Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Influenza vaccine effectiveness in preventing influenza-associated intensive care admissions and attenuating severe disease among adults in New Zealand 2012–2015

Mark G. Thompson [a,*,1], Nevil Pierse [b,*,1], Q. Sue Huang [c], Namrata Prasad [c], Jazmin Duque [a,d], E. Claire Newbern [b], Michael G. Baker [b], Nikki Turner [e], Colin McArthur [f], On behalf of SHIVERS investigation team

[a] Centers for Disease Control and Prevention (CDC), Atlanta, USA
[b] University of Otago, School of Medicine in Wellington, New Zealand
[c] Institute of Environmental Science and Research, Wellington, New Zealand
[d] Battelle, Atlanta, USA
[e] University of Auckland, Auckland, New Zealand
[f] Auckland District Health Board, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 20 March 2018
Received in revised form 8 June 2018
Accepted 15 July 2018
Available online xxxx

Keywords:
Influenza vaccine
Vaccine effectiveness
Intensive care unit
Test negative design
Hospital

ABSTRACT

Background: Little is known about inactivated influenza vaccine effectiveness (IVE) in preventing very severe disease, including influenza-associated intensive care unit (ICU) admissions.
Methods: The Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) project enrolled adults (aged ≥ 18 years) with acute respiratory illness (ARI) in general ward (GW) hospital settings (n = 3034) and ICUs (n = 101) during 2012–2015. IVE was assessed using a test-negative design comparing the odds of influenza vaccination among influenza positives vs. negatives (confirmed by real-time reverse transcription polymerase chain reaction). All models were adjusted for season, weeks from season peak, and a vaccination propensity score.
Results: Influenza virus infection was confirmed in 28% of GW hospital and 41% of ICU patients; influenza vaccination was documented for 56% and 41%, respectively. Across seasons, IVE was 37% (95% confidence intervals [CI] = 23–48%) among GW patients and 82% (95% CI = 45–94%) among ICU patients. IVE point estimates were > 70% against ICU influenza and consistently higher than IVE against GW influenza when stratified by season, by virus (sub)types, and for adults with or without chronic medical conditions and for both adults aged <65 and ≥65 years old. Among hospitalized influenza positives, influenza vaccination was associated with a 59% reduction in the odds of ICU admission (aOR = 0.41, 95% CI = 0.18–0.96) and with shorter ICU lengths of stay (LOS), but not with radiograph-confirmed pneumonia or GW hospital LOS.
Conclusion: Inactivated influenza vaccines prevented influenza-associated ICU admissions, may have higher effectiveness in ICU than GW hospital settings, and appeared to reduce the risk of severe disease among those who are infected despite vaccination.

1. Introduction

Although the preventive benefit of inactivated influenza vaccines (IIVs) has been studied extensively [1,2], the extent to which IIVs avert the most severe manifestations of influenza disease and possibly attenuate disease severity among adults infected despite vaccination remains unclear. To date, there are no statistically significant estimates of influenza vaccine effectiveness (IVE) against influenza-associated intensive care unit (ICU) admissions (ICU influenza) among adults using the established test-negative design (TND) methodology [1,2]. If IIVs reduce the severity of disease, we would expect that influenza infected vaccinees (vaccine failures) would be less likely to be admitted to an ICU (or have other indicators of severe disease) than unvaccinated influenza

* Corresponding authors at: Influenza Division, MS-A32, CDC, 1600 Clifton Rd., GA 30333, USA (M.G. Thompson). The University of Otago, Wellington, PO Box 7343, Wellington South 6242, New Zealand (N. Pierse).
E-mail addresses: isq8@cdc.gov (M.G. Thompson), nevil.pierse@otago.ac.nz (N. Pierse).
[1] Authors Thompson and Pierse made equal contributions.

https://doi.org/10.1016/j.vaccine.2018.07.028
0264-410X/

positives. Multi-center studies from Spain [3] and the United States (US) [4] both observed reduced risk of ICU admission among vaccinated influenza positives, especially among older adults; however, results in the US were not consistent across influenza seasons [5]. Similarly, we would expect that vaccinated influenza positives should require shorter lengths of stay (LOS) in the hospital than unvaccinated positives, which was recently noted in the US among patients aged ≥50 years [4].

We estimated IVE against ICU influenza and examined other indicators of severe outcomes among vaccinated and unvaccinated influenza positive patients as part of the Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) project, which prospectively enrolled hospitalized adults from 2012 to 2015 in Auckland, New Zealand. Although we have previously published seasonal estimates of overall IVE from SHIVERS [6–10], by performing a cross-season analysis, we were able to examine ICU outcomes and differences between vaccinated and unvaccinated influenza positives for the first time.

2. Methods

2.1. Study population

Detailed methods for SHIVERS are previously published [6,7,10,11]. In brief, adult patients (aged ≥ 18 years) were enrolled during 2012–2015 from two hospitals serving a predominantly urban population of 906,000 in Central and Southeastern Auckland, New Zealand. Participation among eligible patients was over 85% [10]. Participants provided verbal consent, and the study was approved by the New Zealand Health and Disability Ethics Committee (NTX/11/11/102). If a patient was intubated or otherwise too ill at admission, a proxy could provide consent.

Eligible hospitalized patients had an overnight admission with a presenting complaint or preliminary diagnosis indicating acute respiratory illness (ARI). Among these adults, study nurses enrolled patients with cough and history of fever (subjective fever or measured temperature ≥ 37.8 °C) with onset ≤ 10 days, defined by the World Health Organization [WHO] as severe acute respiratory infection (SARI). Starting in 2013, a sample of patients with ARI who did not meet the SARI definition (e.g., ARI with cough only or fever only) were also enrolled depending on staff enrollment capacity; these non-SARI respiratory illnesses accounted for 7% of enrollees in 2013 and increased to 25% in 2015.

The analytic sample excluded those without real-time reverse transcription polymerase chain reaction (rRT-PCR) influenza results, participants (or proxies) uncertain of IIV vaccination status, or who received IIV < 14 days before the medical encounter. Patients who tested influenza negative by rRT-PCR but had illness onset > 10 days before admission were also excluded in order to minimize inclusion of possible false rRT-PCR negatives. The analytic sample was limited to weeks of enrollment (18–39) with local influenza circulation.

2.2. Measures

Socio-demographic characteristics (sex, age, and ethnicity) and smoking status were documented. Patients reported illness symptoms and their overall self-rated health [12]. Neighborhood-based social deprivation index [13], the presence of chronic medical condition(s) (full list in Supplemental Table A), vital signs at admission, LOS, admission to ICU, mechanical ventilation, and receipt of influenza antiviral medication were extracted from the medical records. Radiograph results were interpreted using previously validated and published methods [14]. Study data were collected and managed using REDCap electronic data capture tools [15].

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.028.

2.3. Laboratory methods

Nasopharyngeal flocked swabs were collected and tested by rRT-PCR as previously described [11], using US CDC rRT-PCR protocol [16] at Auckland District Health Board Laboratory and using the AusDiagnostic PCR protocol at the Counties Manukau District Health Board laboratory [17], with confirmatory testing, influenza A subtyping and genetic sequencing [9], and B lineage genotyping conducted by the New Zealand National Influenza Centre.

2.4. Vaccination

In New Zealand, southern hemisphere (SH) unadjuvanted trivalent inactivated influenza vaccine (IIV3) is offered free-of-charge to all adults aged ≥ 65 years, pregnant women, and those aged > 6 months with certain chronic medical conditions (http://www.influenza.org.nz). Some adults also receive free IIV3 at their workplace. Hospitalized patients self-reported IIV3 vaccination status (and whether receipt was < 14 days from admission). The compositions of southern hemisphere IIV3 for 2012–2015 are listed in Supplemental Table B.

2.5. Statistical analysis

IVE was assessed using a TND, whereby IVE equals 100% × (1 − odds ratio [ratio of odds of vaccination among influenza-positive cases to the odds of vaccination among influenza-negative controls]) using logistic regression. Although the TND minimizes biases associated with access to IIV3 and healthcare seeking for ARI [18,19], additional adjustments may be needed in studies examining IVE or predictors of disease severity in hospital settings [20,21]. Thus, SHIVERS [6,7] and other studies of IVE in hospital settings [22,23] have employed propensity score regression adjustment to reduce residual confounding [24]. The propensity score is the inverse logit transformation of the linear predictor derived from multivariable logistic regression as a function of the socio-demographic, chronic medical conditions, and other health status variables (listed in full in Supplemental Table A). The propensity score model showed good discrimination between vaccinated and unvaccinated patients; the model correctly predicted 78% of vaccinated patients; the area under the curve was 76% (95% CI = 74–78%); the Hosmer and Lemeshow Test was not significant indicating overall good model fit (Chi-square [8] = 8.88, p = .35). Adjusted IVE models include as covariates the vaccination propensity score plus year/season and weeks from medical encounter to influenza peak season.

As a sensitivity analysis and for comparison with other IVE estimates from SHIVERS [10] and northern hemisphere (NH) IVE platforms during the same time period [1,2], we also calculated IVE adjusting for similar covariates employed in their models: year, weeks from medical encounter to influenza peak, age group, self-rated health status, and presence of underlying medical condition. Other potential confounders (hospital, sex, ethnicity, social deprivation, specific chronic conditions, prior respiratory hospitalization, functional status, obesity, and smoking) did not change the adjusted VE by ≥ 5% which other studies have used as a predetermined threshold for inclusion [25,26]. At the request of reviewers, stratified IVE was also estimated among patients enrolled during weeks when influenza positivity was ≥ 10%, among patients who met SARI criteria (excluding non-SARI acute respiratory illnesses), and among patients with illness onset ≤ 5 days (for patients

Please cite this article in press as: Thompson MG et al. Influenza vaccine effectiveness in preventing influenza-associated intensive care admissions and attenuating severe disease among adults in New Zealand 2012–2015. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.07.028