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Trends in pneumococcal meningitis hospitalizations following the introduction of the 13-valent pneumococcal conjugate vaccine in the United States

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ABSTRACT

Background: The 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in 2010 in the U.S. and its impact on pneumococcal meningitis (PM) is unknown. We assessed the impact of PCV13 on PM hospitalization rates 4 years after the vaccine was introduced.
Methods: This was a retrospective analysis of the National Inpatient Sample from 2008–2014. Patients with an ICD-9-CM code for PM (320.1) were identified and rates calculated using US Census data as the denominator. Data weights were used to derive national estimates. We examined three time periods: 2008–2009 (late post-PCV7), 2010 (transition year), and 2011–2014 (post-PCV13).
Results: During the study period, there were 10,493 hospitalizations due to PM in the U.S. Overall, PM incidence decreased from 0.62 to 0.38 cases per 100,000 over this time (39% decrease; $P < 0.01$). Among children <2 years, the average annualized PM rate decreased by 45% from 2.19 to 1.20 per 100,000 ($P = 0.10$). Annual PM rates decreased in those aged 18–39 years (0.25–0.15 cases per 100,000; $P = 0.02$) and 40–64 years (0.95–0.54 cases per 100,000; $P = 0.03$). A total of 1016 deaths were due to PM, and the case fatality rate was variable over the study period (8.3%–11.2%; $P = 0.96$).
Conclusion: Following the introduction of PCV13, hospitalization rates for PM decreased significantly with no subsequent improvements in case-fatality rate.

1. Introduction

Streptococcus pneumoniae remains a leading cause of serious illness, causing a high burden of morbidity and mortality in the United States and worldwide [1]. Specifically, pneumococcal meningitis (PM) is associated with a high case fatality rate ranging from 8% to 15% [2–4]. In 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in the U.S., changing the epidemiology of PM [5,6] and substantially decreasing the incidence of PM following its introduction [3,7]. PM rates decreased by 64% and 54% among children aged <2 years and individuals aged 65 years or older, respectively, in the post-PCV7 period [7]. However, pneumococcal infections due to serotypes not found in PCV7, especially serotype 19A, began to slowly increase after 2004 [8–11]. Soon thereafter, serotype 19A accounted for almost half of the isolates found within pneumococcal infections [11].

In 2010, the Advisory Committee on Immunization Practices (ACIP) recommended the replacement of PCV7 with the 13-valent pneumococcal conjugate vaccine (PCV13) [12]. PCV13 contains the seven PCV7 serotypes and six additional serotypes (serotypes 1, 3, 5, 6A, 7F, and 19A). Following the introduction of PCV13, the overall number of invasive pneumococcal disease cases decreased and there were significant reductions in pneumococcal bacteremia and pneumonia [13]. However, early studies on invasive pneumococcal disease following the introduction of PCV13 reported that the number of cases of PM had remained steady [13,14]. The national impact of PCV13 on PM incidence remains unknown. Therefore, the primary objectives of this study were to (i) evaluate trends in incidence of PM, and (ii) describe outcomes from PM in the U.S. using the National Inpatient Sample (NIS).

2. Methods

2.1. Data source

The NIS contains discharge data and is annually developed by the Agency for Healthcare Research and Quality (AHRQ) for the

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Healthcare Cost and Utilization Project (HCUP) [15]. The NIS is the largest publicly available all-payer hospital discharge database in the U.S., containing data on approximately 7 million hospital stays each year. The population is formed from a 20% stratified random sample of all acute care hospitals in the U.S. including nonfederal short-term, general, and specialty hospitals. Up to 2011, the sampling design included community hospitals as the primary sampling units and all discharges from these hospitals. In 2012, the NIS was redesigned as a sample of discharges from all participating hospitals. Due to the inclusion of stratification and weighting variables, users can apply data weights to derive national estimates and trends.

In 2014, the sample comprised 44 States and the District of Columbia, providing data on patient- and hospital-level characteristics from 4411 hospitals. Variables include: demographics (age, race, sex), Elixhauser comorbidities, length of hospital stay, in-hospital deaths, and diagnosis codes defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [16]. Prior to 2009, 15 diagnosis codes were available for each patient; thereafter, it was extended to 25 diagnosis fields. The NIS has been used in several prior infectious diseases epidemiologic studies including methicillin-resistant *Staphylococcus aureus*, pneumonia, and pneumococcal meningitis [3,17,18]. The University at Buffalo institutional review board assessed this study as exempt.

2.2. Study design

This was an ecological study of patients from U.S. hospitals within the NIS database from 2008 to 2014. Patients with a meningitis diagnosis were first identified utilizing the clinical classification code (CCS) 76, where CCS is a diagnosis and procedure categorization scheme based on the ICD-9-CM system. CCS code 76 identified both bacterial and viral meningitis cases and excluded meningitis cases caused by tuberculosis or sexually transmitted diseases. A hospitalization due to PM was defined as a primary or secondary discharge diagnosis code of PM (ICD-9-CM: 320.1). All other patients were classified as non-pneumococcal meningitis (non-PM) cases.

2.3. Data and statistical analysis

The main outcome variables were incidence rates for PM and non-PM, in-hospital mortality (IHM) and hospital length of stay (LOS). First, annual incidence rates of meningitis were determined using PM and non-PM discharges as the numerators and annual population estimates from the U.S. Census Bureau as denominators. Data weights were applied to derive national estimates, and incidence rates were presented as meningitis hospitalizations per 100,000 population. We also evaluated trends in annual meningitis hospitalizations from 2008–2014 according to the following age groups: <2 years, 2–4 years, 5–17 years, 18–39 years, 40–64 years, and ≥65 years. IHM was identified by the discharge status item of the NIS, which represents all-cause IHM. To calculate IHM and case-fatality rates, meningitis deaths were considered patients who died with a diagnosis of meningitis during their hospitalization. Case-fatality rate was calculated using weighted in-hospital meningitis deaths as the numerator and total weighted meningitis hospitalizations as the denominator. We further evaluated trends in case-fatality rate from 2008–2014 by age groups. Hospital LOS was expressed as median values given the positive data skew. To evaluate outcome trends based on the introduction of PCV13 to the U.S., the study was divided into three time periods: 2008–2009 (late post-PCV7), 2010 (transition year), and 2011–2014 (after PCV13 introduction). Simple linear regression was applied to evaluate the changes in incidence and outcomes against baseline values from 2008. Statistical significance was assessed at an *a priori* α level of 0.05 and all analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 446,439 hospitalizations involved meningitis during the study period of which 10,493 had a PM diagnosis. The distribution of the ten most common diagnoses comprising the non-PM group from 2008–2014 are presented in Table 1. Non-specific viral meningitis was the most common diagnosis in the non-PM group followed by unspecified meningitis. The median LOS for PM was 9.3 days, and 1016 (9.7%) patients with PM died during their hospitalization.

3.1. Incidence of pneumococcal and non-pneumococcal meningitis

The incidence of PM hospitalizations decreased from 0.62 cases per 100,000 in 2008 (95% CI 0.59, 0.65) to 0.38 cases per 100,000 in 2014 (95% CI 0.36, 0.40; P trend ≤0.01) (Fig. 1). This represents a 39% decrease in PM hospitalization rates following PCV13 introduction. The average annualized rate of PM hospitalizations in children aged <2 years decreased by 45% from 2.19 to 1.20 per 100,000 from 2008 to 2014 (P trend = 0.10) [Appendix A]. The annual rates in children aged 2–4 years increased from 0.24 to 0.42 per 100,000 during the same time period (P trend = 0.10). Following the introduction of PCV13, PM rates decreased among older age groups with significant decreases in annual rates of PM hospitalizations seen in those aged 18–39 years (0.25–0.15 cases per 100,000; P trend = 0.02) and 40–64 years (0.95–0.54 cases per 100,000; P trend = 0.03) [Appendix B]. In the ≥65 age group, PM hospitalizations decreased by 38% (1.02–0.63 cases per 100,000), though this did not reach statistical significance (P trend = 0.08).

Non-PM hospitalization rates also decreased over the study period from 21.3 cases per 100,000 (95% CI 21.1, 21.5) in 2008 to 18.1 cases per 100,000 (95% CI 17.9, 18.3, P trend ≤0.01) in 2014. The average annualized rate of non-PM among hospitalized children aged <2 years peaked in 2010 at 133 cases per 100,000 and subsequently declined to 101 cases per 100,000 in 2014 (P trend = 0.35) [Appendix A]. A similar trend was also seen in those aged 2–4 years (P trend = 0.08). The rates of non-PM among older adults aged ≥65 years (20.4–19.8 cases per 100,000, P trend = 0.97) and those aged 40–64 years (19.5–18.0 cases per 100,000; P trend = 0.07) were steady from 2008 to 2014 [Appendix B]. Rates of non-PM decreased significantly during this time period in those aged 18–39 years (22.0–17.7 cases per 100,000; P trend ≤0.01).

3.2. Mortality

The overall case fatality rate for PM did not vary significantly during the study period from 8.8% (95% CI 7.5, 10.1) in 2008 to 8.3% (95% CI 9.8, 10.3) in 2014 (P trend = 0.96), peaking in 2013 at 11.2% (95% CI 9.6, 12.8) (Fig. 2). The case fatality rate for PM varied based on age during both pre and post-PCV13 time periods with higher rates in older patients [Appendix C]. For non-PM, the case-fatality ratio remained steady across the study period ranging from 3.5% (95% CI 3.4, 3.6) in 2008 to 3.9% (95% CI 3.7, 4.1) in 2014 (P trend = 0.12).

3.3. Hospital LOS

The median hospital LOS for PM was 9.3 days. In patients with PM, the median LOS remained steady at 9.6 days (95% CI 8.9, 10.3) in 2008 to 9.1 days (95% CI 7.8, 10.3) in 2014 (P trend = 0.23). Over the study period, hospital LOS was longer in patients with PM

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