

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

Melissa A Rolfes¹, Brendan Flannery¹, Jessie Chung¹, Alissa O'Halloran¹, Shikha Garg¹, Edward A Belongia², Manjusha Gaglani³, Richard Zimmerman⁴, Michael L Jackson⁵, Arnold S Monto⁶, Nisha B Alden⁷, Evan Anderson⁸, Nancy M Bennett⁹, Laurie Billing¹⁰, Seth Eckel¹¹, Pam Daily Kirley¹², Ruth Lynfield¹³, Maya L Monroe¹⁴, Melanie Spencer¹⁵, Nancy Spina¹⁶, H Keipp Talbot¹⁷, Ann Thomas¹⁸, Salina Torres¹⁹, Kimberly Yousey-Hindes²⁰, James Singleton²¹, Manish Patel¹, Carrie Reed¹, and Alicia M Fry¹ on behalf of the U.S. Flu VE Network, the Influenza Hospitalization Surveillance Network (FluSurv-NET), and the Assessment Branch, Immunization Services Division, Centers for Disease Control and Prevention

¹ Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA

² Marshfield Clinical Research Institute, Marshfield, WI

³ Baylor Scott and White Health, Texas A&M College of Medicine, Temple, TX

⁴ University of Pittsburgh Schools of Health Sciences, Pittsburgh, PA

⁵ Kaiser Permanente Washington Health Research Institute, Seattle, WA

⁶ University of Michigan School of Public Health, Ann Arbor, MI

⁷ Colorado Department of Public Health and Environment, Denver, CO

⁸ Georgia Emerging Infections Program, Atlanta VA Medical Center, Emory University, Atlanta, GA

⁹ University of Rochester School of Medicine and Dentistry, Rochester, NY

¹⁰ Ohio Department of Health, Columbus, OH

¹¹ Michigan Department of Health and Human Services, Lansing, MI

¹² California Emerging Infections Program, Oakland, CA

¹³ Minnesota Department of Health, St. Paul, MN

¹⁴ Maryland Department of Health and Mental Hygiene, Baltimore, MD

Published by Oxford University Press for the Infectious Diseases Society of America 2019. This work is written by (a) US Government employee(s) and is in the public domain in the US.

¹⁵ Salt Lake County Health Department, Salt Lake City, UT

¹⁶ New York State Emerging Infections Program, New York State Department of Health, Albany, NY

¹⁷ Vanderbilt University, Nashville, TN

¹⁸ Oregon Department of Public Health, Portland, OR

¹⁹ New Mexico Department of Health, Sante Fe, NM

²⁰ Connecticut Emerging Infections Program, Yale School of Public Health, New Haven, CT

²¹ Immunization Services Division, Centers for Disease Control and Prevention, Atlanta, GA

Corresponding author:

Melissa A Rolfes

mrolfes1@cdc.gov

Influenza Division; Centers for Disease Control and Prevention

1600 Clifton Rd

MS H24-7

Atlanta, GA 30329

Running title: Effect of flu vaccination in 2017-2018

Summary: During the 2017–2018 influenza season, we estimate that influenza vaccination reduced the risk of medically-attended influenza by 38% and prevented 7 million illnesses, 4 million medical visits, 109,000 hospitalizations, and 8,000 deaths in the United States.

Abstract

Background: The severity of the 2017–2018 influenza season in the U.S. was high with influenza A(H3N2) viruses predominating. 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, and 95% confidence intervals (CI), against medically-attended RT-PCR confirmed influenza virus infection, in the ambulatory setting, using a test-negative design. We estimated influenza type/subtype-specific burden using multipliers applied to population-based rates of influenza-associated hospitalizations. We used a compartmental model to estimate numbers, with 95% credible intervals (CrI), of influenza-associated outcomes prevented by vaccination.

Results: The VE against outpatient medically-attended, laboratory-confirmed influenza was 38% (95% 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 8,000 (95% CrI: 1,100–21,000) 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 U.S. 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

Introduction

The 2017–2018 influenza season in the United States was a high severity season [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]. The Centers for Disease Control and Prevention (CDC) has estimated that there were 49 million influenza illnesses, 960,000 hospitalizations, and 79,000 influenza-associated deaths during 2017–2018, the highest morbidity and mortality since the 2009 pandemic [3].

Influenza vaccination is the primary strategy to prevent influenza illness and its complications. Recent reports estimate that 42% of the U.S. population was vaccinated against influenza during the 2017–2018 season [4, 5]; and 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]. 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.

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].

Influenza vaccine effectiveness

Effectiveness of 2017–2018 influenza vaccination for the prevention of outpatient medically-attended influenza illness was determined through the U.S. 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 seeking outpatient care for acute respiratory illness (including cough) within 7 days of symptom onset at 52 participating health care facilities in five 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 labs used primers and probes from 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 pre-existing health condition associated with increased risk of severe influenza [12, 13].

For all U.S. 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 four 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]. We estimated VE, and 95% confidence

intervals (CI), 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 VE Network study was approved by institutional review boards at each participating site and 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 at <https://www.cdc.gov/flu/about/burden/estimates.htm> [3, 15]. 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 Supplemental Figure 1. 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 U.S. 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]. As data on influenza A subtype was 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 U.S. by month, from August 2017 through April 2018, which were reported at <https://www.cdc.gov/flu/fluview/1718season.htm> (Supplemental Figure 2) [4, 5].

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]. We began the model with all members of the U.S. 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 observed monthly count 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, 18, 19].

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

We estimated the number needed to vaccinate (NNV) to prevent one influenza-associated hospitalization by dividing the number of vaccinated individuals by hospitalizations prevented by

vaccination. When VE 95% confidence intervals 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, incorporating uncertainty in each data input. Briefly, we chose a value at random from the assumed distribution for each of the model inputs (Supplemental Table 1) and calculated the estimated prevented outcome and repeated the process 5,000 times. Distributions for VE and vaccine coverage were truncated at 0.

Sensitivity analysis for vaccine coverage

Because missing responses to the influenza vaccination question were more common in the BRFSS 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]. 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 over-estimation by self-report [21–25].

Results

Among the population eligible for influenza vaccination, 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 and Supplemental Table 2). After applying these rates to the U.S. 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 (Supplemental Table 3). 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 U.S. Flu VE Network, 8,900 people were enrolled and 8,436 were included in analysis for the 2017–2018 influenza season, including 3,050 case-patients with RT-PCR-confirmed influenza and 5,386 controls with non-influenza acute respiratory illness (Table 1; Supplemental Table 4). Influenza A virus infections were identified from November, 2017 through February, 2018 (Supplemental Figure 3). 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 U.S. Flu VE Network, 42% of influenza-positive case-patients and 53% of influenza-negative controls were vaccinated against influenza (Supplemental Table 5). 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, high-risk condition, and calendar time (Figure 2; Supplemental Table 5). 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). 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). 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 (Supplemental table 6). Additionally, over 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). 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).

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 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).

Finally, an estimated 8,000 (95% CrI: 1,100–21,000) 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 credible intervals for estimates of prevented hospitalizations using various vaccine coverage scenarios overlapped with the credible intervals using the reported 2017–2018 coverage (Supplemental Table 7).

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 8,000 deaths related to influenza. In young 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); and 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, vaccine effectiveness, 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 overall. Thus, while vaccination is an important strategy to mitigate some of the burden and severity of the influenza season, improvements in both vaccine effectiveness 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 be underestimating 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 (i.e. herd immunity) against influenza virus infection, largely by reducing the probability of contact with an infected person [26-31]. The magnitude of indirect protection is inconsistent between studies [32]; however, the population benefit of seasonal influenza vaccination would be greater if indirect effects were present and considered in the model [33, 34].

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) [35]. 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]. 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 U.S. [2]. 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 [36]. Even with reduced VE among older adults, vaccination still prevented one influenza-related hospitalization for every 462 people vaccinated. More broadly, we need to better understand the factors that contribute to differences in VE to improve influenza vaccines.

Our estimates of the effect of vaccination rely on large, multi-state 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 two 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 influenza vaccination over the season [37-43]. The current literature 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 telephone surveys have limitations, including lower response rates and possible inaccuracy of vaccination status [21-25, 44, 45]. All results of our sensitivity analysis fell within the credible intervals using reported coverage. Fifth, as we assumed that influenza vaccination would not increase the risk of infection, our credible intervals are truncated at 0 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 and full antigenic and genetic characterization of specimens from the US Flu VE Network is ongoing towards 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 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 [46]. 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 [36, 47, 48]. Also, it is possible that vaccine viruses not propagated in eggs could be advantageous, especially for the A(H3N2) vaccine component. There were two licensed vaccines (cell-culture derived inactivated vaccine and recombinant vaccine) that did not include egg propagated A(H3N2) viruses in 2017–2018 [49]. Efforts to determine the advantages of non-egg 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.

Acknowledgements: We would like to acknowledge the great work and support of the following people: Bret Rosenblum, Samantha Ford, Monika Johnson, Jonathan M. Raviotta, Terrie Sax, Jonathan Steele, Michael Susick, Rina Chabra, Edward Garofolo, Philip Iozzi, Barbara Kevish, Donald B. Middleton, Leonard Urbanski, Pediatric PittNet, University of Pittsburgh Schools of the Health Sciences and UPMC, Pittsburgh, Pennsylvania; Sarah Petnic, Alison Ryan from the California Emerging Infections Program; Amber Maslar, James Meek, Rona Chen from the Connecticut Emerging Infections Program; Stepy Thomas, Suzanne Segler, Kyle Openo, Emily Fawcett, and Andrew Martin from Georgia Emerging Infections Program; Melissa McMahon, Anna Strain, Jamie Christensen from the Minnesota Department of Health; Eva Pradhan, Katarina Manzi from the New York-Albany Emerging Infections Program; Christina Felsen, Maria Gaitan from the University of Rochester School of Medicine and Dentistry; Krista Long, Nicholas Fisher, Emily Hawley, Rory O’Shaughnessy from the Ohio Influenza Hospitalization Surveillance Project; Magdalena Scott, Courtney Crawford from the Oregon Emerging Infections Program. We also acknowledge the work of Tammy Santibanez, Yusheng Zhai, Pengjun Lu, Anup Srivastav, Mei-Chuan Hung in the Immunization Services Division and Charisse Cummings in the Influenza Division at the Centers for Disease Control and Prevention.

Group Authors:

U.S. Flu VE Network: Huong Q McLean, Jennifer P King, Mary Patricia Nowalk, G.K. Balasubramani, Todd M. Bear, Robert Hickey, John V. Williams, Evelyn C. Reis, Krissy K Moehling, Heather Eng

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

Funding: This work was supported by the Centers for Disease Control and Prevention through cooperative agreements: Emerging Infections Programs (CDC-RFA-CK17-1701), the Influenza Hospital Surveillance Project (5U38OT000143), the University of Michigan (1U01 IP001034), Kaiser Permanente Washington Research Institute (1U01 IP001037), Marshfield Clinic Research Institute (1U01 IP001038), University of Pittsburgh (1U01 IP001035), and Baylor Scott and White Healthcare (1U01 IP001039). At the University of Pittsburgh, the project was also supported by the National Institutes of Health through grant UL1TR001857.

Potential conflicts of interest: ASM reports consultancy fees from Sanofi and Seqirus, outside the submitted work. EA reports grants from Sanofi Pasteur, Merck, Pfizer, Micron, MedImmune, and PaxVax; and has received consultancy fees from Abbvie, outside the submitted work. EB reports grants from Seqirus, outside the submitted work. HKT reports grants from Sanofi Pasteur and personal fees from Seqirus, during the conduct of the study. MJ reports grants from Sanofi Pasteur, outside the submitted work. MG reports grants from the CDC, outside the submitted work. RL received payment to co-edit a book on infectious disease surveillance; royalties are donated to the Minnesota Department of Health. RZ reports grants from Sanofi Pasteur, Merck & Co., and Pfizer Inc, outside the submitted work.

References

1. Biggerstaff M, Kniss K, Jernigan DB, et al. Systematic Assessment of Multiple Routine and Near-Real Time Indicators to Classify the Severity of Influenza Seasons and Pandemics in the United States, 2003-04 Through 2015-2016. *Am J Epidemiol* **2017**.
2. Garten R, Blanton L, Elal AIA, et al. Update: Influenza Activity in the United States During the 2017-18 Season and Composition of the 2018-19 Influenza Vaccine. *MMWR Morb Mortal Wkly Rep* **2018**; 67(22): 634-42.
3. Centers for Disease Control and Prevention. Estimated Influenza Illnesses, Medical visits, Hospitalizations, and Deaths in the United States — 2017–2018 influenza season. Available at: <https://www.cdc.gov/flu/about/burden/estimates.htm>. Accessed Oct 29, 2018.
4. Centers for Disease Control and Prevention. Estimates of Influenza Vaccination Coverage and Adults — United States, 2017–18 Flu Season. Available at: <https://www.cdc.gov/flu/fluview/coverage-1718estimates.htm>. Accessed Oct 29, 2018.
5. Centers for Disease Control and Prevention. Estimates of Flu Vaccination Coverage among Children — United States, 2017–18 Flu Season. Available at: <https://www.cdc.gov/flu/fluview/coverage-1718estimates-children.htm>. Accessed Oct 29, 2018.
6. Flannery B, Chung JR, Belongia EA, et al. Interim Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness - United States, February 2018. *MMWR Morb Mortal Wkly Rep* **2018**; 67(6): 180-5.
7. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2017–18 Influenza Season. *MMWR Recommendations and Reports* **2017**; 66(RR-2): 1-20.
8. Gaglani M, Pruszynski J, Murthy K, et al. Influenza Vaccine Effectiveness Against 2009 Pandemic Influenza A(H1N1) Virus Differed by Vaccine Type During 2013-2014 in the United States. *J Infect Dis* **2016**; 213(10): 1546-56.
9. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. *J Infect Dis* **2015**; 211(10): 1529-40.
10. Ohmit SE, Petrie JG, Malosh RE, et al. Influenza vaccine effectiveness in the community and the household. *Clin Infect Dis* **2013**; 56(10): 1363-9.
11. Zimmerman RK, Nowalk MP, Chung J, et al. 2014-2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type. *Clin Infect Dis* **2016**; 63(12): 1564-73.
12. Jackson ML, Chung JR, Jackson LA, et al. Influenza Vaccine Effectiveness in the United States during the 2015-2016 Season. *N Engl J Med* **2017**; 377(6): 534-43.
13. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and Control of Seasonal Influenza with Vaccines. *MMWR Recomm Rep* **2016**; 65(5): 1-54.
14. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* **2013**; 31(17): 2165-8.
15. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. *PLoS One* **2015**; 10(3): e0118369.
16. Chaves SS, Lynfield R, Lindegren ML, Bresee J, Finelli L. The US Influenza Hospitalization Surveillance Network. *Emerg Infect Dis* **2015**; 21(9): 1543-50.
17. Tokars JI, Rolfes MA, Foppa IM, Reed C. An evaluation and update of methods for estimating the number of influenza cases averted by vaccination in the United States. *Vaccine* **2018**; 36(48): 7331-7.

18. Reed C, Angulo FJ, Swerdlow DL, et al. Estimates of the prevalence of pandemic (H1N1) 2009, United States, April-July 2009. *Emerg Infect Dis* **2009**; 15(12): 2004-7.
19. Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: A tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses* **2018**; 12(1): 132-7.
20. Flannery B, Chung J, Ferdinands J. Preliminary Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness against Laboratory-Confirmed Influenza from the US Flu VE and HAIVEN Networks. In: Advisory Committee on Immunization Practices. Atlanta, GA, 2018. Available at: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-06/flu-02-Flannery-508.pdf>.
21. Brown C, Clayton-Boswell H, Chaves SS, et al. Validity of parental report of influenza vaccination in young children seeking medical care. *Vaccine* **2011**; 29(51): 9488-92.
22. Mangtani P, Shah A, Roberts JA. Validation of influenza and pneumococcal vaccine status in adults based on self-report. *Epidemiol Infect* **2007**; 135(1): 139-43.
23. Poehling KA, Vannoy L, Light LS, et al. Assessment of parental report for 2009-2010 seasonal and monovalent H1N1 influenza vaccines among children in the emergency department or hospital. *Acad Pediatr* **2012**; 12(1): 36-42.
24. Irving SA, Donahue JG, Shay DK, Ellis-Coyle TL, Belongia EA. Evaluation of self-reported and registry-based influenza vaccination status in a Wisconsin cohort. *Vaccine* **2009**; 27(47): 6546-9.
25. King JP, McLean HQ, Belongia EA. Validation of self-reported influenza vaccination in the current and prior season. *Influenza Other Respir Viruses* **2018**; 12(6): 808-13.
26. Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. *JAMA* **2000**; 284(13): 1677-82.
27. Monto AS, Davenport FM, Napier JA, Francis T, Jr. Modification of an outbreak of influenza in Tecumseh, Michigan by vaccination of schoolchildren. *J Infect Dis* **1970**; 122(1): 16-25.
28. Pebody RG, Sinnathamby MA, Warburton F, et al. Uptake and impact of vaccinating primary school-age children against influenza: experiences of a live attenuated influenza vaccine programme, England, 2015/16. *Euro Surveill* **2018**; 23(25).
29. Piedra PA, Gaglani MJ, Kozinetz CA, et al. Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. *Vaccine* **2005**; 23(13): 1540-8.
30. Rudenko LG, Slepishkin AN, Monto AS, et al. Efficacy of live attenuated and inactivated influenza vaccines in schoolchildren and their unvaccinated contacts in Novgorod, Russia. *J Infect Dis* **1993**; 168(4): 881-7.
31. Loeb M, Russell ML, Moss L, et al. Effect of influenza vaccination of children on infection rates in hutterite communities: A randomized trial. *JAMA* **2010**; 303(10): 943-50.
32. Mertz D, Fadel SA, Lam PP, et al. Herd effect from influenza vaccination in non-healthcare settings: a systematic review of randomised controlled trials and observational studies. *Euro Surveill* **2016**; 21(42).
33. Arinaminpathy N, Kim IK, Gargiullo P, et al. Estimating Direct and Indirect Protective Effect of Influenza Vaccination in the United States. *Am J Epidemiol* **2017**; 186(1): 92-100.
34. Sah P, Medlock J, Fitzpatrick MC, Singer BH, Galvani AP. Optimizing the impact of low-efficacy influenza vaccines. *Proc Natl Acad Sci U S A* **2018**; 115(20): 5151-6.
35. Flannery B, Chung JR, Monto AS, et al. Influenza Vaccine Effectiveness in the United States during the 2016-2017 Season. *Clin Infect Dis* **2018**.

36. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. *N Engl J Med* **2014**; 371(7): 635-45.
37. 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(1): 246-51.
38. Jimenez-Jorge S, de Mateo S, Delgado-Sanz C, et al. Effectiveness of influenza vaccine against laboratory-confirmed influenza, in the late 2011-2012 season in Spain, among population targeted for vaccination. *BMC Infect Dis* **2013**; 13: 441.
39. Kissling E, Valenciano M, Larrauri A, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case-control study. *Euro Surveill* **2013**; 18(5).
40. Pebody R, Andrews N, McMenemy J, et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection. *Euro Surveill* **2013**; 18(5).
41. 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(8): 1142-9.
42. Sullivan SG, Komadina N, Grant K, Jelley L, Papadakis G, Kelly H. Influenza vaccine effectiveness during the 2012 influenza season in Victoria, Australia: influences of waning immunity and vaccine match. *J Med Virol* **2014**; 86(6): 1017-25.
43. 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(5): 544-50.
44. Centers for Disease Control and Prevention. Interim results: state-specific seasonal influenza vaccination coverage - United States, August 2009-January 2010. *MMWR Morb Mortal Wkly Rep* **2010**; 59(16): 477-84.
45. Zimmerman RK, Raymund M, Janosky JE, Nowalk MP, Fine MJ. Sensitivity and specificity of patient self-report of influenza and pneumococcal polysaccharide vaccinations among elderly outpatients in diverse patient care strata. *Vaccine* **2003**; 21(13-14): 1486-91.
46. Fry AM, Kim IK, Reed C, et al. Modeling the effect of different vaccine effectiveness estimates on the number of vaccine-prevented influenza-associated hospitalizations in older adults. *Clin Infect Dis* **2014**; 59(3): 406-9.
47. Dunkle LM, Izikson R, Patriarca P, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. *N Engl J Med* **2017**; 376(25): 2427-36.
48. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2017-18 Influenza Season. *MMWR Recomm Rep* **2017**; 66(2): 1-20.
49. Barr IG, Donis RO, Katz JM, et al. Cell culture-derived influenza vaccines in the severe 2017-2018 epidemic season: a step towards improved influenza vaccine effectiveness. *NPJ Vaccines* **2018**; 3: 44.
50. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and Control of Seasonal Influenza With Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2017-18 Influenza Season. *Am J Transplant* **2017**; 17(11): 2970-82.

Table 1: Demographic and clinical characteristics of participants enrolled in the U.S. Influenza Vaccine Effectiveness Network — United States, 2017–2018 influenza season

Characteristic	Test result status					Vaccination status			
	Influenza-positive		Influenza-negative		p-value *	Total	Vaccinated		p-value †
	No.	(%)	No.	(%)			No.	(%)	
Overall	3050		5386			8436	4113		
Study site					<0.001				<0.001
Michigan	532	(39)	836	(61)		1368	750	(55)	
Pennsylvania	501	(38)	804	(62)		1305	599	(46)	
Texas	725	(37)	1260	(63)		1985	753	(38)	
Washington	501	(29)	1224	(71)		1725	1022	(59)	
Wisconsin	791	(39)	1262	(61)		2053	989	(48)	
Male sex	1322	(38)	2131	(62)	0.001	3453	1553	(45)	<0.001
Age group (yrs)					<0.001				<0.001
<5 years	262	(24)	847	(76)		1109	551	(50)	
5–17 years	837	(46)	965	(54)		1802	632	(35)	
18–49 years	965	(34)	1894	(66)		2859	1128	(39)	
50–64 years	571	(38)	937	(62)		1508	891	(59)	
≥65 years	415	(36)	743	(64)		1158	911	(79)	
Race/ethnicity					0.02				<0.001
White, non-Hispanic	2171	(36)	3888	(64)		6059	3117	(51)	
Black, non-Hispanic	266	(40)	392	(60)		658	226	(34)	
Other, non-Hispanic	269	(33)	543	(67)		812	418	(51)	
Hispanic	331	(38)	550	(62)		881	339	(38)	

Unknown	13	(50)	13	(50)		26	13	(50)	
Any high-risk condition †	1370	(34)	2633	(66)	0.001	4003	2445	(61)	<0.001
Asthma/pulmonary high-risk condition	537	(32)	1125	(68)	<0.001	1662	994	(60)	<0.001
Cardiovascular high-risk condition	274	(34)	540	(66)	0.12	814	587	(72)	<0.001
Diabetes high-risk condition	232	(34)	449	(66)	0.24	681	480	(70)	<0.001
BMI ≥40 §	179	(32)	381	(68)	0.03	560	360	(64)	<0.001
Other high-risk condition	922	(35)	1704	(65)	0.18	2626	1702	(65)	<0.001
Interval from onset to enrollment					<0.001				<0.001
<3 days	1444	(45)	1759	(55)		3203	1472	(46)	
3–4 days	1066	(35)	2008	(65)		3074	1501	(49)	
5–7 days	540	(25)	1619	(75)		2159	1140	(53)	
Influenza test result ††									
Negative			5386			5386	2842	(53)	
Influenza B positive	958					958	377	(39)	
B/Victoria	39					39	8	(21)	
B/Yamagata	908					908	369	(41)	
Influenza A positive	2103					2103	899	(43)	
A (H1N1)pdm09	318					318	93	(29)	
A (H3N2)	1761					1761	795	(45)	

* P-value calculated using chi-square comparing frequency of participants testing influenza positive versus negative by characteristic.

[†] P-value calculated using chi-square test that compares the frequency of vaccination by participant characteristic.

[‡] Presence of a high-risk health condition is defined as the presence of ≥ 1 medical record-documented International Classification of Disease-10 high risk code from October 1, 2016 to enrollment, as defined by the ACIP guidance for conditions that increase risk for complications from influenza [50].

[§] Body Mass Index (BMI) was calculated as $\text{kg}/(\text{m}^2)$ from height and weight recorded in the electronic medical record. Calculated for adults aged ≥ 18 years only.

^{||} 14 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.

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

Age group	Illnesses		Medical visits		Hospitalization				Death	
	Number prevented	95% CrI *	Number prevented	95% CrI	Number prevented	95% CrI	% prevented	95% CrI	Number prevented	95% CrI
6 months-4 years	2,121,511	(1,445,133, 2,928,929)	1,421,413	(971,080, 1,966,976)	14,790	(10,075, 20,419)	41	(33, 47)	74	(0, 189)
5-17 years	1,366,965	(613,310, 2,178,412)	710,822	(319,168, 1,143,256)	3,748	(1,682, 5,973)	15	(7, 22)	89	(28, 197)
18-49 years	1,138,407	(663,181, 1,610,481)	421,211	(243,149, 603,887)	6,390	(3,722, 9,040)	7	(4, 10)	228	(119, 403)
50-64 years	1,792,530	(673,687, 2,937,768)	770,788	(292,197, 1,263,230)	19,009	(7,144, 31,154)	10	(4, 15)	868	(330, 1,591)
≥65 years	715,073	(0, 2,033,756)	400,441	(0, 1,145,616)	65,007	(0, 184,887)	9	(0, 21)	6,796	(0, 19,844)
All ages	7,134,487	(5,393,925, 9,310,339)	3,724,674	(2,819,761, 4,877,688)	108,944	(38,854, 230,943)	10	(4, 19)	8,054	(1,059, 21,320)

* 95% credible interval (CrI) from 5,000 Monte Carlo simulations.

Table 3: Number needed to vaccinate (NNV) to prevent one influenza A and B-associated hospitalization

— United States, 2017–2018 influenza season

Age group	NNV	95% CrI
6 months-4 years	821	(606, 1,190)
5-17 years	7,811	(4,925, 17,494)
18-49 years	5,758	(4,105, 9,849)
50-64 years	1,311	(808, 3,502)
65+ years	462	(162, >999,999)
All ages	1,223	(578, 3,438)

* 95% credible interval (CrI) from 5,000 Monte Carlo simulations.

Figure legends

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

Figure 2: Adjusted vaccine effectiveness against outpatient medically-attended influenza-associated illness, U.S. 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% CI: -0.91, 0.65).

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











