Review

Estimates of the burden of meningococcal disease in Italy: implications for prevention and control

D. MARTINELLI, F. FORTUNATO, R. PRATO
Department of Medical and Surgical Sciences, University of Foggia

Key words

Meningococcal disease • Incidence • Serogroup B

Summary

Meningococcal disease is an acute, severe bacterial infection caused by Neisseria meningitidis. The most common presentations of invasive meningococcal infection (IMD) are meningitis and sepsis, less common pathologic presentations include focal infections. IMD can develop from initial symptoms to death within 24 hours. As many as 20% of survivors have permanent sequelae. Infants < 1 year of age have the highest incidence and adolescents the highest carriage prevalence.

In Italy, the incidence of IMD was 0.25 confirmed cases per 100,000 in 2011, but this may have been considerably underestimated due to under-detection and under-reporting. Recently, we estimated the impact of the MenC universal vaccination on the burden of meningococcal meningitis in Puglia by assessing the completeness of three registration sources (notifications, hospitalizations, and laboratory surveillance). The sensitivity of the three systems was 36.7% (95% CI: 17.5%-57.9%) and registrations lost nearly 28 cases/year in the period 2001-2013.

In the National Surveillance of Invasive Bacterial Diseases, serogroup B accounted for 64.9% of samples serotyped in 2011. Applying this percentage to the total number of hospitalizations for IMD registered in the same year (n = 256), we obtained an estimated 166 episodes attributable to serogroup B.

Our work highlights the importance of enhancing surveillance for meningococcal disease and strengthening vaccinations against all preventable serogroups.

Brief overview of meningococcal disease

Meningococcal disease is an acute, severe bacterial infection caused by *Neisseria meningitidis*. The bacteria are transmitted by droplet aerosol or secretions from the nasopharynx of colonized people (10% to 20% of adolescents and adults are asymptomatic transient carriers). Meningitis is the most common presentation of invasive meningococcal infection (IMD) and results from the spread of the bacteria through the bloodstream to the brain. Meningococcal sepsis (bloodstream infection or meningococcemia) may occur with or without meningitis (5% to 20% of IMDs). Less common pathologic presentations include pneumonia (5% to 15% of cases), arthritis (2%), otitis media (1%), and epiglottitis (less than 1%) [1, 2].

IMD is a feared, rapidly progressive childhood infection that can develop from initial symptoms (easily misdiagnosed) to death within 24 hours [1, 3]. In the first 8 hours, most children have only non-specific symptoms (irritability, loss of appetite, fever, nausea/vomiting, sore throat, coryza, general aches, leg pain, drowsiness, floppy muscle tone in infants < 1 year of age) that can often resemble those of common viral illnesses. Only about half these children are sent to hospital after the first consultation. Specific meningitis symptoms and signs of sepsis and shock (cold hands/feet, petechiae, purpuric rash, meningism, neck stiffness, photophobia, bulging fontanelle in infants < 1 year of age) are seen later, around 12-15 hours from the onset of the illness, due to the rapid replication of *Neisseria meningitidis* in the body. The last signs (such as confusion/delirium, unconsciousness, seizure, septic shock, multisystem failure, death) develop late, with a median onset of 15-24 hours. Intervention often does not occur until specific late-stage symptoms have already appeared (median time from onset to hospital admission = 19 hours) [3, 4]. Even when the disease is diagnosed early and adequate treatment is started, 5% to 10% of patients die, typically within 24 to 48 hours after the onset of symptoms [2]. Potentially lethal complications of fulminant meningococcal disease include increased intracranial pressure, uncal herniation (included during lumbar puncture), cerebral infarction, status epilepticus, cardiac arrest, metabolic acidosis, primary respiratory failure, multi-system failure, intractable shock, circulatory collapse, disseminated intravascular coagulation [4-6].

As many as 20% of survivors of IMD (all serogroups) have permanent sequelae, such as hearing loss, neurologic damage, or loss of a limb [1]. Most children survive serogroup B meningococcal disease without major sequelae. However, nearly one in ten experience major disabling deficits, including limb amputations, seizures and hearing loss, and more than a third have one or more deficits such as psychological disorders, digit amputations and unilateral hearing loss [7].

Infants younger than one year of age have the highest incidence (17.3-fold increase over average in Europe) [8]

due to a naive/immature immune system, waning of protective maternal antibody levels and exposure to young adult carriers in the household [9, 10]. Adolescents are the population with the highest carriage prevalence (1.8-5.3-fold increase over other age groups) [11]. Close and prolonged contact with a carrier, such as kissing, sneezing or coughing on someone, household crowding, or living in dormitories, sharing of drinks, cigarettes, and utensils, respiratory tract infection, both active and passive smoking, travelling to countries with epidemic or hyperendemic meningococcal infection are associated with an increased risk for the disease [12-14]. Most cases of meningococcal disease occur in previously healthy people without any warning [15].

Under-reporting of meningococcal disease incidence in Italy

IMD is rare in Italy where 0.25 confirmed cases per 100,000 population were observed in 2011, based on surveillance data submitted to The European Surveillance System [16]. Reported incidence, however, may be considerably underestimated due to underdiagnosis (under-ascertainment) and under-reporting affecting IMD surveillance, particularly in some regions [17].
Monitoring the incidence of meningococcal disease is essential to evaluate the impact of the implemented vaccination strategies with the meningococcal serogroup C conjugate vaccine (MenC) or the quadrivalent meningococcal conjugate vaccine (MenACWY), and to advise on the use of the new multicomponent serogroup B meningococcal (4CMenB) vaccine, recently introduced in some Italian regions and under discussion for introduction on a national scale. In a recent study, we estimated the impact of the MenC universal vaccination on the burden of meningococcal meningitis in Puglia by assessing the completeness (sensitivity) of three registration sources (notifications, hospitalizations, and laboratory surveillance) in the period 2001-2013. We found that only 213 cases of meningococcal meningitis out of an estimated 580 (95% CI: 368-1,216) total cases were recorded in at least one of the three sources, with an overall sensitivity of 36.7% (95% CI: 17.5%-57.9%). This means that the routine surveillance systems lost nearly 28 cases/year in the study period [18].

Incidence of meningococcal B disease in Italy

In order to estimate the potential impact of the new 4CMenB vaccine, the distribution of *N. meningitidis* serogroups detected by the National Surveillance of Invasive Bacterial Diseases (referred to as MIB, 2011 and 2013 data) was applied to the total number of both reported and hospitalized cases in each of the 21 Italian regions. Hospitalizations were extracted from the National Hospital Discharge Registry (HDR, 2011 data) [19], where IMD is identified by the ICD9-CM codes

Fig. 1. Number of invasive meningococcal disease cases and estimated distribution of cases attributable to serogroup B, by Italian region, 2013.

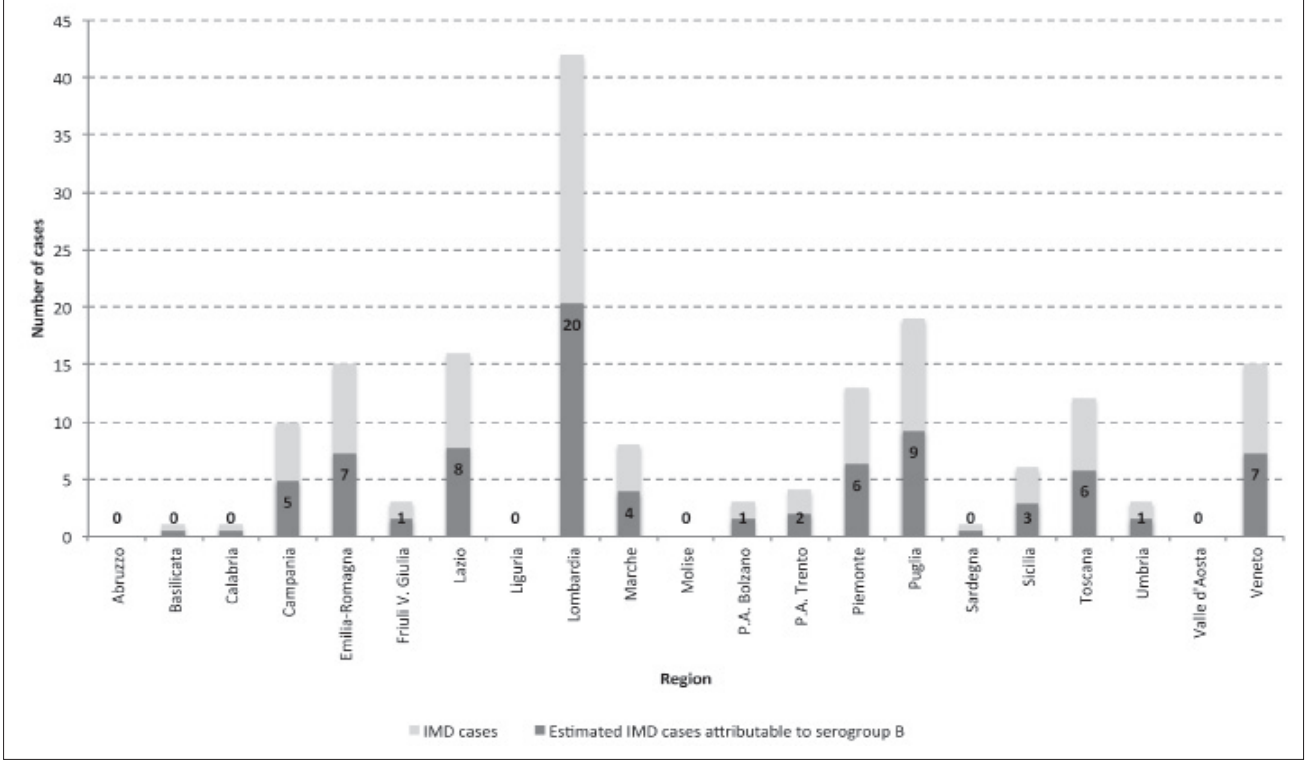
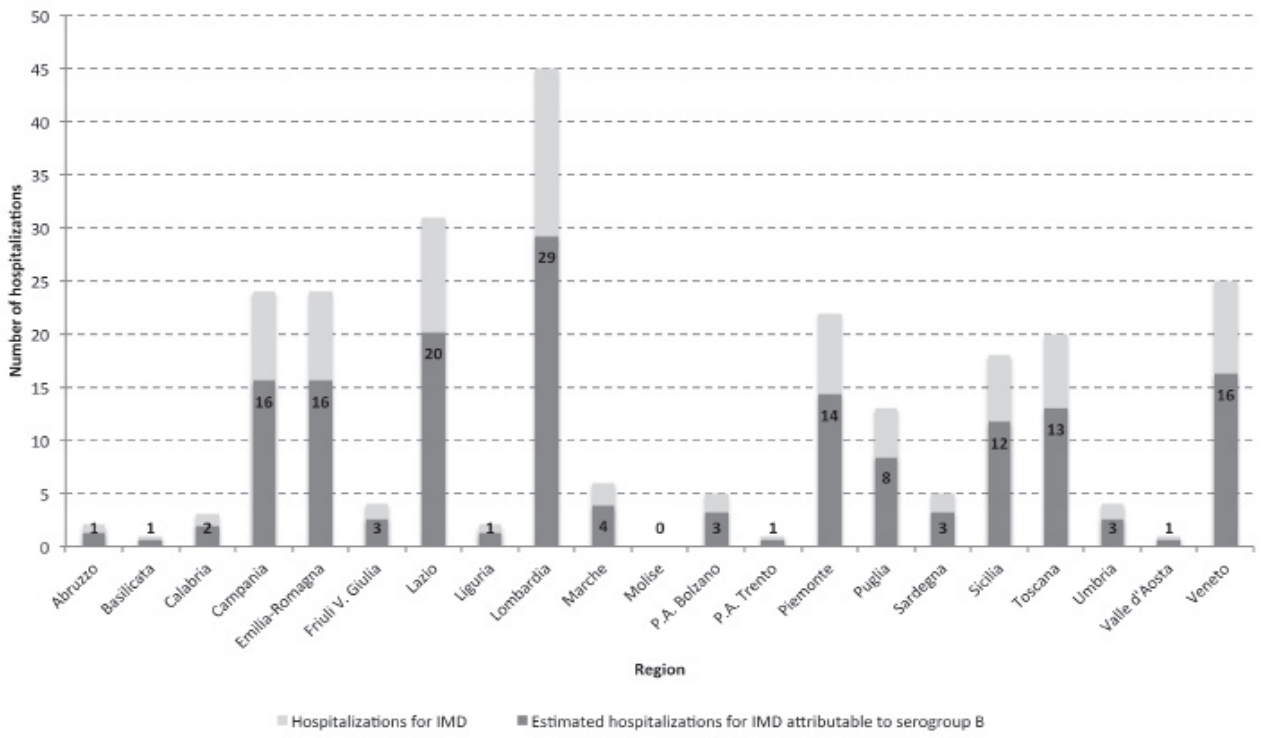


Fig. 2. Number of hospitalizations for invasive meningococcal disease and estimated distribution of cases attributable to serogroup B (% from the MIB surveillance), by Italian region, 2011.



036.x - *Meningococcal infection* as main or secondary diagnosis.

In 2013, a total of 172 cases were notified to the MIB surveillance (incidence rate of 0.29 per 100,000). Among the 116 (67.4%) strains typed, serogroup B accounted for 48.3% of isolates (56 cases, incidence rate of 0.09 per 100.000) [20]. Lombardia reported the highest notification rate (42 cases, incidence rate of 0.43 per 100,000) [20], thus the estimated number of cases that could be attributable to serogroup B was 20. Four regions (Abruzzo, Liguria, Molise, and Valle d'Aosta) reported zero cases (Fig. 1) [20].

A total of 256 hospitalizations for IMD were recorded in the HDR (hospitalization rate of 0.42 per 100,000) in 2011. Out of 22 day-hospitals, 13 reported main diagnosis coded as meningitis and six were coded as sequelae (i.e.: paralytic syndromes, late effects of cerebrovascular disease, disarticulation of elbow, etc). Applying the percentage of the typed B strains in 2011 retrieved from the MIB surveillance (76 cases, 64.9% of samples serotyped [20]) to the total number of hospitalizations for IMD, we obtained an estimated 166 episodes that could be attributable to serogroup B (hospitalization rate of 0.27 per 100,000). Lombardia confirmed the highest rate (45 discharges for IMD; 0.46 per 100,000), with an estimated number of 29 cases that could be attributable to serogroup B. Molise reported zero hospitalizations for IMD (Fig. 2).

Closing remarks

The incidence of invasive meningococcal disease is relatively low in Italy; however, it is a disease with a high fatality rate and high risk of complications [1, 2, 16, 20]. The assessment of the sensitivity of data sources available for monitoring the incidence of meningococcal meningitis showed that they are not sufficiently comprehensive in terms of the cases they contain [18]. Both under-reporting and under-ascertainment affect the Invasive Bacterial Diseases surveillance in some Italian regions [17], complicating efforts to understand their occurrence and burden, particularly when the planning and evaluation of vaccination programmes need timely, reliable incidence data.

Despite significant differences in reporting practices between regions, cases from serogroup B remain dominant in Italy, as the estimated number of discharge records for IMD that could be attributable to group B in our analysis shows.

Our work highlights the importance of enhancing surveillance for meningococcal disease and strengthening vaccination programmes against all preventable meningococcal serogroups.

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■ Correspondence: Rosa Prato, Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi di Foggia, via Napoli 20, 71121 Foggia, Italy - Tel. +39 0 881 588036 - Fax +39 0 881 588047 - E-mail address: rosa.prato@unifg.it