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Southern African Journal of Infectious Diseases

ISSN: 2312-0053 (Print) 2313-1810 (Online) Journal homepage: http://www.tandfonline.com/loi/ojid20

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To cite this article: Susan Meiring, Gregory Hussey, Prakash Jeena, Salim Parker & Anne von Gottberg (2017) Recommendations for the use of meningococcal vaccines in South Africa, Southern African Journal of Infectious Diseases, 32:3, 82-86, DOI: 10.1080/23120053.2017.1359939

To link to this article: http://dx.doi.org/10.1080/23120053.2017.1359939

Published online: 17 Aug 2017.

Southern African Journal of Infectious Diseases 2017; 32(3):82–86
https://doi.org/10.1080/23120053.2017.1359939

South Afr J Infect Dis
ISSN 2312-0053 EISSN 2313-1810

GUIDELINES

Recommendations for the use of meningococcal vaccines in South Africa

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Background: Although meningococcal disease (MD) incidence in South Africa is low, *Neisseria meningitidis* (NM) causes severe disease that is often life-threatening and can cause long-term disabilities. A quadrivalent protein-conjugated meningococcal vaccine (MCV4) is available, and provides protection against 75% of disease causing serogroups in South Africa.
Recommendations: We advise vaccination of persons at high risk of meningococcal disease including those with complement deficiency and asplenia; laboratory personnel from reference laboratories who work with NM; and travellers to Saudi Arabia.
The need for routine vaccine against meningococcal disease in South Africa is controversial given the current burden of disease. However, due to the high morbidity/mortality of MD we recommend that clinicians consider vaccination of healthy infants and children; HIV-infected persons with a CD4 count > 25%; students attending college /university /military academies; and miners.
Conclusion: Protein-conjugated meningococcal vaccine is preferable to the polysaccharide vaccine given the ability of the protein-conjugated meningococcal vaccine to induce immune memory, allow for booster responses and eliminate carriage of the organism in the person vaccinated.

Keywords: guidelines, meningitis, meningococcal vaccines , *Neisseria meningitidis,* South Africa, vaccine

Introduction

Meningococcal disease is a devastating illness with a high mortality rate despite appropriate therapy. Meningococcal conjugate vaccines have become available in South Africa since 2014. The aim of this document is to guide clinicians in decision making regarding when meningococcal vaccine should be used and which vaccine would be most appropriate.

Epidemiology of meningococcal disease in South Africa

Meningococcal disease is caused by the bacterium, *Neisseria meningitidis*, which is a Gram negative intracellular diplococcus. Humans are the sole natural host of this infective organism.[1,2] Up to 10% of the population carry *N. meningitidis* asymptomatically in their nasopharynx and spread the organism from person to person via respiratory droplets. In industrialised countries, teenagers (15-19 years of age) had the highest colonisation rate (25%),[3,4] whilst in the African meningitis belt carriage was lower and peaked at 5% in children 5-14 years of age.[5]

Colonisation with *N. meningitidis* usually confers protection through the production of antibodies to that particular strain.[6] Infrequently, newly acquired hypervirulent carriage strains are able to invade the mucosa and cause bacteraemia and/or meningitis. Disease onset is often rapid and can become life-threatening despite appropriate antibiotic therapy. Sequelae ranging from hearing loss, skin scarring, amputations and neurological fall out are evident in approximately 20% of survivors.[7–9]

Risk factors for acquisition of carriage (which is a prerequisite for disease) include passive smoking, intimate personal contact (kissing), pub attendance, overcrowding, the attendance of mass gatherings and previous antibiotic use. These are all largely behaviour-related and thus may explain the high carriage seen in teenagers and young adults.[3] Other risk factors for disease include HIV infection, other immune deficiencies (especially of the complement components) and asplenia.[10–12]

Meningococcal disease is endemic in South Africa with sporadic cases occurring throughout the year, usually increasing from May to October. Average incidence in the population over the past decade is 1 per 100 000 people, with a peak of 8 per 100 000 people in infants.[13] Over the last decade in South Africa, approximately 17% of people with meningococcal disease have died, with case fatality ratios increasing with age.

The bacterium, *N. meningitidis*, is surrounded by a polysaccharide capsule, which is used to classify the organism into 12 serogroups. Six of these 12 serogroups have been found to cause disease in South Africa, with the majority of disease caused by serogroup W, followed by serogroup B. Prior to 2005, serogroup A was South Africa's predominant disease causing serogroup but only a few cases have been detected over the last 3 years (Figure 1).

Since the 2006 peak in meningococcal disease in South Africa, cases are now at an all-time low, despite limited vaccine use.[14] Meningococcal case-loads are known to wax and wane over periods of 5 to 10 years, therefore South Africa may possibly be on the verge of seeing an increase in meningococcal disease in the near future.

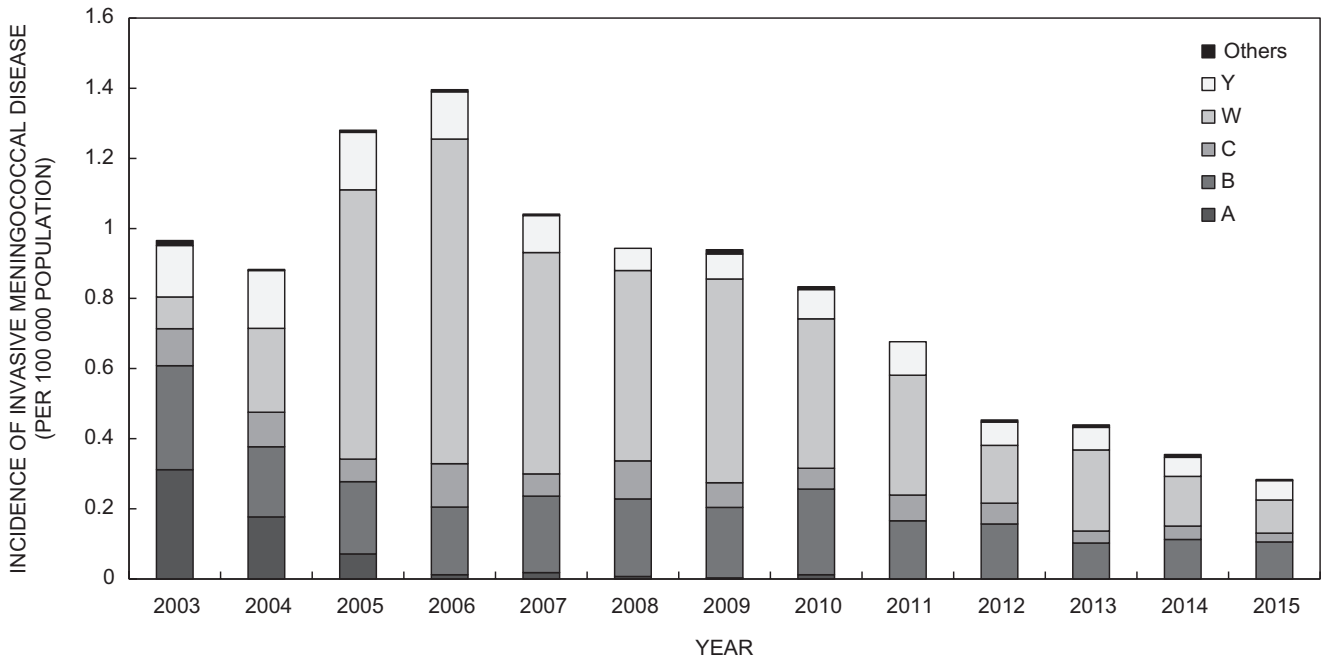

Figure 1: Incidence of invasive meningococcal disease by serogroup, South Africa, 2003-2015 (n = 5118).

Meningococcal vaccines registered in South Africa

Currently there are two types of meningococcal vaccines available in South Africa: a polysaccharide vaccine (Menomune®, Sanofi Pasteur (MPSV4)) and a protein-conjugate polysaccharide vaccine (Menactra®, Sanofi Pasteur (MCV4)). These are both quadrivalent vaccines targeting the polysaccharide capsules of serogroups A, C, W and Y.

The MPSV4 has until 2014 been the only quadrivalent meningococcal vaccine available in South Africa. This **polysaccharide vaccine** elicits a T-cell independent immune response and is thus poorly immunogenic in infants and toddlers. Protection is generally limited to 3-5 years. It has been found that repeated doses may confer immunological hypo-responsiveness.[15] MPSV4 does not eliminate nasopharyngeal carriage and does not induce herd immunity.

MCV4 is a **protein-conjugate polysaccharide vaccine** (polysaccharides are carried by a protein) that induces both B-cell and T-cell immunity; stimulates immune memory; decreases carriage of the organisms; and allows for booster responses. They are immunogenic in infants and are at present licensed for use in persons from 9 months to 55 years of age.[15] Persons 2 years and over generally require a single dose and children from 9 months to 23 months require two doses given 12 weeks apart. Recent studies have shown that antibody levels do decline 5 years following vaccination, therefore booster doses are recommended should a person remain at increased risk for disease.[16,17] MCV4 is safe and immunogenic in HIV-infected children and adults, with a CD4 > 25%, if given in a two-dose schedule.[18,19]

Adverse effects associated with the use of the quadrivalent vaccines are minimal. Vaccine recipients experience mild pain at the injection site for 1-2 days, a low grade fever, headache and/or malaise. There is no increased risk of Guillain-Barre syndrome associated with vaccine use, although vigilance for this adverse effect is essential.[20]

Immunogenicity studies of MCV4 have shown that it is safe and effective to give concomitantly with other childhood vaccines such as measles, mumps, rubella, varicella and the pneumococcal conjugate vaccine.[21]

Recommendations for vaccination

Although the incidence of meningococcal disease is currently low in South Africa, the consequence of acquiring the disease can be devastating with high morbidity and mortality despite adequate treatment. Ideally, all South Africans should be protected against this disease, even though the risk for acquiring it is low. Certain individuals are at higher risk for acquiring the disease and vaccination is recommended in these persons.

Persons with primary immunological disturbances of the immune system (particularly complement deficiency), on immunosuppressive therapy following solid organ transplant and haemopoetic stem cell transplant, acquired immune deficiency (HIV-infection) or those with functional or anatomic asplenia are considered at high risk, and should be offered routine vaccination.[12,17,22,23]

Other groups at increased risk include those with occupational exposure to meningococci in a microbiology laboratory, persons living in crowded living conditions (school/university students in hostels, army recruits and miners) and those travelling to hyperendemic areas. These groups should be offered routine vaccination.[24–26]

In an outbreak setting where the affected population can be clearly defined and the serogroup associated with the disease is identified and covered by the vaccine, vaccination could be used as a control measure. This does not obviate the need for chemoprophylaxis and can be given up to 4 weeks post exposure.[27]

Recommended vaccination schedule

The risk for meningococcal disease could change at any time and under different circumstances and thus our recommendations for vaccination, summarised in Table 1, are divided into the following categories:

The meningococcal vaccine:

i. *Should be considered,*

ii. *Is recommended, or*

iii. *Is required*

A MCV4 vaccine targeting serogroup A, C, W and Y *should be considered* in children between 9 months and 5 years of age. Justification for this includes: the high disease burden in infants; the higher risk of NM clusters in preschools than secondary schools; and, 75% of meningococcal disease in South Africa has been caused by serogroup A, C, W and Y (Figure 1) .[13,28] Protein conjugate vaccines induce T-cell dependent immune response, stimulating immune memory and inducing mucosal immunity, thus eliminating carriage and are effective in children < 2 years of age, unlike the polysaccharide vaccines. Serogroup B vaccines are currently not licenced for use in South Africa. Infants 9 months through to 23 months should be given a two-dose primary series with a dosing interval of 12 weeks, while healthy children 2 years and older require just a single primary dose.

Vaccination with MCV4 *should be considered* in all adolescents and young adults prior to entering their first year of university, college or military training especially if they will be staying in a residence hall. A single primary dose of MCV4 should be given in this instance. A booster dose should be given if meningococcal vaccine had been given more than 5 years previously.

Vaccination with MCV4 *should be considered* for all mine workers staying in hostels. A single primary dose of MCV4 should be given.

Vaccination with MCV4 *is recommended* for all reference/research laboratory workers who routinely work with isolates of *N. meningitidis*. Routine laboratory safety measures should continue to be followed when working with this organism.

Vaccination with MCV4 *is recommended* for all travellers to hyperendemic regions or where epidemics of meningococcus are occurring (e.g. countries of the African meningitis belt). Pilgrims to the Hajj and Umrah, and visitors to Saudi Arabia *are required* to obtain a quadrivalent vaccine at least 10 days prior to entry into the country. A booster is required if the vaccine has been given beyond the previous 3 years for MPSV4 or previous 5 years for MCV4.[29]

Any person attending a mass gathering (i.e. scout jamborees; sporting event) *should consider* vaccination with MCV4 prior to commencement of travel.

Table 1: Suggested recommendations of use of meningococcal vaccine in South Africa

Population Group	Vaccine choice	Recommendation	Primary dosing	Booster
Healthy children and infants	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Children 9 months to 23 months: 2 doses 12 weeks apart Children ≥24 months: 1 dose	
Healthy adolescents or young adults entering university or college (particularly if staying in hostels)	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Single dose prior to entry into university or college	
Military recruits on training or deployment	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Single dose prior to commencing training or deployment	Booster dose required if risk remains high 5 years after primary dose
Miners	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Single primary dose	
Research/reference laboratory workers routinely exposed to *N. meningitidis*	Quadrivalent conjugate vaccine (MCV4)	Recommended	Single primary dose	Booster dose every 5 years if risk remains
Travellers to meningitis belt or other areas where disease is hyperendemic/epidemic	Quadrivalent conjugate vaccine (MCV4)	Recommended	Single primary dose	Booster dose every 5 years should be considered for repeated travel to highly endemic areas
Hajj pilgrims and travellers to Saudi Arabia	Quadrivalent conjugate vaccine	Required	Single primary dose	A booster dose every 3 years for MPSV4 or 5 years for MCV4 is required for repeated travel as per current Saudi regulations
Attendees of mass gatherings	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Single primary dose	
Persons with medical conditions at high risk of acquiring infection: Complement component deficiencies	Quadrivalent conjugate vaccine (MCV4)	Recommended	Two-dose primary schedule 12 weeks apart	Booster every 5 years
Anatomical or functional asplenia	Quadrivalent conjugate vaccine (MCV4)	Recommended	Two-dose primary schedule 12 weeks apart	Booster every 5 years
HIV infection	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Two-dose primary schedule 12 weeks apart	Booster every 5 years
Other immunocompromising conditions	Quadrivalent conjugate vaccine (MCV4)	Should be considered	Two-dose primary schedule 12 weeks apart	Booster every 5 years

Hindu pilgrims of the Kumbh Mela festival to the river Ganges, India *should consider* vaccination with MCV4 prior to commencing their travel.

Persons with terminal complement deficiency and those with functional or anatomical asplenia *are recommended* to be vaccinated with MCV4. A two-dose primary schedule is suggested, followed by a booster dose every 5 years.

Individuals with HIV or other immunocompromising conditions *should consider* vaccination with MCV4. A two-dose primary schedule is recommended to increase the likelihood of attaining a sufficient primary immune response in these persons followed by regular booster doses. HIV-infected individuals should ideally be vaccinated before their CD4 cell count reduces to < 25%.

Vaccination with a single dose of MCV4 *should be considered* following an outbreak of meningococcal disease due to serogroup A, C, W or Y in a well-defined institutional or community setting, following initial chemoprophylaxis, in order to extend protection.

The quadrivalent conjugate vaccines can be administered in conjunction with other childhood immunisations and are safe for use during pregnancy.[21]

There is very limited use for the polysaccharide meningococcal vaccine, viz. in individuals > 55 years of age, if they do not have recurrent risk of meningococcal disease. However, if their risk of meningococcal disease is known to persist for > 5 years, it may be best to use MCV4 first and then boost with either MPSV4 or MCV4 should further boosting doses be required. Either MPSV4 or MCV4 can be used in outbreak settings due to serogroups A, C, W or Y where the risk is not recurrent.

Vaccine funding options

At present, only the quadrivalent polysaccharide vaccine (MPSV4) is available through the public sector to those at high risk of contracting meningococcal disease, viz. for well-defined populations during outbreaks and to travellers to hyperendemic areas.

The conjugated polysaccharide vaccines (MCV4) are available through private pharmacies when prescribed by a doctor; however, funding for this comes from the patients themselves or through their private medical savings plan.

Conclusion

Although meningococcal disease incidence in South Africa is low, *N. meningitidis* causes severe disease that is often life-threatening or with long-term disabilities. A quadrivalent protein conjugated meningococcal vaccine is available, and provides protection against 75% of the disease causing serogroups in South Africa.

We advise vaccination of persons at high risk of meningococcal disease including those with complement deficiency and asplenia; laboratory personal from reference labs who work with *Neisseria meningitidis*; and travellers or Hajj pilgrims to Saudi Arabia.

We recommend that clinicians should consider vaccination of healthy infants and children from 9 months to 5 years of age; first-year students attending college/university/military academies; miners; and those infected with HIV.

Where possible, quadrivalent conjugate meningococcal vaccines are preferable to polysaccharide vaccines given their ability to induce immune memory, allow for booster responses and eliminate carriage of the organism in the person vaccinated.

Conflict of interest statement – SM has received research funding from Sanofi Pasteur; GH has none to declare; PJ has received honoraria from Pfizer for talks on childhood pneumonia; SP has received honoraria from Pfizer for talks and received financial assistance from Sanofi to attend travel medicine conferences; AvG has received research funding from Pfizer and reimbursement of travel expenses for educational and advisory meetings for Pfizer and Sanofi.

Financial support – No financial support was awarded for the completion of this manuscript.

Acknowledgements – The contents of these recommendations were reviewed and supported by the following individuals and organisations:Lee Baker (SASTM); Simon Strachan (PMG); Kerrigan McCarthy (NICD); Chetna Govind (SASCM); Saber Yezli (Saudi Arabia Ministry of Health); National Advisory Group on Immunisation; Tsakani Furumele (CDC-Department of Health, South Africa)

Note

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Received: 10-05-2017 Accepted: 24-07-2017