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Vaccine-associated attenuation of subjective severity among outpatients with influenza

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Abstract

Influenza vaccines can mitigate illness severity, including reduced risk of ICU admission and death, in people with breakthrough infection. Less is known about vaccine attenuation of mild/moderate influenza illness. We compared subjective severity scores in vaccinated and unvaccinated persons with medically attended illness and laboratory-confirmed influenza. Participants were prospectively recruited when presenting for care at five US sites over nine seasons. Participants aged ≥ 16 years completed the EQ-5D-5L visual analog scale (VAS) at enrollment. After controlling for potential confounders in a multivariable model, including age and general health status, VAS scores were significantly higher among 2,830 vaccinated participants compared

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Declaration of Competing Interest

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Disclaimer

The findings and conclusions are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.06.019.

with 3,459 unvaccinated participants, indicating vaccinated participants felt better at the time of presentation for care. No differences in VAS scores were observed by the type of vaccine received among persons aged ≥ 65 years. Our findings suggest vaccine-associated attenuation of milder influenza illness is possible.

Keywords

Influenza; Vaccines

1. Introduction

US Centers for Disease Control and Prevention (CDC) estimates between 4.3 and 20.7 million medical visits and 140,000–710,000 hospitalizations are attributable to influenza annually in the United States [1]. This large burden has substantial economic costs for medical care and societal costs, such as lost wages of patients and caregivers and loss of productivity among sick workers [2]. Given this large annual medical and economic burden on the healthcare system, understanding whether influenza vaccination might attenuate mild illness has important implications for vaccination promotion efforts and pandemic planning. Influenza vaccination has been associated with attenuation of severe disease, especially decreased likelihood of ICU admission and death among vaccinated persons hospitalized with breakthrough influenza virus infection [3]. Less is known about attenuation of illness severity among non-hospitalized vaccinated persons with breakthrough influenza virus infections [3,4]. Previous efforts to quantify subjective severity among outpatients with acute respiratory illness (ARI) have been based on reported symptoms [5–10]. We explore the use of a validated tool, the EQ-5D-5L visual analog scale (VAS) [11,12] as a measure of general subjective severity of illness among outpatients seeking care for an acute respiratory illness (ARI). This tool has been used previously among hospitalized persons with ARI in conjunction with symptom scales [13]. This analysis had two main research questions. First, is vaccination associated with reduced subjective severity among people with medically attended, laboratory-confirmed influenza? Second, if a difference in subjective severity is observed, is there a further difference among recipients aged ≥ 65 years of different influenza vaccine types including so-called enhanced vaccines such as high-dose or adjuvanted influenza vaccines that may induce stronger immune responses than standard-dose influenza vaccines (https://www.cdc.gov/flu/prevent/different-flu-vaccines.htm)?

2. Methods

Consented persons who presented at participating US Influenza Vaccine Effectiveness (Flu VE) Network outpatient study sites with acute respiratory illness including cough within 7 days of illness onset were enrolled during the 2011–2012 through 2019–2020 influenza seasons. Individuals were not tracked across influenza seasons and were considered unique each season. Nasal and throat swabs were tested for influenza virus using molecular assays [14]. Research staff administered a questionnaire at enrollment to collect demographic data, general health status, and symptom history. The visual analog scale (VAS) portion of the EQ-5D-5L consisted of a vertical number line from zero representing ‘‘the worst health

you can imagine" to 100 representing ''the best health you can imagine." Participants were shown the scale on paper or tablet screen and were asked to select the point on the line to rate their ''health today." Two sites assessed VAS subjective health scores during all nine influenza seasons; three sites collected VAS scores in the first seven. Institutional Review Boards reviewed and approved study protocols annually at each site.

In 2011–2012 and 2012–2013, we compared individual VAS scores during acute illness to scores assessed a second time in follow-up questionnaires after participants reported having returned to normal activities. Questionnaires were administered over the phone or online 7–14 days after enrollment. VAS scores at follow up were compared to published population norms for the US population [15].

The main analysis included persons aged ≥ 16 years with laboratory-confirmed influenza who completed the VAS within 3 days of illness onset; a sensitivity analysis included those completing the VAS within 7 days of onset. We excluded participants who were vaccinated 0–13 days before illness onset, missing self-rated general health status, or enrolled by phone (Supplemental Fig. 1). Influenza vaccination status and vaccine type were determined using documented information from electronic medical records and immunization information systems. For participants aged ≥ 65 years enrolled during 2014–2015 through 2019–2020, VAS scores were compared by the type of influenza vaccine received [16].

We compared mean VAS scores by vaccination status and influenza virus type using t-tests. To evaluate factors associated with the highest VAS scores (i.e., feeling the best), we categorized VAS scores into the lowest quartile (0–25), mid-range (26–75), and highest quartile (76–100), and contrasted VAS scores in the lowest versus highest category, excluding scores in mid-range. Using backward elimination, we constructed a multivariable logistic regression model with high vs low VAS score as the outcome and vaccination status, network site, influenza season of enrollment, age, sex, and self-rated general health status as predictors. Presence of one or more medical conditions that put a person at higher risk of severe illness due to influenza was assessed but not retained in the final model because model fit was not improved. P-values < 0.05 were considered statistically significant. In sensitivity analysis, we excluded the 2014–2015 and 2018–2019 seasons when overall influenza vaccine effectiveness was < 30% [17,18]. To assess potential bias in reporting VAS by vaccination status, we conducted a sensitivity analysis comparing high and low VAS scores by vaccination status among persons who tested negative for influenza within 3 days of illness onset. Finally, we conducted a sensitivity analysis with continuous VAS score as the outcome of a multivariable linear model to determine the overall effect of vaccination on subjective severity score.

3. Results

Over nine influenza seasons, 6,289 persons aged ≥ 16 years who tested positive for influenza and completed the Visual Analog Scale (VAS) within 3 days of illness onset were included in primary analyses. VAS scores were approximately normally distributed. The mean VAS score among all participants who completed the VAS within 3 days of illness onset was 48.5 (standard deviation (SD) = 22.2) with a median of 50 (interquartile range 30–65). Most

participants (4,542, 73%) indicated a VAS score in mid-range, 1,092 (17%) were in the lowest VAS quartile, and 655 (10%) were in the highest quartile (Table 1). Among 3,281 participants who completed the VAS 4–7 days after illness onset, the mean VAS score was 52.2 (SD = 21.1).

Among 6,289 participants who completed the VAS, 79% tested positive for influenza A (1,688 A/H3N2, 3,214 A/H1N1pdm09, 59 unknown subtype) and 21% tested positive for influenza B (973B/Yamagata, 322B/Victoria, 23 unknown lineage); <1% (10) tested positive for more than one influenza virus. There was no significant difference in mean VAS scores between those with influenza A (48.2, SD = 22.3) and influenza B (49.9, SD = 22.1) (p-value = 0.31) (Table 2). A total of 465 participants also completed the VAS after reportedly returning to normal activities. Mean VAS score at follow-up among these participants was 80.7 (SD = 13.7). Mean VAS score at follow-up increased with better general health status; the difference in VAS score between acute illness compared with follow up also increased (Supplemental Fig. 2).

Nearly half (2,830, 45%) of participants were vaccinated. Vaccinated participants were more likely to be female, older, and have an underlying health condition compared to unvaccinated participants (Table 3). Vaccinated participants were less likely to report fever or sore throat and had higher average VAS scores (49.5, SD = 22.2) than unvaccinated participants (47.8, SD = 22.3) ($p < 0.01$). In the multivariable model controlling for age, site, sex, influenza season, and general health status, vaccinated participants were more likely than unvaccinated participants to report high VAS scores ($p < 0.01$) (Supplemental Fig. 3). Results were similar after excluding the two influenza seasons when vaccine effectiveness was low. Among those who tested negative for influenza, unvaccinated participants reported an average VAS score of 56.0 (SD = 21.1), and vaccinated participants reported an average VAS score of 55.6 (SD = 21.4). There was no significant difference in the proportion of test-negative participants reporting high versus low scores by vaccination status (results not shown). In the multivariable linear regression model with continuous VAS score as the outcome, vaccination status was significantly ($p < 0.01$) associated with increased VAS scores.

Among 787 persons with laboratory-confirmed influenza aged ≥ 65 years enrolled in the 2014–2015 through 2019–2020 influenza seasons, 210 (27%) were unvaccinated (Table 4). Among the 577 vaccinated persons, 352 (61%) received standard-dose influenza vaccine, 196 (34%) received high-dose influenza vaccine, 17 (3%) received adjuvanted influenza vaccine, and 12 (2%) received an influenza vaccine of unknown type. Persons who received the high-dose influenza vaccine were slightly more likely to report a high VAS score at enrollment than standard-dose recipients (Table 4). However, vaccine type was not associated with higher score versus lower score among persons aged ≥ 65 years after controlling for network site, age, sex, influenza season of enrollment, and general health status ($p = 0.73$).

4. Discussion

Vaccination reduced the subjective severity of medically attended outpatient influenza illness. Unvaccinated participants with laboratory-confirmed influenza felt worse as indicated by lower VAS scores than vaccinated participants with any influenza and influenza A. Persons who rated their general health better before illness had higher VAS scores than participants reporting worse general health. VAS scores were higher among participants interviewed later after illness onset, suggesting rapid recovery from acute illness. During the seasons when VAS was used to assess health status after participants reported returning to normal activities, VAS scores were consistent with reference VAS scores during normal health in the US population [15]. Our findings of reduced subjective severity among vaccinated persons agree with prior findings among working-age adults in one influenza season [19]. In the current analysis, influenza vaccine type received by outpatients aged ≥ 65 years was not associated with VAS score at the time of acute illness. Participants who rated their general health better experienced a larger difference in subjective health between acute illness and follow up than participants who rated their general health as worse. The threshold for seeking outpatient care for ARI might be lower for persons who perceive themselves in worse general health.

Administration of the EQ-5D-5L visual analog scale during interview was simple and could be added to observational studies of vaccine effectiveness for other illnesses, including COVID-19. Studies comparing symptom severity between illnesses caused by respiratory viruses have shown that influenza illness requiring outpatient care might be considered more severe by patients compared to other respiratory viruses [5]. Studies characterizing severity of outpatient ARI should consider adding the VAS to data collection instruments, in addition to a measure of general health status to control for confounding by underlying health status.

Among our study's main strengths was systematic testing of persons with ARI for influenza virus infection using a highly sensitive and specific molecular assay. A previous study from the US Flu VE Network showed an association between lower VAS scores and increased influenza virus RNA load in respiratory specimens from confirmed cases [20]. Another strength of this study was the access to documented vaccination data from electronic medical records and immunization information systems rather than participant report only. We found no difference in subjective severity between unvaccinated and vaccinated influenza-negative participants; differential subjective severity by exposure could introduce bias by care-seeking behavior in observational studies like the test-negative case-control.

Our study was subject to the following limitations. First, enrolled persons might have responded differently to the VAS tool based on their vaccination or disease status, although most participants did not know their influenza test result at enrollment. Second, although we analyzed responses among participants who sought medical care early, some participants seeking care 2– 3 days after onset might have reported lower VAS scores had they been enrolled earlier in illness. Those enrolled 4–7 days after illness onset reported higher VAS scores. Our comparison of acute and follow-up subjective health was limited to data from two influenza seasons and participants who completed the follow-up survey. However, our overall follow-up median VAS score was equivalent to published population norms [15].

Finally, because only persons who felt ill enough to seek outpatient care were interviewed, we might underestimate the benefit of influenza vaccination if vaccination resulted in illness so mild that care was not sought.

Our findings of reduced subjective severity of illness among vaccinated outpatients with breakthrough influenza suggests that attenuation of milder illness is possible. Given the high burden of outpatient and inpatient illness and commensurate costs associated annually with influenza, further research validating findings of vaccine-mediated attenuation of illness on all spectrums of severity could yield valuable data informing decisions to vaccinate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Comparison of characteristics by subjective severity as measured by the Visual Analog Scale[1] (VAS) among 6,289 persons aged ≥ 16 years who tested positive for influenza within 3 days of illness onset, by vaccination status during the 2011–2012 through 2019–2020 influenza seasons.

	All participants			Low VAS (0–25)		High VAS (76–100)	
Characteristic	**N**	**Mean VAS**	**SD**	**N**	**Row %**	**N**	**Row %**
Total	6289	48.5	22.2	1092	17	655	10
Site							
Michigan	1178	46.9	21.9	214	18	109	9
Pennsylvania	1861	51.7	20.9	226	12	218	12
Texas[2]	995	49.7	22.6	158	16	119	12
Washington[2]	1023	47.5	21.1	181	18	70	7
Wisconsin[2]	1232	45.2	24.4	313	25	139	11
Sex[3]							
Female	2722	47.5	22.6	715	19	391	10
Male	1817	50.1	21.6	377	15	262	11
Age group (years)							
16–25	1062	48.8	21.0	157	15	99	9
26–40	1633	48.7	21.8	263	16	156	10
41–55	1663	47.2	22.0	315	19	145	9
56–70	1373	48.8	23.2	260	19	173	13
≥71	558	50.7	23.9	97	17	82	15
Underlying health conditions							
None	3425	48.8	21.8	564	16	349	10
≥1	2864	48.2	22.8	528	18	306	11
General health status							
Excellent	1511	49.6	23.5	271	18	189	13
Very good	2644	50.1	21.8	404	15	303	11
Good	1651	47.3	21.4	293	18	133	8
Fair/Poor	483	41.1	22.0	124	26	30	6
Self-reported symptoms							

Characteristic	All participants N	Mean VAS	SD	Low VAS (0–25) N	Row %	High VAS (76–100) N	Row %
Cough only	377	57.8	21.8	35	9	70	19
Cough and fever/feverishness or sore throat[4]	5638	47.8	22.2	1022	18	561	10
Influenza vaccination status							
Unvaccinated	3459	47.8	22.3	636	18	330	10
Vaccinated	2830	49.5	22.2	456	16	325	11
Illness onset to enrollment (days)							
0–1	1686	48.1	22.5	303	18	183	11
2–3	4603	48.7	22.2	789	17	472	10
Season							
2011–2012	226	42.4	21.5	55	24	14	6
2012–2013	894	48.2	21.8	149	17	92	10
2013–2014	605	50.6	21.3	85	14	66	11
2014–2015	935	48.5	21.7	156	17	87	9
2015–2016	578	46.4	22.9	122	21	56	10
2016–2017	851	48.7	22.3	153	18	92	11
2017–2018	1351	49.2	23.1	243	18	160	12
2018–2019	409	47.2	22.8	77	19	43	11
2019–2020	440	51.3	20.9	52	12	45	10

[1] VAS, Visual analog scale: 0 = worst health you can imagine, 100 = best health you can imagine; SD, standard deviation.

[2] Texas, Washington, and Wisconsin sites administered the VAS during 2011–2012 through 2017–2018 influenza seasons.

[3] Sex unknown for 5 participants.

[3] Presence of fever/feverishness was unknown for 274 participants including 35 who reported low VAS scores and 24 who reported high VAS scores.

Table 2

Unadjusted mean visual analog scale[1] score among 6,289 persons aged ≥ 16 years who tested positive for influenza within 3 days of illness onset, by vaccination status during the 2011–2012 through 2019–2020 influenza seasons.

Influenza virus		All		Vaccinated (N = 2830)		Unvaccinated (N = 3459)		
	N	Mean	SD	Mean	SD	Mean	SD	Difference
Any influenza	6289	48.5	22.2	49.5	22.2	47.8	22.3	1.7*
Any influenza A	4961	48.2	22.3	49.2	22.3	47.3	22.2	1.9*
A/H3N2	3214	48.3	22.3	49.2	22.1	47.4	22.5	1.8
A/H1N1pdm09	1688	47.7	22.1	48.7	22.6	47.0	21.8	1.7
Any influenza B	1318	49.9	22.1	50.9	21.6	49.4	22.4	1.5
B/Victoria	322	51.2	22.1	52.7	21.2	50.5	22.5	2.2
B/Yamagata	973	49.3	22.1	50.3	21.8	49.7	22.3	0.6
Coinfection[2]	10	45.0	26.2	68.3	33.3	35.0	16.6	33.3

SD, standard deviation.

[1] Visual analog scale: 0 = worst health you can imagine, 100 = best health you can imagine.

[2] Those with coinfections were considered separately from the other categories. Of those who tested positive for more than one influenza virus (sub)type, 6 were positive for both influenza A and influenza B, 3 for influenza A/H3N2 and A/H1N1pdm09, and 1 for B/Victoria and B/Yamagata.

* Comparison $p < 0.01$.

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Table 3

Comparison of vaccinated and unvaccinated persons who tested positive for influenza, US Flu VE Network 2011–2012 through 2019–2020 influenza seasons.

	All positives	Vaccinated		Unvaccinated	
		N	Col %	N	Col %
Total	6289	2830	100	3459	100
Site					
Michigan	1178	596	21.1	582	16.8
Pennsylvania	1861	778	27.5	1083	31.3
Texas	995	397	14.0	598	17.3
Washington	1023	507	17.9	516	14.9
Wisconsin	1232	552	19.5	680	19.7
Sex[1]					
Female	3828	1857	65.6	1971	57.0
Male	2456	972	34.4	1484	42.9
Age group (years)					
16–25	1062	286	10.1	776	22.4
26–40	1633	582	20.6	1051	30.4
41–55	1633	694	24.5	969	28.0
56–70	1373	820	29.0	553	16.0
≥71	558	448	15.8	110	3.2
Underlying health conditions					
None	3425	1142	40.4	2283	66.0
≥1	2864	1688	59.7	1176	34.0
General health status					
Excellent	1511	601	21.2	910	26.3
Very good	2644	1205	42.6	1439	41.6
Good	1651	784	27.7	867	25.1
Fair or poor	483	240	8.5	243	7.0
Symptoms					
Fever/feverishness[2]	4823	2119	77.6	2704	82.4

	All positives	Vaccinated		Unvaccinated	
		N	Col %	N	Col %
Sore throat[3]	4329	1917	70.2	2412	73.4
Visual Analog Scale					
0–25 (felt worst)	1092	456	16.1	636	18.4
26–50	2687	1209	42.7	1478	42.7
51–75	1855	840	29.7	1015	29.3
76–100 (felt best)	655	325	11.5	330	9.5
Illness onset to enrollment (days)					
0–1	1686	751	26.5	935	27.0
2–3	4603	2079	73.5	2524	73.0
Season					
2011–2012	226	76	2.7	150	4.4
2012–2013	894	360	12.7	534	15.4
2013–2014	605	194	6.9	411	11.9
2014–2015	935	528	18.7	407	11.8
2015–2016	578	228	8.1	350	10.1
2016–2017	851	403	14.2	448	13.0
2017–2018	1351	624	22.1	727	21.0
2018–2019	409	214	7.6	195	5.6
2019–2020	440	203	7.2	237	6.9

[1]Sex unknown for 5 persons (1 vaccinated, 4 unvaccinated).

[2]A total of 6,011 enrollees answered the question regarding presence of fever/feverishness including 2,729 vaccinated persons and 3,282 unvaccinated persons. The percentages reflect these denominators.

[3]A total of 6,015 enrollees answered the question regarding presence of sore throat including 2,731 vaccinated persons and 3,284 unvaccinated persons. The percentages

Table 4

Influenza vaccination status, vaccine type received, and visual analog scale[1] score category among 787 persons aged ≥ 65 years who tested positive for influenza within 3 days of illness onset during the 2014–2015 through 2019–2020 influenza seasons.

Vaccination status, vaccine type	All N	Low VAS (0–25)	Row %	Mid-Range VAS (26–75)	Row %	High VAS (76–100)	Row %
Unvaccinated	210	41	20	138	66	31	15
Vaccinated	577	93	16	407	71	77	13
Vaccinated, standard dose[2]	333	58	17	236	71	39	12
Vaccinated, high dose[3]	196	27	14	138	70	21	16
Vaccinated, recombinant[4]	19	1	5	14	74	4	21
Vaccinated, adjuvanted[5]	17	3	18	13	76	1	6
Vaccinated, unknown type	12	4	33	6	50	2	17

VAS, Visual Analog Scale.

[1] Visual Analog Scale: 0 = worst health you can imagine, 100 = best health you can imagine.

[2] Influenza vaccine trivalent and quadrivalent egg- or cell-based products containing 15 µg hemagglutinin for each vaccine virus per dose.

[3] Trivalent influenza vaccine egg-based product containing 60 µg hemagglutinin for each vaccine virus per dose.

[4] Quadrivalent influenza vaccine recombinant HA product containing 45 µg hemagglutinin for each vaccine virus per dose (2017–2018 through 2019–2020 influenza seasons).

[5] Trivalent influenza vaccine egg-based product containing 15 µg hemagglutinin for each vaccine virus per dose with MF59 adjuvant.