Vaccine 34 (2016) 1806–1809

Contents lists available at ScienceDirect

Vaccine

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

Evaluating the case-positive, control test-negative study design for influenza vaccine effectiveness for the frailty bias

H. Keipp Talbot[a,*], Hui Nian[b], Qingxia Chen[b], Yuwei Zhu[b], Kathryn M. Edwards[c], Marie R. Griffin[a,d,e]

[a] Departments of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States
[b] Departments of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, United States
[c] Departments of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, United States
[d] Departments of Health Policy, Vanderbilt University Medical Center, Nashville, TN, United States
[e] Mid-South Geriatric Research Education and Clinical Center and Clinical Research Center of Excellence, VA TN Valley Health Care System, Nashville, TN, United States

ARTICLE INFO

Article history:
Received 6 July 2015
Received in revised form 15 January 2016
Accepted 12 February 2016
Available online 28 February 2016

Keywords:
Influenza vaccine
Frailty
Test-negative study design

ABSTRACT

Introduction: Previous influenza vaccine effectiveness studies were criticized for their failure to control for frailty. This study was designed to see if the test-negative study design overcomes this bias.
Methods: Adults ≥ 50 years of age with respiratory symptoms were enrolled from November 2006 through May 2012 during the influenza season (excluding the 2009–2010 H1N1 pandemic season) to perform yearly test-negative control influenza vaccine effectiveness studies in Nashville, TN. At enrollment, both a nasal and throat swab sample were obtained and tested for influenza by RT-PCR. Frailty was calculated using a modified Rockwood Index that included 60 variables ascertained in a retrospective chart review giving a score of 0 to 1. Subjects were divided into three strata: non frail (≤0.08), pre-frail (>0.08 to <0.25), and frail (≥0.25). Vaccine effectiveness was calculated using the formula [1-adjusted odds ratio (OR)] × 100%. Adjusted ORs for individual years and all years combined were estimated by penalized multivariable logistic regression.
Results: Of 1023 hospitalized adults enrolled, 866 (84.7%) participants had complete immunization status, molecular influenza testing and covariates to calculate frailty. There were 83 influenza-positive cases and 783 test-negative controls overall, who were 74% white, 25% black, and 59% female. The median frailty index was 0.167 (Interquartile: 0.117, 0.267). The frailty index was 0.167 (0.100, 0.233) for the influenza positive cases compared to 0.183 (0.133, 0.267) for influenza negative controls ($p = 0.07$). Vaccine effectiveness estimates were 55.2% (95%CI: 30.5, 74.2), 60.4% (95%CI: 29.5, 74.4), and 54.3% (95%CI: 28.8, 74.0) without the frailty variable, including frailty as a continuous variable, and including frailty as a categorical variable, respectively.
Conclusions: Using the case positive test negative study design to assess vaccine effectiveness, our measure of frailty was not a significant confounder as inclusion of this measure did not significantly change vaccine effectiveness estimates.

1. Introduction

The paucity of data from randomized clinical trials of influenza vaccine efficacy in older adults has fueled controversy over influenza vaccine effectiveness in this age group. Since all older adults are recommended to receive yearly influenza vaccine, placebo-controlled trials are considered unethical in this age group in the United States. Observational studies of influenza vaccine effectiveness using large administrative databases have often overestimated vaccine effectiveness due to confounding by frailty, which is very difficult to measure using such databases [1,2]. Frailty, in community dwelling older persons, has been shown to be associated with both a decreased likelihood of vaccination and an increased likelihood of hospitalization and/or death, confounding interpretations of vaccine effectiveness [1,2]. Frailty is the conceptualization of a phenotype of poor physiologic reserve and poor resistance to stressors and hence is associated with a high risk of morbidity and death [3]. Frailty was associated with immune senescence, poor response to vaccination and lower influenza vaccine effectiveness when frail individuals were compared to non-frail,

* Corresponding author. Tel.: +1 615 322 2035; fax: +1 615 343 6160.
E-mail address: Keipp.talbot@vanderbilt.edu (H.K. Talbot).

http://dx.doi.org/10.1016/j.vaccine.2016.02.037
0264-410X/

age-matched participants [4]. In previous studies, frailty scales have predicted vaccine response to polysaccharide pneumococcal vaccine better than age, and have a negative correlation with antibody response to influenza vaccination [5].

Orenstein et al. used simulation models to evaluate which observational study designs would perform best in measuring vaccine effectiveness, and found that the case-control study design with influenza laboratory-confirmation, was a preferred design [6]. Specifically, they demonstrated that the test-negative control study design consistently produced a vaccine effectiveness that was closer to the true vaccine effectiveness and that this relationship held true even as the ratio of influenza to non-influenza influenza-like illness (ILI) changed [6]. In this design, cases are persons with acute respiratory illness and laboratory confirmation of influenza, and controls are persons with acute respiratory illness seeking care in the same site as cases, but who tested negative for influenza. Hence, the term case-positive, test-negative control design effectively described this study design.

The test-negative control study design has been extensively used in both the United States [7,8] and in Europe [9–11] to determine influenza vaccine effectiveness in both outpatients and hospitalized patients. One major assumption when using this approach is that cases and controls are similar with respect to comorbidity or other non-vaccine factors associated with influenza illness. In studies that include older adults, there has been an implicit assumption that frailty is not a confounder, since frailty has not been routinely measured in these studies. Therefore, it is important that this assumption be tested and confirmed in the case-positive, test-negative control study design. Using the study populations from previously reported vaccine effectiveness studies [12], we collected additional data from comprehensive chart reviews to calculate a frailty index using a standardized measure of frailty, to determine if the case-positive, test-negative study design adequately controlled for frailty.

2. Methods

Adults hospitalized with respiratory symptoms were prospectively enrolled from November 2006 through May 2012 during influenza seasons to determine rates of hospital admissions and to evaluate vaccine effectiveness in Nashville (Davidson County), TN in one academic and three community hospitals [12]. The 2009–2010 pandemic H1N1 season was excluded as vaccine became available in Nashville after the peak of the epidemic curve. Recruitment occurred two days per week beginning in November until the defined influenza season had arrived at which time recruitment increased to 4–5 days per week. Adults ≥ 50 years of age with one or more of the following admission diagnoses (*International Classification of Diseases*, 9*th Revision* Number): pneumonia (480–486), upper respiratory infection (465), bronchitis (466), influenza (487), acute exacerbation of chronic obstructive pulmonary disease (490 to 492; 496) or asthma (493), viral illness (079.9) [13], dyspnea (786), acute respiratory failure (518.81), pneumonitis due to solids/liquids (507), or fever (780.6) without localizing symptoms or presenting symptoms of: cough, non-localizing fever, shortness of breath, sore throat, nasal congestion or coryza were eligible for enrollment. Patients or their legally authorized representative provided informed consent. For each participating subject, both nasal and throat swab samples were obtained for RT-PCR. Patient questionnaires and chart review data collection instruments were developed to capture CDC-defined high risk conditions, symptoms, and influenza immunizations [12].

A person's exposure was classified as vaccinated if they received an influenza vaccine at least 2 weeks prior to the onset of symptoms, to allow time to mount an immune response. Study nurses obtained vaccine verification from both traditional (primary care physicians) and non-traditional providers (pharmacies, employers, and grocery stores) to determine the duration between vaccination and illness and to verify patient report for both vaccinated and non-vaccinated patients. Patients were excluded if immunization occurred within two weeks of illness onset since some older adults will mount a seroprotective response as early as 7 days [14] and may be inappropriately assigned to the non-vaccinated group.

Influenza testing was performed in a research laboratory where laboratory assistants were unaware of patient's vaccination status. Influenza positive cases were participants with positive RT-PCR on duplicate testing. Influenza negative controls were participants with an acute respiratory illness who tested negative for influenza by RT-PCR and had an adequate sample demonstrated by evidence of housekeeping genes β-actin or RNase P in the sample. To decrease outcome and exposure misclassification, patients with indeterminate laboratory results, unknown vaccination status, or vaccinated within 2 weeks of presentation were excluded from the analyses. For a sensitivity analysis, patients with more than one admission, only the first influenza positive enrollment or the first enrollment, if none were influenza positive, was included.

2.1. Definitions and covariates

Influenza seasons were defined by the total number of weeks that included all influenza positive specimens from enrolled patients each year. Covariates obtained by self-report or chart review included age in years, sex, race (black, non-black), current smoking (in the past 6 months), home oxygen use, underlying medical conditions (diabetes mellitus, chronic heart or kidney disease, cardiovascular disease, asthma, chronic obstructive pulmonary disease, and asplenia (functional or anatomic), immunosuppression (HIV, corticosteroid use, or cancer), timing of admission relative to the onset of influenza season, and the specific influenza season. All covariates were considered as potential confounding variables.

2.2. Frailty

Frailty was calculated using a modified Rockwood Index. The Rockwood Index [15] includes 70 categories of medical problems and functional issues. For each category present, a point is awarded. The total number of points is divided by 70 giving the final index result giving a score of 0 to 1. This index can be effectively shortened if 30 of the original 70 variables are retained [16]. In our hospitals, clinical nurses regularly documented 60 of the original 70 categories. We ascertained these 60 variables in a retrospective chart review (variables listed in the appendix) and hence divided by 60 to obtain the index. Nurses were masked to influenza testing results at time of abstraction. Frailty was categorized into three strata: non frail (Frailty Index ≤ 0.08), pre-frail (Frailty Index > 0.08 to <0.25), and frail (Frailty Index ≥ 0.25) [17].

2.3. Analysis

Characteristics of participants with and without frailty data were compared using Pearson Chi-square test for categorical covariates and Wilcoxon rank sum test for continuous variables. Vaccine effectiveness estimates were calculated using the formula [1-adjusted odds ratio (OR)] × 100% [18]. Adjusted ORs for individual years and all years were estimated by multivariable logistic regression models with L1 penalty on all covariates except vaccination status (LASSO) [19]. The model outcome was influenza positive cases or negative controls and the exposure of interest was vaccination status while adjusting for the other covariates listed above.