**Clinical characteristics and outcomes of almost 5,000 hospitalised cases of laboratory-confirmed invasive meningococcal disease in England: linkage analysis of multiple national databases**

Chantal Edge,1 Pauline Waight,2 Sonia Ribeiro,2 Mary Ramsay,2 Shamez Ladhani.2,3

1 Speciality Registrar in Public Health, Public Health England, South East Heath Protection Unit, Parkside, Horsham, West Sussex, RH12 1RL, UK

2 Immunisation Department, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK

3 Paediatric Infectious Diseases Research Group, St. George’s University of London, Cranmer Terrace, London SW17 0RE, UK

**Corresponding author:**

Shamez Ladhani, Immunisation Department, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK. Tel: +44 208 327 7155. E-mail: shamez.ladhani@phe.gov.uk

**Key Words:**

meningococcal disease, data linkage, risk factors, vaccine, outcomes

**ABSTRACT**

**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,4,619 of 5,115 (90.30%) laboratory-confirmed IMD cases were successfully linked to a hospitalisation record. Group B meningococci were responsible for 87·33% (n=4,034) of hospitalised IMD cases, ranging from 93·56% (2,294/2,452) in <15 year-olds to 53·52% (152/284) among ≥65 year-olds. Most cases presented with meningitis only (n=2,057, 44·53%), septicaemia only (n=1725, 37·35%) or both meningitis and septicaemia (n=389, 8·42%). Over half the cases (2,526/4,619, 54·69%) were confirmed by PCR only, 22.91% (1,058/4,619) by culture only and 22·41% (1,035/4,619) by both*.* The case fatality rate was 4·46% (206/4,619; 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.

**Funding:** Meningitis Research Foundation ([www.meningitis.org](http://www.meningitis.org)) and Meningitis Now (www.meningitisnow.org)

**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 5,000 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, but 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 2009 England population was used to estimate the annual age-specific and gender-specific incidence ([www.statistics.gov.uk](http://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 was 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. Variable 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 checked with specimen site. Presentation was analysed in terms of meningitis only, septicaemia only, meningitis and septicaemia, or other IMD. For other presentations, cases must have an ‘other’ IMD code (meningococcal heart disease/ carditis/ endocarditis/ myocarditis/ pericarditis, other meningococcal infections, meningococcal arthritis) and be negative for meningitis and septicaemia. See appendix 1 for details of ICD-10 codes used to code clinical presentation,

## Ethics Statement

# PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases (<http://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made>). For meningococcal disease, PHE has specific permissions to link national datasets using available identifiers.

# RESULTS

4,619 of 5,115 (90%) IMD cases confirmed by the Meningococcal Reference Unit linked to hospitalised cases in the HES database, and were coded as A39\* “meningococcal disease” (n=3,935, 76·93%%), G00\* “bacterial meningo-encephalitis” (n=340, 6·65%) or another infection-related ICD-10 code (n=840, 16·42%). Most of the remaining unmatched, MRU-confirmed cases did not have sufficient identifiers for successful linkage or died prior to hospital admission. IMD cases declined over the five-year period, but the age and gender distribution, capsular group and CFR were similar; therefore, all cases were combined for further analysis. The mean annual incidence for hospitalised IMD cases was 1·77 (95% CI, 1·72-1·82) per 100,000 population (Figure 1), with 2,507/4,619 cases (54·28%) diagnosed in children aged <5 years, including 1,115/4,619 cases (24·14%) in infants (<1 year-olds) (Figure 2). MenB was responsible for the majority of cases (n=4,034, 87·33%), followed by MenY (n=242, 5·24%), MenW (n=105, 2·27%), MenC (n=87, 1·88%), and other capsular groups (n=151, 3·27%). MenB was responsible for 93·56% (2,294/2,452) of cases in <15 year-olds and 53·52% (152/284) in ≥65 year-olds (Figure 2).

**Clinical Presentation**

Meningitis only (n=2,057, 44·53%) and septicaemia only (n=1,725, 37·35%) accounted for the majority of clinical presentations, while presentation with both meningitis and septicaemia was less common (n=389, 8·42%). Clinical presentation varied with age (Figure 3a) and capsular group (Table 1).In infants (<1 year-olds), the prevalence of meningitis only and septicaemia only was similar, while septicaemia predominated in toddlers and older children, and meningitis accounted for more than half the adult cases. In older adults, other clinical presentations, particularly pneumonia, predominated.

When assessed by capsular group (**Table 1**), clinical presentation among MenB cases varied with age, with septicaemia only being more common amongst 1-14 year-olds, and meningitis predominating in the other age groups. MenB was also less likely to present with other IMD presentations compared to other capsular groups (RR 0.40; 95%CI, 0.33-0.49; P<0.0001).

**Diagnostic method**

Diagnostic method was available for all 4,619 cases. More than half (2,526/4,619, 54·69%) were confirmed by PCR only, 22·91% (1,058/4,619) by culture only and 22·41% (1,035/4,619) by both culture and PCR(Figure 3b). In a multivariable logistic regression model, confirmation by any culture was independently associated with age, capsular group and clinical presentation (Table 2).

**Case Fatality**

The CFR was 4·46% (206/4,619; 95% CI, 3·88-5·10%) and varied by age, clinical presentation and capsular group (**Table 3**). There were an additional ten deaths after 30 days that were attributed to a complication of IMD on the death certificate, giving an overall CFR of 4·68% (216/4,619, 95% CI, 4·09-5·33%). CFR was low for all age groups except older adults (**Table 3**).

CFR was highest in those presenting with both meningitis and septicaemia, followed by septicaemia only (**Table 3**). CFR was also higher for MenY and MenW compared with MenB cases, although confidence intervals are wide due to small numbers of cases and deaths. When assessed by age-group, IMD deaths in <5 year-olds were mainly due to MenB, with the highest CFR among those presenting with septicaemia. Among 5-24 year-olds, a higher CFR was observed for MenACWY capsular groups than MenB, although differences were non-significant. The highest CFR was among ≥65 year-olds, especially those with MenW disease and those presenting with meningitis and septicaemia, or septicaemia only (Supplementary Table 1).

There was significant interaction between age and capsular group. Therefore, two logistic regression models were developed, one for MenB and another for MenACWY cases. Compared with infants, MenB-associated CFR was significantly higher among adolescents (15-24yrs), adults aged 45-65yrs and older adults (≥65 year-olds)*.* Those presenting with meningitis and septicaemia (389/4,619 [8·42%] cases, 39/389 [10·03%] died) had a 5·3-fold age-adjusted risk of death compared to those presenting with meningitis only (2,057/4,619 [44·53%] cases, 45/2,057 [2·19%] died). Those presenting with septicaemia only (1,725/4,619 [37·34%] cases, 114/1,725 [6·61%] died) had a 4·4-fold higher age-adjusted risk of death than meningitis only cases (Table 4a).

Among MenACWY cases, a higher risk of death was observed among those presenting with meningitis and septicaemia, particularly among adolescents and those aged ≥65 years. A lower risk of death was observed for those with other clinical presentations (Table 4b). In adolescents, after adjusting for age and clinical presentation, the relative risk of death after meningococcal A, C, W or Y disease (8/74 died, 10·81%) compared to MenB disease (29/587 died, 4·94%) was 2·32 (95% CI, 1·00-5·38; P=0·051).

Since both PCR-testing and culture was likely to be performed more routinely in children because of more typical clinical presentations with meningitis and septicaemia, a logistic regression model was developed for <15 year-olds and included age, gender, surveillance year, clinical presentation, capsular group and diagnostic test as the independent variables (Table 4c). In this model, those who died within 30 days were 1·56-fold (95% CI, 1·02-2·39; P=0·040) more likely to have a positive culture result (with or without PCR-confirmation), than diagnosis by PCR alone.

## Exploratory analysis: severe complications associated with CFR

The HES dataset was further explored for severe complications of IMD and association with fatal outcomes using pre-defined ICD-10 codes (Supplementary Table 2). Higher CFRs were seen with most of the complications analysed, including acute kidney disease, hypotension, pulmonary oedema, intravascular coagulation, seizures and cardiac arrest.

# DISCUSSION

Through linkage of multiple national data sources, we have analysed by far the largest cohort of laboratory-confirmed, hospitalised IMD cases in an industrialised country over a relatively short surveillance period of five years. Our results confirm the significant morbidity and mortality associated with this devastating disease, despite declining incidence in recent years. MenB was responsible for the majority of confirmed cases, especially in children and young adults. After adjusting for age, meningitis only and septicaemia only were equally responsible for most clinical presentations among MenB and MenACWY cases, with the highest CFR observed among those with both presentations together. CFR was low across all age groups except ≥65 year-olds and those presenting with MenACWY disease compared to MenB disease. In children, those who died were significantly more likely to have a positive culture result than confirmation by PCR only.

Linkage of large datasets is increasingly becoming recognised as a cost-efficient tool for surveillance of infectious diseases and monitoring trends. Despite the complexities of linking national data sources that were not designed for integration, the increased recording of unique NHS numbers for individual patients in recent years has facilitated linkage of healthcare records. By linking multiple national datasets, we were able to demonstrate that the MRU, which is the currently the focal point for IMD surveillance in England, captured >95% of laboratory-confirmed cases nationally,5 consistent with our previous reports demonstrating high case ascertainment highlighting the advantage of having a single national reference centre.6 We also linked 90% of MRU-confirmed cases to a hospitalisation record, equivalent to an average annual incidence of laboratory-confirmed, hospitalised IMD cases of 1·77/100,000, compared to 2·0/100,000 for all MRU-confirmed cases for the same 5-year period.3 The remaining MRU-confirmed cases either did not have sufficient identifiers for linkage or were not hospitalised, most likely because they died outside the hospital setting.5 Such rapidly fatal cases not only demonstrate the aggressive nature of the infection, but also highlight the importance of prevention through vaccination. On the other hand, understanding the characteristics of hospitalised IMD cases provides an opportunity to identify potentially modifiable risk factors to define priorities for interventions to improve outcomes.

**Clinical disease**

Our analysis reveals a complex interaction between age, capsular group, clinical presentation and fatal outcome. In children, MenB dominated among IMD cases and meningitis was more prevalent in infants, while septicaemia was more common in toddlers and older children. In Liverpool, among >1,000 children admitted to a single hospital over a 31-year period, 53% presented with meningitis and septicaemia, 30% with septicaemia alone and 16% with meningitis only, while only two children (0·17%) had other clinical presentations.7 In our cohort, dual presentation with meningitis and septicaemia accounted for only 9·18%of clinical presentations in <15 year-olds. Possible reasons for differences in clinical presentations include changing epidemiology (e.g. MenC disease is associated with septicaemia, and accounted for almost half the IMD cases in the late 1990’s but is currently rare in the UK), earlier recognition and treatment of suspected IMD cases, and changing clinical practices, such as fewer lumbar punctures being performed in recent years.8,9

In adults, it is noteworthy that 65% of 15-64 year-olds presented with meningitis only. Atypical clinical presentations, including pneumonia and septic arthritis, mainly occurred among ≥65 year-olds, usually due to the less prevalent capsular groups, such as MenW and MenY. The association between these capsular groups and atypical clinical presentations, especially in older adults, is well-reported.10,11

In terms of IMD, the development of septicaemia is often associated with complications and high CFRs and therefore there would be rationale for analysing cases as those with septicaemia in comparison to those without. However, given the higher CFR we found associated with dual presentation, the decision was made to keep clinical presentation grouped into the four aforementioned categories. It is plausible that analysis of septicaemia versus no septicaemia cases may yield further results. In addition, the HES database was used to classify clinical diagnosis of cases, therefore reliant on the diagnosis made by the clinician caring for the patient. This is a potential source of variability that could not be addressed in this analysis and highlights a need to validate this data source against clinical records.

**Case fatality**

Overall, CFR was associated with age, capsular group, clinical presentation and diagnostic method. The significantly higher CFR in ≥65 year-olds with MenB or MenACWY was independent of clinical presentation and is most likely explained by the high prevalence of underlying comorbidities.10,11 In the logistic regression model, clinical presentation with meningitis and septicaemia together, was independently associated with the highest risk of death among MenB and MenACWY cases, with septicaemia only also a significant risk factors in MenB cases. The higher CFR associated with septicaemia compared to meningitis is well-reported, although most of the published studies were undertaken prior to MenC vaccine introduction.7,12 The UK MenC outbreak in the 1990s was particularly associated with septicaemia presentation, with an aggressive clinical course and severe clinical outcomes, including death.13 The higher CFR in those with both septicaemia and meningitis is plausible since it indicates loss of systemic control of infection which can lead to end-organ failure.

The highest burden of MenB disease was observed in infants (26%) and toddlers (31%), who accounted for 57% of all MenB cases and 46% of all MenB deaths. This age-group is particularly susceptible to serious invasive infections by encapsulated bacteria, including meningococci.14 In September 2015, the UK was the first country to introduce the novel, multi-component protein-based MenB vaccine (4CMenB, Bexsero®, GSK Biologicals) into the national infant immunisation programme.15 This vaccine is estimated to protect against 73-88% of circulating MenB strains in the UK and should also protect against other meningococcal capsular groups that share the same vaccine antigens.15 The programme, therefore, has the potential to significantly reduce the burden of IMD – including deaths - in infants and toddlers in the coming years

The age distribution of MenACWY cases was different to MenB cases, with few cases in infants and a small peak associated with a significantly higher CFR among 15-24 year-olds, followed by increasing number of cases diagnosed from 45 years of age. In adolescents, several clinical and social risk factors for IMD have been identified 16, but they do not explain the higher CFR in MenACWY compared to MenB cases. Of particular concern in the UK is the recent emergence of an endemic hypervirulent strain of MenW belonging to ST-11 clonal complex,11 which led to the emergency introduction of an adolescent MenACWY conjugate vaccine programme in August 2015, with a plan to immunise all 14-18 year-olds over two years.4 This programme should provide vaccinated adolescents with direct protection against invasive disease and, because the MenACWY conjugate vaccine also prevents asymptomatic nasopharyngeal carriage,17should also provide indirect (herd) protection to unvaccinated children and adults in the coming years.18

**The role of PCR-testing**

Our study highlighted the importance of a national PCR testing service for confirming the diagnosis of IMD. Confirmation by culture was more likely at the extremes of age, with septicaemia presentations (with or without meningitis) where a higher bacterial load in the blood would be expected and with capsular groups that were more likely to have atypical clinical presentations (MenW, MenY). In children, culture-confirmed cases had a significantly higher CFR compared to by PCR–only. Two previous studies have reported more severe clinical disease and higher CFR associated with increasing meningococcal blood DNA load, especially in those presenting with septicaemia, but neither study assessed these associations in relation to culture positivity.12,19 Culture positivity requires viable bacteria and a higher bacterial load, compared to PCR confirmation, which can detect very small quantities of meningococcal DNA. 20,21 Therefore, culture positivity could indicate uncontrolled bacterial replication, resulting in more severe disease and poor outcomes. However, it is also possible that meningococcal strains identified through culture may be more virulent than those confirmed by PCR only.22 This merits further investigation.

 It is possible that pre-hospital antibiotic treatment could have influenced the results of culture/PCR confirmation. Equally, results may have been affected by the source of the sterile biological material used for testing. This information was not routinely collected as part of the national surveillance dataset, and as such unavailable for analysis, although as a consequence of this linkage work patient sample site data will soon be collected routinely.

**Severe complications**

The exploratory analysis also identified a number of severe complications associated with CFR. It is possible that individuals with more severe clinical outcomes, including death, may have more complete recording on HES compared to those who survived. However, the identified risk factors are biologically plausible and many of the risk factors have been reported in other clinical studies. 23,24 Their presence in any patient with suspected IMD should alert the clinician to a potentially severe course of illness.

# Conclusions

Whilst acknowledging the limitations of linking datasets that were not designed for integration, the large number of laboratory-confirmed cases with clinical and outcome data has allowed us to study, in detail, the complex interactions between age, meningococcal capsular group, clinical presentation, diagnostic method and outcomes. The exclusion of a small number of unlinked cases, laboratory-unconfirmed cases and those that died outside the hospital setting is unlikely to affect our overall findings. We also recognise that the information coded in HES may be limited compared to clinical studies, but the large number of cases over a relatively short period provides true insight into disease characteristics at a population level. Our results provide age- and capsular-group specific data on clinical presentations, risk factors and outcomes of IMD and suggest that the recent introduction of the infant MenB and adolescent MenACWY immunisation programmes could have a significant impact in reducing meningococcal disease and deaths in the UK in the coming years.

**AUTHOR CONTRIBUTIONS**

SNL and MER developed the concept and design of the study. PAW linked the multiple datasets and developed the final database. SR manages the PHE meningococcal database. CE analysed and wrote the first draft of the manuscript. All authors contributed to interpreting the results and revising the manuscript. All authors read and approved the final version of the manuscript.

**Acknowledgements**

The authors thank Professor. Martin Mckee for providing project supervision and assistance during the data analysis, which was performed at the London School of Hygiene and Tropical Medicine.

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**Figure 1.** Mean annual age-specific and gender-specific incidence of hospitalised cases of laboratory-confirmed IMD in England during 2007-11. The numbers above the bars denote the incidence for that age group and gender

**Figure 2**. Number (a) and Proportion (b) of IMD cases caused by different capsular groups in different age groups among hospitalised cases with laboratory-confirmed IMD in England during 2007-11.

**Figure 3**. Prevalence of (a) **clinical presentation** and (b) **diagnostic confirmation** by age group among hospitalised cases with laboratory-confirmed IMD in England during 2007-11

**Table 1. Number (percentages) of different clinical presentations by age group and capsular group among hospitalised IMD cases confirmed in England during 2007-11.**

|  |  |  |  |
| --- | --- | --- | --- |
| Age group | Capsular group | Clinical presentation | Total number of IMD cases |
| **Meningitis only cases/ total IMD cases (%)** | **Septicaemia only cases / total IMD cases (%)** | **Meningitis & septicaemia/ total IMD cases (%)** | **Other presentations / total IMD cases (%)** |
| Total |  | 2057/4619 (45%) | 1725/4619(37%) | 389/4619 (8%) | 448/4619 (10%) | 4619 |
| All ages | MenB | 1807/4034(45%) | 1554/4034(39%) | 344/4034 (9%) | 329/4034 (8%) | 4034 |
| MenC | 33/87(38%) | 35/87(40%) | 8/87 (9%) | 11/87 (13%) | 87 |
| MenW | 47/105(45%) | 28/105(27%) | 6/105  (6%) | 24/105 (23%) | 105 |
| MenY | 91/242(38%) | 69/242(29%) | 27/242 (11%) | 55/242 (23%) | 242 |
| Other | 79/151(52%) | 39/151 (26%) | 4/151 (3%) | 29/151 (19%) | 151 |
| <1 | MenB | 500/1043(48%) | 370/1043(35%) | 107/1043(10%) | 66/1043 (6%) | 1043 |
| MenC | 5/6 (83%) | 1/6(17%) | 0 | 0 | 6 |
| MenW | 10/17(59%) | 6/17(35%) | 0 | 1/17 (6%) | 17 |
| MenY | 5/15(33%) | 2/15(13%) | 5/15 (33%) | 3/15 (20%) | 15 |
| Other | 18/34(53%) | 7/34(21%) | 0 | 9/34 (26%) | 34 |
| 1-4 | MenB | 366/1306(28%) | 714/1306(55%) | 100/1306 (8%) | 126/1251 (10%) | 1251 |
| MenC | 3/12(25%) | 6/12(50%) | 1/12 (8%) | 2/12 (17%) | 12 |
| MenW | 7/18 (39%) | 6/18(33%) | 3/18 (17%) | 2/18 (11%) | 18 |
| MenY | 2/9(22%) | 2/9(22%) | 2/9 (22%) | 3/9 (33%) | 9 |
| Other | 18/47 (38%) | 20/47 (43%) | 0 | 9/47 (19%) | 47 |
| 5-14 | MenB | 132/434(30%) | 194/434(45%) | 51/434 (12%) | 57/434 (13%) | 434 |
| MenC | 2/12(17%) | 6/12 (50%) | 2/12 (17%) | 2/12 (17%) | 12 |
| MenW | 3/7(43%) | 3/7 (43%) | 0 | 1/7 (14%) | 7 |
| MenY | 7/18(39%) | 5/18 (28%) | 3/18 (17%) | 3/18 (17%) | 18 |
| Other | 11/19(58%) | 4/19 (21%) | 1/19 (5%) | 3/19 (16%) | 19 |
| 15-24 | MenB | 415/587 (71%) | 109/587 (19%) | 36/587 (6%) | 27/587 (5%) | 587 |
| MenC | 5/9(56%) | 3/9 (33%) | 0 | 1/9 (11%) | 9 |
| MenW | 9/14(64%) | 2/14 (14%) | 0 | 3/14 (21%) | 14 |
| MenY | 25/51(49%) | 12/51 (24%) | 7/51 (14%) | 7/51 (14%) | 51 |
| Other | 16/23(70%) | 2/23 (9%) | 2/23 (9%) | 3/23 (13%) | 23 |
| 25-44 | MenB | 142/224(63%) | 50/224(22%) | 16/224 (7%) | 16/224 (7%) | 224 |
| MenC | 5/16(31%) | 7/16 (44%) | 2/16 (13%) | 2/16 (13% ) | 16 |
| MenW | ¾(75%) | 0 | ¼ (25%) | 0 | 4 |
| MenY | 10/14(71%) | 2/14 (14%) | 1/14(7%) | 1/14 (7%) | 14 |
| Other | 5/9(56%) | 1/9 (11%) | 1/9 (11%) | 2/9 (22%) | 9 |
| 45-64 | MenB | 182/288(63%) | 72/288 (25%) | 19/288 (7%) | 15/288 (5%) | 288 |
| MenC | 11/23(48%) | 8/23 (35%) | 2/23 (9%) | 2/23 (9%) | 23 |
| MenW | 10/20(50%) | 3/20 (15%) | 0 | 7/20 (35%) | 20 |
| MenY | 23/41(56%) | 10/41 (24%) | 3/41 (7%) | 5/41 (12%) | 41 |
| Other | 10/15(67%) | 3/15 (20%) | 0 | 2/15 (13%) | 15 |
| 65+ | MenB | 70/152 (46%) | 45/152 (30%) | 15/152 (10%) | 22/152 (14%) | 152 |
| MenC | 2/9(22%) | 4/9 (44%) | 1/9 (11%) | 2/9 (22%) | 9 |
| MenW | 5/25(20%) | 8/25 (32%) | 2/25 (8%) | 10/25 (40%) | 25 |
| MenY | 19/94(20%) | 36/94 (38%) | 6/94 (6%) | 33/94 (35%) | 94 |
| Other | ¼(25%) | 2/4(50%) | 0 | 1/4 (25%) | 4 |

**Table 2-** Factors associated with IMD confirmation using any culture (n=2093), as assessed using multivariate analysis. The logistic regression model included variables for; age group, capsular group, clinical presentation, year and sex

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Number of culture-confirmed cases | Odds ratio | 95%CI | P value |
| Capsular group | MenB | 1749 | REF |  |  |
| MenW | 80 | 3·51 | 2·21-5·60 | <0·001 |
| MenY | 197 | 4·29 | 3·04-6·07 | <0·001 |
| Other | 18 | 0·18 | 0·11-0·29 | <0·001 |
| Age | <1 y | 576 | REF |  |  |
| 1-4 y | 547 | 0·60 | 0·51-0·70 | <0·001 |
| 5-14 y | 177 | 0·51 | 0·41-0·63 | <0·001 |
| 15-24 y | 259 | 0·55 | 0·46-0·67 | <0·001 |
| 25-44 y | 109 | 0·65 | 0·49-0·85 | 0·002 |
| 65 y | 224 | 2·37 | 1·72-3·25 | <0·001 |
| Presentation | Meningitis only | 860 | REF |  |  |
| Septicaemia only | 821 | 1·32 | 1·15-1·50 | <0·001 |
| Meningitis and Septicaemia | 199 | 1·38 | 1·10-1·72 | 0·005 |

**Table 3:** Summary of univariate analysis for risk factors associated with death due to meningococcal disease in England during 2007-2011. The median age of fatal cases (17·99; IQR,1·77-63·76 years) was significantly higher than that of survivors (3·74; IQR, 1·03-19·47 years; P<0.0001)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  *Variable* | Total cases | Fatal casesN (CFR, %) | SurvivorsN | P value\* |
| Age group (years) | <1 | 1115 | 37(3·3%) | 1078 | *<0·001* |
| 1-4  | 1392 | 42(3·0%) | 1350 |
| 5-14 | 490 | 11(2·2%) | 479 |
| 15-24 | 684 | 37(5·4%) | 647 |
| 25-44 | 267 | 10(3·7%) | 257 |
| 45-64 | 387 | 18(4·7%) | 369 |
| 65+ | 284 | 51 (18·0%) | 233 |
| Capsular group | MenB | 4034 | 168(4·2%) | 3866 | *<0·001* |
| MenC | 87 | 3(3·4%) | 84 |
| MenW | 105 | 10(9·5%) | 95 |
| MenY | 242 | 24(9·9%) | 218 |
| Other | 151 | 1(0·7%) | 150 |
| Diagnostic confirmation method | Culture & PCR | 1035 | 52(5·0%) | 983 | *<0·001* |
| Culture only | 1058 | 73(6·9%) | 985 |
| PCR only | 2526 | 81(3·2%) | 2445 |
| Any culture vs no culture | 20932526 | 125(6·0%), 81(3.2%) | 19682445 | *<0·001* |
| Any PCR vs no PCR | 25611058 | 133(3·7%)73(6·9%) | 3428985 | *<0·001* |
| Clinical presentation | Meningitis only | 2057 | 45(2·2%) | 2012 | *<0·001* |
| Septicaemia only | 1725 | 114(6·6%) | 1611 |
| Meningitis and septicaemia | 389 | 39(10·0%) | 350 |
| Other IMD | 448 | 8(1·8%) | 440 |

CFR, case fatality rate

*\* Categorical data was compared using Pearson’s X2 test statistic*

Table 4. Factors significantly associated with death (p<0·05) among (a) MenB hospitalised, laboratory-confirmed cases, (b) MenACWY hospitalised, laboratory-confirmed cases, and (c) childhood, hospitalised, laboratory-confirmed cases (<15year-olds) in England during 2007-11. The logistic regression models included variables for: age group, capsular group, diagnostic methods, clinical presentation, year and sex

|  |  |  |  |
| --- | --- | --- | --- |
| (a) Logistic Regression for MenB deaths | Odds ratio | 95%CI | P value |
| Clinical presentation | Meningitis only  | REF |  |  |
| Septicaemia only | 4·44 | 3·01-6·53 | <0·001 |
| Meningitis and septicaemia | 5·29 | 3·18-8·80 | <0·001 |
| Age group | <1yrs | REF |  |  |
| 15-24yrs | 2·49 | 1·60-3·88 | <0·001 |
| 45-64yrs | 2·33 | 1·32-4·13 | 0·004 |
| 65+yrs | 9·51 | 5·90-15·33 | <0·001 |

|  |  |  |  |
| --- | --- | --- | --- |
| (b) Logistic Regression for MenACWY deaths | Odds ratio | 95%CI | P value |
| Clinical presentation | Meningitis only  | REF |  |  |
| Meningitis and septicaemia | 6·06 | 2·44-15·02 | <0·001 |
| Other | 0·26 | 0·07-0·91 | 0·036 |
| Age group | <1yrs | REF |  |  |
| 15-24yrs | 4·22 | 1·45-12·26 | 0·008 |
| 65+yrs | 9·09 | 3·60-22·95 | <0·001 |

|  |  |  |  |
| --- | --- | --- | --- |
| (c) Logistic Regression for childhood deaths (<15 years)  | Odds ratio | 95%CI | P value |
| Clinical presentation | Meningitis only  | REF |  |  |
| Septicaemia only | 9·10 | 4·35-19·02 | <0·001 |
| Meningitis and septicaemia  | 9·73 | 4·08-23·19 | <0·001 |
| Diagnostic method | PCR only | REF |  |  |
| Any culture | 1·56 | 1·02-2·39 | 0·040 |

**Supplementary Table 1**· Cases, deaths and case fatality ratio (CFR) by age and capsular group for hospitalised IMD cases in England during 2007-11. Absolute No refers to the number of deaths divided by the total number of cases in that group. CFR, case fatality rate. 95% CI, 95% confidence interval for the case fatality rat

|  |  |  |  |
| --- | --- | --- | --- |
| Age and Capsular group |  | Case Fatality Ratio (CFR) | Overall CFR |
|  | **Meningitis only** | **Septicaemia only** | **Meningitis and septicaemia** | **Other IMD** |
| All agesAll caps | Absolute no0CFR (95% CI) | 45/2057 2·19 (1·60-2·92) | 114/1725 6·61 (5·48-7·89) | 39/389 10·03 (7·23-13·45) | 8/448 1·79 (0·77-3·49) | 206/4619 4·46 (3·88-5·10) |
| All ages | MenB | Absolute no0CFR (95% CI) | 37/18072·05 (1·46-2·81) | 98/15546·31 (5·15-7·63) | 28/344 8·14 (5·48-11·55) | 3/3290·91 (0·19-2·64) | 168/4034 4·16 (3·57-4·83) |
| MenC | Absolute no0CFR (95% CI) | 00 | 2/35 5·71 (0·70-19·16) | 1/8 12·50 (0·32-52·65) | 000 | 3/87 3·45(0·72-9·75) |
| MenW | Absolute no0CFR (95% CI) | 3/44 6·82 (1·43-18·66) | 4/2814·29 (4·03-32·67) | 2/6 33·33 (4·33-77·72) | 1/24 4·17 (0·11-21·12) | 10/105 9·52(4·66-16·82) |
| MenY | Absolute no0CFR (95% CI) | 5/91 5·49 (1·81-12·36) | 9/69 13·04(6·14-23·32) | 8/27 29·63 (13·75-50·18) | 2/55 3·64 (0·44-12·53) | 24/242 9·92(6·46-14·40) |
| Other | Absolute no0CFR (95% CI) | 000 | 1/39 2·56 (0·06-13·48) | 000 | 000 | 1/151 0·66(0·02-3·63) |
| ACWY | Absolute no0CFR (95% CI) | 8/172 4·65 (2·03-8·99) | 15/133 11·28 (6·45-17·92) | 11/41 26·83(14·22-42·94) | 3/91 3·30 (0·69-9·33) | 37/437 8·47(6·03-11·48) |
| <1 y | MenB | Absolute no0CFR (95% CI) | 000 | 31/370 8·38(5·76-11·68) | 5/107 4·67(1·53-10·57) | 1/66 1·27(0·03-6·85) | 37/1043 3·55(2·51-4·86) |
| MenC | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| MenW | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| MenY | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| Other | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| ACWY | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| 1-4 y | MenB | Absolute no0CFR (95% CI) | 2/366 0·55 (0·07-1·96) | 31/714 4·34 (2·67-6·11) | 7/100 7·00 (2·86-13·89) | 1/126 0·79 (0·02-4·34) | 41/1265 3·24(2·33-4·37) |
| MenC | Absolute no0CFR (95% CI) | 000 | 1/6 16·67 (0·42-64·12) | 000 | 000 | 1/12 8·33(0·21-38·48 |
| MenW | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| MenY | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| Other | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| ACWY | Absolute no0CFR (95% CI) | 000 | 1/14 7·14(0·18-33·87) | 000 | 000 | 1/40 2·50(0·06-13·16) |
| 5-14 y | MenB | Absolute no0CFR (95% CI) | 3/132 2·27 (0·47-6·50) | 3/194 1·55 (0·32-4·45) | 2/51 3·92(0·48-13·46) | 000 | 8/434 1·84(0·80-3·60) |
| MenC | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| MenW | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| MenY | Absolute no0CFR (95% CI) | 1/7 14·29(0·36-57·87) | 1/5 20·00 (0·51-71·64) | 1/3 33·33(0·84-90·57) | 000 | 3/18 16·67(3·58-41·42) |
| Other | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| ACWY | Absolute no0CFR (95% CI) | 1/12 8·33(0·21-38·48) | 1/14 7·14(0·18-33·87) | 1/5 20·00 (0·51-71·64) | 000 | 3/37 8·11(1·70-21·91) |
| 15-24 y | MenB | Absolute no0CFR (95% CI) | 17/415 4·10(2·40-6·48) | 8/109 7·34 (3·22-13·95) | 3/36 8·33(1·75-22·47) | 1/27 3·70 (0·09-18·97) | 29/587 4·94(3·33-7·02) |
| MenC | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| MenW | Absolute no0CFR (95% CI) | 1/9 11·11 (0·28-48·25) | 1/2 50·00 (1·26-98·74) | 000 | 000 | 2/14 14·29(1·78-42·81) |
| MenY | Absolute no0CFR (95% CI) | 2/25 8·00(0·98-26·03) | 2/12 16·67 (2·09-48·41) | 2/7 28·57(3·67-70·96) | 000 | 6/51 11·76(4·44-23·87) |
| Other | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| ACWY | Absolute no0CFR (95% CI) | 3/39 7·69 (1·62-20·87) | 3/1717·65 (3·80-43·43) | 2/7 28·57(3·67-70·96) | 000 | 8/74 10·81(4·78-20·20) |
| 25-44 y | MenB | Absolute no0CFR (95% CI) | 4/142 2·82(0·77-7·06) | 5/50 10·00 (3·33-21·81) | 000 | 000 | 9/224 4·02(1·85-7·49) |
| MenC | Absolute no0CFR (95% CI) | 000 | 000 | 1/2 50·00(1·26-98·74) | 000 | 1/16 6·25(0·16-30·23) |
| MenW | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| MenY | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| Other | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| ACWY | Absolute no0CFR (95% CI) | 000 | 000 | 1/4 25·00(0·63-80·59) | 000 | 1/34 2·94(0·07-15·33) |
| 45-64 y | MenB | Absolute no0CFR (95% CI) | 3/182 1·65 (0·34-4·47) | 10/72 13·89(6·87-24·06) | 2/19 10·53 (1·30-33·14) | 000 | 15/2885·21(2·94-8·44) |
| MenC | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| MenW | Absolute no0CFR (95% CI) | 1/10 10·00(0·25-44·50) | 000 | 000 | 000 | 1/20 5·00(0·23-24·87) |
| MenY | Absolute no0CFR (95% CI) | 000 | 000 | 1/3 33·33(0·84-90·57) | 000 | 1/41 2·44(0·62-12·86) |
| Other | Absolute no0CFR (95% CI) | 000 | 000 | 000 | 000 | 000 |
| ACWY | Absolute no0CFR (95% CI) | 2/44 4·55 (0·56-15·47) | 000 | 1/5 20·00 (0·51-71·64) | 000 | 3/86 3·49(0·73-9·86) |
| ≥65 y | MenB | Absolute no0CFR (95% CI) | 8/70 11·43 (5·07-21·28) | 10/45 22·22 (11·20-37·09) | 9/15 60·00 (32·29-83·66) | 2/20 10·00 (1·23-31·70) | 29/152 19·08(13·17-26·23) |
| MenC | Absolute no0CFR95% CI | 000 | 1/4 25·00(0·63-80·59) | 000 | 000 | 1/9 11·11(0·28-48·25) |
| MenW | Absolute no0CFR95% CI | 000 | 3/8 37·50 (8·52-75·51) | 2/2 100(0·16-1·00) | 1/10 10·00 (0·25-44·50) | 6/25 24·00(9·36-45·13) |
| MenY | Absolute no0CFR95% CI | 2/19 10·53 (1·30-33·14) | 6/36 16·67 (6·37-32·81) | 4/6 66·67 (22·28-95·67) | 2/33 6·06 (0·74-20·23) | 14/94 14·89(8·39-23·72) |
| Other | Absolute no0CFR95% CI | 000 | 1/250.00 (1·26-98·74) | 000 | 000 | 1/4 25·00(0·63-80·59) |
| ACWY | Absolute no0CFR95% CI | 2/26 7·69 (0·95-25·13) | 10/48 20·83 (10·47-34·99) | 6/9 66·67 (29·92-92·51) | 3/45 6·67(1·40-18·27) | 21/128 16·41(10·45-23·98) |

**Supplementary Table 2·** Cases, deaths and case fatality ratios (CFR), along with odds of death for complications after adjusting for age in years and capsular group) among hospitalised IMD cases confirmed in England during 2007-11

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Complication | Number and % of IMD cases | CFR | CFR if meningitis also coded | CFR if septicaemia also coded | Odds of death  |
| Acidosis | 107(2·32%) | 21·50(14·14-30·49) | 10·26 (2·87-24·22) | 30·12(20·53-41·18) | 5·21(3·17-8·56, P<0·001) |
| Acute Kidney failure | 151(3·27%) | 17·22 (11·57-24·20) | 25·00 (14·39-38·37) | 31·37 (22·55-41·31) | 3·29(2·16-5·01,P<0·001) |
| Pneumonia | 185(4·01%) | 14·05 (9·39-19·91) | 32·89 (22·58-44·63) | 26·09 (17·48-36·29) | 1·76(1·15-2·68, P=0·009) |
| Hypotension | 228(4·94%) | 10·09 (6·50-14·75) | 14·78 (8·85-22·61) | 27·71 (18·45-38·62) | 4·19(2·54- 6·92, P<0·001) |
| Pulmonary edema | 51 (1·10%) | 17·65 (8·40-30·87) | 15·38 (1·92-45·45) | 23·26 (11·76-38·63) | 4·20(1·99-8·87, P<0·001) |
| Intravascular coagulation | 63 (1·36%) | 15·87 (7·88-27·26) | 0 | 20·69 (11·17-33·35) | 5·43(2·75-10·72,P<0·001) |
| Seizures | 83(1·80%) | 7·23(2·70-15·07) | 5·77 (1·21-15·95) | 16·13 (5·45-33·73) | 2·12(0·97-4·63, P=0·060) |
| Cardiac arrest | 51(1·10%) | 43·14(29·35-57·75) | 58·33 (27·67-84·83) | 50·00 (34·19-65·81) | 17·71(9·54-32·87, P<0·001) |

**Appendix 1**

The following ICD-10 codes were considered as presentation with meningitis: A390, G0\*, A87; septicaemia: A391, A392, A393, A394, A41, A40, P36, other presentation A398, A399, A395. Cases were analysed in the following categories; presentation with meningitis only (positive for any meningitis code but negative for any septicaemia code), septicaemia only (positive for any septicaemia code but negative for any meningitis code), concurrent meningitis and septicaemia, other presentations (including those with no codes for meningitis or septicaemia).