaccine to be 22% more effective in prevention of both probable influenza infections and influenza-related hospital admissions. With 2 studies with nearly identical results and 1 with sharply different results, what are we to think?

The primary outcome of the VHA study was hospitalization, with a primary diagnosis of pneumonia or influenza (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], codes 480–487, which include noninfluenza causes of pneumonia), with inclusion of nonspecific outcomes biases toward the null [5]. In contrast, Izurieta et al required a rapid influenza diagnostic test followed by dispensing of oseltamivir or a diagnosis of influenza (ICD-9-CM, codes 487–488), thereby more accurately detecting differences in effectiveness.

The VHA study was conducted at a time when VHA usage of the high-dose vaccine was uncommon (15.6% of patients). It is well known that patients are selected for different therapies based on clinical considerations, which causes the problem known as confounding by indication [6]. Richardson et al [1] attempted to address this through statistical techniques, including propensity score analysis. However, even if propensity score analysis could correct for the powerful clinical tendency to reserve scarce higher-dose vaccine for sicker patients, it cannot correct for differential timing of vaccination among the 2 groups (eg, using high-dose vaccine first for the sickest or most frail patients) nor for differential allocation of high-dose vaccine in different geographic areas (influenza activity may have differed in timing or intensity in different areas), resulting in differential person-time at risk.

In contrast, Izurieta et al identified vaccinees who went to community pharmacies that offered both vaccines, ensuring equal access to vaccine and similar timing of influenza exposure for both vaccine groups within a given community. Of their 2545275 elderly patients, 36.5% received the high-dose vaccine (similar to national usage that year), substantially reducing the risk of confounding. Finally, the blinded, randomized, experimental trial of DiazGranados et al [2] is the design least susceptible to bias or confounding and is considered to provide the most reliable results.

What should we think of the study by Richardson et al? As Rothman states in his textbook Modern Epidemiology, “Only infrequently can nonrandomized studies provide a valid estimate of the efficacy of a treatment. In most [such] situations, the measured differences between the experiences of patient groups receiving alternative therapies are primarily the result of underlying differences between the groups . . .” [6].

Note

Potential conflicts of interest. All authors are employees of and are recipients of stock or options in, Sanofi Pasteur, the manufacturer of the high-dose influenza vaccine discussed herein. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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