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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

Table 2
Case fatality ratios of invasive meningococcal disease by serogroup and age group

Category	Case fatality ratio
Global	5%–10% [12]
Overall	
Industrialized region	7.3%–15.7% [15,26]
Undeveloped region	9.1%–26.4% [29,30]
Serogroup	
A	
C	9% [24]
W	13% [24]
Y	13% [24]
B	5.3%–12.5% [15,24,31]
Age group	
<1 year	2% [24]
Serogroup B	8.1% [32]
Serogroup C/Y	4.9% [32]
1–<5 years	5%–7% [24]
Serogroup B	2.7% [32]
Serogroup C/Y	6.9% [32]
5–<10 years	4% [24]
Serogroup B	16.6% [32]
Serogroup C/Y	10.4% [32]
10–<19 years	4% [24]
20–<65 years	8% [24]
Serogroup B	9.5% [32]
Serogroup C/Y	13.9% [32]
≥65 years	39% [24]
Serogroup B	41.3% [32]
Serogroup C/Y	21.3% [32]

Table 3
Sequelae associated with invasive meningococcal disease

Sequela	Rate
Clinical diagnosis	
Meningitis	8.2%–28% [24,26] (unique study vs. review)
Meningococcemia	1.5%–33% [24,26]
Meningitis + meningococcemia	3.5%–37% [24,26]
Serogroup	
B	28%–41.3% [24,26,35]
C	22.2%–34% [24,35]
W	15% [24]
Y	54% [24]
Condition	
Arthritis/vasculitis	4.7% [36]
Skin scarring	6.4%–48% [26,31,35]
Amputation/limb loss	.8%–14% [26,31]
Seizures	1.4%–13.9% [31,37–39]
Cognitive impairment[a]	2.9%–7.5% [26,40]
Hearing loss	2%–9.3% [26,31,37,39]
Visual abnormalities[a]	2.7%–13.7% [26,40]
Neuromotor disability[a]	1.2%–8.1% [26,40]
Neurologic impairments	13.5% (adult) [26], 2.4%–10.1% (pediatric) [26,35], 3.6% (all) [31]
Growth impairment	6%–13.1% [26]
Renal dysfunction	2%–8.7% [31,39]

[a] Includes values for all-cause bacterial meningitis.

W and Y IMD [24]. Between 1998 and 2007 in the United States, the overall CFR for serogroup W was highest (16.3%), followed by serogroups C (14.7%), Y (12.0%), and B (10.6%) [4,34]. CFRs may also vary by clinical presentation of IMD, with septic shock and combined meningitis/septic shock causing more deaths than meningitis alone [24].

Morbidity

Long-term consequences of meningococcal infection may be severe. Up to 20% of survivors experience permanent significant sequelae, with these proportions varying by age and the severity of infection [8,24]. Although associations between severity of sequelae and serogroups have been inconsistent [24], one study from Great Britain reported more severe sequelae associated with serogroup C disease than serogroup B [26].

Sequelae may be physical, neurologic, cognitive, and psychiatric (Table 3). Skin necrosis, seizures, deafness, ataxia, and amputation represent several types of sequelae reported among IMD survivors [28]. Overall, the most frequently reported long-term sequelae are hearing loss, cognitive defects, and visual abnormalities [26].

Among physical sequelae, skin scarring occurs most frequently and is associated with meningococcemia [26]. Amputation, also associated with meningococcemia, occurs less frequently and may range from loss of a digit to loss of single or multiple limbs. Amputation rates range from .8% to 14% depending on study sample size [26]. In addition, bone growth plates may be sufficiently damaged during acute IMD infection to cause differences in limb length or arrest of growth altogether [26].

Neurologic effects of IMD include deficits in memory and executive function, unilateral or bilateral hearing loss, seizures, and chronic pain. Hearing loss has been reported in approximately 2%–6% of survivors [26,37]. Epilepsy has been recorded in 2% of children diagnosed with serogroup B IMD [37], and the global rate of unprovoked seizures in meningococcal meningitis survivors is estimated at 1.4% [38]. Children diagnosed with all-cause bacterial meningitis as infants were estimated to have a substantially higher risk for severe or moderate disabilities at 5 years of age compared with controls, but these risks varied depending on infecting organism [40]. Survivors of IMD may experience mild to severe cognitive sequelae, including difficulty concentrating, low academic achievement, and deficits in executive function that have consequences into adulthood for educational achievement [26,41]. Significant differences were reported in cognitive and behavioral assessments between IMD survivors and control groups [26]. In a large Danish study, 11% fewer meningococcal meningitis patients completed high school, and 7.9% fewer patients achieved higher education [42].

Psychiatric effects of meningococcal disease may be short-lived or may manifest as long-term consequences, especially for pediatric patients and their parents. Two studies documented an increased risk for post-traumatic stress disorder (PTSD) in children diagnosed with meningococcal disease, and parents or caregivers may also experience long-term effects from the stress associated with an acute and potentially fatal illness in a child [26,43]. Most of the studies assessing the burden of IMD focus on the acute phase or soon after hospitalization, meaning the mid- to long-term psychiatric impact of IMD are probably under-recognized.

Reduction in the quality of life (QoL) in IMD patients is dependent on the type and severity of sequelae. One study reported a reduction in QoL in 23% of IMD survivors who completed a survey designed to assess emotional and physical health [44]. In a second study, survivors with intellectual and behavioral deficits scored worst, suggesting that cognitive impairment may be an equally important contributor to loss of

Table 4
Direct and indirect costs associated with invasive meningococcal disease

Clinical presentation	Cost (USD for study year also shown)					
	Direct			Indirect		
	Pediatric cost (range; USD)	Adult cost (range)	Overall cost (SD)	Pediatric cost (range)	Adult cost (range)	Overall
Meningococcal disease						
Developed countries	€6,800 [25][a] [$8,976] £157,101–£136,401 [45] ($247,434–$214,831)[b]	€8,250 [25][a] [$10,890]	$65,980 [46][c] $46,736 ($109,924.40) [39][c]			
Undeveloped countries	$175 ($62–$1,442) [47][d,e] $1,289 ($207–$7,076) [48][b,e] $162 ($115–$248) [49][f,e]		$90–$244 [50][g]	$46 ($0–$863) [47][d,e]		
By clinical presentation						
Meningococcemia	$79,648 [46][c]					
Meningitis	$56,202 [46][c]					
Other	$69,269 [46][c]					

Outbreak containment	Large-scale cost (range)	Small-scale cost (range)	Large-scale cost (range)	Small-scale cost (range)
Developed countries	$55,755 ($26,371–$91,046) [51][b]	$41,857 ($14,085–$69,629) [51][b]	$579,851 ($105,484–$1,081,627) [51][b]	$299,641 ($42,254–$557,028) [51][b]
Undeveloped countries	$2,222 ($.31–$6,465) [51][b]		$3,407,590 ($58,363–$9,726,937) [51][b]	
Sequelae			With (annual)	Without (annual)
Annual			€4,147.69 [25][a] ($5,474.95)	€489 [25][a] ($646)
Lifelong			€1,183,272–€3,149,676 [52][h] ($1,514,588–$4,031,585)	

SD = standard deviation; USD = United States dollar.
[a] Cost reported in 2013 euro.
[b] Cost reported in 2010 USD.
[c] Cost reported in 2009 USD.
[d] Cost reported in 2012 USD.
[e] Includes values for all-cause bacterial meningitis.
[f] Cost reported in 2005 USD.
[g] Cost reported in 2006 USD.
[h] Cost reported in 2012 Euro.

QoL as physical impairment [26]. In a high-income country, the estimated effects of IMD sequelae in terms of quality-adjusted life-years lost differed by type and severity of sequela. If 1.0 represents 1 year in perfect health, quality-adjusted life-years lost for sequelae from most to least severe were calculated to be .94 for severe neurologic disability, .74 for blindness, .46 for cognitive deficits, .39 for amputation with substantial disability, and .19 for hearing loss [25].

Economic Burden of Disease

Costs associated with meningococcal disease vary by clinical presentation and geographic region and may be categorized as direct, indirect, and societal (Table 4). Direct costs are associated with treatment of the acute phase of IMD, usually described in terms of hospitalization costs. Indirect costs encompass follow-up treatment and expenses associated with disease sequelae. Societal costs may be measured in terms of loss of QoL as a result of meningococcal infection.

Direct costs

The economic burden of IMD depends on the economic status of the country and whether health care is government-sponsored or private. Treatment costs frequently comprise a greater proportion of the per capita gross domestic product in low-income countries. Costs to rural households in low-income countries are generally lower than for urban households but may comprise a greater proportion of household income [50]. Between 1990 and 2010, average costs per IMD case during outbreaks in high-income and low-income countries were estimated at $41,857 to $55,755 and $2,222 (USD), respectively [51].

Developed countries. The total one-year direct cost burden of IMD in U.S. hospitals has been estimated at $76 million (USD), which corresponds to $65,980 per case. Costs vary by clinical diagnosis; treatment for septicemia costs approximately 40% more than treatment for meningitis ($79,648 vs. $56,202 per case) [46]. In Europe, pediatric hospitalization costs in Italy have been estimated at €6,800 ($8,976 for same study year) per stay, and at €8,250 ($10,890) for adult hospitalizations [25]. A study of two IMD cases in Spain estimated costs in the year of acute illness to range from €121,896 ($156,027) to €168,251 ($215,361), depending on clinical diagnosis [52]. In the United Kingdom, acute costs per case for septicemia and meningitis treatment, respectively, were estimated at £157,101 ($247,434) and £136,401 ($214,831) [45].

Undeveloped countries. The average cost per household per IMD case in sub-Saharan Africa was estimated at $90 without sequelae and $244 if sequelae were present [50]. One study of pediatric all-cause bacterial meningitis in Senegal estimated a mean cost per acute episode of $1,289 (range, $207–$7,076) [48]. A study of economic health care burden in Kenya reported a median cost for pediatric all-cause bacterial meningitis of $162 (range, $115.16–$248.14) [49]. In Vietnam, the median direct cost associated with all-cause bacterial meningitis treatment in children aged <5 years was estimated at $175 (range, $62–$1,442), which included medication, medical supplies, diagnostics, bed-days, and outpatient costs [47]. The limitation of

studies reporting all-cause bacterial meningitis is the lack of specificity for meningococcal meningitis.

Indirect costs

Beyond the expenses associated with diagnosis and hospitalization, financial input is necessary to address sequelae in IMD survivors. Costs are highly dependent on severity of the sequelae and can vary between and within countries.

Developed countries. Costs associated with caring for those who have survived meningococcal disease can be overwhelming. Although IMD is relatively rare compared with other infectious diseases, approximately 20% of survivors require continued treatment for sequelae after the primary infection is resolved, placing a substantial burden on health services and families. Excluding initial hospitalization, approximately $37 million are spent for follow-up care in the first year after diagnosis [46]. Among patients enrolled in a managed care program in the United States between 1998 and 2009, those reporting sequelae incurred substantially higher costs for office visits, home health care costs and medical equipment, and pharmacy costs [39]. A Spanish study reported lifelong costs for treatment of an IMD patient diagnosed with severe sequelae, including neurologic deficits, at €1.18 million to €3.14 million ($1.51 million to $4.01 million), including €121,896 to €168,251 ($156,026 to $215,361) for medical costs in the first year after diagnosis and an average of €32,509 ($41,612) per year for the rest of the patient's life for social care costs. An Italian study reported the average annual cost per person with sequelae as approximately €4,100 ($5,412), whereas survivors without sequelae were estimated to pay nearly 10-fold less (€489 [$646]) in follow-up costs in the first year after IMD diagnosis [25].

Undeveloped countries. The enormous costs associated with surviving meningococcal disease are even more overwhelming for those living in low-income countries. Although actual dollar figures may be relatively low compared with indirect costs reported in high-income countries, the resources required to provide for a survivor may comprise a disproportionately large portion of household annual income. Indirect costs associated with hospitalization for pediatric all-cause bacterial meningitis in Vietnam were estimated at $46 [47]. Over the course of a lifetime, these expenses may fluctuate, depending on need for rehospitalization or for long-term care of a patient with severe sequelae. Total costs for a 30-year lifetime of care for Senegalese pediatric all-cause bacterial meningitis survivors were estimated at $36,336 (range, $477–$99,528) [48].

Societal costs

Costs associated with a lifetime of care for survivors of IMD place substantial burdens on government health care resources or health insurance providers. Not unexpectedly, survivors with sequelae require greater investment of societal resources, and those with severe sequelae require the greatest input [52].

A Vietnamese study estimated the mean (standard deviation) cost for treating all-cause bacterial meningitis from a societal perspective at $727 ($865), which is approximately fourfold higher than the cost of care during the acute phase of disease [47]. A Spanish study of two cases of IMD estimated that social care costs within one year of diagnosis ranged from €28,665 to €33,330 ($36,691 to $42,662) and cost approximately €27,000 ($34,560) per year for the rest of the patient's life [52]. Lifelong rehabilitation costs from a government perspective in the United Kingdom were estimated to range from £1.368 to £3.038 million ($2.155 to $4.785 million) for meningococcal septicemia and from £1.721 to £4.474 million ($2.711 to $7.047 million) for meningococcal meningitis [45].

Outbreaks of meningococcal disease in particular are associated with high societal costs encompassing IMD treatment, containment strategies, and community disruption or anxiety. Costs associated with reactions to outbreaks are largely borne by public health departments, which are given the difficult task of budgeting financial and human resources to address outbreaks. These departments must coordinate targeted vaccination in the outbreak population and prophylactic antibiotic administration in close contacts of the disease case. In high-income countries for the period 1990 to 2010, outbreak management costs such as those above were estimated at $299,641 per small containment strategy and $579,851 per large containment strategy. Management costs for low-income countries for the same period were estimated at $3,407,590 per large containment strategy [51]. A study of costs associated with the management of a cluster of IMD in England reported that managing two cases of meningococcal infection cost nearly 17 times more than the management of a single case (£317 vs. £5,584 [$502 vs. $8,845]). The largest component of this difference in cost was attributed to additional health department staff time required to manage the outbreak rather than costs associated with prophylactic antibiotics or medical equipment [53].

Neglected Burden of Disease

The burden of meningococcal disease is most often measured quantitatively in terms of fatality rates and cost of treatment, which leaves other more qualitative categories of disease burden underrepresented. In addition, most of the available data on the burden of disease refer to the acute phase of disease. Because little data are available describing these neglected aspects, these components may not be sufficiently emphasized in the collection of data that policymakers consider when evaluating vaccination programs aimed toward proactively preventing rather than managing meningococcal disease. Prevention of IMD through vaccination obviates these less visible, but nonetheless important, burdens of disease (Table 5).

Long-term cognitive and psychiatric burden

Cognitive, psychosocial, and psychiatric sequelae are usually only considered in the short term and are systematically neglected as long-term sequelae when considering the effects of IMD. Very few studies have aimed to assess this particular burden in depth and even fewer with a long-term perspective. Only through additional long-term follow-up studies will these less obvious defects be detected and described rigorously.

Consequences of treatments administered during hospitalization for meningococcal disease are not often considered in descriptions of IMD burden. Sedatives and analgesics are frequently given to IMD patients and may exert negative influences on neuropsychological health. A Dutch study evaluating IMD patients four or more years after hospital discharge reported an association between the use of morphine, fentanyl, and

Table 5
Neglected burden of invasive meningococcal disease and all-cause bacterial meningitis

Burden	Description
Cognitive impairment	Learning disabilities, behavioral deficits, lower educational achievement [25,26,41,42,54,55]
Psychological stress	Post-traumatic stress disorder–like symptoms (in patients and caregivers); depressive symptoms [23,26,43,56–59]
Family burden	Loss of income often required to allow a caregiver to devote sufficient time to the survivor; siblings also may be negatively affected; emotional stress in caregivers [47,48]
Adaptive measures	Rehabilitation costs, special education plans, medical devices (hearing devices, prostheses) [26,48]
Legal burden	Cost of retaining lawyers for malpractice suits; lost productivity associated with legal complaints; damages awarded to plaintiff [60–62]
Fear of meningococcal disease	Increased clinical work and testing (bloodwork, cerebrospinal fluid sampling), unnecessary treatments or hospitalizations ordered by treating physicians to rule out meningococcal disease
Social crisis management	Logistical planning associated with managing outbreaks (vaccine purchase, storage, administration, and follow-up surveillance) [63]

opioids and poorer performance on tests evaluating verbal, visual, and executive function [54].

Several reports have noted significant negative psychological effects among children surviving IMD, including emotional and behavioral issues. As many as 62% of children treated for IMD experienced symptoms consistent with post-traumatic stress, and approximately 10% of children met diagnostic criteria for PTSD [26]. Among children hospitalized with meningococcal septic shock, adolescents aged 12–17 years reported lower global self-worth than age-matched controls, particularly among patients with skin scarring [56]. How these experiences in childhood may influence adult psychological well-being is unknown.

Significant cognitive deficits relating to number and word fluency have also been detected among IMD survivors evaluated 4–16 years after hospitalization [55]. One of the few studies to report data related to educational achievement in adults after pediatric all-cause bacterial meningitis concluded that economic self-sufficiency is compromised in meningitis survivors, with a substantial component of the deficiency stemming from strain placed on the family [42].

Family burden

Coping with an IMD diagnosis imparts a substantial emotional and psychological burden on family members or caregivers, especially when potentially faced with a new reality of economic sacrifice and loss of QoL. Studies of the effects on QoL after diagnosis with meningococcal disease specifically (as opposed to pneumococcal or general bacterial meningitis) are somewhat rare. The burden of IMD on a family may be described in economic terms such as loss of income to care for a survivor but should also include the less easily quantifiable facets of the emotional burden experienced by parents who must care for a child with physical, psychological, or cognitive disabilities.

In a study of all-cause pediatric meningitis in Vietnam, approximately half of caregivers lost income because of the child's illness, and nearly one third were forced to use additional sources of payment, such as borrowing and sale of household assets, to cover medical costs. In addition, paid work days lost due to caring for the ill child were estimated at 16.6 days. Overall, the economic burden of caring for a child with all-cause bacterial meningitis represented approximately 83% of the household's monthly income [47]. Sequelae that are severe enough, and last long enough, to prevent a child in a low-income country from attending school may place an additional burden on family members to provide childcare while the primary household earners are at work. Among pediatric all-cause bacterial meningitis survivors in Senegal who did not attend school, 61% were kept home because of meningitis sequelae, and 81% of households reported an adult foregoing work to care for the child [48].

Hospitalization for IMD may elicit negative psychological effects in both patients and caregivers (i.e., children and their parents) [57]. Parents of critically ill children are placed under enormous stress; short-term studies of emotional health in mothers of children with IMD indicated a substantial increased risk for developing PTSD [26]. Problems of emotion, hyperactivity, and behavior were observed at a three-month follow-up time point among 60 IMD survivors aged 3–6 years. Approximately, 43% of the parents of those children were considered at risk for psychiatric disorders, and 19%–38% were considered at risk for PTSD [58]. In a study of 86 parents of children diagnosed with IMD in the United Kingdom, 23% of mothers and 11% of fathers were considered at risk for PTSD 12 months after their child was hospitalized [59].

The long-term psychological effects of IMD on caregivers are not well characterized. In a survey of 164 parents of children hospitalized with meningococcal septic shock, most parents recovered from the initial psychological distress associated with caring for a child hospitalized for a potentially fatal illness, but after 4 years or more, nearly one quarter of parents were considered at risk for psychiatric disorders [23].

Adaptive measures

Consequences of IMD with sequelae may require extensive follow-up treatment and adaptive measures necessary to reintroduce an IMD survivor into society. As hearing loss, motor deficits, and cognitive deficits are among the most frequently reported sequelae, hearing devices, physiotherapy, and specialized education are necessary to restore a survivor to a QoL as close to normal as possible. Although limb amputation is not as common as other types of sequelae, costs associated with prosthetics may be much higher than costs for other adaptive measures. In high-income countries, costs associated with these services are frequently covered by government-sponsored health care, but in low-income countries, these types of adaptive measures are often out of the financial reach of the average household. In Senegal, for example, approximately 83% of caregivers of children with all-cause bacterial meningitis were aware of treatments or adaptive measures that would benefit their child but did not access the treatment due to an inability to cover the cost [48].

Sequelae sometimes may not be linked to a past episode of IMD because of a substantial length of time between hospitalization and manifestation of the effects of the disease, thus requiring intervention at a much later time. For example, effects

on cartilage growth during acute infection may only show a clinical effect many years later as asymmetric or arrested limb growth [26], rendering a link between the effect and the infection difficult to discern and therefore difficult to report as part of the burden of IMD.

Legal burden

Clinical presentation of meningococcal disease may vary in onset and severity and often mimic symptoms of less severe infections. These characteristics may consequently render a timely and accurate diagnosis difficult. Patients who are not diagnosed correctly may turn to legal action with claims of medical malpractice (noniatrogenic/misdiagnosis) to secure compensation for lost QoL. The financial outlay and lost productivity associated with legal complaints place a substantial financial burden on both plaintiff and defendant, whether the defendant is a privately practicing physician, a health care network, or a government-run public health ministry. Out-of-court settlements and damages awarded to plaintiffs are also components of the legal burden associated with meningitis, for example (all-cause bacterial meningitis in this case) [60]. In a study of malpractice cases brought due to all-cause meningitis contracted after otolaryngologic procedures, untimely diagnosis and permanent deficits were the two most frequently reported allegations [61]. As a practical example, the United Kingdom's Joint Committee on Vaccination and Immunization has recently agreed that these legal costs and compensation for factors other than QoL losses may represent additional costs to governmental health services and should be taken into account in the cost-effectiveness analysis when assessing the use of meningococcal B vaccine as part of the national immunization program [62].

Fear of meningococcal disease

One of the most important challenges for a practitioner in the first line of health care (i.e., in a primary care or emergency room setting), is the possibility of missing a case of IMD in the initial stages of the disease, when IMD is clinically indistinguishable from any other general syndrome of an infectious disease. This "fear of meningococcal disease" is partially related to the legal burden associated with IMD regarding misdiagnosis by the treating physician or the "the risk of doing nothing." In an effort to provide the most comprehensive care for a patient and rule out IMD as a diagnosis, physicians may invest specific work time, order additional bloodwork, cerebrospinal fluid sampling, or other potentially invasive tests. After the diagnostic workup, doubtful or inconclusive cases may be hospitalized for initial observation or empirical therapy while awaiting the clinical course. In many of these cases, these procedures and measures are later shown to have been unnecessary on a final diagnosis after ruling out IMD. To our knowledge, no report in the literature has attempted to specifically measure this burden.

Social crisis management costs

Meningococcal disease outbreaks constitute a major public health burden owing not only to their unpredictability but also to the expenses associated with treating close contacts of an infected person and implementing strategies to contain the outbreak [63]. Outbreaks may be brief or last several years; the public health resources required to manage an outbreak include expenses for prophylactic antibiotics and less tangible costs associated with vaccination campaigns, educational campaigns, and surveillance. Outbreaks at U.S. universities have placed severe financial burdens on the universities, which were required to quickly coordinate vaccine purchase, storage and handling, and campus-wide advertisement campaigns to support vaccination clinics aimed at preventing disease spread [64].

Discussion

Considering the facets of meningococcal disease burden outlined previously, particularly those that are underreported or overlooked, the optimal strategy to reduce overall IMD burden is prevention through vaccination. Vaccines protecting against IMD caused by serogroups A, C, W, Y, and more recently, B, are now available, and public health authorities must evaluate such vaccines from different perspectives before recommending them in national immunization programs. A recent example of a successful meningococcal vaccination strategy is the phased introduction of the serogroup A conjugate vaccine PsA-TT (Meningococcal A conjugate vaccine), which was implemented in Africa starting in 2010 to control cyclical serogroup A IMD outbreaks [65]. Among countries participating in surveillance, the incidence of serogroup A meningitis decreased by more than 10-fold [65]. The vaccination program also nearly eliminated serogroup A carriage in those who were and were not vaccinated, providing evidence for a herd effect and further protection from disease [66]. Significant effects on disease incidence and carriage combined to make this vaccine extremely effective.

Vaccines may be costly to produce; thus, the economic investment they require may present a barrier—if not the main barrier—to recommendation [67]. Few studies have examined the nonclinical/economic burdens of meningococcal disease, which greatly affect the body of data considered during cost-effectiveness evaluations.

Immunization with a MnB vaccine would optimize IMD control [68]. Current MnB clinical disease burden is likely underestimated in countries where molecular diagnostics are not routinely used due to limitations in the detection of *N meningitidis* caused by interference of early antibiotic treatment with microbiological culture detection methods [69]. In addition to this likely underestimation of disease burden, vaccine efficacy modeling has focused on direct protection to estimate cost-effectiveness and numbers needed to vaccinate. The types of static models used are susceptible to inaccurate estimation due to the comparatively lower incidence of IMD than other vaccine-preventable infectious diseases [69]. The severity of sequelae, long-term outcomes, and litigation costs that could be reduced by prophylactic vaccination should be important aspects of the burden of meningococcal disease considered during economic evaluation [26,69].

A MnB vaccine (4CMenB) was recently approved for inclusion in the national immunization program in the United Kingdom only after multiple iterations of cost-effectiveness modeling and price negotiations with the vaccine manufacturer [70]. In March 2014, the UK's Joint Committee on Vaccination and Immunization issued a statement supporting the introduction of the 4CMenB vaccine to the routine infant immunization program but only at a cost-effective price per dose [71]. Initial cost-effectiveness estimates indicated that vaccination would not be cost-effective at any price, but after adjusting inputs into the original model, the outcome favored recommendation. This example highlights the need for careful review of the often

speculative parameters involved in cost-effectiveness evaluations for vaccines, particularly for new vaccines without a history of widespread use, and for vaccines targeting rarer infectious diseases for which changes in incidence may be difficult to track. Methodology intended to evaluate the cost-effectiveness of curative treatments places preventive treatments such as vaccines at a disadvantage [67].

Summary and Future Considerations

The global clinical burden of IMD is substantial, persistent, and unpredictable. Surviving patients may experience sequelae ranging from skin scarring to hearing impairment to limb amputation, which undoubtedly reduce the patient's QoL. Major economic burdens are also incurred during hospitalization and after discharge. On a larger scale, management of meningococcal disease outbreaks in communities or university campuses requires extensive financial outlays by public health resources. In addition, considering that most cases occur in otherwise healthy subjects, the most effective strategy to reduce the total burden of meningococcal disease is prevention through vaccination.

Less easily quantifiable outcomes and costs associated with meningococcal disease (Table 5) are consistently neglected when calculating disease burden. Consequently, these factors are not usually included in cost-effectiveness analyses when proposed vaccination programs are evaluated by public health authorities for inclusion in national immunization programs. To improve the accuracy of cost-effectiveness analyses for meningococcal vaccines, or any new vaccine, the medical community must advocate for a change in the methods by which these vaccines are evaluated from the health economic perspective, and must ensure that all disease burden is measured and accounted comprehensively.

No modern health system can afford to use a speculative economic model that inhibits introduction of a potentially effective disease-prevention strategy. Health economics should serve as guides for, rather than determinants of, immunization policy [67]. No matter how meningococcal disease burden is interpreted, IMD is now a vaccine-preventable disease.

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