Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study

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Summary

Background Bacterial meningitis continues to be a substantial cause of morbidity and mortality, but the epidemiological trends after adjunctive dexamethasone recommendations are unknown in the USA. We aimed to describe the changing patterns among the most common bacterial causes in the USA after conjugate vaccination and to assess the association between adjunctive dexamethasone and mortality.

Methods For this population-based observational study, we searched information available from hospital discharges about incidence and inpatient mortality for the most important causes of community and nosocomial bacterial meningitis based on International Classification of Diseases coding across all hospitals in the USA between 1997 and 2010 with the HealthCare Cost Utilization Project (HCUP) network database. We calculated incidences according to US Census Bureau data and used a negative binomial regression model to evaluate the significance of changes over time. We assessed mortality from pneumococcus for three periods 1997–2001 (baseline), 2002–04 (transition years), and 2005–08 (after corticosteroid recommendations were available).

Findings Streptococcus pneumoniae incidence fell from 0.8 per 100 000 people in 1997, to 0.3 per 100 000 people by the end of 2010 (RR 0.3737, 95% CI 0.1825–0.7656). Mortality from pneumococcal meningitis decreased between 2005 (0.049 per 100 000 people) and 2008 (0.024 per 100 000 people) compared with between 2002 (0.073 per 100 000 people) and 2004 (0.063 per 100 000 people; RR 0.5720, 95% CI 0.4303–0.7582). The incidence of Neisseria meningitidis infection decreased from 0.721 per 100 000 people in 1997, to 0.123 per 100 000 people in 2010 (RR 0.1386, 95% CI 0.048–0.4284), which has placed this pathogen close to common bacterial causes of nosocomial meningitis such as staphylococcus and Gram-negative bacteria and to Haemophilus influenzae.

Interpretation S pneumoniae continues to be the leading identifiable cause of bacterial meningitis in the USA, but with a significant decrease in incidence and mortality associated with the introduction of conjugated vaccines and a mortality decrease that is associated with the introduction of recommendations for use of adjunctive dexamethasone for pneumococcal meningitis.

Funding National Center for Research Resources.

Introduction Bacterial meningitis continues to cause substantial neurological morbidity and mortality worldwide. The epidemiology of bacterial meningitis continues to shift with the ongoing introduction of conjugate vaccines for the most common meningital pathogens. Streptococcus pneumoniae remains the leading cause of bacterial meningitis and is associated with a 30% mortality rate. Besides timely antibiotic treatment, only adjunctive dexamethasone decreases pneumococcal meningitis mortality in adults. The addition of adjunctive dexamethasone to antibiotic treatment in bacterial meningitis was endorsed by the Infectious Diseases Society of America (IDSA) guidelines in 2004 and has now become routine practice. Nationwide implementation of adjunctive dexamethasone in the Netherlands was associated with a 20–30% decrease in mortality of cases of pneumococcal meningitis. The effect of adjunctive dexamethasone in the mortality of patients with bacterial meningitis in the USA is unknown. The objective of our study was to assess the temporal association between conjugate vaccine introduction of pneumococcal seven-valent conjugate vaccine (PCV7) in 2000 and the meningococcal conjugate vaccine (MCV4) introduced in 2005, the trends of the most important community-acquired and nosocomial meningital pathogens in the USA from 1997 to 2010, and to explore whether the introduction of adjunctive dexamethasone was associated with a decrease of mortality from pneumococcal meningitis.

Methods Data source We searched information available for all principal diagnoses including bacterial meningitis based on International Classification of Diseases (ICD) 9 coding across the USA during 14 years between 1997 and 2010 with the Agency for Healthcare Research and Quality National Inpatient Sample database (NIS), which is part of the Healthcare Cost and Utilization Project (HCUP) network. The HCUP-network national inpatient sample is the largest publicly available inpatient care database in the USA and is a free online query system that provides access to health statistics and information about hospital
inpatient and emergency department use across the USA since 1988. The database contains data from roughly 8 million hospital stays each year from about 1000 hospitals and is designed to be a representative cross-section of institutions comprising about 20% of the US community hospitals including public hospitals, academic medical centres, and specialty hospitals such as obstetrics and gynaecology, ear, nose, and throat, orthopaedic, and paediatric institutions (appendix). The database is based on statewide data collected by individual state and private data organisations, hospital associations, and the federal government.

Procedures
We obtained information from the NIS database starting from 1997 until 2010 because this was when the greatest number of states was represented (22 in 1997 and 46 states included in 2010; appendix) and statistics on the specific diagnosis of bacterial meningitis per organism were available since 1997. After an initial analysis, we excluded all causes that did not have a specific ICD code 9 or if data were incomplete for the years included in the study. We calculated mortality, incidence, routine discharge, home health care, length of stay, and charges for admission to hospital for bacterial meningitis caused by specified pathogens if this information was available.

Statistical analyses
We calculated all rates by dividing the annual rate of hospitalisation and mortality by the annual population of the USA according to the US Census Bureau with rates expressed as hospitalisation and mortality per 100 000 people. To assess the changes in the meningitis incidence rate, we analysed the differences between the first and the last years of the study with NIS data. We also assessed annual meningitis hospitalisation rates from 1997–2010 by age group (age <1 year, 1–17 years, 18–44 years, 45–64 years, 65–85 years, and >85 years) for pneumococcal and meningococcal meningitis that were adjusted for specific denominators per age group based on US Census Bureau information. To assess the changes in mortality rate from pneumococcus, we divided the available information into three periods: 1997–2001 (baseline), 2002–04 (transition years; because this was the period of time when the first evidence of corticosteroids affecting pneumococcal meningitis mortality appeared in 2002 and when guidelines made this recommendation widely available in 2004), and 2005–08 (after corticosteroid recommendations). To estimate the effect of corticosteroids, we calculated the average weighted pneumococcal mortality rates for the baseline years and for the years after the recommendation of corticosteroids. All analyses were done with SAS 9.3 (SAS Institute) assuming statistical significance at p<0·05. We did a negative binomial regression model to assess the significance of rate changes across time.7,8 Hospitalisation charges were adjusted for the USA inflation index from 1997 until 2010 and also accounted for the number of discharges in the NIS, weighted for national estimates changes from 1997 until 2010 (appendix).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Incidence of admittance to hospital due to bacterial meningitis was available in the NIS for 50 822 cases reported from 1997 to 2010 for five of the most commonly identified bacterial pathogens: S pneumoniae, Neisseria meningitidis, Haemophilus influenzae, staphylococcus species, and Gram-negative bacteria (figure 1). The most common identifiable bacterial pathogen was S pneumoniae, with 21858 cases and an incidence rate of 0·306 per 100 000 people (95% CI 0·250–0·374) by the end of 2010. N meningitidis accounted for 12 833 cases and an incidence rate of 0·123 per 100 000 people (0·082–0·185) in 2010. During these 14 years, 3404 cases of H influenzae meningitis were reported with a rate of 0·058 per 100 000 people (0·036–0·071) by the end of 2010. H influenzae has now been displaced as one of the most common causes of meningitis by other bacterial causes such as staphylococcal species (6031 cases) and Gram-negative bacteria (6696 cases) between 1997 and 2010 with an incidence rate of 0·250–0·374 by the end of 2010.
During the study, we noted a decrease in the number of cases and mortality of patients with pneumococcal meningitis. In the USA, the incidence of pneumococcal meningitis decreased from 1997 to 2010 (figure 1) with an incidence rate in 1997 of 0.81 (95% CI 0.6729–0.997) per 100 000 people and 0.3 (0.25–0.3748) per 100 000 people in 2010 (relative risk [RR] 0.3738, 95% CI 0.1825–0.7656; p<0.0001). This decrease has been consistent in all age groups and was greater in children younger than 1 year (rate 12.4 in 1997 vs 2.06 in 2010), in the age group 1–17 years (rate 0.65 in 1997 vs 0.25 in 2010), and in patients older than 65 years (rate 1.05 in 1997 vs 0.36 in 2010; table 1). Information about in-hospital mortality from pneumococcal meningitis was available with 3401 deaths reported between 1997 and 2008. The in-hospital mortality of pneumococcal meningitis has decreased during the baseline period (1997–2001) and after corticosteroid recommendations (2005–08 (0.073 per 100 000 people) compared with 2002–04 (0.024 per 100 000 people; RR 0.5720; 95% CI 0.401–0.8185; p<0.0001). This decrease has been consistent across all age groups and was greater in children younger than 2 years, and for unvaccinated children between age 24 and 59 months at high risk for pneumococcal infection. *p value obtained based on the comparison between 1997 and 2010.*

Relative risk (RR) and 95% CI of in-hospital mortality (per 100 000 people) for H. influenzae. There has been a decrease in the incidence rates of the least common of the five meningal pathogens of our study. There has been a decrease in the incidence rates of H. influenzae meningitis across the USA (figure 1) with an incidence rate of 0.10 in 1997 and a rate of 0.058 per 100 000 people in 2010 (RR 0.5720; 95% CI 0.401–0.8185; p<0.0022). We were unable to estimate the percent in-hospital mortality data and age distribution based on ICD9 coding for H. influenzae because of an insufficient number of cases during the 14-year study period.

Staphylococcus species and Gram-negative bacteria are more commonly encountered in the nosocomial setting. These pathogens showed a reduction in the incidence rate for Gram-negative organisms with a rate of 0.21 per 100 000 in 1997 and 0.12 per 100 000 in 2010 (RR 0.3891; 95% CI 0.3825–0.9071; p<0.0163). For staphylococcus, we also noted reduction, with a rate of 0.17 per 100 000 in 1997 and 0.11 per 100 000 in 2010 (RR 0.6481; 95% CI 0.45–0.9215; p<0.0157). At the end of the observation period, both pathogens were more common causes of bacterial meningitis than were the community-acquired pathogens N meningitidis and H influenzae (figure 1).
As total incidence decreased during the study period, discharge home rates for pneumococcal meningitis decreased from a rate of 0.45 per 100 000 people (95% CI 0.3678–0.5395) in 1997 to 0.15 (95% CI 0.1201–0.1872) per 100 000 in 2010 (table 1). Patients being discharged on home health care decreased from a rate of 0.11 (95% CI 0.1003–0.1255) in 1997 to 0.07 (95% CI 0.0638–0.0829) per 100 000 (table 1). For meningococcal meningitis, the incidence of the total discharge home rates decreased from 0.48 per 100 000 people (95% CI 0.29–0.82) in 1997 to 0.065 per 100 000 in 2010 (95% CI 0.038–0.1112; table 2). Information about home health discharges for this pathogen was insufficient to calculate estimates.

The median length of stay did not change significantly for all the pathogens and remained roughly 8–11 days for the community-acquired pathogens (S pneumoniae, H influenzae, and N meningitidis) and roughly 14–16 days for the nosocomial pathogens (staphylococcus and Gram-negative bacteria; table 3). After adjustment of charges of hospitalisation on the basis of US inflation calculations, the charges of hospitalisation increased for all the mentioned pathogens with hospitalisation related to Gram-negative bacteria, staphylococcal, and pneumococcal meningitis continuing to have the highest costs.

**Discussion**

The epidemiology of bacterial meningitis in the USA continues to develop as vaccination strategies targeting the most common community-acquired pathogens are introduced. During the study period (1997–2010), the most pivotal changes have been the introduction of the conjugate vaccines for S pneumoniae (Prevnar-7; Wyeth) in 2000 and N meningitidis (Menactra; Aventis Pasteur) in 2005.10 These improved vaccines induce a T-cell-dependent response that improves immune response in infants and leads to a booster response with subsequent doses. The introduction of these vaccines has been associated with a significant reduction in the incidence rate of both S pneumoniae and N meningitidis (p<0.0001; tables 1, 2). This finding is consistent with other studies done in the USA that have shown a reduction in the incidence rate after the introduction of these two vaccines,2,9 and with more recent information from a population observational study done in England with data from the past 50 years suggesting more prominent reductions after the introduction of conjugated vaccines and different catch-up boosters implemented for disease control.11 Furthermore, because the conjugate vaccines might also provide herd immunity by decreasing nasopharyngeal colonisation, we noted that even non-
targeted groups for vaccination had significant decreases in incidence rate (tables 1, 2).

*S. pneumoniae* remains the leading cause of bacterial meningitis in the USA with an incidence rate of 0·3 per 100 000 people in 2010. On the one hand, when comparing this result with other studies done in industrialised countries, similar results were noted in the Netherlands where *S. pneumoniae* was the most common cause with 51% of the cases.9 On the other, our findings were discordant with a recent laboratory based surveillance study done in England and Wales that reported *N. meningitidis* as a more common pathogen with 43% of the cases closely followed by *S. pneumoniae* with 36% of the cases of bacterial meningitis.9 These results need to be interpreted in the context of local epidemiological factors and vaccine schedule implementation policies.

The mortality of pneumococcal meningitis has remained high in the past several decades despite the availability of appropriate antibiotic treatment.26 Besides timely antibiotic treatment, the use of adjunctive dexamethasone in high-income countries has been the only measure associated with a decrease in mortality in pneumococcal meningitis.13 The nationwide implementation of adjunctive dexamethasone in the Netherlands has been associated with an absolute decrease of 10% in the mortality of pneumococcal meningitis.6

In adults, adjuvant corticosteroids significantly reduced mortality associated with bacterial meningitis;19 however, in children, findings of studies show conflicting results with those in the USA showing no benefit.14,15 An epidemiological study that used the same database (NIS) did show a reduction in the mortality from pneumococcal meningitis from 1994 to 2004 with an estimated decrease of 30% in mortality overall 4 years after the introduction of PCV7 (2001–04), which was mainly driven by a decrease in the number of cases in patients younger than 2 years and patients aged 65 years or older.6 The reason for the decrease in mortality in this study remains unclear. On the basis of our analysis, there was a more prominent reduction between 2005 and 2008 after corticosteroids were recommended, which might suggest a contributory effect of this particular intervention on mortality.

The compliance with IDSA recommendation guidelines on administration of steroids for bacterial meningitis is unknown, and although direct causality cannot be established, to our knowledge, this is the first study in the USA at a nationwide level showing a more prominent decrease (figure 2) in the mortality rate of *S. pneumoniae* meningitis temporally associated with the recommendations of corticosteroids based on findings of a 2002 randomised trial1 and the introduction of adjunctive dexamethasone in clinical practice since 2004.4

The incidence of meningococcal meningitis now approaches the incidence of *Staphylococcus* species and Gram-negative bacteria, two of the most common causes of nosocomial meningitis. Vaccination against *N. meningitidis* has been available since the 1970s (monovalent, bivalent, and quadrivalent polysaccharide vaccines) and has been used on only high-risk populations such as military recruits, splenectomised patients, patients with terminal complement deficiencies, and in outbreaks.1

The meningococcal conjugate vaccine A, C, Y, and W135 (MCV4, Menactra) was approved in January, 2005, for use in people aged 11–55 years and recommended to be given to adolescents and first year university students.17 In our study, we recorded the most significant decrease in incidence since 2006 until 2010 in the targeted population for meningococcal vaccination (infants and adolescents; table 2), which suggests a protective effect of the conjugate vaccination, which was first available in 2005 with vaccine recommendations widely established by the US Advisory Committee on Immunization Practices (ACIP) in 2007 and booster policies in 2009.17 One notable finding in our study was the reduction in the total number of cases between 2002 and 2006 even before the implementation of MCV4. This finding is consistent with previous studies documenting decreased incidence even before the availability of conjugated vaccines18–20 and has been difficult to explain but could be related to cyclical nature of disease, antigenic variation, population immunity after peaks of disease noted in the 1990s,21,22 and also environmental factors like smoking, low socioeconomic status, and crowding that have changed over time and might have contributed to decreased incidence.20,22,23

*H. influenzae* is the less common meningeal pathogen including nosocomial causes such as staphylococcal and Gram-negative microorganisms. This result confirms the effect of the *H. influenzae* vaccine that was first introduced in 1990.1 *H. influenzae* accounted for 45% of all cases of community-acquired bacterial meningitis in 1986, with the greatest burden of disease arising in children younger than 5 years and serotype B accounting for 95% of cases.4

After the *H. influenzae* type b vaccine (Hib) was first introduced in children in 1987 and recommended for patients aged 2 months since 1991, the total number of cases per 100 000 of Hib meningitis decreased by 94% from 2·9 to 0·2 between 1986 and 1996.21

The success of the Hib vaccine has not only been based on vaccine-related immunity but also on a subsequent decrease in nasopharyngeal colonisation and herd immunity in unvaccinated participants.24 In low-incidence populations such as in the USA, the persistence of cases despite wide availability of vaccines is probably related to non-Hib serotypes (type f) and non-typeable *H. influenzae* strains.24 Nosocomial meningitis is most commonly caused by staphylococci and by Gram-negative pathogens and usually arises after craniotomy or head trauma, placement of a ventricular or lumbar catheters, or after intrathecal infusions of drugs or anaesthesia.22 Because there are no vaccination strategies against these pathogens, prevention focuses on standardisation of the neurosurgical procedure and perioperative antibiotic prophylaxis.22 Findings of this study show that the
incidence of these nosocomial pathogens have had only a slight decrease from 1997 to 2010 and now their incidence exceeds *N meningitidis* and *H influenzae*. There is not a specific ICD9 code for nosocomial meningitis and this diagnosis could be included in several ICD9 codes (eg, 320.82 meningitis due to Gram-negative bacteria, not elsewhere classified or 320.9 meningitis due to unspecified bacterium), which makes it difficult to appropriately assess the incidence of this common surgical complication. Future epidemiological studies could be done associating diagnostic related groups with specific microbiological causes of bacterial meningitis.

Finally, the discharge home rates did not vary greatly for pneumococcal and meningococcal meningitis with home health discharge rates decreasing over time for pneumococcal meningitis, suggesting more ill patients are being admitted with pneumococcal meningitis. The length of stay was stable for the community-acquired pathogens (*S pneumoniae, H influenzae*, and *N meningitidis*) and for the nosocomial pathogens (staphylococcus and Gram-negative bacteria; table 3) but the cost of admittance to hospital increased substantially for all pathogens after adjustment for inflation. The costs were higher with the nosocomial meningitis pathogens and with pneumococcal meningitis, which is associated with the worst prognosis. Taking into account that among high-risk patients aged 19–64 years the pneumococcal vaccination coverage was only 18.5% in 2010, these findings highlight the importance and effect of enhancing and improving vaccination strategies.

Our study had several advantages. First, the data provided from our study was obtained from a nationwide data sample representing a large proportion of the US inpatient community hospital population, compared with previous reports that used focal surveillance areas. Second, although direct causality cannot be established, to our knowledge, this is the first study in the USA documenting a decrease in the mortality of pneumococcal meningitis temporally associated with conjugate vaccination and the recommendation of adjunctive dexamethasone with a reduction that was more prominent after this recommendation was widely available per guidelines. Third, this is the first study to our knowledge documenting the epidemiology of the most common pathogens of both community-acquired and nosocomial-acquired meningitis in the USA (panel).

Our study also had limitations. First, because the information was available through the NIS database and included measuring disease burden from specific pathogens using ICD coding only, there might be an under-reporting of cases. With the national inpatient sample, it was not possible to establish the incidence of group B streptococci and *Listeria monocytogenes* because ICD9 coding for the specific diagnosis of meningitis due to these pathogens are not available. Second, the direct effect of adjunctive dexamethasone on pneumococcal meningitis mortality cannot be established because of insufficient knowledge about compliance rates with IDSA recommendations of use of steroids in cases of pneumococcal meningitis. Preliminary data in a large academic centre in the USA estimates compliance rates are close to 45% (unpublished). Furthermore, the mortality rates presented in this study are lower than those reported in others. This finding could be explained by the fact that only in-hospital mortality was available accounting for about 75% of all deaths that happened after bacterial meningitis.

In summary, the epidemiology and mortality of bacterial meningitis in the USA continue to change as new conjugate vaccines against *S pneumoniae* and *N meningitidis* are introduced and adjunctive dexamethasone has been incorporated into clinical guidelines. Nosocomial meningitis pathogens such as staphylococci and Gram-negative bacteria are important pathogens associated with longer duration of stay and higher costs. Further epidemiological research will be needed to assess the long-term effectiveness of new vaccination strategies such as PCV13 for invasive pneumococcal disease and to assess the effect and compliance with the use of adjunctive dexamethasone in patients that present with pneumococcal meningitis.

**Contributors**

All authors had full access to all of the data (including statistical reports and tables) in the study. RH had idea of designing the study. RLC collected data, and MJL was in charge of the statistical analysis. RH designed analysis reviewed and gave the final approval of the report.

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**Panel: Research in context**

**Systematic review**

We searched PubMed for reports published in English before April 4, 2014, with the terms “mortality”, “bacterial meningitis”, and “corticosteroids”, to assess the association between steroid treatment and mortality from pneumococcal meningitis in the USA. We identified one multicentre retrospective study done in children, a prospective study that identified patients with pneumococcal meningitis with prospective data from a multicentre pneumococcal surveillance study at eight children’s hospitals, and a report of retrospective data for mortality of bacterial meningitis between 1942 and 1962 in a hospital in Detroit, MI, USA. We also searched PubMed for reports published in English in the USA with the terms “bacterial meningitis”, “United States”, and “epidemiology”, most studies were based on focal surveillance areas. To our knowledge, this is the first study documenting the association between mortality and corticosteroid use and epidemiological trends and morbidity at a nationwide level in the USA.

**Interpretation**

Our findings show a reduction in mortality in cases of pneumococcal meningitis that is temporally associated with conjugate vaccination, being more prominent after the introduction corticosteroids. *Streptococcus pneumoniae* remained the most common cause of bacterial meningitis; in 2010, the incidence of *Neisseria meningitidis* was similar to that of staphylococcal and Gram-negative meningitis. *Haemophilus influenzae* had the lowest incidence throughout the study period. Hospitalisation costs have increased substantially with discharge home percentages remaining relatively stable. These findings emphasise the importance of timely administration of corticosteroids and conjugate vaccination for populations at risk.
Declaration of interests
We declare no competing interests.

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