



Contents lists available at ScienceDirect

Vaccine

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

Risk stacking of pneumococcal vaccination indications increases mortality in unvaccinated adults with *Streptococcus pneumoniae* infections

Jacob B. Morton^{a,b}, Haley J. Morrill^{a,b}, Kerry L. LaPlante^{a,b,c}, Aisling R. Caffrey^{a,b,d,*}

^a Veterans Affairs Medical Center, Infectious Diseases Research Program and Center of Innovation in Long Term Services and Supports, Providence, RI, United States

^b University of Rhode Island, Department of Pharmacy Practice, College of Pharmacy, Kingston, RI, United States

^c Warren Alpert Medical School of Brown University, Division of Infectious Diseases, Providence, RI, United States

^d Brown University School of Public Health, Providence, RI, United States

ARTICLE INFO

Article history:

Received 26 October 2016

Received in revised form 9 February 2017

Accepted 14 February 2017

Available online xxxxx

Keywords:

Risk stacking

Pneumococcal vaccination

Streptococcus pneumoniae

Mortality

ABSTRACT

Background: Several chronic disease states have been identified as pneumococcal vaccination indications due to their ability to increase pneumococcal disease development and subsequent mortality. However, the risk of mortality according to the number of these disease states present is unknown. We sought to determine the impact of concomitant, multiple risk factors (stacked risks) for pneumococcal disease on 30-day mortality in adults.

Methods: This was a national case-control study of unvaccinated older Veterans (≥ 50 years of age) admitted to Veterans Affairs medical centers from 2002 to 2011 with serious pneumococcal infections (pneumonia, bacteremia, meningitis) based on positive *S. pneumoniae* blood, cerebrospinal fluid, or respiratory cultures, respectively. Cases were those not alive 30 days following culture, while controls were alive. Using logistic regression, we quantified risk of 30-day mortality among patients with stacked risk factors, including age ≥ 65 years, alcohol abuse, chronic heart disease, chronic liver disease, chronic respiratory disease, diabetes mellitus, immunodeficiency, and smoking.

Results: We identified 9730 serious pneumococcal infections, with an overall 30-day mortality rate of 18.6% (1764 cases, 7966 controls). Infection types included pneumonia (62%), bacteremia (26%), and bacteremic pneumonia (11%). Along with eight individual risk factors, we assessed 247 combinations of risk factors. Most cases (85%) and controls (74%) had at least two risk factors. Mortality increased as risks were stacked, up to six risk factors (one: OR 1.5, CI 1.08–2.07; two: OR 2.01, CI 1.47–2.75; three: OR 2.71, CI 1.99–3.69; four: OR 3.27, CI 2.39–4.47; five: OR 3.63, CI 2.60–5.07; six: OR 4.23, CI 2.69–6.65), with each additional risk factor increasing mortality an average of 55% ($\pm 13\%$).

Conclusions: Among adults ≥ 50 years with serious pneumococcal disease, mortality risk increased approximately 55% as vaccination indications present increased. Mortality with six stacked indications was double that of two indications.

Published by Elsevier Ltd.

1. Introduction

Serious *Streptococcus pneumoniae* infections, including pneumonia, bacteremia, and meningitis, are a major cause of morbidity and mortality among older adults [1–3]. Since the 1980s, vaccines to prevent pneumococcal disease have been used on a global scale to mitigate the risks associated with these bacterial infections [4]. The Advisory Committee on Immunization Practices (ACIP)

recommends administration of the pneumococcal vaccination to adults with certain risk factors for pneumococcal disease, including age ≥ 65 years, alcoholism, heart disease and heart failure, chronic respiratory disease, hepatic dysfunction, immunodeficiency, and smoking, in an effort to prevent invasive pneumococcal disease (IPD) and subsequent poor outcomes [3].

Recent research has revealed that the presence of multiple, concomitant risk factors (risk stacking), particularly those conditions identified by ACIP as indications for pneumococcal vaccination, increases the likelihood of developing pneumococcal disease beyond the risk posed by individual risk factors alone [5,6]. As our population ages, it is becoming more common for patients to

* Corresponding author at: University of Rhode Island, 7 Greenhouse Road, Kingston, RI 02881, United States.

E-mail address: Aisling_Caffrey@uri.edu (A.R. Caffrey).

have two or more risk factors [6]. However, the impact of risk stacking on outcomes, namely mortality, of adults who end up developing pneumococcal disease remains unknown. Furthermore, current data on risk stacking are limited in that there is no information regarding the impact of risk stacking “at-risk” conditions (e.g., alcoholism, heart disease, liver disease, cigarette smoking) with “high-risk” conditions (e.g., immunodeficiency) [5–7]. As such, the purpose of this study was to quantify the impact of stacking risk factors for developing pneumococcal disease on 30-day mortality among unvaccinated older adults.

2. Methods

Using national Veterans Health Administration databases, we conducted a nested case-control study of older Veterans (age ≥ 50 years) with positive *S. pneumoniae* blood, cerebrospinal fluid, or respiratory cultures between January 1, 2002 and December 31, 2011. We defined serious pneumococcal infections as culture-positive pneumonia, bacteremia, and meningitis. Cases were those individuals who died from any cause within 30 days of positive culture, and controls were those alive at 30 days. Patients were allowed to be included in the study multiple times if they had multiple positive cultures. Positive cultures from the same patient within a 30-day period were considered the same infection. We utilized national VA datasets, created from electronic medical records and administrative data, to collect patient demographics, health factors, medical history, vaccination history, medication use, clinical outcomes, and culture data. Pneumonia was identified from positive sputum cultures in addition to International Disease Classification, Ninth Revision (ICD-9) diagnosis codes. Bacteremia and meningitis were defined by positive blood and cerebrospinal fluid cultures, respectively. Patients receiving a pneumococcal vaccination within five years of positive culture were excluded. We utilized ICD-9 and procedure codes to identify the presence of disease states within one year of the positive culture date. Medication use within 30 days of positive culture, particularly the use of immunosuppressants (corticosteroids, monoclonal antibodies, antineoplastic agents), was also assessed.

We quantified the impact of individual, as well as combinations of multiple risk factors (stacked risks) for developing pneumococcal disease on 30-day all-cause mortality. Selected risk factors were those that were previously identified as commonly occurring among older Veterans with pneumococcal disease, and that were also indications for pneumococcal vaccination identified by ACIP [1,3]. These included age ≥ 65 years (age), alcohol abuse, chronic heart disease including chronic heart failure (CHD), chronic liver disease (CLD), chronic respiratory disease, including asthma and chronic obstructive pulmonary disease (CRD), diabetes mellitus (DM), immunodeficiency (IC), and smoking.[3] Age was included as a dichotomous variable, as opposed to a continuous variable, to reflect the actual vaccination indication of age ≥ 65 years. Immunodeficiency was defined as the presence of a solid malignancy, hematologic malignancy, HIV, or an AIDS-defining illness within one year of positive culture. Smoking status was defined as documentation of active cigarette smoking, smoking cessation counseling, or receipt of smoking cessation prescription products (varenicline, nicotine replacement products) within one year of positive culture. We determined all possible two, three, four, five, six, seven, and eight indication combinations and defined each combination as a unique variable. Odds ratios (ORs) and 95% confidence interval (CIs) were calculated using logistic regression. Separate models were run for each mutually exclusive combination of vaccine indications. The reference group for each model consisted of those individuals without any of the aforementioned risk factors. This common reference group was selected in order

to quantify the impact of stacking different combinations of indications as compared to those with none of the aforementioned indications for vaccination. Risk factors were deemed significant at a two-tailed *p*-value of 0.05 or less. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Approval by the Institutional Review Board and Research and Development Committee of the Providence Veterans Affairs Medical Center was obtained prior to initiating the study.

3. Results

We identified 9730 serious pneumococcal infections in 9468 unvaccinated individuals, with a 30-day mortality rate of 18.6% (1764 cases and 7966 controls; Table 1). The primary infection types, determined from positive cultures, included pneumonia (cases *n* = 871, 49.4%; controls *n* = 5204, 65.3%), bacteremia (cases *n* = 585, 33.2%; controls *n* = 1969, 24.7%), and bacteremic pneumonia (cases *n* = 305, 17.3%; controls *n* = 755, 9.5%). Meningitis accounted for <1% of infections among cases and among controls.

There were 574 episodes (5.9%; 49 cases, 2.8%, 525 controls, 6.6%) of pneumococcal disease among individuals with none of the eight aforementioned risk factors. In addition to the eight individual risk factors, there were 247 unique combinations of risk factors. There were three individual risk factors (age, CHD, and IC) and 89 stacked risks significantly associated with an increased risk of mortality (Figs. 1 and 2). One risk factor (smoking) was associated with a decreased risk of mortality (OR 0.52, CI 0.31–0.87).

The risk of 30-day mortality among patients with one of any of the eight risk factors was 50% higher compared to those with none of the eight risk factors (OR 1.50 95% CI 1.08–2.07). The risk of 30-day mortality increased as risk factors were stacked, up to six risk factors (one: OR 1.50, CI 1.08–2.07; two: OR 2.01, CI 1.47–2.75; three: OR 2.71, CI 1.99–3.69; four: OR 3.27, CI 2.39–4.47; five: OR 3.63, CI 2.60–5.07; six: OR 4.23, CI 2.69–6.65). The addition of each risk factor increased the risk of 30-day mortality by an average of 55% ($\pm 13\%$; median: 56%, interquartile range 51–60%), with the greatest increase between two and three stacked risk factors (70%). There were no statistically significant odds ratios among patients with seven (OR 1.65, CI 0.36–7.52) or eight (OR 2.14, CI 0.25–18.71) risk factors.

Among the 89 significant stacked risks, age was the most common risk factor present (50/89; 56.2%), followed by IC (49/89,

Table 1
Demographics of unvaccinated older adults with pneumococcal disease.

	Alive at 30 days (<i>n</i> = 7966)	Not alive at 30 days (<i>n</i> = 1764)
Age (years), (SD)	67 (± 11)	71 (± 11) [*]
Gender, Male	7795 (97.5)	1740 (98.6) [*]
Race		
American Indian	98 (1.2)	14 (0.8)
Asian or Pacific Islander	63 (0.8)	11 (0.6)
Black	1054 (13.2)	238 (13.5)
White	6297 (79.0)	1354 (76.8) [*]
Unknown	454 (5.7)	147 (8.3) [*]
Pneumococcal Disease Risk Factors within previous year		
Alcohol abuse	1261 (15.8)	313 (17.7) [*]
Chronic heart disease	1999 (25.1)	611 (34.6) [*]
Chronic heart failure	1324 (16.6)	489 (27.7) [*]
Chronic liver disease, any severity	705 (8.9)	320 (18.1) [*]
Chronic respiratory disease	3609 (45.3)	911 (51.6) [*]
Diabetes mellitus	1709 (21.5)	476 (27.0) [*]
Immunodeficiency	2535 (31.8)	747 (42.3) [*]
Cigarette smoking	3777 (47.4)	674 (38.2) [*]

Note: Results reported as *n* (%) unless otherwise specified.

^{*} *p* < 0.05.

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