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BRIEF REPORT

Waning Vaccine Effectiveness Against Influenza-Associated Hospitalizations Among Adults, 2015–2016 to 2018–2019, United States Hospitalized Adult Influenza Vaccine Effectiveness Network

Jill M. Ferdinands,[1] Manjusha Gaglani,[2] Emily T. Martin,[3] Arnold S. Monto,[3] Donald Middleton,[4] Fernanda Silveira,[4] H. Keipp Talbot,[5] Richard Zimmerman,[4] and Manish Patel[1]

[1]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [2]Baylor Scott & White Health System, Temple, Texas, USA, [3]University of Michigan School of Public Health, Ann Arbor, Michigan, USA, [4]University of Pittsburgh and University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA, and [5]Vanderbilt University Medical Center, Nashville, Tennessee, USA

We observed decreased effectiveness of influenza vaccine with increasing time since vaccination for prevention of influenza A(H3N2), influenza A(H1N1)pdm09, and influenza B/Yamagata–associated hospitalizations among adults. Maximum vaccine effectiveness (VE) was observed shortly after vaccination, followed by an absolute decline in VE of about 8%–9% per month postvaccination.

Keywords. adults; hospitalization; influenza; vaccine effectiveness; waning.

Annual influenza vaccination is recommended in the United States (US) for all individuals aged ≥6 months, but the optimal timing of vaccination remains a subject of debate [1]. Mounting evidence that vaccine-induced immunity wanes over the course of an influenza season [1, 2] suggests that early vaccination (ie, in July and August) may result in suboptimal immunity before the end of the influenza season, particularly among older adults. To balance the need to immunize before influenza circulation with concern about waning immunity, US guidelines recommend that vaccination be offered by the end of October. A better understanding of the extent of intraseason waning of influenza vaccine protection is vital for reducing uncertainty regarding the best time to vaccinate. Here, we report estimates of intraseason waning of vaccine protection against influenza-associated hospitalizations observed among adults enrolled in the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN).

METHODS

Study participants were adults (≥18 years of age) hospitalized for acute respiratory illness (ARI) presenting with new or worsening cough or sputum production of ≤10 days' duration at hospitals participating in the HAIVEN study during the 2015–2016 through 2018–2019 influenza seasons. HAIVEN study procedures have been described previously [3]. In brief, adults admitted with ARI were identified by review of electronic medical records. After providing consent, participants/proxies were interviewed to collect information about demographics, vaccination, and illness characteristics. Respiratory specimens were tested for influenza by reverse-transcription polymerase chain reaction. Patients testing positive for influenza were cases and those testing negative were controls. Diagnosis codes from medical encounters in the past year were used to identify comorbidities known to increase risk of serious influenza complications ("high-risk conditions") [1].

Participants were considered vaccinated if they had documented evidence in medical records or immunization registries of receipt of ≥1 dose of influenza vaccine at least 14 days before illness onset. Individuals who received vaccine 1–13 days before illness onset were excluded. To examine the association between influenza vaccine effectiveness (VE) and time since vaccination, we used methods previously used by the US Influenza Vaccine Effectiveness Network [4]. In brief, we pooled data for each influenza subtype across seasons for which ≥50 cases were enrolled (2015–2016 and 2018–2019 for influenza A(H1N1)pdm09; 2016–2017 and 2017–2018 for influenza A(H3N2) and influenza B/Yamagata) and restricted each pooled dataset to cases and 3 controls per case matched on illness onset date with nearest neighbor matching to reduce confounding by calendar time. We excluded analysis of influenza A(H3N2) during the 2018–2019 season due to the antigenic drift of circulating strains that resulted in overall VE near zero. We had insufficient cases to assess waning VE against influenza B/Victoria viruses. We used multivariate logistic regression models with influenza-associated hospitalization as the outcome and time in days between vaccination and symptom onset as the predictor to estimate VE as a function of time since vaccination and median absolute decline in VE per 30 days postvaccination. Unvaccinated individuals were the reference group and assigned a value of zero days since vaccination. We examined alternative specifications of time since vaccination (eg, splines); however, because the association between time since vaccination and VE was approximately

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Correspondence: J. Ferdinands, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS A-32, Atlanta, GA 30333 (jferdinands@cdc.gov).

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linear for all influenza subtypes, time since vaccination was assumed linear in final models. Bootstrapping was used to estimate 95% confidence intervals (CIs). Models were adjusted for site, season, age, race, calendar time of illness onset, days between onset and specimen collection, past year hospitalizations, and 1 or more indicators of underlying health status (which varied depending on season due to data collection differences). In subgroup analysis, we restricted to participants aged ≥65 years. Characteristics of participants were compared using χ^2 tests or Fisher exact tests for categorical variables and *t* test or Wilcoxon rank-sum test for continuous variables. CIs excluding the null or *P* values < .05 were considered statistically significant. Analyses were conducted in R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.3 (Cary, North Carolina) software. Institutional review boards at participating hospitals and the Centers for Disease Control and Prevention approved study procedures.

RESULTS

Datasets included 3016 participants for analysis of VE against influenza A(H3N2), 1492 participants for analysis of VE against influenza A(H1N1)pdm09, and 1060 participants for analysis of VE against influenza B/Yamagata–associated hospitalizations. The mean participant age was 61, 59, and 60 years in the influenza A(H3N2), A(H1N1)pdm09, and B/Yamagata analyses, respectively. Age and underlying health status were significantly different for influenza cases and controls within each subtype (Supplementary Tables 1–3). Cases were less likely to have received influenza vaccine ($P \leq .01$ for all). Overall, 34% of vaccinees received vaccination by the end of September, 77% by the end of October, 92% by the end of November, and 97% by the end of December (Supplementary Table 4). The median (interquartile range) interval between vaccination and influenza onset was 108 (75–140) days, 125 (92–156) days, and 110 (77–144) days for the influenza A(H3N2), A(H1N1)pdm09, and B/Yamagata analyses, respectively.

Adjusted VE against influenza A(H3N2)–associated hospitalizations decreased with increasing time since vaccination ($P = .05$), with average decline in VE of 7.5% (95% CI, .3%–16.3%) per 30 days postvaccination (Table 1; Supplementary Figure 1). Similarly, adjusted VE against influenza A(H1N1)pdm09–associated hospitalizations decreased with increasing time since vaccination ($P = .003$), with average decline in VE of 8.5% (95% CI, 3.0%–17.0%) per 30 days postvaccination (Supplementary Figure 2), and adjusted VE against influenza B/Yamagata–associated hospitalization decreased with increasing time since vaccination ($P = .02$), with average decline in VE of 8.0% (95% CI, 1.4%–21.9%) per 30 days postvaccination (Supplementary Figure 3). Average and maximum VE estimates are provided in Supplementary Figures 1–3.

Among adults aged ≥65 years, the average decline in VE per 30 days postvaccination was 10.8% (95% CI, 2.6%–23.8%) against influenza A(H3N2)–associated hospitalizations (n = 1580, $P = .02$; Supplementary Figure 4); 9.6% (95% CI, – 3.3% to 32.7%) against influenza A(H1N1)pdm09–associated hospitalizations (n = 528, $P = .14$; Supplementary Figure 5); and 10.8% (95% CI, 1.4%–33.9%) against influenza B/Yamagata–associated hospitalizations (n = 536, $P = .03$; Supplementary Figure 6).

DISCUSSION

In combined data from recent US influenza seasons, we observed statistically significant decreases in effectiveness of influenza vaccine with increasing time since vaccination for prevention of influenza A(H3N2), influenza A(H1N1)pdm09, and influenza B/Yamagata–associated hospitalizations among adults. Maximum VE was observed shortly after vaccination, followed by an absolute decline in VE of about 8%–9% per

Table 1. Estimated Decline in Influenza Vaccine Effectiveness per Month Postvaccination Among Adults Enrolled in the United States Hospitalized Influenza Vaccination Network (HAIVEN), 2015–2016 Through 2018–2019

Influenza Type/Subtype	Influenza Seasons Included	No. of Cases/Controls	Estimated VE Decline per Month, Absolute % (95% CI)	*P* Value[a]
Influenza A(H3N2)[b]				
Aged ≥18 y	2016–2017, 2017–2018	754/2262	7.5 (.3–16.3)	.05
Aged ≥65 y	2016–2017, 2017–2018	395/1185	10.8 (2.6–23.8)	.02
Influenza A(H1N1)pdm09[c]				
Aged ≥18 y	2015–2016, 2018–2019	373/1119	8.5 (3.0–17.0)	.003
Aged ≥65 y	2015–2016, 2018–2019	132/396	9.6 (–3.3 to 32.7)	.14
Influenza B/Yamagata[b]				
Aged ≥18 y	2016–2017, 2017–2018	265/795	8.0 (1.4–21.9)	.02
Aged ≥65 y	2016–2017, 2017–2018	134/402	10.8 (1.4–33.9)	.03

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

[a] *P* value for test of association between interval in days between vaccination and onset and influenza positivity.

[b] VE models adjusted for study site, season, age group, race, days from illness onset to specimen collection, self-reported health (poor/fair vs good/very good/excellent), and self-reported past year hospitalizations.

[c] VE models adjusted for study site, season, age group, sex, race, days from illness onset to specimen collection, past year respiratory illness–associated hospitalizations, immunosuppressive disorders, and lung disorders.

month. Rate of decline was similar across influenza subtypes. Among older adults, we observed a slightly faster rate of decline of 10%–11% per month.

In the first successful trial of inactivated influenza vaccine in 1943, Francis et al observed that antibodies to influenza declined by about one-third in 4–5 months after vaccination [5], consistent with observations of repeat infections from early ferret studies and experimental human challenge trials. Our results are broadly consistent with these early studies as well as recent observational studies and a post hoc analysis from a randomized controlled trial that reported decreasing VE with increasing time since vaccination [2, 6]. The pattern and magnitude of waning VE that we observed was similar to the 6%–11% decline in VE per month observed against outpatient influenza illnesses during the 2011–2015 US influenza seasons. Our findings for influenza A(H3N2) viruses are consistent with those of Petrie et al and Belongia et al, who observed modest waning of influenza VE during the influenza A(H3N2)–predominant 2007–2008 US season [6, 7]. Unlike other researchers [2], we observed similar rates of decline in VE across types/subtypes. Similar to other studies, we saw greater waning among older adults, consistent with the hypothesis that immunosenescence may contribute to faster waning.

An alternative explanation for an observed decline in vaccine protection includes emergence and circulation of a drifted variant less well-matched to the vaccine strain. However, antigenic drift was minimal among influenza viruses circulating during the seasons we analyzed [8]. Additionally, an observed pattern of decreasing vaccine protection could arise from bias introduced by changes in the composition of the at-risk population over the course of the season or from the leaky vaccine effect [9]. However, these effects would likely be smaller than the amount of waning we observed and are unlikely to fully explain the waning VE we report [10]. Study designs other than the test-negative design may be better suited to identify waning VE [11]. Our study lacked serological markers of immune protection with which to correlate temporal trends in postvaccination antibody levels with observed VE. Additionally, our study did not examine variation in waning VE by vaccine type or prior vaccination history, nor did it consider indirect effects of vaccination.

Optimal timing of vaccination depends upon a number of factors, including extent of waning vaccine protection and potential changes in vaccine coverage if vaccine administration were delayed or compressed [12]. Our results contribute to evidence suggesting that influenza vaccine protection may wane significantly in a matter of months. The public health implications of these findings warrant closer examination because even a 1- to 2-month delay in annual vaccination could improve VE by 10%–20%. If such an approach does not encroach on the annual influenza season, delay vaccine delivery, or reduce vaccine uptake, it could lead to appreciable gains in public health benefits given the large burden of influenza morbidity and mortality annually in the US.

Supplementary Data

Supplementary materials are available at *Clinical 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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References

1. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20 influenza season. MMWR Recomm Rep **2019**; 68:1–21.
2. Young B, Sadarangani S, Jiang L, Wilder-Smith A, Chen MI. Duration of influenza vaccine effectiveness: a systematic review, meta-analysis, and meta-regression of test-negative design case-control studies. J Infect Dis **2018**; 217:731–41.
3. Ferdinands JM, Gaglani M, Martin ET, et al; HAIVEN Study Investigators. Prevention of influenza hospitalization among adults in the United States, 2015–2016: results from the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN). J Infect Dis **2019**; 220:1265–75.
4. Ferdinands JM, Fry AM, Reynolds S, et al. Intraseason waning of influenza vaccine protection: evidence from the US influenza vaccine effectiveness network, 2011–12 through 2014–15. Clin Infect Dis **2017**; 64:544–50.
5. Francis T, Pearson HG, Salk JE, Brown PN. Immunity in human subjects artificially infected with influenza virus, type B. Am J Public Health **1944**; 34:317–34.

6. Petrie JG, Ohmit SE, Truscon R, et al. Modest waning of influenza vaccine efficacy and antibody titers during the 2007-2008 influenza season. J Infect Dis **2016**; 214:1142–9.
7. Belongia EA, Sundaram ME, McClure DL, Meece JK, Ferdinands J, VanWormer JJ. Waning vaccine protection against influenza A (H3N2) illness in children and older adults during a single season. Vaccine **2015**; 33:246–51.
8. Centers for Disease Control and Prevention. FluView past weekly surveillance. Available at: https://www.cdc.gov/flu/weekly/pastreports.htm. Accessed 25 August 2020.
9. Ray GT, Lewis N, Klein NP, Daley MF, Lipsitch M, Fireman B. Depletion-of-susceptibles bias in analyses of intra-season waning of influenza vaccine effectiveness. Clin Infect Dis **2020**; 70:1484–6.
10. Tokars JI, Patel MM, Foppa IM, Reed C, Fry AM, Ferdinands JM. Waning of measured influenza vaccine effectiveness over time: the potential contribution of leaky vaccine effect. Clin Infect Dis **2020**; 71:e633–41.
11. Durham LK, Longini IM Jr, Halloran ME, Clemens JD, Nizam A, Rao M. Estimation of vaccine efficacy in the presence of waning: application to cholera vaccines. Am J Epidemiol **1998**; 147:948–59.
12. Ferdinands JM, Alyanak E, Reed C, Fry AM. Waning of influenza vaccine protection: exploring the trade-offs of changes in vaccination timing among older adults. Clin Infect Dis **2020**; 70:1550–9.