

Effects of Influenza Vaccination in the United States During the 2017–2018 Influenza Season

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(See the Editorial Commentary by Neuzil and Fitzpatrick on pages 1854–5.)

Background. The severity of the 2017–2018 influenza season in the United States was high, with influenza A(H3N2) viruses predominating. Here, we report influenza vaccine effectiveness (VE) and estimate the number of vaccine-prevented influenza-associated illnesses, medical visits, hospitalizations, and deaths for the 2017–2018 influenza season.

Methods. We used national age-specific estimates of 2017–2018 influenza vaccine coverage and disease burden. We estimated VE against medically attended reverse-transcription polymerase chain reaction–confirmed influenza virus infection in the ambulatory setting using a test-negative design. We used a compartmental model to estimate numbers of influenza-associated outcomes prevented by vaccination.

Results. The VE against outpatient, medically attended, laboratory-confirmed influenza was 38% (95% confidence interval [CI], 31%–43%), including 22% (95% CI, 12%–31%) against influenza A(H3N2), 62% (95% CI, 50%–71%) against influenza A(H1N1) pdm09, and 50% (95% CI, 41%–57%) against influenza B. We estimated that influenza vaccination prevented 7.1 million (95% CrI, 5.4 million–9.3 million) illnesses, 3.7 million (95% CrI, 2.8 million–4.9 million) medical visits, 109 000 (95% CrI, 39 000–231 000) hospitalizations, and 8000 (95% credible interval [CrI], 1100-21 000) deaths. Vaccination prevented 10% of expected hospitalizations overall and 41% among young children (6 months–4 years).

Conclusions. Despite 38% VE, influenza vaccination reduced a substantial burden of influenza-associated illness, medical visits, hospitalizations, and deaths in the United States during the 2017–2018 season. Our results demonstrate the benefit of current influenza vaccination and the need for improved vaccines.

Keywords. influenza; vaccination; prevented illnesses; burden.

The 2017–2018 influenza season in the United States was a high severity season $[1, 2]$ $[1, 2]$ $[1, 2]$ $[1, 2]$ $[1, 2]$. Circulation of influenza viruses was widespread for an extended period throughout the country. Influenza A(H3N2) viruses predominated, but influenza A(H1N1)pdm09 and B viruses also circulated [\[2\]](#page-7-1). The Centers for Disease Control and Prevention (CDC) has estimated

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that there were 48.8 million influenza illnesses, 959 000 hospitalizations, and 79 400 influenza-associated deaths during 2017–2018, the highest morbidity and mortality since the 2009 pandemic [\[3\]](#page-7-2).

Influenza vaccination is the primary strategy to prevent influenza illness and its complications. Recent reports estimate that 42% of the US population was vaccinated against influenza during the 2017–2018 season [\[4,](#page-7-3) [5\]](#page-7-4); the mid-season estimates of the effectiveness of influenza vaccine were 36% against all influenza A and B virus infections and 25% against A(H3N2) virus infections [\[6\]](#page-7-5). Here, we report end-of-season vaccine effectiveness (VE) and apply it with vaccine coverage to estimate the number of influenza-associated illnesses, medical visits, hospitalizations, and deaths prevented by influenza vaccination.

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METHODS

Influenza Vaccine Composition

The recommended composition of the 2017–2018 Northern Hemisphere trivalent influenza vaccine included an A/Michigan/45/2015 (H1N1)–like virus, an A/Hong Kong/4801/2014 (H3N2)–like virus, and a B/ Brisbane/60/2008–like virus (Victoria lineage). In addition, quadrivalent vaccines included a B/Phuket/3073/2013–like virus (Yamagata lineage) [\[7\]](#page-7-6).

Influenza Vaccine Effectiveness

Effectiveness of 2017–2018 influenza vaccination for the prevention of outpatient medically attended influenza illness was determined through the US Influenza Vaccine Effectiveness (Flu VE) Network, which has been described in detail previously [8–11]. Briefly, study staff recruited, consented, and enrolled patients aged ≥6 months who sought outpatient care for acute respiratory illness (including cough) within 7 days of symptom onset at 52 participating healthcare facilities in 5 research sites in Michigan, Pennsylvania, Texas, Washington, and Wisconsin. Patients who received an antiviral medication in the 7 days before enrollment or who were enrolled in the prior 14 days were not eligible. Study staff collected a combined nasal and throat swab from patients aged ≥2 years or a nasal swab only from children aged <2 years. Reverse-transcription polymerase chain reaction (RT-PCR) was used to detect influenza viruses, including subtype and lineage. All diagnostic laboratories used primers and probes from the CDC and passed proficiency testing. Staff interviewed patients for demographic data, current health status, symptoms, and reported receipt of 2017–2018 influenza vaccine. We looked for International Classification of Diseases codes assigned to medical encounters in the year prior to enrollment to determine whether participants had a preexisting health condition associated with increased risk of severe influenza [[12](#page-8-0), [13](#page-8-1)].

For all US Flu VE Network sites, a participant's vaccination status was based on documented receipt of 2017–2018 influenza vaccine in electronic immunization records (medical records, state immunization systems, and employee health records). In addition, at 4 sites (excluding Wisconsin), we considered adults aged ≥18 years vaccinated if they reported timing and place of vaccination without documented receipt. We excluded children (aged 6 month–8 years) who were partially vaccinated. We used a test-negative design to estimate VE, contrasting the odds of influenza vaccination among participants with RT-PCR–positive influenza (cases) to the odds of vaccination among participants who were negative for influenza (controls) using a logistic regression model [[14\]](#page-8-2). We estimated VE and 95% confidence intervals (CIs) against any influenza and by influenza virus type or subtype in separate models and stratified models by participant age (6 months–4 years, 5–17 years, 18–49 years, 50–64 years, and ≥65 years). We adjusted all logistic regression models, a priori, for network site, calendar time (in bi-week increments), participant age, and high-risk status.

The Flu VE Network study was approved by institutional review boards at each participating site and the CDC.

Estimates of Influenza-associated Outcomes

The methods for estimating age-specific influenza burden have been detailed elsewhere, and estimates from the 2017–2018 season are available from the CDC [\[3,](#page-7-2) [15](#page-8-3)]. This method uses mathematical multipliers to calculate illnesses, medical visits, and deaths from data on hospitalized cases reported through the Influenza Hospitalization Surveillance Network (FluSurv-NET), as illustrated in [Supplementary Figure 1.](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data) For this analysis, we restricted burden estimates to those aged ≥6 months. We further estimated the burden by influenza virus type and subtype using virologic distributions observed in the US Flu VE Network patients for illnesses and medical visits and the distributions observed in FluSurv-NET to estimate hospitalizations and deaths for each (sub)type [[16\]](#page-8-4). As data on influenza A subtype were missing for 60% of FluSurv-NET patients with influenza A virus infection, we used multiple imputation (70 imputations) to estimate the rate of hospitalization for each subtype, including patient age, surveillance site, and admission time period (October–December, January, February, or March– May) in the imputation model.

Influenza Vaccine Coverage

We obtained annual estimates of influenza vaccination coverage in the United States by month, from August 2017 through April 2018, which were reported by the CDC ([Supplementary Figure](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data) [2\)](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data) [\[4,](#page-7-3) [5\]](#page-7-4).

Influenza-associated Outcomes Prevented by Vaccination

We estimated the effect of seasonal influenza vaccination on disease burden using a mathematical compartmental model, stratified by age group [[17\]](#page-8-5). We began the model with all members of the US population unvaccinated and susceptible to influenza. Each month the susceptible population was divided, based on observed data, into those who became infected (using data on estimated illness), those who were vaccinated and protected against influenza (using data on vaccine coverage and effectiveness), and those who remained susceptible to infection. Each month we estimated age-specific rates of illness (and medical visits, hospitalizations, and deaths) by dividing the monthly illnesses by the prior month's susceptible population. Using these rates among susceptible persons, we estimated the number of outcomes that would have occurred in the same population without influenza vaccination. We calculated the prevented outcomes as the difference between outcomes in the absence of vaccination and those estimated under current levels of vaccination [[15,](#page-8-3) [18](#page-8-6), [19\]](#page-8-7).

Estimates of VE in adult outpatients and inpatients during 2017–2018 were similar in the United States, thus we assumed that VE estimates from the US Flu VE Network applied to all influenza outcomes and were also constant across the season [[20](#page-8-8)]. We applied (sub)type-specific VE estimates to the (sub)type-specific models.

We estimated the number needed to vaccinate (NNV) to prevent 1 influenza-associated hospitalization by dividing the number of vaccinated individuals by hospitalizations prevented by vaccination. When VE 95% CIs included the null, the undefined value of NNV was indicated as >999 999. Our estimates of NNV were stratified by age group.

We used a Monte Carlo algorithm to estimate a 95% credible interval (CrI) around the estimates of prevented outcomes, incorporating uncertainty in each data input. Briefly, we chose a value at random from the assumed distribution for each of the model inputs ([Supplementary Table 1](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data)) and calculated the estimated prevented outcome and repeated the process 5000 times. Distributions for VE and vaccine coverage were truncated at 0.

Sensitivity Analysis for Vaccine Coverage

Missing responses to the influenza vaccination question were more common in the telephone survey in 2017–2018 compared with 2016–2017. We conducted sensitivity analyses to assess the effect of differences in vaccine coverage on estimates of prevented hospitalizations [\[4\]](#page-7-3). We explored the following scenarios for age group–specific coverage: as observed in 2016–2017; 2017–2018 coverage assuming individuals with missing responses were vaccinated; 2017–2018 coverage assuming individuals with missing responses were unvaccinated; and reducing coverage by 3%–17% to account for overestimation by self-report [21–25].

RESULTS

Among the population eligible for influenza vaccination and aged ≥6 months, we estimated there were 47.9 million illnesses, 22.1 million medical visits, 953 000 hospitalizations, and 79 400 deaths associated with influenza in 2017–2018. Adults aged ≥65 years accounted for 15% of illnesses but 70% and 90% of all hospitalizations and deaths, respectively.

Influenza A(H3N2) was associated with the highest rates of illness, affecting 9% of children aged 6 months–4 years and 15% of adults aged 50–64 years ([Figure 1](#page-3-0) and [Supplementary](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data) [Table 2](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data)). After applying these rates to the US population, influenza A(H3N2) was associated with an estimated 28.4 million illnesses, 13.0 million medical visits, 587 000 hospitalizations, and 49 000 deaths overall [\(Supplementary Table 3\)](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data). Influenza A(H1N1)pdm09 virus infections were less common, with 4.6 million illnesses. Influenza B virus infections accounted for 15.7 million illnesses, 32% of all influenza illnesses.

Vaccine Effectiveness

From the US Flu VE Network, 8900 people were enrolled and 8436 were included in analysis for the 2017–2018 influenza season, including 3050 case-patients with RT-PCR–confirmed influenza and 5386 controls with noninfluenza acute respiratory illness ([Table 1](#page-4-0); [Supplementary Table 4](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data)). Influenza A virus infections were identified from November 2017 through February 2018 [\(Supplementary Figure 3\)](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data). Influenza A(H3N2) viruses accounted for 84% of influenza A virus infections; and influenza B virus infections occurred later in the season with a peak in mid-March.

Among those enrolled in the US Flu VE Network, 42% of influenza-positive case-patients and 53% of influenza-negative controls were vaccinated against influenza [\(Supplementary](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data) [Table 5](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data)). Of the vaccinated participants aged <65 years with known vaccine type, 97% received quadrivalent inactivated influenza vaccine (IIV4) and 3% received trivalent inactivated influenza vaccine (IIV3). Of vaccinated adults aged ≥65 years with known vaccine type, 51% received high-dose IIV3, 47% received standard-dose IIV4 or IIV3, and 2% received adjuvanted IIV3.

VE against any influenza A or B virus infection was 38% (95% CI, 31%–43%) after adjustment for study site, age, highrisk condition, and calendar time ([Figure 2;](#page-5-0) [Supplementary](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data) [Table 5\)](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data). The VE estimates against any influenza virus infection varied by age group and were statistically significant in all age groups except for people aged ≥65 years [\(Figure 2](#page-5-0)). The adjusted VE against A(H3N2) was 22% (95% CI, 12%–31%) overall but also varied by age and was only statistically significant in children aged 6 months–4 years. The adjusted VE against A(H1N1) pdm09 was 62% (95% CI, 50%–71%) and VE against influenza B was 50% (95% CI, 41%–57%).

Vaccine-prevented Burden

We estimated that influenza vaccination prevented 7.1 million (95% CrI, 5.4 million–9.3 million) illnesses and 3.7 million (95% CrI, 2.8 million–4.9 million) medical visits [\(Table 2](#page-6-0)). Prevented illnesses included 2.3 million illnesses due to A(H3N2) viruses and 1.4 million illnesses due to A(H1N1)pdm09 viruses; 48% and 70% of which, respectively, were prevented among children [\(Supplementary Table 6\)](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data). Additionally, more than 3 million illnesses from influenza B viruses were prevented with vaccination.

Overall, an estimated 109 000 (95% CrI, 38 900–231 000) hospitalizations were prevented by vaccination, or 10% (95% CrI, 4%–19%) of expected hospitalizations ([Table 2](#page-6-0)). However, the percent of expected hospitalizations prevented by vaccination varied by age group, from a low of 7% (95% CrI, 4%–10%) in adults aged 18–49 years, who had the lowest vaccine coverage, to a high of 41% (95% CrI, 33%–47%) in children aged 6 months–4 years, who had high vaccine coverage and the highest VE [\(Figure 3](#page-6-1)).

The burden of influenza-associated hospitalizations was greatest in adults aged ≥65 years, and our model estimated that influenza vaccination prevented approximately 65 000 influenza-associated hospitalizations (95% CrI, 0–185 000; 9% of expected, 95% CrI, 0%–21%) in this age group despite lower VE

Figure 1. Adjusted rates of influenza-associated (A) illnesses, (B) medical visits, (C) hospitalizations, and (D) deaths, by age group and influenza (sub)type—United States, 2017–2018 influenza season.

compared with other age groups. Using the estimated vaccine coverage and the overall prevented hospitalizations, we estimate that 462 people (95% CrI, 162–>999 999) aged ≥65 years needed to be vaccinated for each influenza-associated hospitalization prevented [\(Table 3](#page-6-2)).

Finally, an estimated 8000 (95% CrI, 1100–21 000) influenza-associated deaths were prevented by vaccination (9% of expected deaths, overall; 95% CrI, 1%–20%). Influenza vaccination prevented an estimated 39% (95% CrI, 30%–45%) of influenza-related mortality in children aged 6 months–4 years.

In sensitivity analysis, all CrIs for estimates of prevented hospitalizations using various vaccine coverage scenarios overlapped with the CrIs using the reported 2017–2018 coverage [\(Supplementary Table 7](http://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciz075#supplementary-data)).

DISCUSSION

During the 2017–2018 season, currently available influenza vaccines reduced the risk of any influenza-associated medically

attended illness by 38% and A(H3N2)-associated illness by 22%. When modeled with burden and vaccine coverage, we estimated that influenza vaccination prevented 7.1 million illnesses, 109 000 hospitalizations, and 8000 deaths related to influenza. In children aged 6 months–4 years, the benefits of vaccination were greatest, with 41% of all expected hospitalizations prevented by vaccination. VE against A(H1N1)pdm09 and B viruses was greater in all age groups than for A(H3N2); accordingly, the benefit of vaccination against these viruses was greater than against A(H3N2) viruses. Nevertheless, our results suggest that currently available vaccines provided substantial benefit during a season with high rates of influenza-associated medical visits, hospitalizations, and deaths.

The population benefit of influenza vaccination in our model depends on burden, VE, and vaccine coverage. During 2017–2018, the benefit of influenza vaccination was substantial mainly because of the high burden of influenza-associated disease. Vaccination prevented 109 000 hospitalizations, but this number represents only 10% of expected hospitalizations

Table 1. Demographic and Clinical Characteristics of Participants Enrolled in the US Influenza Vaccine Effectiveness Network—United States, 2017–2018 Influenza Season

^aP value calculated using χ² comparing frequency of participants testing influenza positive vs negative by characteristic.

^bP value calculated using χ^2 test that compares the frequency of vaccination by participant characteristic.

c Presence of a high-risk health condition is defined as the presence of ≥1 medical record–documented International Classification of Disease, 10 Edition, high risk code from 1 October 2016 to enrollment, as defined by the Advisory Committee on Immunization Practices guidance for conditions that increase risk for complications from influenza [[26](#page-8-9)].

^dBody mass index was calculated as kg/m² from height and weight recorded in the electronic medical record. Calculated for adults aged ≥18 years only.

^e Fourteen influenza B viruses were of unknown lineage; 34 influenza A viruses were of unknown subtype. There were 25 coinfections that are each counted twice in the table above: 11 A(H3N2) and A(H1N1)pdm09, 9 B/Yamagata and A(H3N2), 3 B/Victoria and B/Yamagata, 1 A(H1N1)pdm09 and B/Yamagata, and 1 B/Yamagata and A of unknown subtype.

overall. Thus, while vaccination is an important strategy to mitigate some of the burden and severity of the influenza season, improvements in both VE and vaccine coverage are needed and would result in a greater reduction in burden, enhancing both the public health and economic benefits of annual influenza vaccination. Our model of prevented illness may underestimate

the population benefit of vaccination as it only accounts for direct effects of vaccination. Various studies suggest that influenza vaccination, particularly of school-aged children, may also provide indirect protection (ie, herd immunity) against influenza virus infection, largely by reducing the probability of contact with an infected person [27–32]. The magnitude of indirect

Figure 2. Adjusted vaccine effectiveness (VE) against outpatient, medically attended influenza-associated illness, US Flu VE Network—2017–2018 influenza season. The *y*-axis scale has been truncated for simplicity; however, for adults aged ≥65 years, the 95% confidence interval around the adjusted VE estimate against influenza A(H1N1) pdm09 extends beyond the lower limit of the *y*-axis (adjusted VE = 0.19, 95% confidence interval, –.91, .65).

protection is inconsistent between studies [\[33](#page-8-10)]; however, the population benefit of seasonal influenza vaccination would be greater if indirect effects were present and considered in the model [[34,](#page-8-11) [35](#page-8-12)].

VE against circulating A(H3N2) viruses and prevented fraction of A(H3N2) disease were lower than with influenza A(H1N1)pdm09 and B viruses. Reduced vaccine protection against A(H3N2) viruses is likely multifactorial and was also observed during the 2016–2017 influenza season with the same A(H3N2) vaccine reference virus (A/Hong Kong/4801/2014) [\[36](#page-8-13)]. Antigenic characterization indicated that most circulating A(H3N2) viruses in 2017–2018 remained antigenically similar to the cell-propagated A/Hong Kong/4801/2014 reference virus, suggesting limited antigenic drift between the seasons [\[2\]](#page-7-1). However, A(H3N2) viruses continued to evolve, and several viral genetic groups circulated. Further, many circulating A(H3N2) viruses were poorly inhibited by antisera raised against egg-adapted viruses used for production of the majority of influenza vaccines in the United States [\[2\]](#page-7-1). The higher VE against A(H3N2) viruses that we observed in young children may suggest that the immune response to the current A(H3N2) vaccine virus differs by age. This deserves more attention as young children had higher VE despite being vaccinated with

egg-based vaccines. Among older adults, egg adaptation of A(H3N2) vaccine viruses may have contributed to reduced effectiveness despite increasing use of high-dose vaccine, which was shown previously to be more effective than standard-dose influenza vaccines in previous A(H3N2) predominant seasons [\[37](#page-8-14)]. Even with reduced VE among older adults, vaccination still prevented 1 influenza-related hospitalization for every 462 people vaccinated. More broadly, we need to better understand the factors that contribute to differences in VE in order to improve influenza vaccines.

Our estimates of the effect of vaccination rely on large, multistate research and surveillance platforms, but there are limitations to the available data. First, multipliers are used to scale surveillance data to national burden estimates. Data to calculate the multipliers often lag by 2 years; thus, we use multipliers measured during previous influenza seasons. Any changes in testing practices, care-seeking behavior, or disease severity patterns that occurred during 2017–2018 would not be reflected in the multipliers. Our estimates of the effect of vaccination will be revised on CDC websites as data are updated. Second, we imputed subtype-specific hospitalization rates because subtyping was not performed systematically in FluSurv-Net. Third, our model does not currently account for possible waning effectiveness of

Table 2. Estimates of Influenza A- and B-Associated Illness, Medical Visits, Hospitalizations, and Deaths Prevented by Influenza Vaccination—United States, 2017–2018 Influenza Season

aThe 95% CrI is from 5000 Monte Carlo simulations.

The 95% Crl is from 5000 Monte Carlo simulations.

Figure 3. Estimated percent of expected influenza-associated hospitalizations prevented by vaccination—United States, 2017–2018 influenza season.

influenza vaccination over the season [38–44]. The current lit erature is inconsistent about the amount of waning that occurs; however, including any amount of waning effectiveness in the model would have reduced our estimated population benefit. Fourth, vaccination coverage estimates from self-report and tele phone surveys have limitations, including lower response rates and possible inaccuracy of vaccination status [21–25, [45,](#page-8-15) [46](#page-8-16)]. All results of our sensitivity analysis fell within the CrIs using reported coverage. Fifth, as we assumed that influenza vaccina tion would not increase the risk of infection, our CrIs are trun cated at zero and thus skewed in favor of a population benefit. Finally, the role of genetic and antigenic diversity on the VE and estimated population benefit deserves further investigation; full antigenic and genetic characterization of specimens from the US Flu VE Network is ongoing toward this effort.

Our results highlight the large burden of influenza-associated illnesses, medical visits, hospitalizations, and deaths during 2017–2018 and the value of current vaccines to reduce the burden of disease, even with a VE of 38% against influenza

Table 3. Number Needed to Vaccinate to Prevent 1 Influenza A- and B-Associated Hospitalization—United States, 2017–2018 Influenza Season

Age Group	Number Needed to Vaccinate	95% Credible Interval ^a
6 mo-4 y	821	(606, 1190)
5–17 v	7811	(4925, 17 494)
$18 - 49$ v	5758	(4105, 9849)
$50 - 64$ y	1311	(808, 3502)
$65 + y$	462	(162, >99999)
All ages	1223	(578, 3438)

^aThe 95% credible interval is from 5000 Monte Carlo simulations.

A and B viruses and 22% against A(H3N2) viruses. Given the substantial burden of influenza-associated illness, efforts to improve influenza vaccines are imperative. An A(H3N2) vaccine component with improved effectiveness could substantially reduce the number of influenza-associated hospitalizations among older adults [\[47](#page-8-17)]. Several studies have suggested that vaccines with a higher dose of antigen may offer protective advantages over standard-dose inactivated influenza vaccines in older adults [\[37,](#page-8-13) [48](#page-8-17), [49\]](#page-8-18). Also, it is possible that vaccine viruses not propagated in eggs could be advantageous, especially for the A(H3N2) vaccine component. There were 2 licensed vaccines (cell culture–derived inactivated vaccine and recombinant vaccine) that did not include egg-propagated A(H3N2) viruses in 2017–2018 [[50\]](#page-8-19). Efforts to determine the advantages of nonegg-based and enhanced vaccines are ongoing. At this time, vaccination remains an important component of influenza prevention; and our results indicate that current vaccines prevented a substantial burden of illness during the 2017–2018 influenza season.

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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