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Review article

Deciphering the Burden of Meningococcal Disease: Conventional and Under-recognized Elements

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A B S T R A C T

Invasive meningococcal disease remains a substantial global public health burden despite being vaccine-preventable worldwide. More than one million cases are reported annually, with average fatality rates ranging from 10% to 40% depending on clinical presentation and geographic location. Survivors may suffer debilitating sequelae that reduce the quality of life for the patient and family members responsible for their care. Major financial burdens are associated with acute treatment and follow-up care, and outbreak management often places extensive financial strains on public health resources. Although the clinical and financial aspects of meningococcal disease burden are straightforward to quantify, other burdens such as lifelong cognitive deficits, psychological stress, adaptive measures for reintegration into society, familial impact, and legal costs are systematically overlooked. These and other facets of disease burden are therefore not systematically considered in cost-effectiveness analyses that public health authorities take into consideration when making decisions regarding vaccination programs. Changing the approach for measuring meningococcal disease burden is necessary to accurately understand the societal consequences of this devastating illness. In this article, the conventional and under-recognized burdens of meningococcal disease are presented and discussed.

Invasive meningococcal disease (IMD) is caused by the gram-negative commensal bacterium *Neisseria meningitidis*, whose only known reservoir is the human nasopharyngeal tract [1]. With more than 1.2 million cases reported worldwide each year, IMD represents a significant global public health concern [2]. Meningococcal disease is potentially fatal within 24 hours of onset of illness and has an average case fatality ratio (CFR) ranging from approximately 10%–20%, which can reach as high as 40% in patients with septicemia [3–7]. Among survivors, up to 20% may experience permanent or long-term sequelae [8].

The highest rates of IMD are reported in infants younger than 1 year, adolescents, and young adults [1,9]. Geographic region and season are known to influence IMD incidence, which ranges from <1 case to more than 1,000 cases per 100,000 population [1,5,10,11]. Worldwide, most meningococcal disease is caused by six serogroups, defined based on differential expression of bacterial capsular polysaccharides: A, B, C, W, X, and Y [12,13]. Serogroups A and C are frequently associated with hyperendemic disease, whereas serogroup B is often the cause of sporadic disease and outbreaks in developed countries [1,5,14].

Meningococcal disease is dynamic and highly unpredictable, manifesting as isolated cases or outbreaks. Outbreak cases may occur in closely grouped temporal clusters or may be spread across several years. For example, during a serogroup B outbreak in the

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United States, four cases were reported within one month, with a fifth case identified retrospectively [15], whereas cases associated with a separate outbreak were spread across 2 years [16]. Long intervals between cases and erratic transmission patterns make meningococcal disease exceptionally difficult to predict.

This review article presents the global clinical and economic burden of IMD, highlighting other unconventional aspects of disease burden that are frequently overlooked.

Clinical Burden of Disease

Clinical presentation

N meningitidis commonly colonizes the nasopharyngeal tract, but a transition between asymptomatic carriage and invasive disease can occur within 2 weeks of acquisition [1]. After attachment to epithelial cells of the upper respiratory tract, bacteria may spread to the bloodstream or other epithelial surfaces, leading to systemic disease [1,17]. The underlying mechanisms of this shift are not fully understood.

Certain groups are at increased risk for IMD because of physiological, genetic, or environmental characteristics [9,18]. By age group, infants and adolescents/young adults are at highest risk [9]. In some countries, increased risk for IMD in adolescents and young adults may be attributed to increased social mixing behavior, including bar attendance, smoking, or more than one kissing partner [19]. Host genetic factors, mainly polymorphisms in the complement factor H gene, may have roles in susceptibility to IMD [20]. Polymorphisms in the plasminogen activator inhibitor 1 gene, genes encoding Fc receptors of immunoglobulins, and Toll-like receptors are also thought to correlate with disease susceptibility and severity [18]. Functional or anatomic asplenia, complement deficiencies, and chronic underlying illnesses such as membranous glomerulonephritis and immunodeficiency are also considered risk factors for IMD [9,21]. Environmental factors contributing to increased risk include confined living conditions such as military barracks and university dormitories, which are associated with higher nasopharyngeal carriage rates [19]. Travel to countries or regions with hyperendemic meningococcal disease and routine handling of *N meningitidis* in a laboratory are also risk factors [9,22]. Importantly, most IMD cases occur in otherwise healthy individuals without identifiable risk factors in nonepidemic circumstances [18,23].

Meningococcal disease onset is characteristically sudden and may progress to severe disease in as little as 15–24 hours [3]. Symptoms are variable and often difficult to distinguish from other illnesses, at least during the early stages. Patients may present with fever, sudden headache, neck stiffness, rash, nausea and/or vomiting, sensitivity to light, and altered mental status. Meningococcal disease among infants may have less specific symptoms, but a bulging fontanelle may be observed. The number of patients presenting with specific clinical features may also differ between industrialized and developing countries and between outbreaks [1]. Diagnoses are generally made by confirming the presence of *N meningitidis* in a normally sterile site such as blood or cerebrospinal fluid via detection of meningococcal antigens in seroagglutination assays or by PCR for meningococcal genes [17].

IMD may manifest in multiple clinical presentations (Table 1), with the most common clinical diagnoses being meningitis and meningococcemia; these may sometimes present together. Presentation may also differ depending on the infecting *N meningitidis* serogroup. For example, among 879 cases of IMD in the Netherlands between 1999 and 2011, serogroup Y was most frequently associated with meningococcemia, serogroup B with meningitis, and serogroup C with combined meningococcemia and meningitis [24].

Table 1
Clinical presentation of invasive meningococcal disease and case fatality ratios

Clinical presentation/syndrome	Proportion of IMD diagnoses	Case fatality ratio
Meningococcal disease		10%–40% [5]
Meningococcemia	17%–37% [24,25]	13.2%–40% [5,26]
Meningitis	≥50% [11]	2%–9% [24,26]
Meningococcemia + meningitis	4%–22% [24,25]	14%–16.5% [24,26]
Pneumonia	5%–15% [17]	
Chronic meningococcemia	Rare[a] [17]	
Conjunctivitis/endophthalmitis	Rare[a] [17]	
Epiglottitis	Rare[a] [17]	
Pericarditis/myocarditis	Rare[a] [17]	
Peritonitis	Rare[a] [27]	
Septic arthritis/osteomyelitis	Rare[a] [17]	

IMD = invasive meningococcal disease.
[a] Rare diagnoses, <5% of cases.

Meningitis accounts for at least 50% of IMD cases worldwide [11]. In the United States between 2001 and 2005, meningitis was diagnosed in 70% of children aged ≤19 years with IMD [28]. Approximately, 20% of IMD is attributed to meningococcemia. Symptoms include sudden fever, a nonblanching rash that may worsen to purpura fulminans, hypotension, multiorgan failure, and other manifestations of septicemia [5,11,17].

Meningococcal pneumonia occurs in ≤15% of patients but may be underdiagnosed due to the inability to distinguish *N meningitidis* in sputum samples as being invasive or carriage in origin. Meningococcal pneumonia tends to occur in older adults more often than younger adults; the median age of these patients in the United States has been reported at 68.5 years, compared with 18 years for meningococcal meningitis or meningococcal bacteremia [4]. Less frequently reported meningococcal diagnoses include epiglottitis, septic arthritis, urethritis, conjunctivitis, and pericarditis [17].

Mortality

CFRs of 10%–20% persist among those who contract meningococcal disease (Table 2) [4]. Globally, an estimated 135,000 deaths are attributed to IMD annually [2]. Risk factors for fatal outcomes of all-cause bacterial meningitis include reduced consciousness, tachycardia, and low cerebrospinal fluid white blood cell count [33]. IMD mortality is greatest in the elderly, reaching as high as 20% in the United States [26]. In U.S. children from 2001 to 2005, CFRs were 3.8% in those aged ≤5 years, 9.5% in those aged 6–10 years, and 21.2% in those aged ≥11 years [28]. In less developed countries, meningococcal meningitis incidence is substantially higher, especially in the sub-Saharan "Meningitis Belt." In 2014, approximately 9.1% of IMD cases in Africa were fatal although CFRs varied widely by country, reaching as high as 26.4% [29]. Fatality rates in Latin American countries range from 10% to 20% although higher CFRs have been associated with specific serogroups during outbreaks [30].

Some studies have detected associations between serogroup and mortality rate, with serogroups C and Y having higher CFRs [26], whereas others have not found consistent associations [24,28]. A Dutch study reported a CFR of 13% each for serogroup