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Correspondence

Stratified Estimates of Influenza Vaccine Effectiveness by Prior Vaccination: Caution Required

To the Editor—Ohmit and colleagues recently reported intriguing results from the Household Influenza Vaccine Effectiveness (HIVE) study [1]. An unexpected finding of this study was that the vaccine effectiveness (VE) estimate suggested no protection with repeated vaccination (VE, −45%; 95% confidence interval [CI], −226 to 35), whereas for participants not vaccinated in the prior season, the vaccine was protective (VE, 62%; 95% CI, 17–82).

Like investigators in Europe, the United States, and Canada, we have been reporting VE estimates for trivalent inactivated vaccines using a general practice sentinel surveillance scheme in Victoria, Australia [2]. To examine whether repeated vaccination might attenuate VE in our data, we calculated VE estimates for 2011 and 2012 stratified by vaccination status in the prior season using a logistic regression model, where VE = 1 – odds ratio × 100. Participants are asked whether they had been vaccinated in the

Table 1. Adjusted Vaccine Effectiveness Estimates for 2011 and 2012 From the Victorian General Practitioner Sentinel Surveillance System and Crude Vaccine Effectiveness Estimates for the Household Influenza Vaccine Effectiveness Study

	Victorian GP Sentinel Surveillance Data[a]						HIVE Study Data[b]		
	2011			2012			2010–2011		
Vaccination Status	Cases/ Noncases	Adjusted VE[c]	95% CI	Cases/ Noncases	Adjusted VE[c]	95% CI	Cases/ Total	Crude VE	95% CI
A. Stratification by prior seasonal vaccine receipt									
Stratum 1. Vaccinated in prior season									
Unvaccinated (study season)	17/40	Ref		20/35	Ref		8/117	Ref	
Vaccinated (study season)	9/39	67%	(−16 to 90)	36/66	−22%	(−175 to 45)	62/625	−45%	(−251 to 31)
Stratum 2. Not vaccinated in prior season									
Unvaccinated (study season)	124/263	Ref		169/199	Ref		43/458	Ref	
Vaccinated (study season)	4/12	19%	(−173 to 76)	1/17	94%	(54–99)	12/241	47%	(−2 to 75)
B. Vaccination status classified into mutually exclusive categories									
Vaccination status									
Neither season	124/263	Ref		169/199	Ref		43/458	Ref	
Study season only	4/12	20%	(−172 to 76)	1/17	94%	(53–99)	12/241	47%	(−2 to 75)
Study and prior seasons	9/39	48%	(−25 to 78)	36/66	32%	(−19 to 61)	62/625	−6%	(−60 to 30)
Prior season only	17/40	−23%	(−136 to 36)	20/35	33%	(−22 to 64)	8/117	27%	(−57 to 70)
C. Vaccinated in either season vs neither season									
Vaccination status									
Neither season	124/263	Ref		169/199	Ref		43/458	Ref	
Either season	30/91	12%	(−49 to 48)	57/118	43%	(12–64)	82/983	11%	(−32 to 39)

Three different analyses are presented for both data sets: A, stratified by prior season's vaccination status; B, comparing mutually exclusive vaccination status categories; and C, comparing vaccination in either season with neither season.

Abbreviations: CI, confidence interval; GP, general practitioner; HIVE, household influenza vaccine effectiveness; VE, vaccine effectiveness.

[a] Estimates made for patients seeking care from a sentinel general practitioner within 8 days of symptom onset. Patients are excluded if vaccinated <14 days prior to symptom onset (or no vaccination date).

[b] Data taken from table 3 of Ohmit et al [1].

[c] All models adjusted for age group (<18, 18–49, ≥50 years; <9 subjects not included due to too few data), high-risk health status, week, and time between onset and polymerase chain reaction request.

previous year and provide the vaccination date for the current year. The vaccines had the same composition in the 3 seasons (2010–2012). As seen in Table 1*A*, vaccination appeared to be beneficial regardless of prior vaccination in 2011, although neither estimate was statistically significant. Conversely, in 2012, among those vaccinated in the prior season (stratum 1), vaccination was possibly not protective (VE, –22%; 95% CI, −175 to 45), whereas among those not vaccinated in the prior season (stratum 2), vaccination was protective (VE, 94%; 95% CI, 53–99). We noted that 36 of 37 vaccinated influenza-positive cases in 2012 were also vaccinated in 2011, leading to these extreme observations. Antigenic analysis suggested that vaccine mismatch was not a contributing factor as 24 of 26 viruses characterized by hemagglutination inhibition assay were antigenically similar to the vaccine strain.

However, by stratifying on prior vaccination status, the effectiveness of vaccination in both seasons is estimated by comparison with vaccination in the prior season only. We believe that estimates should also be reported with reference to people vaccinated in neither season. Thus, we reexamined our data with vaccination status classified into 4 mutually exclusive categories: (1) vaccination in neither season; (2) vaccination in the study season only; (3) vaccination in both the study and prior seasons; and (4) vaccination in the prior season only. Finally, we examined the effect of vaccination in either season compared with neither season. As seen in Table 1*B*, vaccination in both the study season and the prior season compared with neither season was nonsignificantly protective in 2011 (VE, 48%; 95% CI, −25 to 78) and 2012 (VE, 32%; 95% CI, −19 to 61). Similarly, vaccination in either season compared with neither season was protective and significantly so in 2012 (VE, 43%; 95% CI, 12–64; Table 1*C*). By comparison, the crude VE from the HIVE study [1] (Table 1) comparing vaccination in both seasons with neither season would be –6% (95% CI, −60 to 30), and for either season vs neither season VE would be 11% (95% CI, −32 to 39). These estimates are quite different from the crude VE reported from the stratified analysis (VE, −45%; 95% CI, −251 to 31).

We acknowledge that our estimates are inconsistent across the 2 years examined and may be affected by sparse data bias. Moreover, those vaccinated in neither season likely represent a mix of people who were vaccination-naive and experienced. Indeed, most VE studies do not consider the effects of prior vaccination in their choice of cases and noncases. However, both Ohmit's study and this analysis highlight the need to improve our understanding of the effect of repeated vaccination on estimates of VE from observational studies.

Notes

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