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Prior season vaccination and risk of influenza during the 2014–2015 season in the U.S

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To the Editor—The recent article by Skowronski and colleagues [1] raises the possibility that repeated influenza vaccination may increase one's likelihood of influenza illness during some seasons. During the 2014–2015 season in Canada, individuals reporting influenza vaccination in three consecutive seasons experienced increased likelihood of influenza A(H3N2)-associated illness to those who reported no vaccination during the 2014–2015 season in Canada [2]. In contrast, individuals reporting vaccination during 2014–2015 but in neither of the two prior seasons had decreased risk of A(H3N2)-related illness compared to the consistently unvaccinated. The authors hypothesize that repeat vaccination with the same A(H3N2) vaccine component increased the likelihood of infection with antigenically-drifted A(H3N2) viruses. However, similar conditions in the United States during the 2014–2015 season were not associated with increased risk of illness among individuals vaccinated in two consecutive seasons or with significant protection for those vaccinated only in 2014–2015 [3]. Differential VE against multiple A(H3N2) clades that circulated during 2014–2015

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complicates interpretation of subgroup analyses of VE by prior vaccination [4]. In addition, differences in ascertainment of prior season vaccination status may contribute to some of the difference observed in the U.S. and Canadian studies. For comparison, we conducted additional analyses of data from the U.S. Influenza Vaccine Effectiveness (Flu VE) Network to investigate the effects of vaccination in three consecutive seasons on vaccine effectiveness against A(H3N2)-associated illness during the 2014–2015 season.

The U.S. Flu VE Network conducts annual studies of vaccine effectiveness (VE) using the test-negative study design that is also used in Canada. In the Canadian study, current and prior season vaccination status is based on a combination of patient self-report and sentinel practitioner documentation. In the U.S. Flu VE Network, current season vaccination status is also based on a combination of patient self-report and electronic immunization records, however prior season vaccination is based on immunization records only. Misclassification of vaccine history may result from inaccurate self-report or incomplete immunization records. One study that compared self-reported influenza vaccination to an immunization registry found that patients over-reported vaccination by approximately 10 percent [5]; recall of prior seasons' vaccination may be less accurate. To minimize misclassification of vaccination history in two prior seasons, we considered documented doses only among patients aged ≥9 years with medical records available for at least two years prior to enrollment, and excluded patients who reported 2014–2015 influenza vaccination that was not documented. After adjusting for age and other potential confounding variables, we found no statistically significant association between vaccination in three consecutive seasons and A(H3N2)-related illness during 2014–2015 (Table). However, we observed the highest point estimate among persons vaccinated in 2014–2015 only. A sensitivity analysis restricted to the main genetic group (clade 3C.2a) of antigenically drifted A(H3N2) and influenza negatives resulted in similar estimates (data not shown). Although the higher point estimate for vaccination only in 2014–2015 is consistent with potential negative interference from prior vaccination [1], our results do not support evidence of increased likelihood of influenza due to A(H3N2) viruses among repeatedly vaccinated individuals compared to those unvaccinated in three consecutive seasons.

The U.S. Advisory Committee on Immunization Practices recommends annual vaccination for all persons aged ≥6 months to prevent influenza and its complications. This policy results in annual revaccination among a substantial part of the population receiving influenza vaccines. In previous seasons, the U.S. Flu VE Network has reported modest effects of repeated vaccination on vaccine effectiveness [6–8], similar to findings for two of three A(H3N2) seasons in the Canadian study [1]. Analyses for 2014–2015 from Canada are the first to report statistically significantly increased likelihood of influenza A(H3N2) among revaccinated individuals compared to unvaccinated, although one other study reported increased likelihood of influenza A(H3N2)-related illness among persons vaccinated in 2014–2015 in a population with a large percentage of repeat vaccination [9]. Similar to the U.S., a multi-country European study reported higher VE among persons vaccinated only in 2014–2015 without prior season vaccination, but observed no increased likelihood of influenza A(H3N2)-related illness among those vaccinated both seasons compared to those not vaccinated [10]. As Skowronski and colleagues point out, underlying differences between the repeatedly vaccinated and the much smaller group of infrequently vaccinated

patients or routinely unvaccinated need careful attention when considering implications for vaccination recommendations. We contend that ascertainment of vaccination status itself is also an essential consideration.

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Table

Unadjusted and adjusted vaccine effectiveness stratified by combinations of prior (2012–13 and/or 2013–14) and current (2014–15) influenza vaccination status among patients aged ≥9 years with at least two years of available medical records.

	Influenza-Positive Cases			Influenza-Negative Controls		Unadjusted Vaccine Effectiveness		Adjusted[a] Vaccine Effectiveness	
Vaccination History	**Total**	**N**	**Row (%)**	**N**	**Row (%)**	**VE %**	**(95% CI)**	**VE %**	**(95% CI)**
Current and both prior (2012–13 and 2013–14)	1980	452	(22.8)	1528	(77.2)	−7%	(−25 to 9)	−2%	(−24 to 15)
Current and 1 prior (2012–13 or 2013–14)	587	119	(20.3)	468	(79.7)	8%	(−16 to 27)	7%	(−20 to 27)
No current but both prior (2012–13 and 2013–14)	314	71	(22.6)	243	(77.4)	−5%	(−41 to 21)	5%	(−29 to 31)
No current but 1 prior (2012–13 or 2013–14)	542	118	(21.8)	424	(78.2)	0%	(−27 to 21)	−2%	(−31 to 21)
Current but neither prior (2014–15 only)	386	66	(17.1)	320	(82.9)	26%	(1 to 44)	26%	(0 to 46)
Unvaccinated all 3 seasons	1714	372	(21.7)	1342	(78.3)	REF		REF	

[a]Adjusted for site, age (natural cubic spline), presence of any high-risk condition, and calendar time (2-week intervals)