Invasive meningococcal disease: timing and cause of death in England, 2008-2015

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# Abstract

# Background

# *Neisseria meningitidis* is a major cause of bacterial meningitis and septicaemia, with death often occurring rapidly after onset of the first symptoms. Later death can also occur later, but may be due to other causes, such as underlying comorbidities. The study aimed to assess the timing and cause of death in patients with invasive meningococcal disease (IMD) prior to the introduction of two new meningococcal immunisation programmes in England

**Methods**

Public Health England (PHE) conducts IMD surveillance in England through its national meningococcal reference unit. Laboratory-confirmed IMD cases diagnosed during 2008-2015 were linked to weekly and annual electronic death registration records as well as the online Patient Demographic Service (PDS).

**Results**

Overall, 6,734 of 6,808 (99%) laboratory-confirmed IMD cases matched to PDS, including 668 fatalities. Of these, 667 linked to an annual death registrations compared to 405 to weekly registrations. In total, 429/667 (64.3%) of all deaths and 428/502 (85.3%) of IMD-related deaths occurred within one day of diagnosis. At 30 days after IMD diagnosis, 498/667 (74.7%) had died and 98.4% (490/498) were IMD-related. Serogroup B contributed to 64% (323/502) of IMD-related deaths, followed by serogroup W (84/502, 17%) and serogroup Y (70/502, 14%). Deaths occurring after 30 days were less likely to be IMD-related, mainly among ≥65 year-olds, with malignancy, chronic respiratory and cardiac conditions predominating.

**Conclusions**

Most IMD-related deaths occurred within a day of diagnosis and nearly all IMD-related deaths occurred within 30 days of diagnosis. The rapidity of death highlights the importance of prevention through vaccination.

# Introduction

*Neisseria meningitidis* is one of the leading causes of bacterial meningitis and septicaemia worldwide and is associated with significant morbidity and mortality (1){Jafri, 2013 #6048}. Disease onset is often sudden with non-specific illness but progression can be very rapid, with death often occurring with hours of the first symptoms (2). Twelve different meningococcal serogroups are identified based on their unique polysaccharide capsule, which is known to be a major virulent factor. In Europe, four serogroups (B, C, W and Y) are responsible for nearly all cases of invasive meningococcal disease (IMD) (1). The different serogroups have different propensities for causing invasive disease and fatal outcomes in different age groups, especially among those with underlying co-morbidities.

In the UK, MenC, which was associated with high case fatality rates (CFR) especially in teenagers, is now rare because of the success of the MenC immunisation programme that was implemented two decades ago (3). At the same time, MenB cases in the UK and across the UK have been declining over the same period most likely to secular trends. From 2009, however, England experienced a national outbreak of group W meningococcal (MenW) disease caused by a single hypervirulent strain belonging to the ST-11 clonal complex, which was associated with high morbidity and mortality across all age groups (4). This led to the implementation of an emergency meningococcal ACWY (MenACWY) conjugate vaccine programme for teenagers as a national outbreak response in August 2015 (5). At the same time, the United Kingdom also became the first country to offer the novel, protein-based, multi- component MenB vaccine (4CMenB) to all infants as part of a free national childhood immunisation programme (6).

In England, Public Health England (PHE) has been conducting IMD surveillance for several decades (7). Confirmed cases are identified through the national Meningococcal Reference Unit and linked with weekly reports of IMD-related death registration records provided by the Office for National Statistics (ONS) using pre-specified ICD-10 codes. This linkage is usually performed retrospectively, is time-consuming, and requires the recording of IMD on the death certificate which may not happen for rapidly fatal cases, unusual clinical presentations or atypical age groups, such as older adults. Given all the changes in the epidemiology of IMD, it was important to optimise the surveillance of IMD-related deaths in order to rapidly monitor outcomes in addition to the number of laboratory-confirmed cases nationally. Linkage with other available national surveillance databases could facilitate linkage and accelerate reporting of IMD-related deaths in a regular and timely manner. Here, we aimed to evaluate existing and new models of estimating IMD-related deaths and its implications for future surveillance strategies.

# Methods

## Surveillance

Public Health England routinely conducts enhanced national surveillance of invasive meningococcal disease in England using both clinical and laboratory reporting mechanisms (7). The MRU provides species confirmation, grouping, typing and subtyping for all invasive *Neisseria meningitidis* isolates. The MRU also provides non-culture polymerase chain reaction (PCR) confirmation of meningococcal diagnosis (including genogroup and geno-subtype analysis) for >10,000 clinical specimens that are routinely submitted every year by National Health Service (NHS) hospitals across England.

## Sources of death notification

For this analysis, all confirmed IMD cases diagnosed in England during 2008-2015 were included. We excluded subsequent surveillance years to avoid any confounding due to implementation of the infant MenB in September 2015 and the adolescent MenACWY immunisation programmes in August 2015 in the UK. Data on deaths up to a year after IMD diagnosis were obtained from 3 sources; weekly Office for National Statistics death registration (W-ONS) extracts of IMD-related ICD-10 codes (A39.0-A39.9), annual national ONS death certificate records (A-ONS) the NHS patient demographic system (PDS), a national electronic database containing full demographic details of all patients registered with the National Health Service (NHS).

Annual-ONS data are obtained 6 months after the end of each year and provides records of all certified deaths across England, including the date and cause of death. Confirmed IMD cases were also linked to the Annual-ONS records and as IMD-related or not IMD-related based on the recorded ICD-10 code and free-text searches for serious infections (meningitis, septicaemia, pneumonia, sepsis) in the text fields of the death registration records. PDS provides up-to-date status for all patients registered within the NHS, including death status and date of death, but not the cause of death. The different datasets were linked to using any combination of full name, date of birth and individual NHS number. All datasets were combined into a single dataset for analysis. Data are mainly descriptive and analysed by age group and serogroups for the combined 8-year surveillance period of 2008-2015 inclusive.

# Results

There were 6,808 IMD cases reported in England during the eight-year surveillance period (2008-2015). Overall, cases declined across all age groups by more than 30% from 1,171 in 2008 to 797 in 2015. Children aged <5 years were responsible for nearly half the cases (n=3,352) (**Figure 1**). Most cases were caused by MenB (79%) followed by MenW (8%), MenY (8%) and MenC (3%). The proportion of cases caused by MenB declined from 90% (1,051/1,171) in 2008 to 56% (450/797) in 2015. Over the same period, the proportion of MenW cases increased from 1% to 25% and MenY from 3% to 13%. The contribution of MenC cases remained between 2-4%, while other capsular groups were rare (1-4%).

## Deaths following IMD

Of the 6,808 laboratory-confirmed IMD cases, 6,734 (99%) cases matched to a PDS record and 668 were identified to have died; of these 668 deaths, 667 linked to an Annual-ONS record and 405 to the Weekly-ONS record. Nearly all deaths reported through the Weekly-ONS deaths (396/405, 96%) occurred within 30 days of IMD diagnosis, with only 9 occurring after this period (Table 1). Annual-ONS death certificate records identified an additional 262 deaths compared to the Weekly-ONS and only one less than PDS. Annual-ONS identified 22-25% more deaths and IMD-related deaths than Weekly-ONS at all time-points between 1 day to 180 days after IMD diagnosis.

## Timing of death and Association with age

Annual-ONS records were used as the most complete data source for the number and cause of death among laboratory-confirmed IMD cases (Table 1). Most IMD-related deaths occurred rapidly after disease onset. Overall, 429/667 (64.3%) of all deaths and 428/502 (85.3%) of all IMD-related deaths (as recorded on the death certificate) occurred within one day of diagnosis. At 30 days after IMD diagnosis, these proportions were 74.7% (498/667) and 98.4% (490/498), respectively; there were only additional 12 IMD-related deaths recorded (12/502, 2.4%) after this time. The CFR at 30 days correlated well with overall IMD-related deaths (Figure 2). After 180 days, there were 43 additional deaths in this cohort and 92.8% (502/541) were IMD-related according to the Annual-ONS death registration record.

In children (<15 year-olds), 88.7% (173/195) of deaths occurred within a day of diagnosis, 93.8% (183/195) within 7 days, and 94.7% (190/195) within 30 days after IMD diagnosis; all but two deaths (193/195, 99.0%) in children were IMD-related. In adults (15-64 year-olds), 71.7% (66+26+50=142/198) deaths and 90.4% (141/156; i.e. all but 1 IMD-related) occurred within a day of diagnosis, compared to 74.7% (148/198) and 94.2% (147/156; again all but 1 IMD-related) within 7 days, and 78.8% (156/198) and 98.7% (154/156, all but 2 IMD-related), respectively within 30 days. In adults, 38 of the 42 deaths (90.5%) that were not IMD-related were among 45-64 year-olds.

In older adults aged ≥65 year, all 114 and 134 deaths within one and seven days after diagnosis were IMD-related, as were 96.1% (146/152) of the deaths within 30 days of diagnosis. There were only 7 additional IMD-related deaths (7/153, 4.6%) occurring more than 30 days after IMD diagnosis among ≥65 year-olds compared to 115 additional that were not IMD-related.

## Analysis by capsular group

Where serogroup was known, MenB contributed to 64% (323/502) of IMD-related deaths, followed by MenW (84/502, 17%) and MenY (70/502, 14%). IMD-related deaths associated with MenB occurred across all ages and especially among infants aged <1 year (72 deaths) and toddlers aged 1-4 years (84 deaths) (**Supplement Tables**). Notably, all MenC and MenW fatalities in children and young adults (<25 year-olds) occurred within 1 day of diagnosis and all were IMD-related. MenC fatalities occurred across all age groups, including older adults, except infants. More than half of the IMD-related fatalities among MenW cases (44/84, 52.4%) were in older adults aged ≥65 years. There were no MenY fatalities in children aged <5 years, and 47/70 (67.1%) of the IMD-related fatalities among MenY cases were in ≥65 year-olds.

Whilst nearly all deaths within 30 days were IMD-related, those that occurred after 30 days and, especially after 180 days, were less likely to be IMD-related, particularly for MenY (70/131 [53.4%] were IMD-related), followed by MenC (23/30, 76.7%), MenW (84/106, 79.2%) and MenB (323/395, 81.8%). More detailed serogroup-specific analysis by age-group and time since IMD diagnosis identified that, in addition to the interval between diagnosis and death, those that were not related to IMD invariably occurred among ≥65 year-olds, followed by 45-64 year-olds (**Supplement Tables**), particularly for MenY and MenB, and to a lesser extent, MenW. Fatalities among MenC cases up to 90 days after diagnosis, on the other hand, were all due to IMD. The main causes of death that were not IMD-related were malignancy, followed by chronic respiratory and cardiac conditions (Table 2).

# Discussion

We undertook a detailed review of deaths in patients with laboratory-confirmed IMD over an 8-year period in England using multiple data sources with the aim of identifying an optimal method for rapidly reporting IMD case fatality rates as part of national surveillance. This was important because of the emergence of a highly virulent MenW:cc11 clone since 2009/10 that was associated with high morbidity and mortality across all age groups (4) and the implementation of two new meningococcal vaccines into the UK national immunisation programme in 2015 (6). We found that the Weekly-ONS reports were poor at capturing fatalities among IMD cases when compared to both PDS and Annual-ONS, even those that occurred within 30 days of IMD diagnosis. PDS, on the other hand, provided accurate and timely death status for IMD patients. More importantly, linkage with Annual-ONS data confirmed that fatal cases within 30 days of IMD diagnosis were almost all due to IMD across all age-groups. Notably, all deaths among IMD cases aged <45 years occurred within 30 days of diagnosis. Among older adults aged ≥65 years and, to a lesser extent 45-64 year-olds, deaths continued to occur across the surveillance period but were increasingly less likely to be IMD-related. A number of the late deaths in older adults were due to pneumonia (Table 3), highlighting the importance other preventive interventions such as influenza and pneumococcal vaccination in this vulnerable population. Overall, our results confirm low CFR associated with IMD across all age groups except older adults and that nearly all IMD-related deaths occurring very rapidly after diagnosis.

**CFR for meningococcal disease**

The use of multiple independent national data sources provides a more accurate estimate of overall and IMD-related deaths in England, by age group and meningococcal capsular group. Nearly all IMD-related deaths (85.3%) occurred within a day of diagnosis and, in some cases, the diagnosis may only be confirmed post-mortem (8). The rapid progression of IMD from first symptoms to death is well-described, especially in children (2); in our cohort, nearly 90% of all deaths in children and more than 90% of all deaths in 15-24 year-olds with IMD occurred within a day of diagnosis, highlighting the critical value of prevention through vaccination. In keeping with the literature, too, we have previously reported that only 18 of 3,411 (0.5%) of IMD cases had underlying risk factors for IMD (7) and, therefore, it is not surprising that 97.6% (490/502) deaths within 30 days of diagnosis were IMD-related, with very few (n=12) IMD-related deaths occurring after this period. For clinicians and the families of patients with IMD, these results provide reassurance that the risk of death decreases rapidly after the first few days of the illness and that, in previously healthy patients of any age, late deaths due to any cause are rare. Deaths occurring more than 30 days after diagnosis were nearly all in ≥65 year-olds, followed by among 45-64 year-olds, mainly in those with MenB and MenW, and nearly always due to a serious underlying comorbidity that would have been present at the time of IMD, especially malignancy, or due to old age (Table 3).

## Surveillance

In terms of surveillance, the weekly-ONS data were used to rapidly monitor IMD-related deaths during the national MenC outbreak in the UK that started in the mid-1990s (3). At that time, this was the quickest data source for rapidly monitoring fatalities during a national outbreak associated with high morbidity and mortality. Since then, however, real-time access to PDS had vastly improved national surveillance because of access to accurate patient demographics, the general practice they are registered with (for completion of surveillance questionnaires) and, if died, their date of death.

Annual-ONS data provided more information relating to both the date and the cause of death, which could be attributed to infection in nearly all cases. A major disadvantage of Annual-ONS data is that the information only become available in the second half of the following year and, as such, in only useful for retrospective confirmation of deaths and cause of death in patients with laboratory-confirmed IMD identified through national surveillance. Access to PDS, however, and our demonstration that nearly all deaths within 30 days are IMD-related now allows us to report CFR and monitor outcomes across age-groups, serogroups and time in near real-time.

**Strengths and Limitations**

The strength of this analysis is the availability of multiple national datasets with reliable identifiers to link across the datasets. We were able to link 8 years’ worth of data during a national outbreak of MenW:cc11 disease and prior to the introduction of two new meningococcal immunisation programmes in England. The paucity clinical information within the analysed databases, however, is an important a limitation of the study, especially because the information recorded on death registrations is known to be limited (9). Underlying comorbidities, for example, may be less well documented on the death certificate, although it is very likely that significant underlying illnesses such as malignancy and chronic diseases would be recorded. At the same time, most IMD cases occur in previously healthy individuals, unlike many other infectious diseases. On the other hand, our primary data source was laboratory-confirmed IMD cases, which we linked to the weekly and annual death registration records. We were, therefore, certain of the diagnosis and aetiology of the infection-related deaths. More detailed clinical information for cases would have allowed for more detailed ascertainment of the cause of death, such as duration of illness, presenting symptoms, laboratory investigations, time to treatment, transfer to intensive care, management of organ failure, and so on. Another important limitation was the lack of information on sequelae, which can be severe and long-term, including epilepsy, blindness deafness and limb amputations (10).

**Conclusions**

Our analysis provides a detailed assessment of deaths in patients with confirmed IMD during a national outbreak due to MenW:cc11 and prior to the introduction of two new national meningococcal immunisation programmes in 2015. We found that most IMD-related deaths occurred within a day of diagnosis and that nearly all IMD-related deaths were captured within 30 days of diagnosis, making this interval ideal for timely surveillance of IMD-related deaths nationally. The rapidity of death in patients with confirmed IMD highlights the importance of prevention through vaccination.

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**Figure 1.** Number of cases of laboratory-confirmed invasive meningococcal disease (IMD) by calendar year and capsular group in England, 2008-2015

*NK=not known*

**Figure 2.** Number of cases of laboratory-confirmed invasive meningococcal disease (IMD) by age group with outcomes and case fatality ratest (CFR) at 1 day, 30 days, 180 days and any time after IMD diagnosis in England, 2008-2015

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age** |  | **1 day** | **7 days** | **14 days** | **30 days** | **90 days** | **180 days** | **Death at any time** |
| **<1y****N=1501** | *Weekly-ONS (% of Weekly-ONS deaths in this age-group)**Annual ONS (% of all Annual-ONS deaths in this age-group)**IMD-related deaths (% of all IMD-related deaths in this age-group)**Overall CFR / IMD-related CFR in this age-group* | 63/69 (91.3%)68/76 (89.5%)68/74 (91.9%)4.5% / 4.5% | 67/69 (97.1%)72/76 (94.7%)72/74 (97.3%)4.8% / 4.8% | 6974/76 (97.4%)744.9% / 4.9% | 6974/76 (97.4%)744.9% / 4.9% | 6974/76 (97.4%)744.9% / 4.9% | 6975/76 (98.7%)745.0% / 4.9% | 697674 5.1% / 4.9% |
| **1-4y****N=1850** | *Weekly-ONS (% of Weekly-ONS deaths in this age-group)**Annual ONS (% of all Annual-ONS deaths in this age-group)**IMD-related deaths (% of all IMD-related deaths in this age-group)**Overall CFR / IMD-related CFR in this age-group* | 72/84 (85.7%)76/88 (86.4%)76/88 (86.4%)4.1% / 4.1% | 78/84 (92.9%)82/88 (93.2%) 82/88 (93.2%)4.4% / 4.4% | 81/84 (96.4%)85/88 (96.6%)85/88 (96.6%)4.6% / 4.6% | 82/84 (97.6%)86/88 (97.7%)86/88 (97.7%)4.6% / 4.6% | 8488884.8% / 4.8% | 8488884.8% / 4.8% | 8488884.8% / 4.8% |
| **5-14y****N=659** | *Weekly-ONS (% of Weekly-ONS deaths in this age-group)**Annual ONS (% of all Annual-ONS deaths in this age-group)**IMD-related deaths (% of all IMD-related deaths in this age-group)**Overall CFR / IMD-related CFR in this age-group* | 29/31 (93.5%)29/31 (93.5%)29/31 (93.5%)4.4% / 4.4% | 29/31 (93.5%)29/31 (93.5%)29/31 (93.5%)4.4% / 4.4% | 30/31 (96.8%)30/31 (96.8%)30/31 (96.8%)4.6% / 4/6% | 30/31 (96.8%) 30/31 (96.8%)30/31 (96.8%)4.6% / 4.6% | 3131314.7% / 4.7% | 3131314.7% / 4.7% | 3131314.7% / 4.7% |
| **15-24y****N=1,019** | *Weekly-ONS (% of Weekly-ONS deaths in this age-group)**Annual ONS (% of all Annual-ONS deaths in this age-group)**IMD-related deaths (% of all IMD-related deaths in this age-group)**Overall CFR / IMD-related CFR in this age-group* | 59/63 (93.7%)66/72 (91.7%)66/69 (95.7%)6.5% / 6.5% | 6369/72 (95.8%)696.8% / 6.8% | 6369/72 (95.8%)696.8% / 6.9% | 6369/71 (95.8%)696.8% / 6.8% | 6371/72 (98.6%)697.0% / 6.8% | 6371/72 (98.6%)697.0% / 6.8% | 6372697.1% / 6.8%  |
| **25-44y****N=438** | *Weekly-ONS (% of Weekly-ONS deaths in this age-group)**Annual ONS (% of all Annual-ONS deaths in this age-group)**IMD-related deaths (% of all IMD-related deaths in this age-group)**Overall CFR / IMD-related CFR in this age-group* | 23/28 (82.1%)26/32 (81.3%)26/31 (83.9%)5.9% / 5.9% | 24/28 (85.7%)27/32 (84.4%)27/31 (87.1%)6.2% / 6.2% | 26/28 (92.9%)29/32 (90.6%)29/31 (93.5%)6.6% / 6.6% | 27/28 (96.4%)31/32 (96.9%)317.1% / 7.1% | 27/28 (96.4%)31/32 (96.9%)317.1% / 7.1% | 27/28 (96.4%)31/32 (96.9%)317.1% / 7.1% | 2832317.3% / 7.1% |
| **45-64y****N=661** | *Weekly-ONS (% of Weekly-ONS deaths in this age-group)**Annual ONS (% of all Annual-ONS deaths in this age-group)**IMD-related deaths (% of all IMD-related deaths in this age-group)**Overall CFR / IMD-related CFR in this age-group* | 41/46 (89.1%)50/94 (53.2%)49/56 (87.5%)7.6% / 7.4% | 43/46 (93.5%)52/94 (55.3%) 51/56 (91.1%)7.9% / 7.7%  | 44/46 (95.7%)55/94 (58.5%)53/56 (94.6%)8.3% / 8.0%  | 45/46 (97.8%)56/94 (59.6%)54/56 (96.4%)8.5% / 8.2%  | 4659/94 (62.8%)568.9% / 8.5% | 4663/94 (67.0%)569.5% / 8.5% | 46945614.2% / 8.5% |
| **≥65y****N=670** | *Weekly-ONS (% of Weekly-ONS deaths in this age-group)**Annual ONS (% of all Annual-ONS deaths in this age-group)**IMD-related deaths (% of all IMD-related deaths in this age-group)**Overall CFR / IMD-related CFR in this age-group* | 59/84 (70.2%)114/274 (41.6%)114/153 (74.5%)17.1% / 17.1% | 74/84 (88.1%)134/274 (48.9%)134/153 (87.6%)20.1% / 20.1% | 77/84 (91.7%)140/274 (51.1%)139/153 (90.8%)20.9% / 20.7%  | 80/84 (95.2%)152/274 (55.5%)146/153 (95.4%)22.7% / 21.8% | 84172/274 (62.8%)15325.7% / 22.8% | 84182/274 (66.4%)15327.1% / 22.8% | 8427415340.9% / 22.8% |
| **All cases \*****N=6,798** | *Weekly-ONS (% of Weekly-ONS deaths in this age-group)**Annual ONS (% of all Annual-ONS deaths in this age-group)**IMD-related deaths (% of all IMD-related deaths in this age-group)**Overall CFR / IMD-related CFR in this age-group* | 346/405 (85.4%)429/667 (64.3%)428/502 (85.3%)6.3% / 6.3% | 378/405 (93.3%)465/667 (69.7%)464/502 (92.4%)6.8% / 6.8% | 390/405 (96.3%)482/667 (72.3%)479/502 (95.4%)7.1% / 7.0% | 396/405 (97.8%)498/667 (74.7%)490/502 (97.6%)7.3% / 7.2% | 404/405 (99.8%)526/667 (78.9%)5027.7% / 7.4% | 404/405 (99.8%)541/667 (81.1%)5028.0% / 7.4% | 4056675029.8% / 7.4% |

Table 1. Timing and cause of death in patients with laboratory-confirmed invasive meningococcal disease (IMD) in England identified through three different sources, with overall and IMD-related case fatality rates (CFR) by age group. Weekly-ONS = deaths identified through weekly reports by the Office for National Statistics (ONS) using pre-defined ICD-10 codes; Annual-ONS = deaths identified through annual electronic death registration records provided by the ONS

\* Age not known for 11 cases

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Meningococcal serogroup** | **MenB** | **MenC** | **MenW** | **MenY** | **TOTAL** |
| Malignancy | 25 | 2 | 12 | 26 | **65** |
| Respiratory disease\* | 16 | 1 | 3 | 5 | **25** |
| Cardiovascular disease | 6 | 1 | 2 | 14 | **23** |
| Neurological disease | 5 | -  | 2 | 4 | **11** |
| Hepatic disease | 7 | -  | -  | 2 | **9** |
| Inflammatory disease | 3 | -  | -  | 1 | **4** |
| Renal disease | 1 | -  | -  | 2 | **3** |
| Other causes \*\* | 9 | 3 | 3 | 7 | 22 |
| **Total**  | **72** | **7** | **22** | **61** | **162 \*\*\***  |

**Table 2. Cause of death were recorded in the death certificate to be due to causes other than invasive meningococcal disease (IMD) in patients with laboratory-confirmed IMD in England, 2008-2015.**

\* Eleven of the 25 cases with a respiratory cause of death were due to pneumonia

\*\* Other causes of death were mainly related to old age, including senility and dementia

\*\*\* Three additional cases were due to serogroups other than A, B, C, W or Y.