Understanding Suboptimal Influenza Vaccine Effectiveness Within the Agent, Host, and Environment Paradigm

To the Editor—In their recent publication, Ohmit et al report reduced influenza vaccine effectiveness (VE) of 31% (95% confidence interval [CI], 7% to 55%) for the 2010–2011 season. Authors describe these findings as substantially lower than reported by other established VE networks for the same season, cited instead in the range of 52%–60% [1]. In fact, an earlier publication by the Canadian sentinel surveillance system using the test-negative design also reported suboptimal vaccine protection for the 2010–2011 season with overall adjusted VE against medically attended laboratory-confirmed influenza of 37% (95% CI, 17%–52%) [2]. The Canadian estimate was driven by predominant circulation of influenza A(H3N2) virus, and the participation of adults aged 20–49 years in whom VE against the dominant circulating H3N2 variant was just 39% (95% CI, 0%–63%) [2].

In trying to understand suboptimal VE estimates, Ohmit et al focused their analysis on the effects of repeat immunization. In the Canadian publication, we also highlighted that >70% of participants vaccinated in 2010–2011 had been previously immunized in both 2008–2009 and 2009–2010 [2], a high proportion of repeat immunization similar to that noted in other seasons and by Ohmit et al [1]. Earlier studies have hypothesized that prior influenza immunization may positively or negatively interfere with current vaccine protection [3, 4].

The number, nature, and antigenic distance specified by virus mutations across sequential circulating variants and vaccine components and their interactions with preexisting immunity (differentially determined by historic prime/boost exposures), likely modulate VE estimates in intricate and as yet impenetrable ways. Each of these considerations will further separately vary for individual components of the trivalent vaccine and in overall VE estimates depending on the proportionate mix of circulating subtypes and variants in a given study setting.

In the Canadian publication for the 2010–2011 season, suboptimal VE was observed despite findings of vaccine match to the dominant circulating H3N2 variant based on conventional hemagglutination inhibition (HI), an assay that may also lack resolution [2]. Additionally applying gene sequencing, we reported evidence of substantial mutation in key antigenic sites of the hemagglutinin surface protein [2], with 8 amino acid (AA) substitutions relative to the 2010–2011 World Health Organization (WHO)–recommended vaccine strain (A/Perth/16/2009-like) [5]. We also highlighted that the egg-adapted vaccine strain actually used by manufacturers that season (A/Victoria/210/2009 NYMC X-187) itself showed 4 further AA mutations relative to the WHO-recommended strain, rendering the vaccine even more divergent from the dominant circulating influenza variant (90.8% identity) [1].

It is noteworthy that each of the above observations for the 2010–2011 season has again been echoed during the most recent 2012–2013 season, including suboptimal VE < 50% for the H3N2 component despite report of vaccine match based on HI [6–8], antigenic-site mutations in circulating viruses [6], as well as changes in the egg-passaged vaccine strain (IVR-165) relative to WHO recommendation [5], and the possible effects of prior immunization [6]. Understanding suboptimal VE thus remains critical, but its further exploration will require broad consideration of complex factors within the full epidemiologic triad of agent, host, and environment interactions. Differentiating their separate effects and varying contributions from year to year will require in-depth and adequately powered immunepidemiologic investigation across multiple seasons.

Note

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