

# WHO position paper on meningococcal vaccines

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## Epidemiology of meningococcal disease

- In most countries *Neisseria meningitidis* is a leading cause of meningitis and fulminant septicaemia, but no reliable global disease burden estimate is currently available.
- Invasive meningococcal infections are usually caused by serogroups A, B, C, W-135, X, or Y. Their relative prevalence varies with time and geographic location.
- In the African “meningitis belt” serogroup A disease dominates, but outbreaks caused by serogroups C, W135, and X, have also occurred.
- Endemic disease occurs primarily in children and adolescents, with highest attack rates in infants aged 3-12 months, whereas in meningococcal epidemics, rates may rise in older children and young adults.

## Meningococcal disease

- When exposure to the pathogen results in invasive meningococcal disease (IMD) symptoms usually occur after 1–4 days. Meningitis and septicaemia are the most common IMD manifestations.
- Whereas symptoms of IMD in infants and young children may be uncharacteristic and often misleading, a petechial or purpuric rash is typical of meningococcal septicaemia. In older children and adults signs of meningitis include neck rigidity, photophobia and altered mental status.
- Most untreated cases of meningococcal meningitis and/or septicaemia are fatal, and even with appropriate care, up to 10% of patients die.
- 10% to 20% of survivors of meningococcal meningitis are left with permanent sequelae, including mental retardation, deafness, or epilepsy.

## Diagnosis and treatment

- The gold standard for laboratory diagnosis of IMD is isolation of *N. meningitidis* from a normally sterile body fluids (mostly blood or cerebrospinal fluid).
- Methods based on rapid polymerase chain reaction (PCR) can complement standard laboratory procedures as they are less affected by prior antibiotic therapy.
- Antimicrobial therapy should be started promptly while awaiting laboratory confirmation of diagnosis. Depending on bacterial susceptibility and availability of appropriate drugs, therapy is usually based on penicillin G, ceftriaxone, cefotaxime or chloramphenicol.

## The vaccines (I)

- Currently available meningococcal vaccines include polysaccharide and polysaccharide-protein conjugate vaccines.
- Although purified capsular polysaccharide antigens elicit protective antibody responses\*, conjugate vaccines are more immunogenic and induce immunological memory.
- Both polysaccharide and conjugate vaccines are available against meningococci of serogroups A, C, W-135 and Y, but not of group X.
- Serogroup B-vaccines based on bacterial protein have been used in some countries to limit outbreaks. These vaccines are strain-specific and not widely available.
- In terms of serious adverse events, all meningococcal vaccines are considered safe, including for use in pregnancy, although minor local reactions are common and transient fever may occur.

\* *Serum bactericidal activity  $\geq 1:4$  in hSBA or  $\geq 1:8$  in rSBA (human or rabbit source of complement) is widely used as an immunologic correlate of protection.*

## Polysaccharide vaccines

- Meningococcal polysaccharide vaccines consist of purified, heat-stable, and lyophilized capsular polysaccharides.
- Available in bivalent (A and C), trivalent (A,C,W-135), and quadrivalent (A,C,W-135,Y) formulations.
- Short-term efficacy 85% -100% in children  $\geq 2$  years and in adults. High effectiveness in closed high-risk adult populations, such as college students and military recruits.
- Little impact on carriage.
- Serogroup C polysaccharide is poorly immunogenic in children aged <18–24 months.
- Serogroup C polysaccharide may induce hypo-responsiveness to repeated doses.

## Conjugate vaccines

- Currently licensed meningococcal conjugate vaccines are either monovalent (A or C) or quadrivalent (A,C, W-135, Y).
- A combination vaccine *based on Haemophilus influenza* type b and *Neisseria meningitidis* serogroup C vaccines (HibMenC) is also marketed.
- Current evidence does not show significant replacement disease after the introduction of meningococcal conjugate vaccines.

## Monovalent serogroup C conjugate vaccines

- MenC conjugate vaccines are licensed for children aged >2 months as well as adults.
- These vaccines are highly immunogenic (>90%), although protective antibody titres are not long-lasting in young children.
- Large-scale MenC conjugate vaccination has drastically reduced the incidence of serogroup C-disease in many countries.
- Persistent disease reduction despite waning antibody titers is attributed in part to herd protection through reduced nasopharyngeal carriage.



## Monovalent serogroup A conjugate vaccine

- A MenA conjugate vaccine mainly intended for the African Meningitis Belt was licensed in 2010.
- This vaccine induces functional antibody responses against meningococcal serogroup A that are significantly higher and more persistent than those induced by a corresponding polysaccharide vaccine.
- The MenA conjugate vaccine has been used successfully in large vaccine campaigns in Burkina Faso, Mali, and Niger and is being introduced in other countries of the meningitis belt.

## Quadrivalent meningococcal conjugate vaccines

- Two quadrivalent meningococcal conjugate vaccines are currently available.
- A,C,W-135,Y-D conjugated to diphtheria toxin and licensed for individuals 2-55 years of age.
- A,C,W-135,Y-CRM conjugated to CRM-197 and licensed for individuals aged 2 to 55 years (in some countries for individuals  $\geq 11$  years).
- Recent estimates suggest that within 3 to 4 years after vaccination, the effectiveness A,C,W-135,Y- D is 80% - 85%.
- Immunogenicity, of the A,C,W-135,Y-CRM vaccine is proven non-inferior to the A,C,W-135,Y-D vaccine.

## WHO position / Recommendations (I)

- WHO recommends that countries with high (>10 cases/100 000 population/year) or intermediate (2-10 cases/100 000 population/year) endemic rates of invasive meningococcal disease and countries with frequent epidemics introduce appropriate large scale meningococcal vaccination programmes.
- In these countries, the vaccine may be administered through routine immunization programmes, supplementary immunization activities (SIAs), for example during outbreaks, or through private immunization services.
- Depending on the national epidemiology and socioeconomic resources, countries should select and implement the most appropriate control policy.

## WHO position / Recommendations (II)

- In countries where the disease occurs less frequently (<2 cases per 100 000 population/year), meningococcal vaccination is recommended for defined risk groups, such as children and young adults residing in closed communities, e.g. boarding schools or military camps.
- Laboratory workers at risk of exposure to meningococci should also be vaccinated. Similarly, travellers to high-endemic areas should be immunized against the prevalent serogroup(s).
- In addition, meningococcal vaccination should be offered to all individuals suffering from immunodeficiency including asplenia, terminal complement deficiencies, or advanced HIV infection.

## WHO position / Recommendations (III)

- Monovalent MenA conjugate vaccine should be given as one single intramuscular dose to individuals 1-29 years of age. The possible need for booster doses is not yet established for this vaccine.
- For monovalent MenC conjugate vaccine one single intramuscular dose is recommended for children aged  $\geq 12$  months, teenagers and adults. Children 2-11 months of age require two doses administered at an interval of at least 2 months and a booster about 1 year thereafter. If the primary series is interrupted, one should resume without repeating the previous dose. It is not yet known whether booster doses will be needed for long-term protection in healthy individuals who received primary vaccination when aged  $\geq 12$  months.

## WHO position / Recommendations (IV)

- Quadrivalent conjugate vaccines (A,C,W-135,Y-D and A,C,W-135,Y-CRM) should be administered as one single intramuscular dose to individuals aged  $\geq 2$  years.  
A,C,W-135,Y-D is licensed also for children 9-23 months of age, and given as a 2-dose series, 3 months apart, beginning at age 9 months.
- If the primary series is interrupted, vaccination should be resumed without repeating the previous dose.
- Polysaccharide vaccines can be used to control outbreaks in countries where limited economic resources or insufficient supply restrict the use of meningococcal conjugate vaccines.

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### WHO position / Recommendations (V)

- In the case of serogroup A or C outbreaks, bivalent A, C polysaccharide vaccine is recommended for mass campaigns. However, due to the limited efficacy of polysaccharide vaccines in children <2 years of age, in confirmed group C-outbreaks MenC conjugate vaccines should be used for protection of those aged 2-24 months. Similarly, during group A-outbreaks, MenA conjugate vaccine is the preferred option for protection of children 12-24 months of age.
- Meningococcal outbreaks caused by the W-135 or Y serogroups require trivalent (A,C,W-135) or quadrivalent (A,C,W-135,Y) polysaccharide vaccines.
- Meningococcal polysaccharide vaccines should be administered to individuals aged  $\geq 2$  years as one single dose; most polysaccharide vaccines require subcutaneous injection. One booster 3-5 years after the primary dose may be given to persons considered to be at continued high risk of exposure, including some health workers.

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### WHO position / Recommendations (VI)

- For all countries, knowledge of meningococcal disease burden is critical to making appropriate use of available vaccines.
- Countries considering the use of meningococcal vaccines should develop the surveillance systems to characterize meningococcal disease epidemiology including standard clinical case definition, field investigation of cases and outbreaks, and laboratory capacity for the confirmation and characterization of *N. meningitidis*.
- Continued surveillance of invasive meningococcal disease should dictate the need and timing of repeat mass vaccination campaigns.



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### WHO position / Recommendations (VII)

- The ongoing efforts to control invasive group A disease should be completed in all countries in the African meningitis belt.
- WHO underlines the importance of ensuring high quality surveillance in countries introducing the serogroup A meningococcal conjugate vaccine to document its impact on invasive disease and indirect benefits from reduction in carriage.
- This effort should also be used to strengthen the routine EPI programme and pharmacovigilance infrastructure in these countries.

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### WHO position / Recommendations (VIII)

- Further studies are needed to determine the frequency of possible repeat doses of meningococcal vaccines in immunodeficient individuals.
- Further research into the development and testing of protein based vaccines against serogroup B is highly encouraged. The lack of a vaccine against group X meningococci is a cause for concern given the outbreaks caused by meningococci of this serogroup in the past few years.
- As the assumed correlation between SBA titres ( $\geq 1:4$  in hSBA or  $\geq 1:8$  in rSBA) and protection against group A, W-135 or Y meningococcal disease have not yet been adequately documented there is a need for rigorous phase IV effectiveness studies to establish the reliability of this correlate beyond group C disease.