Incidence, complications and mortality of invasive meningococcal disease (IMD) in Europe: results from a systematic literature review

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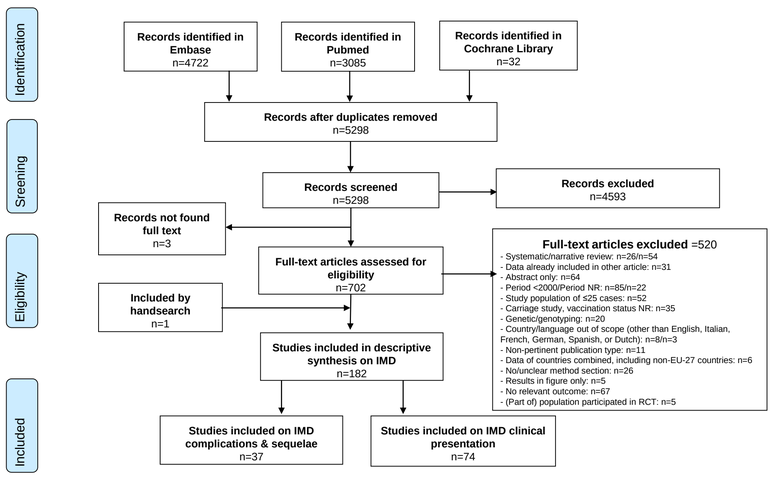
BACKGROUND

- Invasive meningococcal disease (IMD) is a serious bacterial infection caused by Neisseria meningitidis, which is classified into serogroups based on different capsular polysaccharides and external protein membranes.
- Among 12 distinct serogroups reported in the literature, six of them (A, B, C, W, X, Y) are the causative agent for almost all IMD and responsible for the greatest clinical disease burden.
- Nevertheless, serogroup epidemiology may vary temporally, geographically and with age, and even if most of IMD are preventable by vaccination, it continues to be a global public health concern due to its epidemic potential, mortality and sequelae.
- Approximately 500,000-1,200,000 cases of IMD occur each year, with 50,000-135,000 deaths worldwide[1]. Even with appropriate treatment, 5-10% of patients die within 24-48 h of developing symptoms. Moreover, several studies have reported severe long-term sequelae for 10–20% of survivors[2]. The severity of IMD manifestations ranges from transient bacteremia, with mild and non-specific symptoms, to fulminant sepsis with multi-organ failure.
- The objectives of this review are to systematically identify IMD clinical burden in EU-27.

METHODS

- PubMed, Embase and Cochrane Library databases were searched for publications from 2000 to 3 January 2018 with search strings for meningococcal disease and the countries of interest to characterize the burden of IMD in EU-27 countries. Articles were selected by screening the titles and abstracts, followed by screening of the full-text articles. Language other than English, Italian, French, German, Spanish, or Dutch was an exclusion criteria.
- Reported data covered the period from 1977 to 2017 for IMD clinical presentation, and 1974 to 2016 for IMD incidence.

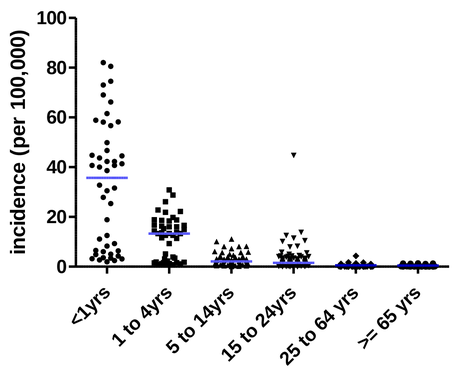
Figure 1: Example of PRISMA Flow diagram for IMD clinical presentation
The number of records identified, included and excluded, and the reasons for exclusions



RESULTS

- Out of 182 identified articles with IMD data reported in EU-27, 74 papers presented data on clinical presentation (data from 16 EU countries) and 37 presented data on complications/sequelae (data from 11 EU countries) (Figure 1).
- Here we report the results incidence, mortality, acute events and complications/sequelae for all countries, age groups and serogroups. (PROSPERO registration number: CRD42018084136)
- The **highest incidence of IMD was reported in infants <1 years old** (median of 36/100,000) in publications from 2003-2017.
  - Data for <14 years were reported in 2003-2017, data for 15-24 years in 2006-2017, data for 25-64 years in 2002-2017 and data for >65 years in 2002-2016.

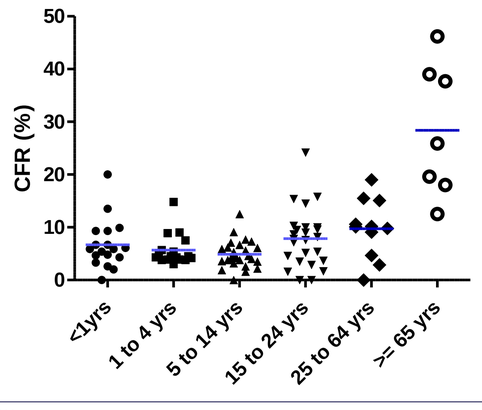
Figure 2A: Incidence per age group (all serogroups)



Blue line: median

For all IMD cases**, CFRs were higher in adults** (mean of 10%) and **older adults** (mean of 28%) compared to other age groups.

Figure 2B: Case-fatality rates per age group (all serogroups)



Blue line: mean

IMD clinical presentation for the overall population

- The main outcomes reported in our analysis were **meningitis** (range: 3.6-89.2% of the cases, n=207 estimates); **meningococcemia** corresponding to a meningococcal sepsis (range: 0.0-100%, n=169 estimates) and **meningitis + meningococcemia** (range: 0.0-64.5%, n=99 estimates).
- Other clinical features reported were septic shock (range: 3.6-76.2%, n=23 estimates); fulminant meningococcemia (range: 5.0-100%, n=9 estimates); bacteremia + meningitis (range: 17.7-44.6%, n=4 estimates); bacteremia (range: 10.7-60.6%, n=12 estimates); pharyngitis (25.0%, n=1 estimate); septic shock + meningitis (range: 11.2-30.8%, n=13 estimates); pneumonia (range: 0.0-76.9%, n=16 estimates); Waterhouse Friderichsen syndrom (range: 0.2-20.0%, n=4 estimates); arthritis (range: 0.0-14.8%, n=15 estimates); epiglottitis/supraglottitis (range: 0.0-8.3%, n=6 estimates); pericarditis (range: 0.0-3.7%, n=6 estimates); encephalitis (range: 0.9-3.7%, n=2 estimates); other (range: 0.2-7.5%, n=6 estimates).

Figure 3: clinical presentation of IMD

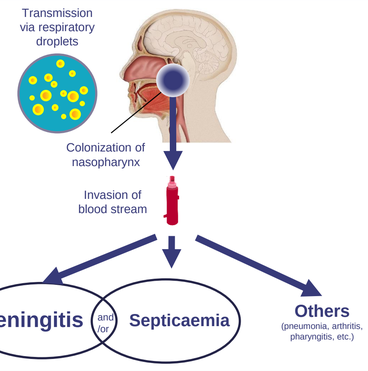
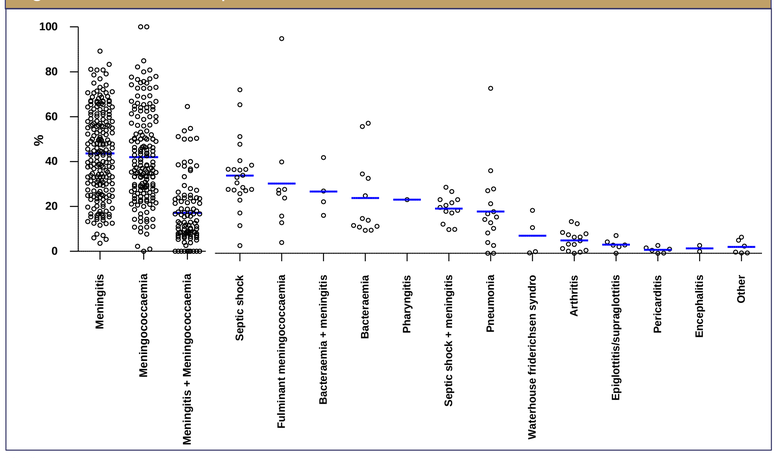


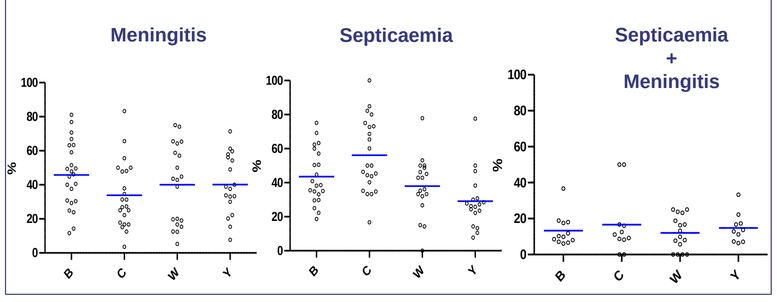
Figure 4: IMD clinical presentation of IMD



Blue line: mean.
Each point corresponds to one estimate.
One estimate was the percent of cases presenting the clinical form.

- The highest rate of **meningitis** was reported for **serogroup B** (range from 11.6-81.1%, n=23 estimates).
- The highest rate of **septicaemia** was reported for **serogroup C** (range from 16.70-100%, n=22 estimates).
- A rate around **15% of meningitis+ meningococcemia** was reported for all serogroups.

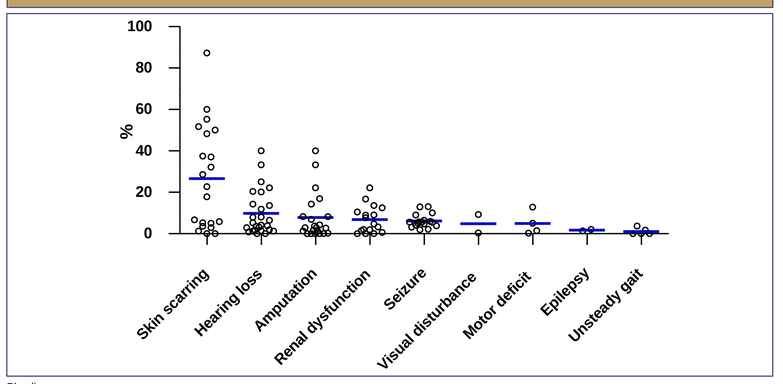
Figure 5: IMD clinical presentation – per serogroup



Blue line: mean. No data for Serogroup A presented

- The three most common complications reported after an IMD were:
  - **Skin scarring** (range: 0.0-87.3%, n=21 estimates);
  - **Hearing loss** (range: 0.0-40.0%, n=26 estimates);
  - **Amputation** (range: 0.0-40.0%, n=22 estimates);
- Less reported common complications were renal dysfunction (range: 0.0-22.2%, n=9 estimates); Seizure (range: 2.0-13.0%, n=17 estimates); Visual disturbance (range: 0.4-9.4%, n=2 estimates); Motor deficit (range: 0.3-12.9%, n=4 estimates); Epilepsy (range: 1.4-2.1%, n=2 estimates); Unsteady gait (range: 0.0-3.7%, n=5 estimates).

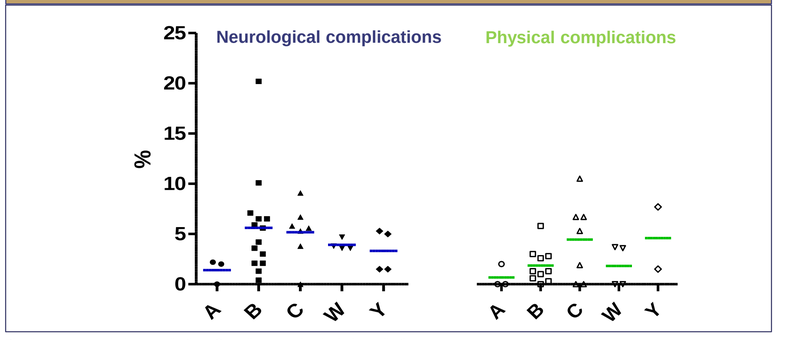
Figure 6: % complications after IMD



Blue line: mean

- The highest rate of **neurological complications** was reported for **serogroup B** (range: 0.4-20.2%, n=13 estimates) followed by:
  - Serogroup C (range: 0.0-9.1%, n=7 estimates).
  - Serogroup W (range: 3.6-4.7%, n=4 estimates).
  - Serogroup Y (range: 1.5-5.3%, n=4 estimates).
- The highest rate of **physical complications** was reported for the **serogroup C** (range: 0.0-10.5%, n=7 estimates), followed by:
  - Serogroup Y (range: 1.5-7.7%, n=2 estimates).
  - Serogroup B (range: 0.0-5.8%, n=9 estimates).
  - Serogroup W (range: 0.0-3.7%, n= 4 estimates).

Figure 7: Neurological and physical complications per serogroup



Blue line: mean neurological complications, Green line: mean for physical complications
Neurological complications: motor deficit, epilepsy, seizure, visual disturbance, hearing loss, unsteady gait and psychomotor deficit.
Physical complications: skin scarring, amputation, renal failure, cardiovascular, respiratory, haematological, Disseminated Intravascular Coagulation (DIC), multiple system failure.

IMD sequelae

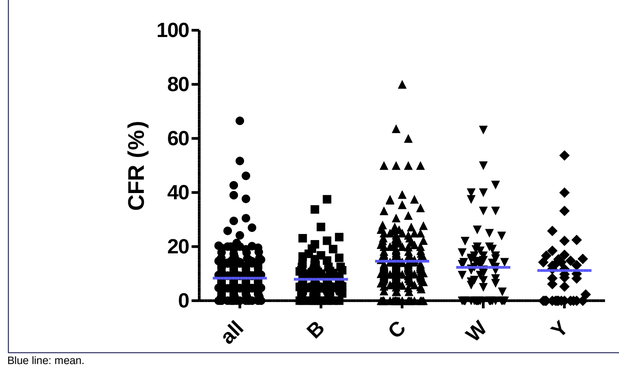
- Typically, a sequela is a chronic condition that is an **irreversible complication** which follows a more acute condition.
- Overall the rate of sequelae reported was up to **57%** (range: 0.0-57.4%, n= 34 estimates without information on serogroups).
- Our results showed the risk to develop sequelae by serogroups:
  - Serogroup B (range: 2.9-37.6%, n=8 estimates)
  - Serogroup C (range: 12.5-34.0%, n=3 estimates)
  - Serogroup W (range: 10.7-15.4%, n=2 estimates)
  - Serogroup Y (range: 12.0-53.8%, n=2 estimates)

Figure 8A: % sequelae per serogroup (all ages)

Blue line: mean.
No data for serogroup A presented

- Among vaccine- preventable IMD, **serogroup C, W and Y had the highest CFR**, with a mean of respectively 14.6%, 12.4% and 11.2%.
- Although B is the most prevalent serogroup, CFR is below 8%.

Figure 8B: Case-fatality rates (CFR) per serogroup (all ages)



Blue line: mean.

DISCUSSION

- The clinical course of IMD is frequently complicated by neurologic and physical complications. Most commonly, meningococcal infection presents as either meningitis or meningococcemia, or a combination of both. IMD outcomes can also manifest in the form of pneumonia, myocarditis, endocarditis, pericarditis, arthritis, conjunctivitis, urethritis, pharyngitis, etc.
- In those who survive meningococcal infection, around 18% will suffer from long-term complications (figure 8A). This percentage may be up to 36% among younger people.[3]
- The clinical course of IMD is frequently complicated by neurologic and physical complications including seizures and focal neurologic deficits such as hearing loss, limb weakness, difficulties with sight, speech, language and communication.
- Meningitis sequelae can have an enormous financial and emotional impact on families. In the United Kingdom, a study demonstrated that sequelae were linked with significant detriments to the quality of life.[4]
- Based on this literature review we can highlight that
  - Serogroup C induced more often meningococcemia that can explain its highest proportion of physical complications.
  - Serogroup B induced more often meningitis that can explain its highest proportion of neurological complications.
  - Serogroup Y caused more often sequelae than other serogroups.
- Limitations:
  - Sequelae and clinical outcomes definitions differed per study
  - Few data for serogroup A due to its low circulation in Europe.
  - Few data for serogroup W as the data on the increased incidence observed in Europe were not published at the time this literature review was performed.
  - Some distorted estimates were observed in some studies due to the low number of cases and the diversity of context (studies including outbreaks). This may impact the large range observed.
  - Limitation due the study design (cohort, case control study, retrospective study) – no standardized protocol and tool.
  - Difference in terms of follow-up period.
  - Data gaps on impact of sequelae on quality of life.

CONCLUSIONS

This review reports the IMD clinical burden and the results of its incidence, mortality, acute events and complications/sequelae for EU countries, for all age groups and serogroups. It highlights the important morbidity of IMD with variation according to serogroup and age groups. It can be noticed than 18% of IMD survivors are affected by a broad range of long-term complications (neurological or not), which can impact their quality of life and the family members responsible for their care. It can differ by serogroup and age groups, and reach up to 36% among younger people.[3]
Recent studies showed an increased incidence and spread of W & Y hypervirulent strains (with increased CFR in older adults) in different parts of the world. This justifies an accurate surveillance and prompt action from national health authorities.
The unpredictability of infection, striking otherwise healthy people, coupled with the poor prognosis for some patients despite appropriate management suggests the best strategy to control the burden of IMD is through immunization for disease prevention.
These results highlight the burden of IMD, and are in line with WHO "Defeating meningitis by 2030" goals[5] :
- Eliminate meningitis epidemics
- Reduce cases and deaths from vaccine-preventable meningitis by 80%
- Decrease the impact of sequelae by 50%

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DISCLOSURES

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