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Commentary

Is the Emergence of the *N. meningitidis* Serogroup W ST-11 Hajj Outbreak Unraveling in the New Era of WGS?

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Neisseria meningitidis, or meningococcus, frequently colonizes the oropharyngeal mucosa without causing any detectable symptoms but is also a major cause of bacterial meningitis and septicemia worldwide. The epidemiology and incidence of invasive meningococcal disease (IMD) are unpredictable over time and across geographic regions. In non-epidemic areas such as Europe and US the incidence rate is low, 0.5–5 cases per 100,000 population per year, whereas in the epidemic region of sub-Saharan Africa rates of up to 1000 cases per 100,000 population per year have been recorded. Twelve different serogroups based on the polysaccharide capsule have been identified, but only six of them (A, B, C, W, X and Y) account for 90% of the IMD globally (Harrison et al., 2009). The annual Islamic Hajj pilgrimage to Mecca, Saudi Arabia, has historically been associated with outbreaks of serogroup A. However, during the Hajj pilgrimages of 2000 and 2001, there was an epidemiological shift from serogroup A disease to serogroup W. Serogroup W has previously only been associated with sporadic cases but has emerged as a cause of worldwide outbreaks and continued to cause disease in the sub-Saharan Africa including Niger, South Africa and a large epidemic in Burkina Faso 2002 (Taha et al., 2000; von Gottberg et al., 2008; Traore et al., 2006).

In this issue of EBioMedicine, Mustapha et al. (2015) investigate the genomic epidemiology of serogroup W ST-11 strains from 1970 to 2013 in order to discriminate sporadic W ST-11 strains from Hajj outbreak strains. Antigen-encoding gene profiles, the presence of recombinant alleles and whole genome phylogenetic analyses compared to the Hajj reference genome (strain ID: *M7124*) divided the collection of 270 strains into two clusters: Cluster 1 (Hajj cluster), which consisted of closely related strains collected during, or after the Hajj 2000 epidemic, and Cluster 2 with sporadic strains heterogeneous in nature, consisting of both pre- and post-Hajj (Mustapha et al., 2015).

Capsular switch is a mechanism whereby the bacterium can escape the immunity against a particular serogroup by horizontal gene transfer of the polysialyltransferase gene (*siaD*) or the capsule biosynthesis operon, and has been reported in several outbreaks (Swartley et al., 1997). Mustapha et al. (2015) propose, in line with previous studies (Mayer et al., 2002), that the serogroup W ST-11 diverged through capsular switching from an ancestral serogroup C ST-11 strain based on its high relatedness to serogroup C ST-11 strains and the fact that the majority of ST-11 strains have historically been expressed by serogroup C strains. However, only two serogroup B ST-11 strains and 17 serogroup C ST-11 strains were included in the analysis of this study and therefore it cannot be excluded that serogroup W ST-11 strains arose from another serogroup. Furthermore, they found a group of SNPs specific to the Hajj cluster located in four recombinant regions which were not present in any of the more heterogeneous strains in Cluster 2, which suggests that this allelic replacement is due to recombination with donor sequences from other non-ST-11 isolates or commensal *Neisseria* species. Also, two of these recombinant regions encode three antigens and/or virulence proteins: FHbp, nitrite reductase and nitric oxide reductase, which the authors hypothesize, may have been associated with the emergence of the Hajj clone. Another possible key factor is that the strains belonging to the Hajj cluster carry a unique allele of *fHbp* that is not present in Cluster 2, nor is it cross-reactive with the variants circulating in Cluster 2. This may have led to a novel antigenic type being introduced in a naïve population. Although the meningococcal capsule is a known virulence factor, the virulence of a strain is probably more dependent on the genotype of the isolate. The success of the Hajj strain was therefore probably due to a two-step process including capsular switch and the subsequent evolvement from sporadic W ST-11 strains by sequence variation within antigen-encoding genes and/or virulence genes.

In concordance with previous genomic studies of ST-11 clonal complex strains (Lucidarme et al., 2015), Mustapha et al. (2015) show the co-circulation of both Hajj-related and endemic W ST-11 strains across the sub-Saharan Africa. The majority of W ST-11 strains in South Africa from 2003 to 2013 were Hajj-related strains, as well as the ones circulating in the UK in 2000–2004, whereas endemic W ST-11 strains have been circulating in the US, Brazil and Chile. Although the study includes genomes extracted from public databases to create a large global collection of strains, strains from UK or South Africa are largely overrepresented (89%), which may make it difficult to draw any further phylogeographic conclusions.

The reasons for the fluctuating incidence of invasive meningococcal disease ranging from endemicity to epidemic outbreaks are yet to be understood. Analysis of hyperinvasive complexes such as the ST-11 clonal complex will continue to be important both from a historical

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perspective but also because of recent events such as the introduction of this clonal complex into the MSM community as well as its continued increase in South Africa (von Gottberg et al., 2008), South America (Abad et al., 2014) and in England and Wales (Ladhani et al., 2015). The high-resolution that WGS data generates, together with the access of large collections of genomes from open access repositories, will continue to provide insights regarding the transmission, evolution and virulence of the hyperinvasive complexes.

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