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Review article

The Global Evolution of Meningococcal Epidemiology Following the Introduction of Meningococcal Vaccines

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A B S T R A C T

Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* is associated with high morbidity and mortality. Although IMD incidence is highest in infants, a second peak occurs in adolescents/young adults. The incidence of IMD and the predominant disease-causing meningococcal serogroups vary worldwide. Epidemiologic data have guided the development of meningococcal vaccines to reduce the IMD burden. In Europe, serogroup C IMD has been substantially reduced since the introduction of a serogroup C conjugate vaccine. Serogroup B predominates in Europe, although cases of serogroup Y IMD have been increasing in recent years. In the United States, declines in serogroup C and Y disease have been observed in association with the introduction of quadrivalent (serogroups ACWY) meningococcal conjugate vaccines; serogroup B persists and is now the most common cause of outbreak associated disease. In the African meningitis belt, a conjugate vaccine for serogroup A has been effective in decreasing meningitis associated with that serogroup. Outbreaks of the previously rare serogroup X disease have been reported in this region since 2006. In recent years, outbreaks of serogroup B IMD, for which vaccines have only recently been approved by the U.S. Food and Drug Administration and the European Medicines Agency, have occurred in Europe and the United States. Targeting meningococcal vaccination to adolescents/young adults may reduce the morbidity and mortality associated with IMD and has the potential to impact the larger community through herd benefits.

Invasive meningococcal disease (IMD) is a condition, too often fatal, caused by invasion of the bacterium *Neisseria meningitidis* into the blood stream and subsequent development of septic shock and purpura fulminans in a subset of patients. When the bacterium gains access to the central nervous system, meningitis results. The morbidity and mortality resulting from either condition is substantial, with a case-fatality rate (CFR) approximating 10% in developed countries [1–3]. Many survivors experience permanent debilitating sequelae such as hearing loss, neurologic impairments, or limb loss [3,4]. The incidence of IMD varies by geographic region and ranges from <.5 to .9 cases per 100,000 population in North America and Europe to 10 to 1,000 cases per 100,000 population in the African meningitis belt. Incidence is highest in infants and young children, with a second smaller peak in adolescents and young adults (Figure 1) [8,9]. Colonization of the nasopharynx is a prerequisite for IMD, and humans are the only host for this organism. Colonization is typically asymptomatic; however, *N. meningitidis* can translocate from the nasopharynx to the blood stream, resulting in disease. Transmission may occur following close contact with an infected or colonized individual.

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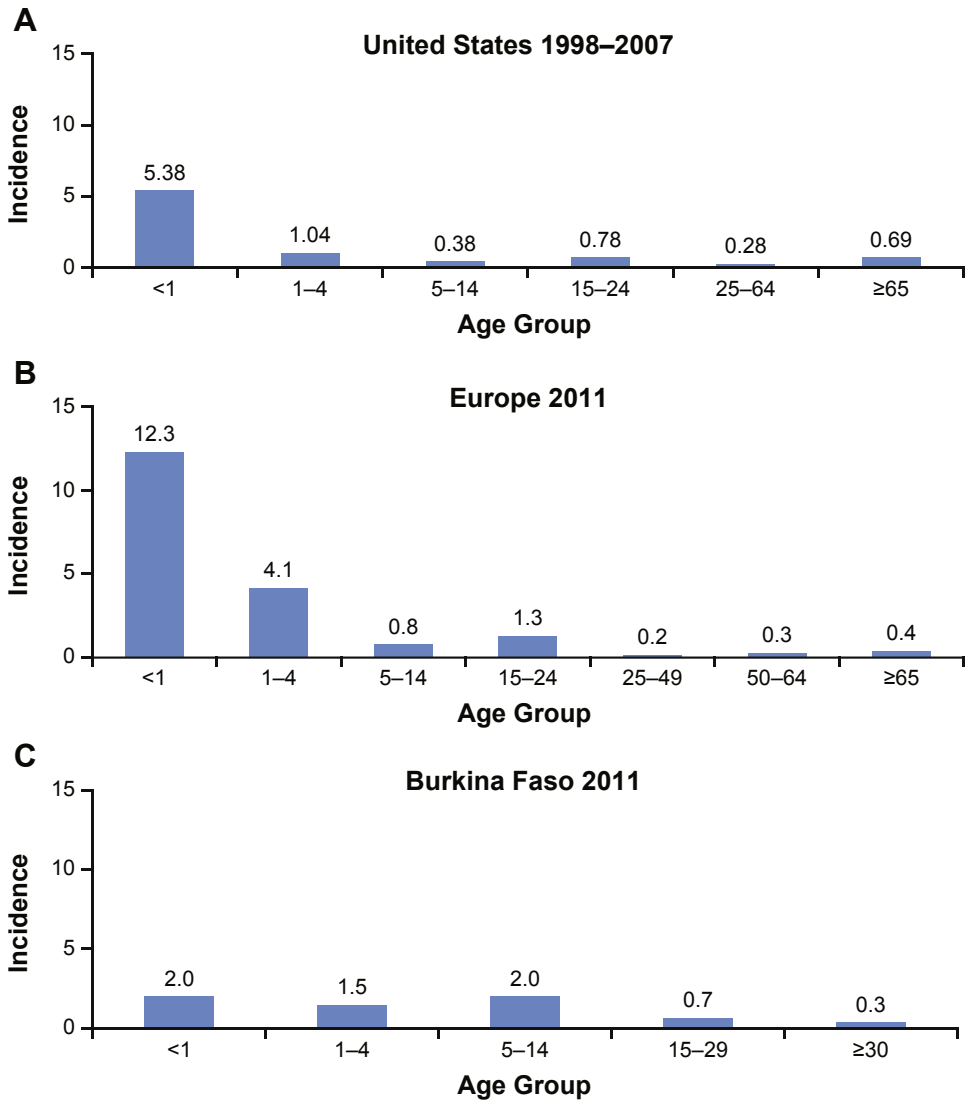

Figure 1. Universality of meningococcal epidemiology: highest incidence in infancy with second peak during adolescence (all serogroups). (A) Invasive meningococcal disease in the United States, 1998–2007, cases per 100,000 population [5]; (B) invasive meningococcal disease in Europe after introduction of MenCC, 2011; cases per 100,000 population [6]; (C) meningococcal meningitis in Burkina Faso after introduction of MACV, 2011, cases per 100,000 population [7].

N. meningitidis is a gram-negative diplococcus in which most pathogenic isolates are encapsulated [10,11]. The major categorization of *N. meningitidis* is by capsular polysaccharide serogroup, of which there are 13. Most cases of IMD are caused by serogroups A, B, C, W-135 (referred to as serogroup W herein), X, and Y [12], with serogroup prevalence differing according to geographic region (Figure 2). A more detailed molecular characterization scheme termed multilocus sequence typing is derived from the analysis of seven housekeeping genes and groups isolates into sequence types and sets of related sequence types called clonal complexes [14,15]. The ability to characterize strains by multilocus sequence typing and sequence types is important for characterizing outbreaks to determine if they are due to a single strain circulating within the community and for identification of hypervirulent strains.

Because of rapid bacterial multiplication in the bloodstream and the subsequent progression of disease, immediate antibiotic treatment and hospital admission with supportive care of patients is required when IMD is suspected [16]. In addition to antibiotic prophylaxis for secondary prevention in close contacts, vaccination may also be of value in controlling meningococcal outbreaks [17]. Effective vaccines are available for serogroups A, C, W, and Y [18], and vaccines for serogroup B (MnB) have recently been approved [19].

Although it is well documented that infants experience high rates of IMD, meningococcal carriage rates in infants in western countries are relatively low, rising as high as 25%–33% by young adulthood in the United Kingdom [20,21]. In the African meningitis belt, carriage rates are highest in individuals aged 5–14 years (5%) [22]. Although carriage isolates are genetically heterogeneous in nature, isolates that cause IMD usually represent a subset of those carried [14]. The properties that make these hyperinvasive strains more pathogenic have not yet been completely identified, but it has been postulated that the presence of viral genetic material incorporated and expressed by *N. meningitidis* (a bacterial prophage) [23,24] may be a virulence