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Meningococcal vaccine

A new vaccine to combat meningococcal disease in India

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Meningococcal meningitis is caused by *Neisseria meningitidis,* a gram-negative, aerobic, encapsulated diplococcus. Meningococci are divided into numerous serogroups based on the composition of their capsular polysaccharide (Ps) antigens. At least 13 serogroups have been described: A, B, C, D, 29E, H, I, K, L, W-135, X, Y and Z. Out of these 13, six (A, B, C, W135, X and Y) can cause epidemics. The incubation period averages 3–4 d (range 1–10 d), which is the period of communicability. Bacteria can be found for 2–4 d in the nose and pharynx, and for up to 24 h after starting antibiotics. *N. meningitidis* is a leading cause of meningitis worldwide and a significant public health problem and dreaded disease in most countries. Morbidity and mortality rates from the disease remain high. Apart from epidemics, at least 1.2 million cases of bacterial meningitis are estimated to occur every year, 135,000 of which are fatal—of these, ~500,000 and ~50,000 respectively are caused by meningococci. Many outbreaks of meningococcal meningitis have been documented, with major outbreaks mainly seen in large cities of northern, western and eastern India like New Delhi, Mumbai, Kolkata and northeastern states. In 2011, 245 people died in India, the vast majority (179) in West Bengal, while 467 and 341 people in 2009 and 2010 respectively died of this disease. The meningococcal conjugate vaccines (MCV) are preferred for reasons of immunogenicity and persistence of immunity but are unavailable in India. Only the quadrivalent and bivalent meningococcal Ps vaccines (MPV) are available in India. The quadrivalent MPV is preferred for Haj pilgrims, international travelers and students in that it provides protection against emerging W-135 and Y disease in these areas. A single-dose 0.5mL injection is recommended.

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Meningococcal meningitis has been recognized as a serious problem for almost 200 years. It was first identified definitely by Vieusseux in Geneva in 1805. The causative organism, *N. meningitidis,* is a gram-negative, aerobic, encapsulated diplococcus that grows best on enriched media, such as Mueller-Hinton or chocolate agar at 37°C and in an atmosphere of 5–10% CO_2. Meningococcal disease is still associated with a high mortality rate and persistent neurologic defects among survivors, particularly among infants and young children.[1]

There are numerous meningococcal serogroups based on the composition of their capsular Ps antigens. They are identified by agglutination reactions to specific sera directed against Ps antigens. At least 13 serogroups have been described, of which six (A, B, C, W135, X and Y) can cause epidemics. Geographic distribution and epidemic capabilities differ according to the serogroup. More than 99% of meningococcal infections are caused by serogroups A, B, C, 29E and W-135.[2] In Europe and the Americas, serogroup B is the predominant serogroup causing meningococcal disease, followed by serogroup C. Serogroup A is the main global epidemic cause, while serogroups A and C remain the predominant causes in Africa and Asia.[3] In the African "meningitis

belt" (a region of savanna that extends from Ethiopia in the east to Senegal in the west), this disease frequently occurs in epidemics during the hot and dry weather (December to March). The incubation period averages 3–4 d (range 1–10 d), which is the period of communicability. Bacteria can be found for 2–4 d in the nose and pharynx and for up to 24 h after starting an antibiotic regimen. Bacteria are transmitted from person to person through droplets of respiratory or throat secretions. The most common symptoms are stiff neck, high fever, sensitivity to light, confusion, headache and vomiting.[1]

N. meningitidis is the leading cause of meningitis worldwide and a significant public health problem and dreaded disease in most countries. Morbidity and mortality rates from the disease remain high. Apart from epidemics, at least 1.2 million cases of bacterial meningitis are estimated to occur every year, 135,000 of which are fatal - ~500,000 and ~50,000 respectively are due to meningococci.[4] Meningococcal meningitis most commonly affects individuals from age 3 y to adolescence. It rarely occurs in individuals older than 50 y. In developing countries, the mortality rate from bacterial meningitis is often higher (20–40%) than in developed countries. The disease is found more in males than females.[5]

Early complications of bacterial meningitis include seizures, increased intracranial pressure, cerebral venous thrombosis, sagittal sinus thrombosis and hydrocephalus. The risk of cerebral herniation from acute meningitis is about 6–8%. Infrequent suppurative complications include septic arthritis, purulent pericarditis, endophthalmitis and pneumonia. Of survivors, 10% developed allergic complications manifested as cutaneous vasculitis or arthritis. In fulminant meningococcemia, severe Disseminated Intravascular Coagulation (DIC) may develop, leading to hemorrhagic diathesis with bleeding into the lungs, urinary tract and gastrointestinal tract. Ischemic complications of DIC also are common. Late complications may include communicating hydrocephalus (which can present with gait difficulty, mental status changes and incontinence) and hearing loss.[6] Bacterial meningitis may result in brain damage, hearing loss or a learning disability in 10–20% of survivors, as well as amputations due to systemic DIC.[7] The Waterhouse-Friderichsen syndrome may develop in 10–20% of children with meningococcal infection; this syndrome is characterized by large petechial hemorrhages in the skin and mucous membranes, fever, septic shock and DIC.[8] Even when the disease is diagnosed early and adequate treatment is started, 5–10% of patients die, typically within 24–48 h of the onset of symptoms.[7] In a review of 493 episodes in adults, the overall case-fatality rate was 25%. In another study, patients with meningococcal meningitis had a case-fatality rate of 8%.[9]

Many outbreaks of meningococcal meningitis have been documented, which typically have occurred at a periodicity of ~20 y. Each epidemic has lasted for a decade. Major outbreaks of meningococcal disease are mainly seen in large cities of northern, western and eastern India like New Delhi, Mumbai, Kolkata and northeastern states. There is relative sparing of central and southern India. The important contributing factors in major outbreaks may be overcrowding or vulnerability to importation of new strain or a suitable climatic condition. The epidemic period coincides with the November – March dry season, with reduced incidence with onset of monsoon and again increased afterwards. Most of the epidemics in India being reported from the drier northern parts of the country than the more humid south supports the current view of the seasonal effect of the disease.[10] Endemic disease occurs primarily in infants and children, with the highest attack rates in infants aged 3–12 mo. During an epidemic, the disease is found in children; however, shift is noted from young children to adolescents and young adults later. Overall carriage rates are lower in India than other similar settings. High carriage rates are found in close household contacts, which justifies antibiotic prophylaxis. The highest proportion of cases and deaths have occurred in age groups < 1 y followed 1–4 y.[10]

In 2011, 245 people died of meningococcal meningitis in India, the vast majority (179) in West Bengal, while 467 and 341 people in 2009 and 2010 respectively died of this disease.[11] Globally more than 50% of meningococcal disease in infants aged < 1 y is attributed to serogroup B, against which no vaccine is yet available due to diversity of circulating strains and molecular mimicry between serogroup B Ps and neural adhesion molecules. However, novel group-common meningococcal B vaccines have been in advanced clinical development.

MPV

The MPVs are bivalent (A + C) or quadrivalent (A, C, Y, W135), contain 50 μg of each Ps in lyophilized form. These are stored at 2–8°C and reconstituted with sterile water. Serogroup A Ps induces antibody in some children as young as three months of age, although a response comparable with that in adults is not achieved until age 4–5 y. Serogroup C Ps is poorly immunogenic in young children. The bivalent MPVs have good immunogenicity, with clinical efficacy rates ≥ 85% among those ≥ 5 y of age. The Y and W-135 Ps are immunogenic in older children and adults; although clinical protection has not been documented. In infants and children < 5 y, measurable levels of antibodies against A and C Ps, as well as clinical efficacy decrease substantially during the first three years after vaccination. Protective antibody levels are usually achieved within 7–10 d of vaccination. Antibody levels also decrease in healthy adults, but antibodies are still detectable up to 10 y after vaccination. MPVs are safe; the most common side effects are local pain and redness at site of injection.[12]

MCV

The MCVs induce a T-cell-dependent response, resulting in an improved antibody response in infants, priming of immunologic memory and a booster response to subsequent doses, and herd immunity through protection from nasopharyngeal carriage. Serogroup C MCVs (conjugated to CRM_{197} or TT) has been part of routine vaccination in UK since 1999, with a schedule of three doses at a 4- to 8-weeks interval at age < 6 mo, two doses at age 6–12 mo, and one dose in

older children. The MCVs were licensed on the basis of safety and immunogenicity studies without data on clinical efficacy. A dramatic decline in meningococcal disease among vaccinated subjects was noted following introduction of the vaccine. Effectiveness within the first year of vaccination was 88–98% among different age groups; efficacy dropped to 80% after the first year. No serotype replacement has been observed to date.[10]

A serogroup A MCV was introduced in late 2010 nationwide in Burkina Faso and in selected regions of Mali and Niger. These countries reported in 2011 the lowest number of confirmed meningitis cases ever recorded during an epidemic season. Other countries in the African meningitis belt are preparing for introduction; Cameroon, Chad and Nigeria are introducing the vaccine in selected regions, and Mali and Niger are completing their nationwide campaigns. It is hoped that all 25 countries in the African meningitis belt will have introduced this vaccine by 2016. High coverage of the target age group of 1–29 y is expected to eliminate serogroup A epidemics from this region of Africa.[7] A quadrivalent A, C, Y and W-135 MCV has been licensed for those aged 11–55 y in USA (2–55 y in Canada). This vaccine contains 4 μg each of A, C, Y and W-135 Ps conjugated to 48 μg of DT. This vaccine had comparable immunogenicity to the MPS, is associated with minor local side effects such as pain and swelling, and can be safely administered concomitantly with other vaccines.[12]

Recommendations for Meningococcal Vaccine in India

MCVs are preferred but unavailable in India. The quadrivalent and bivalent MPVs are available in India. Quadrivalent MPV is preferred for Haj pilgrims, international travelers and students given that it protects against emerging W-135 and Y disease in these areas. A 0.5mL dose is administered subcutaneously or intramuscularly. In children aged < 2 y, two doses are recommended three months apart. Revaccination (MCV preferred) 2–5 y after MPV may be considered for those children at high risk of infection or who were vaccinated at age < 4 y.[12]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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