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CHANGING TRENDS IN THE EPIDEMIOLOGY OF ACUTE BACTERIAL MENINGITIS IN "AFRICAN MENINGITIS BELT": A CRITICAL REVIEW

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ABSTRACT

In "African meningitis belt" Regional prevalence of meningococcal meningitis in epidemic years ranges from 400-1000 cases per 100,000 populations. In recent time, there have been outbreaks of meningitis serotype C in Nigeria, initially limited to a few areas in Kebbi and Sokoto states in 2013 and 2014. In 2015, however, there were more than two thousand five hundred (2500) cases of the disease across three states in Nigeria as well as eight thousand five hundred (8500) cases in Niger. Studies of the epidemiology of meningococcal disease demonstrate significant differences in Serogroup distributions by geographic regions. The introduction of MenC vaccines in Europe, MenACWY in the United States and Canada, and MACV in Africa appear to be associated with declines in vaccine type disease and shifts in serotype distributions in those geographic regions. Therefore, although, the exact genes involved in capsular switching have not been well elucidated, reductions in the morbidity and mortality associated with Invasive Meningococcal Disease (IMD) may be achieved with the introduction of Serogroup appropriate vaccines based on epidemiologic data.

KEYWORDS: Epidemiology "African meningitis Belt" Meningococcemia, Cerebrospinal Meningitis, Cerebrospinal fluid, Serogroup C.

INTRODUCTION

Epidemiology of community-acquired bacterial meningitis worldwide has changed in the past decades as a result of the introduction of conjugate vaccines against N. meningitides Serogroup C.[1] However, within almost six months of the recent epidemics of acute bacterial meningitis in Nigeria, (from 13th December, 2016 to 2nd June, 2017) a total of 14,473 suspected cases of Cerebrospinal Meningitis (CSM) were reported from 25 States and of the reported cases, 998 (6.9%) were laboratory tested; of which 460 (46.6%) were confirmed positive for bacterial meningitis. *Neisseria meningitides* Serogroup C remains the predominant (80.6%)[2] Serogroup implicated. Epidemiologically, this outbreak emphasizes the potential for serotype shifts following introduction of Men A conjugate vaccine (MenAfrivac), which protects against the most prevalent type of *Neisseria Meningitides* (Serogroup A).

Epidemiology

"African meningitis belt" is a region of twenty five sub-Saharan countries stretching from Senegal in the west to Ethiopia in the east, with a total population of about five hundred million (500million) people.[3] Since the introduction of the Men A conjugate vaccine (MenAfrivac), which protects against the most prevalent type of *Neisseria Meningitides* (Serogroup A) by the government of Nigeria, with support from the Global Alliance for Vaccine Initiative (GAVI), occurrence of the disease has reduced significantly in all states at risk, including North-Western states. However, Despite overall decrease in serotype A meningococcal infections, the risk of other types of Neisseria meningitides persists, as evidenced by the Laboratory tests that confirmed the predominance of Neisseria meningitides Serogroup C, in the most recent outbreak of meningococcal meningitis in Nigeria.[3]

Epidemics of meningococcal meningitis in the African meningitis belt usually occur during the dry season that ranges from January to June when the incidence can reach as high as 1,000 cases per 100,000 population. During outbreaks, the rate of endemic disease remains relatively high at 10 to 25 cases per 100,000 population.[4] Between 1990 and 2010, the predominant serotype associated with outbreaks in the meningitis belt has been Serogroup A.[5,6,7] which necessitated introduction of a Serogroup A polysaccharide conjugate vaccine (MACV)[8] that was administered in the sub-region.[9,10,11,12] It was reported that, in the period between 1995 and 2004, alone, an estimated 60,000 deaths occurred during meningococcal outbreaks in this region.[5] In 2005, before the introduction of MACV, the Case Fatality Rate (CFR) among countries in the meningitis belt ranged from 4% in Mali to 26% in Benin.[8] However, with the introduction of MACV, the

overall CFR within the region has reduced and has been relatively stable at 8.5%, 9.1%, and 9.1% in 2012, 2013, and 2014, respectively.[10, 11, 12]

Additionally, use of MACV in the region has been accompanied by an overall reduction in epidemic activity among countries in the meningitis belt.[10, 12] Successful vaccination program within the sub-region demonstrated clear evidence of shift in serotypes. For example, in Burkina Faso, more meningitis cases were reported during the 2012 meningitis season than in the 2011 season, primarily because of an increase in Serogroup W cases[13], while, Chad where MACV was not used, Serogroup A still predominated.[14]

Recent Meningococcal Outbreaks: Outbreaks of Serogroup C disease in men having sex with men have been reported since 2013 in three European countries: Germany, France, and Belgium.[15] This strain is related to the outbreak strain identified in New York City from 2010 to 2013. Two years later, two large outbreaks of meningococcal Serogroup C Invasive Meningococcal Disease (IMD) occurred in Africa. Between January and May 2015, Niger's Ministry of Public Health notified the World Health Organization of 8,500 suspected cases of meningococcal meningitis, including five hundred and seventy three (573) deaths.[16] This is the first large-scale meningitis outbreak caused by N. meningitides Serogroup C to hit any country in Africa's meningitis belt.[17] At the same time, Nigeria notified the World Health Organization of six hundred and fifty two (652) suspected cases of meningococcal disease, including fifty (50) deaths, apparently due to Serogroup C.[17] Both of these outbreaks emphasize the potential for serotype shifts following introduction of meningococcal conjugate vaccines with limited coverage of clinically relevant isolates.

Studies of the epidemiology of meningococcal disease demonstrate significant differences in Serogroup distributions by geographic regions. The introduction of MenC vaccines in Europe, Men ACWY in the United States and Canada, and MACV in Africa appear to be associated with declines in vaccine type disease and shifts in serotype distributions in those geographic regions.[18]

Epidemiologic surveillance will continue to be important in providing data on which national and regional health authorities can base vaccination policies. Further reductions in the morbidity and mortality associated with Invasive Meningococcal Disease (IMD) may be achieved with the introduction of Serogroup appropriate vaccines informed by epidemiologic data.[18] This is similar to what happed in Europe where introduction and widespread use of meningococcal vaccines for Serogroup C in Europe and for Serogroup A, C,W, and Y in US and Canada, led to significant reductions in IMD associated with these serotypes.

Possible molecular basis for paradigm shift. Polysaccharide capsule is the most important virulence determinant of Neisseria meningitides, a normal commensal of the human nasopharynx that occasionally causes invasive meningococcal disease (IMD).[21] Although evidence of capsular switching has not been extensive so far, an increased prevalence of Serogroup either not covered in existing vaccines (e.g., Serogroup X in Africa) or contained in vaccines that are not in common use (e.g., Serogroup Y in Europe) has been observed.[18] Sequence type (ST)-11 clonal complex (cc11), a hyper virulent meningococcal lineage, is a leading cause of IMD globally.[22, 23] Cc11 is a highly genetically diverse lineage associated with IMD caused by capsular Serogroup including Serogroup C,[22, 24] Serogroup C cc11 strains were associated with endemic IMD cases implicated in epidemics in the African "meningitis belt" in the 1970s.[22, 25, 26]

The capsule gene cluster, cps, is a 24-kb genetic island horizontally acquired by N meningitides that is not present in closely related N. lactamica and N. gonorrhoeae.[27, 28] A recent study described cps architecture and gene content.[27] All known meningococcal Serogroups had cps containing five gene regions involved in capsule synthesis, transport and assembly (cps regions A–E).[29] The transferase gene, located in region A, determines Serogroup phenotype.[29, 30] Capsular Serogroup diversity among meningococci within the same clonal complex is driven by "capsular switching"—lateral exchange of capsule biosynthetic genes through homologous recombination[31, 32] However, for a recombination event to result in change of capsular phenotype, allelic changes must include region A genes, particularly the transferase gene.[31,33] Meningococcal capsular switching is relatively common and has been associated with the emergence and persistence of IMD.[31, 34, 35, 36]

Phylogenomic study of seven hundred and fifty (750) meningococcal cc11 isolates[24] revealed a highly complex population structure with extensive genetic diversity among cc11 strains. Serogroup C cc11 strains formed several clusters linked to multiple epidemiological instances of Serogroup C disease.[24, 37, 38] Given the preponderance of Serogroup C among cc11 strains, it is regarded to be the main capsule type with Serogroups W, B and Y representing capsular switch variants.[38, 39, 40]

CONCLUSION

Finding of epidemiologic studies have shown that, after a peak in incidence of Serogroup C meningococcal meningitis in the early 2000s, several countries introduced the Men C vaccine in their vaccination programs[39, 40], which resulted in a sharp decrease in Serogroup C meningococcal meningitis cases and provided long-term herd immunity.[39, 40] Therefore, although, the exact genes involved in capsular switching have not been well elucidated, reductions in the

morbidity and mortality associated with Invasive Meningococcal Disease (IMD) may be achieved with the introduction of Serogroup appropriate vaccines based on epidemiologic data.[18] This is similar to what happed in developed countries, where introduction and widespread use of Serogroup appropriate vaccines led to significant reductions in IMD associated with these serotypes.

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