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Clinical diagnoses and outcomes of 4619 hospitalised cases of laboratory-confirmed invasive meningococcal disease in England: Linkage analysis of multiple national databases

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Summary *Background:* Invasive meningococcal disease (IMD) is rare but remains one of the most feared infectious diseases worldwide. We linked multiple national datasets to describe disease characteristics and outcomes of IMD in England over a five-year period.
Methods: IMD cases confirmed by Public Health England (2007–11) were linked with national hospitalisation records and death registrations. Cases were analysed by age, gender, capsular group, clinical presentation, diagnostic test and outcome. Risk factors for death were assessed using multivariable logistic regression.
Results: Overall, 4619 of 5115 (90.30%) laboratory-confirmed IMD cases were successfully linked to a hospitalisation record. Group B meningococci were responsible for 87.33% (n = 4034) of hospitalised IMD cases, ranging from 93.56% (2294/2452) in <15 year-old to 53.52% (152/284) among ≥65 year-old. Most cases presented with meningitis only (n = 2057, 44.53%), septicaemia only (n = 1725, 37.35%) or both meningitis and septicaemia (n = 389, 8.42%). Over half the cases (2526/4619, 54.69%) were confirmed by PCR only, 22.91% (1058/4619) by culture only and 22.41% (1035/4619) by both. The case fatality rate was 4.46%

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(206/4619; 95% CI, 3.88—5.10%) and varied by age, clinical presentation and capsular group. Children under 15 years who died within 30 days of diagnosis were significantly more likely to have been diagnosed by culture than by PCR alone (OR, 1.56; 95% CI, 1.02—2.39; P = 0.040). *Conclusions:* We identified complex interactions between age, meningococcal capsular group, clinical presentation, diagnostic method and death. The recent introduction of two new meningococcal immunisation programmes in the UK should significantly reduce IMD cases and deaths in the coming years.

Introduction

Invasive meningococcal disease (IMD) remains a significant burden to public health worldwide despite vaccination programmes and awareness campaigns.[1] Like most infectious diseases, IMD follows secular trends, with periods of high and low disease activity as new meningococcal strains are introduced into populations, and others are removed naturally or through effective vaccination programmes.

The United Kingdom has one of the highest incidences of IMD among industrialised countries,[1] and was the first country to introduce the meningococcal group C (MenC) conjugate vaccine into the national immunisation programme in 1999/2000.[2] Consequently, MenC disease is now rare and capsular group B (MenB) is the main cause of IMD, especially in children and young adults.[3] Capsular groups W (MenW) and Y (MenY) usually cause disease in older adults with underlying co-morbidities although, since 2009, the UK has been experiencing a year-on-year increase in MenW disease due to expansion of a single hypervirulent strain belonging to clonal complex 11 (cc11).[4]

The provision of a national reference service for IMD confirmation ensures high case ascertainment for national surveillance in England, but the service does not routinely collect clinical or outcome data.[5] Monitoring the clinical characteristics of IMD cases, and factors associated with disease outcomes, is essential in informing national policy in terms of both investigation and management of suspected IMD cases in the clinical setting, as well as considerations for introduction of preventive measures such as vaccination to protect those who are most vulnerable and monitoring the impact of such interventions in the population.

We recently linked five national IMD datasets to estimate disease burden in England over a five-year period.[5] Within this dataset, we linked almost 5000 confirmed cases with hospitalisation records and national death registrations. The objective of this study was to describe the age distribution, clinical characteristics, meningococcal capsular groups, diagnostic method, outcomes and risk factors for death, among hospitalised patients with laboratory-confirmed IMD in England during 2007—2011, with the aim of identifying potentially modifiable factors that might help reduce the morbidity and mortality associated with this devastating infection.

Methods

The Meningococcal Reference Unit (MRU) at Public Health England (PHE) provides a national service for species confirmation, grouping, typing, subtyping, and antimicrobial susceptibility testing of all invasive *Neisseria meningitidis* isolates. The MRU also provides free non-culture polymerase chain reaction (PCR) confirmation of meningococcal diagnosis for clinical specimens routinely submitted by National Health Service (NHS) hospitals in England and Wales.

In 2014, PHE initiated a data linkage project to estimate the total burden of IMD in England using multiple independent national data sources; details of the data linkage are published elsewhere.[5] Briefly, the five datasets were (i) cases confirmed by PHE MRU; (ii) Hospital Episode Statistics (HES); (iii) electronic notification of confirmed IMD cases by NHS hospitals to PHE via LabBase2; (iv) private laboratory reports of IMD confirmations to PHE; and (v) individual death registration data obtained from the Offices for National Statistics (ONS) for surveillance purposes. Linkage was performed using unique patient NHS Number, surname, forename, date of birth, date of specimen, postcode and reporting laboratory. Clinical diagnosis in HES was cross-checked with sample site of the clinical specimen (e.g. CSF confirmation indicated meningitis). The case fatality rate (CFR) was defined as a fatal outcome within 30 days of a positive laboratory test. On inspection of death certificate information, 10 cases were identified that died after 30 days and were attributed to a complication of IMD. However, there was no difference between the 30-day and the overall case fatality rates therefore for the subsequent analysis 30-day CFR was used.

Data analysis

All analyses were performed using Stata version 14·0 (StataCorp LP, College Station, TX, USA). The dataset was analysed in terms of age, capsular group, clinical presentation, diagnostic test and outcomes of hospitalised IMD cases. The mid-year England population was used to estimate the annual age-specific and gender-specific incidence (www.statistics.gov.uk). For univariate analysis, medians and interquartile range were used to summarise age distribution and compared using the Mann—Whitney U test. All other categorical data were compared using Pearson's chi-squared test. Risk factors for death were assessed using multivariable logistic regression using the following variables: age group, gender, capsular group, diagnostic method, clinical presentation and year of diagnosis. Variables with a P value <0.05 in the model were considered significant.

Clinical presentation of cases was determined by interrogation of ICD-10 codes contained within HES records for each case. All potential codes associated with an admission were analysed, with clinical diagnosis cross