Epidemiology of Meningococcal Disease in Light of Recent Hajj-Associated Outbreaks

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(See the article by Wilder-Smith et al. on pages 679–83)

Neisseria meningitidis serogroup W135 (hereafter, W135) was first identified in 1968 [1]. W135 was initially considered to be a rare cause of invasive disease. However, during the 1990s, it accounted for 2.6%–4% of reported cases of invasive meningococcal disease in the United Kingdom, France, and the United States [2]. After the annual Muslim pilgrimage (the Hajj) in 2000, more than 400 cases of W135 infection in pilgrims and in their close contacts were reported from 16 countries [3]. The outbreak recurred in 2001. The first international outbreak of meningococcal disease associated with the Hajj occurred in 1987 and was caused by N. meningitidis serogroup A (MenA). After that outbreak, Saudi Arabia introduced vaccination against MenA as a condition for receiving a Hajj visa; as a result, there was a marked decrease in Hajj-associated outbreaks.

The incidence of W135 meningococcal disease in Hajj pilgrims in England and Wales was 30 cases per 100,000 pilgrims in 2000 [4]. In 2001, because quadrivalent A/C/Y/W135 meningococcal vaccine was not available for most pilgrims, the incidence in England and Wales remained 28 cases per 100,000 pilgrims. Similar rates were reported in France and Singapore [2, 5].

Hajj pilgrims who became carriers of W135 have been shown to transmit the organism to their household contacts after returning home [2, 6]. Wilder-Smith et al. [5], in this issue of Clinical Infectious Diseases, provide the first quantitative assessment of the risk of invasive W135 disease among household contacts of pilgrims: rates of 18 and 28 cases per 100,000 contacts were observed in 2000 and 2001, respectively, which is similar to the incidence among Hajj pilgrims. Spread of the Hajj-associated W135 strain to persons in the general community who do not have known contact with Hajj pilgrims has also been reported [7].

As a result of the Hajj-associated outbreak of disease due to W135, vaccination with quadrivalent A/C/Y/W135 vaccine was made a requirement for a Hajj visa in May 2001 [8]. The W135 component of the vaccine seems protective: no W135 disease was observed among Hajj pilgrims in Singapore who had received the quadrivalent vaccine in 2001, whereas the incidence was unchanged in those vaccinated with bivalent A/C vaccine [5]. There are no data available to determine what effect, if any, receipt of W135 vaccine has on acquisition of W135 carriage. Wilder-Smith et al. [5] demonstrate that, among Hajj pilgrims from Singapore who had received quadrivalent vaccine, the rate of carriage was 15% upon return to Singapore; none of these pilgrims had been carriers before departure from Singapore [6]. Household contacts of these pilgrims had carriage rates of 3.4% for the Hajj-associated strain of W135. Although no W135 meningococcal disease occurred in vaccinated pilgrims, its incidence in their household contacts did not change after introduction of the use of quadrivalent vaccine. Therefore, the quadrivalent vaccine does not seem to prevent acquisition of W135 or transmission of the organism to close household contacts.

The optimal method of protecting household contacts of Hajj pilgrims remains to be determined. Vaccination with quadrivalent vaccine would not protect young children and would be difficult to implement. Administration of chemoprophylaxis to returning Hajj pilgrims, to eradicate meningococcal carriage and thereby prevent transmission to household contacts, would be expensive and difficult to implement.

Why did it take 32 years after the identification of W135 for the first large outbreak of disease to be observed? Meningococci can be differentiated serologically on the basis of the presence of cell-surface components: capsular polysaccharide (which determines the serogroup), class 2
or 3 outer membrane protein (which determines the serotype), class 1 outer membrane protein (which determines the subtype), and lipopolysaccharide epitopes. Protective immunity is based on the presence of bactericidal antibody directed against both capsular polysaccharide and 1 or more of the other surface antigens (i.e., serotype or subtype proteins) and against lipopolysaccharide epitopes. There is no cross-reactivity between capsular polysaccharides. MenA strains appear to have unique outer membrane proteins, but MenB, MenC, MenY, and W135 share many serotype and subtype antigens.

The complete genomes of MenA and MenB strains have been sequenced, which has helped explain why meningococci continue to be a major health problem [9, 10]. Both genomes have an extraordinary large number and diversity of repeating sequences—much larger than those of any other bacterial pathogen sequenced to date. These repetitive elements include large multiple arrays, many of which specify production of surface-exposed proteins. Gene conversions resulting from recombination of multiple repeating units permit the marked antigenic variation characteristic of meningococci, as demonstrated by the ever increasing number of serotypes and subtypes identified.

In addition, the genomes contain many copies of uptake sequences coding for proteins responsible for recognition and uptake of DNA from the microbial environment. Recombination events resulting from uptake of DNA are much more common than are point mutations as the means of genetic change in meningococci [10, 11]. Capsule switching results from acquisition of capsule biosynthetic genes in vivo, in a carrier colonized concurrently with 2 different meningococcal serogroups [12]. Capsule switching can involve serogroups B, C, Y, and W135, the capsules of which are composed of polysialic acid or of sialic acid linked to glucose or galactose [12]. Capsule switching has been observed during outbreaks in the Czech Republic, in western Norway, in Oregon and Washington (in the United States), and in Spain [12–15]. Exchange of genetic material between strains can also result in changes in the outer membrane proteins that distinguish serotypes and subtypes [16]. Meningococci also import DNA from commensal neisseriae at extremely high rates in patients with mixed colonization in the nasopharynx [17]. Antigenic variations of capsule and of surface proteins resulting from these genetic mechanisms greatly enhance the ability of meningococci to evade host immune responses.

A number of studies have demonstrated that isolates of the Hajj-associated strain of W135 all belonged to the serologic type W135:2a:P1,5,2 and belonged to a single clone of the ET-37 complex [3, 5, 6, 18]. It is of great interest that MenB and MenC strains associated with outbreaks during the past 20 years in Canada, the United States, the United Kingdom, Spain, and Czechoslovakia also belonged to the 2a: P1.5,2 ET-37 complex [13, 15, 19–24]. W135 strains genetically similar to the Hajj outbreak strain have been circulating worldwide since at least 1970 [3]. Therefore, emergence of a new W135 clone or capsule switching between MenB or MenC ET-37 and W135 does not explain the outbreak. The most important factor may be the widespread use of MenA or bivalent MenA/C vaccines. Campaigns of mass vaccination with MenA/C vaccine in Africa have been followed by increased prevalence in the carriage of W135 [25–27]. Replacement of MenC ET-37 by MenB ET-37 was observed following mass immunization with MenC vaccines in Spain and the Czech Republic [15, 28].

The effect of mass use of serogroup-specific vaccines, whether pure polysaccharide or polysaccharide conjugates, on the epidemiology of meningococcal carriage remains to be determined. The use of MenA and A/C vaccines in sub-Saharan Africa during the past 20 years and among Hajj pilgrims since 1987 may have altered meningococcal ecology such that W135 has replaced other carrier strains. During the Hajj, close contact between large numbers of adults from all over the world for several weeks under crowded conditions facilitates transmission of meningococci.

Alterations in carrier epidemiology induced by vaccination and rapid genetic change in the surface antigens responsible for inducing protective antibodies indicate that the problem of Hajj-associated epidemics of meningococcal disease may not be solved by the use of quadrivalent A/C/Y/W135 vaccine. Indeed, control of meningococcal disease, in both endemic and epidemic form, will not be achievable until a serogroup B vaccine effective against all serotypes and subtypes has been developed, as well as conjugated versions of the A/C/Y/W135 polysaccharide vaccines effective in infants, and until they are available at a price that is affordable in developing countries.

References


