Low Influenza Vaccine Effectiveness Against A(H3N2)-Associated Hospitalizations in 2016–2017 and 2017–2018 of the Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN)

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Background. The 2016–2017 and 2017–2018 influenza seasons were notable for the high number of hospitalizations for influenza A(H3N2) despite vaccine and circulating strain match.

Methods. We evaluated vaccine effectiveness (VE) against hospitalization in the test-negative HAIVEN study. Nasal-throat swabs were tested by quantitative reverse transcription polymerase chain reaction (RT-PCR) for influenza and VE was determined based on odds of vaccination by generalized estimating equations. Vaccine-specific antibody was measured in a subset of enrollees.

Results. A total of 6129 adults were enrolled from 10 hospitals. Adjusted VE against A(H3N2) was 22.8% (95% confidence interval [CI], 8.3% to 35.0%), pooled across both years and 49.4% (95% CI, 34.3% to 61.1%) against B/Yamagata. In 2017–2018, the A(H3N2) VE point estimate for the cell-based vaccine was 43.0% (95% CI, –36.3% to 76.1%; 56 vaccine recipients) compared to 24.0% (95% CI, 3.9% to 39.9%) for egg-based vaccines. Among 643 with serology data, hemagglutinin antibodies against the egg-based A(H3N2) vaccine strain were increased in influenza-negative individuals.

Conclusions. Low VE for the A/Hong Kong/4801/2014 vaccine virus in both A(H3N2) seasons emphasizes concerns for continued changes in H3N2 antigenic epitopes, including changes that may impact glycosylation and ultimately reduce VE.

Keywords. adults; case-control study; hospitalization; influenza; vaccine; vaccine effectiveness.

The 2016–2017 and 2017–2018 US influenza seasons were characterized by use of the A/Hong Kong/4801/2014 (H3N2)-like vaccine virus coupled with a 2-year predominance of A(H3N2) viruses in the northern hemisphere. Additionally, 2017–2018 was notable for being the most severe influenza season since the 2009 A(H1N1) pandemic. During the US 2017–2018 season, it is estimated that 45 million people were infected, the highest since the 2009 pandemic, and 61 000 people died [1].

In both seasons, vaccine effectiveness (VE) was low against medically attended acute respiratory illness [1,2]. Factors that

potentially reduce VE against influenza have included prior vaccination [3–5] and intraseason waning [6–8]. Specific to the 2016–2017 and 2017–2018 season, several studies have noted the presence of an egg-adaptation mutation in the egg-produced vaccine virus that may have precluded the ability of the vaccine to elicit a protective response against circulating viruses [9–11]. However, the degree to which this adaptation influenced observed effectiveness estimates remains unclear. These evaluations require the use of large surveillance systems with access to documented vaccination product information.

Our objective was to determine the effectiveness of influenza vaccine against hospitalization with laboratory-confirmed influenza during the 2016–2017 and 2017–2018 seasons using a test-negative study in a 10-hospital network called the US Hospital Adult Influenza Vaccine Effectiveness Network (HAIVEN) for yearly VE surveillance. The test-negative design compares influenza-positive patients to those negative using sensitive quantitative reverse transcription polymerase chain reaction (RT-PCR) testing [12]. Secondary analysis objectives

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included exploratory analyses by vaccine product and by prior vaccination.

METHODS

HAIVEN consists of 4 sites located in Texas (2 hospitals), Tennessee (3 hospitals), Pennsylvania (3 hospitals), and Michigan (2 hospitals). The methods have been described elsewhere [13]. Patients age ≥ 18 years hospitalized in the 2016–2017 and 2017–2018 seasons were selected for participation based on a standardized case definition indicating acute respiratory illness.

Upon obtaining informed consent from the participant, an enrollment interview collected data on demographics, health history, and vaccination. Throat and nasal swab specimens were collected for laboratory confirmation of influenza and respiratory syncytial virus (RSV) by RT-PCR using standard Centers for Disease Control and Prevention assays or multiplex PCR-based assays for clinical care.

Vaccination Status

Participants were considered vaccinated if they had documented or plausible self-reported vaccination (with inclusion of location of vaccine receipt) administered ≥ 14 days prior to illness onset [13]. Information was also collected regarding vaccination in the prior season using documented and self-reported data following similar methods to current-year vaccination.

Statistical Analyses

Patient characteristics were compared between influenza-positive and -negative individuals and vaccinated and unvaccinated individuals using a Pearson χ^2 test. Study data was analyzed in a test-negative design [12] with VE calculated as $(1 - \text{the adjusted odds ratio of the association between vaccination and infection}) \times 100\%$. Odds ratios were determined using generalized estimating equations models with a logit link and exchangeable correlation structure to account for individuals who were enrolled more than once ($n = 60$ individuals for 2016–2017; $n = 113$ individuals for 2017–2018). An independent correlation structure was used in subgroup analyses with small cluster and sample size (vaccination habit, prior vaccination, and study site-specific models). Adjusted models for overall, strain-specific, and product-type-specific estimates included terms for enrollment hospital, age (in groups of 18–49, 50–64, 65–74, ≥ 75 years), race, tertiles of calendar time from site-specific and influenza-type specific peaks, days from illness onset to specimen collection (categorized as 0–1, 2–4, 5–10 days), self-reported health (categorized as poor/fair vs good/very good/excellent) and self-reported hospitalizations in the year prior to enrollment. Logistic regression was used for age-group-specific models, which included these same covariates except for categorical age in the adjusted models and differences between age-specific strata were evaluated by

an interaction term in the adjusted model. For analyses specific to vaccine product type, VE was evaluated among all enrollees with available documentation of vaccination (excluding those with self-reported data only), including documentation of product received. VE against RSV was also calculated as a negative control outcome, given that influenza vaccine is not expected to impact RSV [14–16]. This analysis compared RSV-positive to RSV-negative enrollees, restricting participants to those enrolled during times of RSV circulation and including the same adjustment factors as in the main influenza VE model.

For strain-specific analyses of VE against hospitalization, participants infected with other influenza strains were excluded, as were participants enrolled outside of periods of circulation of the strain under analysis. Stratified, adjusted models, using model variables above when applicable, were created by participant subgroup (Supplementary Figure 1). Two secondary analyses were a priori selected based on prior findings from HAIVEN and other literature: a comparison of product-specific VE [17–21] and an evaluation of VE by prior vaccination (ie, separately for individuals with single and 2-year vaccination compared to the unvaccinated group) [3, 4, 22]. A sensitivity analysis was performed for timing of sample collection (within 4 days versus more than 4 days) based on effects seen in prior studies [23–26].

Serology

Sera from clinical blood specimens taken during hospital admission were collected and tested from both seasons by the University of Michigan site's laboratory for characterization of preinfection antibody levels. We have previously demonstrated that similar specimens from HAIVEN participants in previous seasons were collected soon enough after symptom onset such that antibodies to the infecting strain were not increased [27]. Specimens from both years were tested by hemagglutination inhibition (HAI) assay for antibodies against egg-based vaccine antigens, including ether-split egg-based vaccine antigen (Sanofi Pasteur) representing the A/Hong Kong (H3N2) vaccine strain. Specimens from 2017–2018 were tested by HAI against ether-split vaccine antigen (Sanofi Pasteur) representing the A/Singapore (H3N2) vaccine for 2018–2019 to evaluate the presence of cross-reactive antibodies to the subsequent year's vaccine. Antineuraminidase antibody was measured using methods as previously described [9] by neuraminidase inhibition assay (NAI). NAI targets included the representative neuraminidases from A/Hong Kong (H3N2) (both study years) and A/Singapore (H3N2) (2017–2018 only). Logistic regression models were used to determine the independent reduction in odds of infection associated with HAI or NAI holding the other constant.

RESULTS

A total of 7398 subjects were enrolled (3290 in 2016–2017 and 4108 in 2017–2018), and 1269 were excluded (Supplementary

Table 1) for a final analysis sample of 6129. Overall, 21.1% (n = 1291) of participants were 75 years of age or older and 22.6% (n = 1388) of participants were 65 to 74 years of age (Table 1). Age distribution varied by site and season (Supplementary Table 2A–D). The most commonly reported race and ethnicity was white, non-Hispanic (n = 3979, 65.0%) and race varied by site. High-risk conditions were present in 98% (n = 2554) of participants in the first analysis year and 95.3% (n = 3359) in the second year (Supplementary Table 3). Half of participants (n = 3065) self-reported poor or fair health, 2809 enrollees (45.8%) had a Charlson Comorbidity Index greater than 3, and 2364 enrollees (39.2%) self-reported 3 or more markers of frailty. Overall, 3790 (61.8%) participants reported being hospitalized at least once in the past year. Over one-fifth of participants (n = 1343; 21.9%) reported being hospitalized 4 or more times during the year prior to study enrollment. Vaccination uptake at the 4 sites ranged from 70.2% (468 of 667, Michigan site) to 74.4% (656 of 882, Pennsylvania site) in the first year of analysis and was lower in the second year, ranging from 64.5% (747 of 1158, Texas site) to 69.4% (409 of 589, Tennessee site) (Supplementary Table 3).

Influenza Infection

Influenza A(H3N2) strains from the vaccine-like clade 3c.2a predominated nationally during both the 2016–2017 and 2017–2018 seasons [28, 29]. Influenza was identified in 17.8% (463 of 2605) of participants during the 2016–2017 season but in 25.8% (910 of 3524) of participants during the 2017–2018 season. Percent of participants with influenza ranged from 13.7% (62 out of 451, Texas site) to 21.1% (141 out of 667, Michigan site) in the 2016–2017 season and ranged from 23.1% (268 out of 1158, Texas site) to 28.7% (271 out of 943, Michigan site) in the 2017–2018 season (Supplementary Table 3). Influenza detection increased with age in both years. The majority of influenza detections (61.1%) were influenza A(H3N2) (839 of 1373 total detections) followed by 21.6% influenza B/Yamagata (n = 296) (Table 2).

Overall Influenza Vaccine Effectiveness

In an adjusted model pooled across all influenza strains and both years, VE against any influenza-associated hospitalization was 33.5% (95% confidence interval [CI], 23.6%–42.0%; Table 2). Effectiveness against A(H3N2) hospitalization was lower (22.8%; 95% CI, 8.3%–35.0%) than against B/Yamagata (49.4%; 95% CI, 34.3%–61.1%). The point estimate for the VE for each influenza type was higher in 2017–2018 than in 2016–2017, however CIs overlapped. Effectiveness in 2016–2017 against A(H3N2)-associated hospitalization had a CI including the null (18.0%; 95% CI, –9.2% to 38.3%). A total of 328 of 2605 (12.6%) and 422 of 3524 (12.0%) individuals required intensive care unit (ICU) admission in 2016–2017 and 2017–2018, respectively. Among this subgroup of individuals, VE comparing ICU patients with and without A(H3N2) was 23.7% (95% CI,

–75.4% to 66.8%; 36 total A(H3N2) infections) for 2016–2017 and 27.0% (95% CI, –56.3% to 65.9%; 41 total A/H3N2 infections) for 2017–2018. VE against RSV, the negative control, was –28.1% (95% CI, –85.7% to 11.7%) in 2016–2017 and –8.1% (95% CI, –52.1% to 23.2%) in 2017–2018, confirming that positive VE was not observed against a virus with no biologic association to the vaccine. The negative control estimate was lowest for the 18–49 years age group –199.7% (95% CI, –579.0% to –32.2%) in 2016–2017 and –169.7% (95% CI, –469.7% to –27.7%) in 2017–2018.

Effect of Vaccine Type

Analyses of cell-based vaccines were performed for the 2017–2018 season only, given the small numbers in the cell-based vaccine group in 2016–2017 (n = 9). In 2017–2018, 66 individuals (2.8% of all vaccinated participants in that season) received a non-egg-based type of vaccine product, including 65 Flucelvax (Seqirus) and 1 Flublok Quadrivalent (Sanofi) vaccines. The individual receiving Flublok was excluded from comparative analyses. In addition, we excluded 608 individuals who had unknown vaccine type, leaving 2915 individuals. Overall, the point estimate for the cell-based VE against A(H3N2) was higher than for egg-based vaccines, but CIs overlapped (cell based, 43.0% [95% CI, –36.3% to 76.1%] vs egg based, 24.0% [95% CI, 3.9% to 39.9%]); the difference in VE was not statistically significant ($P = .52$) (Table 3). Point estimates against B/Yamagata were similar (cell based, 51.5% [95% CI, –77.0% to 86.7%]) vs egg based, 50.6% [95% CI, 30.2% to 65.1%]) with $P = .98$ for the difference in VE. In a model restricting the egg-based vaccine group to only those receiving standard-dose vaccine, excluding high-dose recipients, the egg-based VE estimate was 26.6% (95% CI, 5.1% to 43.3%) comparable to the estimate against A(H3N2), combining standard and high dose recipients.

Effect of Prior Vaccination

Prior vaccination was evaluated in the 2017–2018 season, finding that over three-quarters of the study population in this year had documentation or a self-report of influenza vaccination in the previous year, thus receiving 2 consecutive vaccines containing the A/Hong Kong (H3N2) vaccine strain. Previous-year vaccine receipt was common among individuals with vaccination in the current year (n = 1739, 87.3% in 2016–2017; n = 2182, 83.3% in 2017–2018). VE against influenza A(H3N2) hospitalization in 2017–2018 was higher among the subgroup of individuals vaccinated in 2016–2017 (30.0%; 95% CI, 5.5% to 48.2%) than among those not vaccinated previously (5.7%; 95% CI, –63.7 to 45.7); however, the sample size for those unvaccinated in 2016–2017 was very small (Supplementary Figure 1) and the P value for the interaction was 0.34.

Timing of Sample Collection

Although enrollment was permitted for up to 10 days after the onset of symptoms, most samples were collected within 7 days

Table 1. Overall Hospitalized Adult Influenza Vaccine Effectiveness Network Study Population, Combined Years (N = 6129)^a

Characteristic	Overall	Influenza Positive	Influenza Negative	PValue	Vaccinated	Not Vaccinated	PValue	Received Cell-Based Vaccine	
								2016–2017	2017–2018
Season									
2016–2017	2605 (42.5)	463 (17.8)	2142 (82.2)	<.001	1886 (72.4)	719 (27.6)	<.001	9 (0.5)	–
2017–2018	3524 (57.5)	910 (25.8)	2614 (74.2)		2350 (66.7)	1174 (33.3)		–	66 (2.8)
Study site									
Michigan	1610 (26.3)	412 (25.6)	1198 (74.4)	.002	1089 (67.6)	521 (32.4)	.002	2 (0.4)	31 (5.0)
Pennsylvania	1716 (28.0)	385 (22.4)	1331 (77.6)		1229 (71.6)	487 (28.4)		1 (0.2)	12 (2.1)
Tennessee	1194 (19.5)	246 (20.6)	948 (79.4)		851 (71.3)	343 (28.7)		6 (1.4)	15 (3.7)
Texas	1609 (26.3)	330 (20.5)	1279 (79.5)		1067 (66.3)	542 (33.7)		0 (0.0)	8 (1.1)
Sex									
Female	3467 (56.6)	777 (22.4)	2690 (77.6)	.984	2406 (69.4)	1061 (30.6)	.584	6 (0.6)	34 (2.5)
Male	2662 (43.4)	596 (22.4)	2066 (77.6)		1830 (68.7)	832 (31.3)		3 (0.4)	32 (3.2)
Age group, y									
18–49	1376 (22.5)	274 (19.9)	1102 (80.1)	<.001	759 (55.2)	617 (44.8)	<.001	2 (0.6)	15 (3.7)
50–64	2074 (33.8)	415 (20.0)	1659 (80.0)		1323 (63.8)	751 (36.2)		5 (0.8)	33 (4.7)
65–74	1388 (22.6)	317 (22.8)	1071 (77.2)		1043 (75.1)	345 (24.9)		0 (0.0)	6 (1.0)
75+	1291 (21.1)	367 (28.4)	924 (71.6)		1111 (86.1)	180 (13.9)		2 (0.4)	12 (1.8)
Race and ethnicity									
White, non-Hispanic	3979 (65.0)	858 (21.6)	3121 (78.4)	.21	2908 (73.1)	1071 (26.9)	<.001	5 (0.4)	39 (2.5)
Black, non-Hispanic	1723 (28.2)	411 (23.9)	1312 (76.1)		1061 (61.6)	662 (38.4)		3 (0.7)	25 (3.9)
Other race, non-Hispanic	183 (3.0)	43 (23.5)	140 (76.5)		117 (63.9)	66 (36.1)		0 (0.0)	1 (1.6)
Hispanic, any race	235 (3.8)	58 (24.7)	177 (75.3)		147 (62.6)	88 (37.4)		1 (2.0)	1 (1.0)
Vaccinated in prior season									
Yes	4614 (76.2)	956 (20.7)	3658 (79.3)	<.001	3921 (85.0)	693 (15.0)	<.001	8 (0.5)	58 (2.7)
No	1438 (23.8)	395 (27.5)	1043 (72.5)		275 (19.1)	1163 (80.9)		1 (0.8)	6 (4.1)
High risk in past year									
Yes	5913 (96.5)	1304 (22.1)	4609 (77.9)	<.001	4130 (69.8)	1783 (30.2)	<.001	7 (0.4)	59 (2.6)
No	216 (3.5)	69 (31.9)	147 (68.1)		106 (49.1)	110 (50.9)		2 (8.7)	7 (8.4)
Self-reported health									
Poor	961 (15.7)	155 (16.1)	806 (83.9)	<.001	679 (70.7)	282 (29.3)	<.001	3 (1.0)	8 (2.1)
Fair	2104 (34.3)	442 (21.0)	1662 (79.0)		1529 (72.7)	575 (27.3)		2 (0.3)	24 (2.9)
Good	1918 (31.3)	480 (25.0)	1438 (75.0)		1322 (68.9)	596 (31.1)		2 (0.4)	23 (3.0)
Very good	828 (13.5)	211 (25.5)	617 (74.5)		518 (62.6)	310 (37.4)		2 (0.9)	8 (2.8)
Excellent	318 (5.2)	85 (26.7)	233 (73.3)		188 (59.1)	130 (40.9)		0 (0.0)	3 (3.3)
Charlson comorbidity index									
0	504 (8.2)	159 (31.5)	345 (68.5)	<.001	272 (54.0)	232 (46.0)	<.001	1 (0.9)	10 (6.3)
1	1080 (17.6)	264 (24.4)	816 (75.6)		602 (55.7)	478 (44.3)		0 (0.0)	8 (2.5)
2–3	1736 (28.3)	382 (22.0)	1354 (78.0)		1194 (68.8)	542 (31.2)		2 (0.4)	22 (3.3)
4+	2809 (45.8)	568 (20.2)	2241 (79.8)		2168 (77.2)	641 (22.8)		6 (0.6)	26 (2.1)
Frailty level									
0	1096 (18.2)	313 (28.6)	783 (71.4)	<.001	696 (63.5)	400 (36.5)	<.001	1 (0.3)	13 (3.4)
1	1323 (21.9)	294 (22.2)	1029 (77.8)		886 (67.0)	437 (33.0)		2 (0.5)	17 (3.5)
2	1253 (20.8)	263 (21.0)	990 (79.0)		873 (69.7)	380 (30.3)		3 (0.8)	14 (2.8)
3	1086 (18.0)	240 (22.1)	846 (77.9)		771 (71.0)	315 (29.0)		1 (0.3)	10 (2.3)
4	912 (15.1)	178 (19.5)	734 (80.5)		681 (74.7)	231 (25.3)		2 (0.7)	7 (1.9)
5	366 (6.1)	62 (16.9)	304 (83.1)		266 (72.7)	100 (27.3)		0 (0.0)	4 (3.0)
Days from onset to specimen collection									
0–2	2253 (36.8)	533 (23.7)	1720 (76.3)	<.001	1599 (71.0)	654 (29.0)	.081	3 (0.4)	20 (2.3)
3–4	1734 (28.3)	425 (24.5)	1309 (75.5)		1175 (67.8)	559 (32.2)		4 (0.8)	16 (2.3)
5–7	1481 (24.2)	306 (20.7)	1175 (79.3)		1020 (68.9)	461 (31.1)		2 (0.5)	19 (3.3)
8–10	661 (10.8)	109 (16.5)	552 (83.5)		442 (66.9)	219 (33.1)		0 (0.0)	11 (5.2)
Self-reported number of hospitalizations in past year									
0	2339 (38.2)	679 (29.0)	1660 (71.0)	<.001	1469 (62.8)	870 (37.2)	<.001	3 (0.5)	21 (2.5)
1	1153 (18.8)	264 (22.9)	889 (77.1)		790 (68.5)	363 (31.5)		2 (0.5)	15 (3.6)
2	772 (12.6)	151 (19.6)	621 (80.4)		550 (71.2)	222 (28.8)		1 (0.4)	5 (1.7)
3	522 (8.5)	105 (20.1)	417 (79.9)		395 (75.7)	127 (24.3)		1 (0.6)	7 (3.1)
4+	1343 (21.9)	174 (13.0)	1169 (87.0)		1032 (76.8)	311 (23.2)		2 (0.4)	18 (3.2)

Data are n (%). Row percents are displayed for all columns except the Overall.

^aSixty participants had 2–4 enrollments (giving a total of 69 additional enrollments) in 2016–2017; 113 participants had 2–6 enrollments (giving a total of 134 additional enrollments) in 2017–2018.

Table 2. Overall and Strain-Specific, Vaccine Effectiveness Against Hospitalization With Laboratory-Confirmed Influenza, Hospitalized Adult Influenza Vaccine Effectiveness Network 2016–2018 (N = 6129)

Outcome	Year	Vaccinated ^a Positives, n/Total (%)	Unvaccinated Positives, n/Total (%)	Unadjusted VE (95% CI)	Adjusted ^b VE (95% CI)
Influenza, all	2016–2017	302/1886 (16.0)	161/719 (22.4)	33.4 (17.5 to 46.3)	30.6 (12.4 to 45.0)
	2017–2018	557/2350 (23.7)	353/1174 (30.1)	26.6 (14.2 to 37.3)	34.2 (21.9 to 44.6)
	2016–2018 (2 y)	859/4236 (20.3)	514/1893 (27.2)	31.0 (21.7 to 39.2)	33.5 (23.6 to 42.0)
A/H3N2	2016–2017	214/1658 (12.9)	95/596 (15.9)	21.4 (–2.2 to 39.5)	18.0 (–9.2 to 38.3)
	2017–2018	343/2044 (16.8)	187/970 (19.3)	14.9 (–3.7 to 30.1)	23.8 (5.3 to 38.7)
	2016–2018 (2 y)	557/3702 (15.0)	282/1566 (18.0)	18.8 (5.0 to 30.6)	22.8 (8.3 to 35.0)
A/H1N1 pdm09	2016–2017	7/391 (1.8)	4/150 (2.7)	...	...
	2017–2018	48/1567 (3.1)	56/729 (7.7)	61.92 (43.4 to 74.4)	56.1 (33.1 to 71.2) ^c
	2016–2018 (2 y)	55/1958 (2.8)	60/879 (6.8)	60.5 (42.5 to 72.8)	53.7 (31.4 to 68.7) ^c
B/Yamagata	2016–2017	56/1356 (4.1)	39/502 (7.8)	45.0 (15.1 to 64.3)	47.9 (16.8 to 67.3)
	2017–2018	119/1615 (7.4)	82/738 (11.1)	36.2 (14.1 to 52.5)	50.2 (31.4 to 63.8)
	2016–2018 (2 y)	175/2971 (5.9)	121/1240 (9.8)	42.0 (26.1 to 54.4)	49.4 (34.3 to 61.1)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

^aAll denominators exclude other influenza types and any enrollments occurring outside of influenza type-specific periods for each site.

^bAdjusted VE models are adjusted for enrollment hospital, age (18–49, 50–64, 65–74, ≥75 y), race, tertiles (for 1 y) or 6 quantiles (for 2 y) of calendar time including a site-specific and influenza-type specific peak for each year, days from illness onset to specimen collection (0–1, 2–4, 5–10 d), self-reported health (poor/fair vs good/very good/excellent), and self-reported past year hospitalizations.

^cVE could not be calculated due to small numbers in 2016–2017. Adjusted VE models for A/H1N1 are adjusted for site instead of enrollment hospital due to small case numbers per hospital.

(n = 5468, 89.2%) and 3987 specimens (65.1%) were collected within 4 days. While influenza detection rate was lower among individuals enrolled ≥ 4 days after illness onset compared to within 4 days of onset ($P = .04$ in 2016–2017 and $P = .004$ in 2017–2018), the difference in VE was not statistically significant between individuals enrolled within 4 days after onset compared to individuals enrolled more than 4 days after onset (35.1% vs 21.4% in 2016–2017; 39.9% vs 21.3% in 2017–2018; P values for interaction, respectively, $P = .42$ in 2016–2017 and $P = .13$ in 2017–2018).

Serology

Serum specimens collected upon hospital admission were obtained from 643 enrollees from 1 hospital within the Michigan site during the 2016–2017 (n = 379) and the

2017–2018 (n = 264) seasons (Supplementary Table 6). One hundred specimens (15.6%) were from individuals with influenza A (H3N2) and 498 specimens (77.4%) were from vaccinated individuals (Supplementary Table 6). HAI and NAI titers against A/Hong Kong (H3N2), representing titers against the egg-adapted vaccine strain in both seasons, were significantly higher among vaccinated individuals in both years (Figure 1). Similarly, vaccinated individuals in 2017–2018 had higher HAI and NAI titers that were cross-reactive against A/Singapore (H3N2), which was selected as the vaccine strain for the following year. In the 2016–2017 season, increasing levels of the vaccine-like A/Hong Kong (H3N2) HAI antibody were found to significantly reduce the odds of infection per log₂ increase in titer (odds ratio [OR], 0.76; 95% CI, .63–.91), but NAI antibodies against A/Hong Kong (H3N2) were not associated with

Table 3. Overall and Strain-Specific, Vaccine Effectiveness of Flucelvax Versus Egg-Based Vaccines Against Hospitalization With Laboratory-Confirmed Influenza, Hospitalized Adult Influenza Vaccine Effectiveness Network 2017–2018 (N = 2915)

Outcome	Comparison Groups (1 vs 2)	Group 1 ^a Positives, n/Total (%)	Group 2 ^a Positives, n/Total (%)	Unadjusted VE (95% CI)	Adjusted VE (95% CI)
2017–2018 Influenza, all	Flucelvax vs unvaccinated	14/65 (21.5)	353/1174 (30.1)	35.6 (–18.4 to 64.9)	40.1 (–15.2 to 68.8) ^b
	Egg-based vs unvaccinated	399/1676 (23.8)	353/1174 (30.1)	26.1 (12.5 to 37.5)	34.5 (21.1 to 45.7) ^b
	Flucelvax vs egg-based	14/65 (21.5)	399/1676 (23.8)	12.8 (–59.8 to 52.4)	8.5 (–75.9 to 52.3) ^b
A/H3N2	Flucelvax vs unvaccinated	7/56 (12.5)	187/970 (19.3)	39.9 (–35.4 to 73.3)	43.0 (–36.3 to 76.1) ^c
	Egg-based vs unvaccinated	248/1459 (17.0)	187/970 (19.3)	13.5 (–6.8 to 29.9)	24.0 (3.9 to 39.9) ^c
	Flucelvax vs egg-based	7/56 (12.5)	248/1459 (17.0)	30.5 (–55.8 to 69.0)	24.9 (–78.8 to 68.5) ^c
B/Yamagata	Flucelvax vs unvaccinated	3/43 (7.0)	82/738 (11.1)	39.9 (–99.1 to 81.9)	51.5 (–77.0 to 86.7) ^d
	Egg-based vs unvaccinated	83/1135 (7.3)	82/738 (11.1)	36.6 (12.6 to 54.0)	50.6 (30.2 to 65.1) ^d
	Flucelvax vs egg-based	3/43 (7.0)	83/1135 (7.3)	5.2 (–213.5 to 71.4)	1.8 (–254.0 to 72.8) ^d

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

^aAll denominators exclude other influenza types, any enrollments occurring outside of influenza type-specific periods, and unknown vaccine types for each site.

^b P values calculated for adjusted VE for all influenza types were: .13 for Flucelvax vs unvaccinated, <.001 for egg-based vs unvaccinated, and .79 for Flucelvax vs egg-based.

^c P values calculated for adjusted VE for A/H3N2 were: .21 for Flucelvax vs unvaccinated, .02 for egg-based vs unvaccinated, and .52 for Flucelvax vs egg-based.

^d P values calculated for adjusted VE for B/Yamagata were: .27 for Flucelvax vs unvaccinated, <.001 for egg-based vs unvaccinated, and .98 for Flucelvax vs egg-based.

Figure 1. Antibody titers by hemagglutination inhibition (HAI) and neuraminidase inhibition (NAI) against vaccine antigens in 2016–2017 (A) and 2017–2018 (B). The A/Hong Kong/4801/2014 (A/Hong Kong) strain was included in both the 2016–2017 and 2017–2018 influenza vaccines; the A/Singapore/INFIMH-16-0019/2016 strain was subsequently selected as the H3N2 strain included in the 2018–2019 vaccine. Error bars represent 95% confidence intervals.

protection (OR, 0.99; 95% CI, .82–1.19). The point estimates were similar in 2017–2018 for both HAI (OR, 0.80; 95% CI, .64–1.00) and NAI (OR, 1.02; 95% CI, .86–1.22) antibodies against vaccine-like A/Hong Kong (H3N2), but neither were statistically significant.

DISCUSSION

In this analysis of 2 years of a prospective, multicenter, test-negative study of influenza VE in prevention of hospitalization, we found VE of 33.5% against any influenza-associated hospitalization and a low VE of 22.8% for the A/Hong Kong/4801/2014 vaccine strain. VE was similarly low across adult age groups and levels of frailty and chronic comorbidities (Supplementary Figure 1). These estimates are similar to the Ambulatory US Flu VE Network results for A(H3N2) in the 2016–2017 and 2017–2018 seasons (33% [2] and 22% [1], respectively) and the Canadian Sentinel Practitioner Surveillance Network results (42% [30] and 17% [31]).

Overall, evaluations in recent years have found VE to be consistently lower against A(H3N2) compared to A(H1N1)

pdm09 or influenza B [32–34]. VE against hospitalization in the HAIVEN study was higher in 2015–2016 (51%) against A(H1N1)pdm09 [13]. In some years, most notably in 2014–2015, low VE against A(H3N2) has been attributed to difficulties with matching the vaccine strain to the clade of the subsequently circulating virus [35]. However, our resulting VE in these 2 seasons is unexpectedly low even when considering the degree of antigenic match. Antigenic studies indicate that most circulating viruses in the United States during those years were similar to the A/Hong Kong/4801/2014 strain used in the vaccine [36], yet a VE below 25% was observed in both years. This pattern, found even in years when the vaccine strain was antigenically similar, prompts concern for additional, continued changes in A(H3N2).

In recent years, mutations resulting from egg adaptation that change glycosylation have modified antigenic sites available for antihemagglutinin antibody binding such that the vaccine strain may elicit antibodies to sites that are unavailable in circulating viruses. The A/Hong Kong/4801/2014 strain acquires a specific egg-adaptation mutation during propagation in eggs, altering antigenic sites (T160K) [11]. The seed virus for the cell-based vaccine included in our analysis was propagated without the use of eggs [17], avoiding this change. We have previously demonstrated that vaccinated individuals enrolled in HAIVEN (2017–2018 season) had antibodies specific to the egg-propagated A/Hong Kong/4801/2014 virus and antibody titers against cell-grown A/Hong Kong/4801/2014 and other A(H3N2) 3c.2a2 and 3c.2a1 viruses were lower [9]. The 2016–2017 and 2017–2018 US vaccine evaluation landscape included the increasing use of quadrivalent influenza vaccines grown in cell systems, in contrast to growth in eggs, although initially produced with seed stock originating in eggs. By the 2017–2018 season, production of cell-based vaccines began using cell-based seed stocks for the H3N2 strain [17], and use of these vaccines became more common in the United States. Our findings are consistent with modest increases in VE for cell-based vaccines observed in studies in hospitalized adults [18, 19], across a large health plan [20], and in a Department of Defense sentinel surveillance study [37]. Complementing these findings is an immunogenicity study where cell-based vaccine elicited an antibody response slightly higher than egg-based vaccine but lower than high-dose or recombinant products [21]. In our product-type specific analyses for the 2017–2018 season, the point estimate for the VE for the cell-based vaccine was higher than for egg-based vaccines, but this difference was not statistically significant and this estimate (43%) is at the low end of the range expected from a well-matched vaccine. Our estimates for egg-based vaccines were similar when excluding those receiving high-dose vaccine. Recently, a dedicated analysis of high- versus standard-dose vaccination in HAIVEN participants in the 2015–2017 seasons has found the increase in VE for high-dose to be moderate, and not statistically significant, in

seasons with low to moderate overall VE [38]. While the egg adaptation is one explanation proposed for the low VE observed in 2017–2018, other factors impacting VE, including prior vaccination and the role of neuraminidase antibodies, cannot be ruled out. Ongoing observational studies and randomized trials of egg- and non-egg-based influenza vaccine products will shed light on these potential hypotheses of the impact of egg adaptation going forward, and more mechanistic studies are needed.

In both seasons, increasing HAI, but not NAI, antibody against egg-adapted A/Hong Kong (H3N2) vaccine strain was associated with protection. This appears to be inconsistent with low VE against influenza A(H3N2) in these 2 seasons and it is possible this association is affected by unmeasured antibody with better specificity to the circulating virus. We have demonstrated in a smaller subset of this population that antibody titers against cell-grown viruses, although present only at low levels, were better correlates of protection [9]. Interestingly, antibody titers against both the hemagglutinin and neuraminidase of A/Singapore (H3N2) were higher among individuals vaccinated with A/Hong Kong (H3N2) relative to unvaccinated individuals. This suggests cross-reactivity between these antigens. For hemagglutinin, the cross-reactivity is not surprising; A/Singapore (H3N2) and A/Hong Kong (H3N2) are antigenically similar with both expected to have the same egg-related mutation demonstrated to drive antibody response. However, neuraminidase cross-reactivity between the 2 strains was unexpected given that A(H3N2) viruses predominant in 2017–2018 were reassortants with hemagglutinin and neuraminidase segments from separate 3c.2A subclades [39]. NAI titers did not protect against infection, a finding that may be related to issues with the quality of the antibody [40] or with continued antigenic change of the neuraminidase [39]. Increased antigenic characterization of the neuraminidase of circulating viruses is potentially needed to understand future patterns of circulation and severity, and to aid in vaccine strain selection.

Limitations of this study include its small sample size for evaluation of product-specific effects, given the low uptake of newer vaccine products observed in 2016–2017 and 2017–2018. This study is also limited by challenges inherent in observational studies of VE, particularly those conditional upon hospital admission. The majority of adults of all ages in HAIVEN have chronic health conditions, a population not fully captured in ambulatory-based studies with differing VE estimates [1, 2, 41, 42]. While presenting an opportunity to study this important and high-risk population, the potential for bias arising from differential vaccination and hospital admission patterns as they impact the test-negative design is an area for further attention. Analyses of the association between vaccination and a negative control outcome (RSV) resulted in a strongly negative point estimate. As VE for the prevention of RSV using influenza vaccine should be zero, this largely negative VE raises concern for bias in the age stratified estimate for 18–49 year olds, leading to an underestimation of VE in that age group. While we have

previously found minimal bias in the test-negative design as applied to hospitalized adults using testing of other respiratory viruses as a control [43], more work to understand the 18 to 49-year-old population is needed, particularly in years with low influenza VE. In this analysis, we also evaluated the potential for bias in our estimates when including individuals for whom sample collection occurred >4 days after symptom onset, potentially raising the possibility of false-negative results. While this was not statistically significant, our finding of reduced VE and reduced overall detection rate in this group should prompt further attention to the importance of timing of sample collection in studies of respiratory virus hospitalization.

In summary, we found that VE for prevention of A(H3N2) hospitalization was under 25% in both years where the A/Hong Kong/4801/2014 vaccine strain was used. Following the 2017–2018 season, the A(H3N2) component of the vaccine was updated to A/Singapore/INFIMH-16–0019/2016 A(H3N2)-like virus and since has been updated for the 2019–2020 season. Active surveillance of influenza VE against hospitalization is a key component in understanding prevention of severe morbidity. Given challenges with VE against A(H3N2) infection, and increasing variety of vaccine products, efforts to monitor VE with prospective collection of viruses and product-specific vaccine documentation is critical to inform seasonal vaccination strategies from year to year. Longer-term vaccine development plans support testing of future universal influenza vaccines with longer-lasting, broader protection; however, these products are likely to be years away. Until then, ongoing investment is needed to monitor changes in A(H3N2) strains and their impact on VE against severe disease, coupled with continued, appropriate use of antivirals in hospitalized adults [44].

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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