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# Advances in Meningococcal Disease Prevention for the UK Traveller

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**Introduction**

*Neisseria meningitidis,* is the leading cause of bacterial meningitis worldwide. in developed countries, most cases are caused by endemic disease although there are appreciable cyclical fluctuations in meningococcal disease incidence, resulting in outbreaks and epi-demics. A well documented area is the "African Meningitis Belt" where the disease is endemic.

The causative organism, is a Gram-negative diplo-coccus with 13 diverse polysaccharide capsules that form antigenically distinct groups identified as A, B, C, X, Y, Z, W135, 29E, H, I, K, L and Z. These are fur-ther subdivided by serotype and sulphonamide sensi-tivity. The relative importance of the causative serogroups also varies with age - 70% of cases under 5 years are attributable to group B in the UK, but this falls to 50% in those over 10 years of age.[1] In 1999, the UK was the first country to introduce immunisation against meningococcal C disease and with excellent outcomes.[2]

For the UK traveller, meningococcal disease is an important disease to consider prevention. it is well known that international travel as well as migration has helped the spread of meningococcal disease around the world. Different serogroups are emerging in different areas. Serogroup A and to a lesser degree serogroup C have dominated in the past in epidemics, mainly in Africa. Serogroup W135 first emerged in Saudi Arabia and rapidly spread to other areas, particularly West Africa. Meningococcal disease occurs in all countries and risk assessment is an important consideration for those undertaking travel abroad.

**Transmission**

infection is acquired by inhaling infected droplets of respiratory secretions from the nose and throat or by direct contact (especially kissing) with a patient or carrier. Frequent or prolonged contact encourages transmission of the infection.

*N. meningitidis* colonises 8 - 25% of healthy indi-viduals of all ages; the duration of meningococcal car-riage can vary from days to many months. About one in four (25%) of adolescents and 5 to 11% of young adults may be asymptomatic carriers at any one time, while the rate in the general adult population is 1%. Meningococcal disease may occur, usually within days, after the new acquisition of *N. meningitidis* in the nasopharynx. The incubation period is from 1 to 10 days, most commonly less than 7 days. Humans are the only known carrier of the meningococcus (in the upper respiratory tract) and act as a reservoir for transmission of the disease.

Meningococcal disease shows marked seasonal varia-tion: peak level in the winter, low level in the summer. The winter seasonal onset of the disease in the UK usually coincides with that of influenza. Generally, in temperate climates most epidemics occur usually dur-ing the winter-spring period, while in tropical areas they occur during the dry season.

Transmission occurs from nasopharyngeal carriers via respiratory droplets. Risk factors include smoking, living closely to others (schools, colleges, military bar-racks, students in halls of residence, Hajj and other pilgrimages), poor living conditions, overcrowding. Travel,

population displacements, migration, and pilgrimages can facilitate the circulation of pathogenic meningococcal strains within and outside individual countries.

*Epidemiology*
Meningococcal meningitis occurs sporadically in small clusters throughout the world with seasonal variations. in temperate regions the number of cases increases in winter and spring. Serogroups B and C together predominate in Europe. in North America serogroups B, C, and Y predominate while in South America are serogroups B, and C. in the past, impor-tant outbreaks due to *Neisseria meningitidis* serogroup C were reported in Canada and USA (1992-93) and in Spain (1995-97).

New Zealand has experienced in the late 1990s appreciable activity of meningococcal meningitis with an annual average of 500 cases (mostly due to serogroup B). in Australia, serogroups B, and C pre-dominate. in Asia, serogroups A, and C are usually the cause of meningococcal disease. Table 1 and figure 1 show the global distribution of meningococcal serogroups around the world.

In Africa generally, epidemics are usually associat-ed with *Neisseria meningitidis* serogroups A, W135, C, and X. Serogroup W135 was first seen during an epidemic in the West African nation of Burkina Faso in 2002. it infected 12,000 people and killed 1,500. it was the first time this serogroup was identified as the main causal agent in a major epidemic. The WHO reports that there is increasing evidence of serogroup W135 being associated with outbreaks of considerable size. in 2000 and 2001 several hundred pilgrims attending the Hajj in Saudi Arabia were infected with serogroup W135.

Globally, meningococcal disease affects up to 1.2 million people per year, causing 135,000 deaths. The highest burden is in the "meningitis belt" of Africa.

*The African 'Meningitis Belt':* This is an area that stretches from Senegal in the west to Ethiopia in the east (Figure 2), with an estimated total population of 300 million people.[4] This hyperendemic area carries the highest burden of meningococcal disease in Sub-Saharan Africa. The risk is highest in the Savannah during the dry season, between end of November and June. During these months, the nights are cold; there are dust winds, and higher incidence of acute respiratory infections. The risk decreases with the arrival of the rainy season. The epidemic cycles in the "meningitis belt of Africa" last between 8 to 15 years. Because of socioeconomic problems (mainly poor living conditions) in these countries, households are usually overcrowded and this is made worse during population movements such as large population dis-placements due to pilgrimages or war and traditional regional markets.

The main serogroups in the meningococcal belt of Africa are A (the predominant serogroup), B, C, W135, and X. Major epidemics happen every few years - a pattern seen nowhere else in the world. Attack rates range from 100 to 800 (sometimes as high as 1000) per 100 000 population. The highest attack rates are seen in young children. In 1996, Africa had its worst year and reported over 250 000 cases and 25 000 deaths. in 2006, 41,526 cases (18,292 in 2005) were reported to the WHO from the 'meningitis belt', and 3967 deaths (2575 in 2005). The countries most affected in 2006 were: Burkina Faso, Chad, Ethiopia, Niger, Benin, and Central African Republic.

During the 10 years between 1996 and 2006, the estimated number of cases of meningococcal disease was around 700,000 cases, according to the WHO, with a 10% mortality rate (around 70,000 people died).

**Table 1**
***Global serogroup distribution of meningococcal disease and serogroup importance***

| |
|---|
| *Serogroup A* causes the highest incidence of meningococcal disease and causes very large epidemics. Repeated pandemics of serogroup A disease have taken place in sub-Saharan Africa, now known as the meningitis belt. |
| *Serogroup B* is a major cause of sporadic or endemic disease, but prolonged outbreaks in Europe, Cuba, Chile, the US Pacific Northwest and, recently, New Zealand have caused significant morbidity and mortality. |
| *Serogroup C* has caused major epidemics (eg, sub-Saharan Africa, Brazil) and case clusters and local outbreaks in the United States, Canada, and Western Europe, especially among adolescents and young adults. |
| *Serogroup W-135* caused worldwide outbreaks in 2000-2002 associated with the Hajj pilgrimage and significant disease in parts of the African meningitis belt. |
| *Serogroup Y* strains have caused increased rates of disease in the United States and Israel since the mid-1990s. |
| *Serogroup X* has been responsible for localized recent outbreaks in parts of sub-Saharan Africa such as Niger. Only rarely does it cause meningococcal disease in other parts of the world. |

**Figure 1**
***Global serogroup distribution of meningococcal disease***

*Neisseria meningitidis* Serogroup Distribution Varies Globally

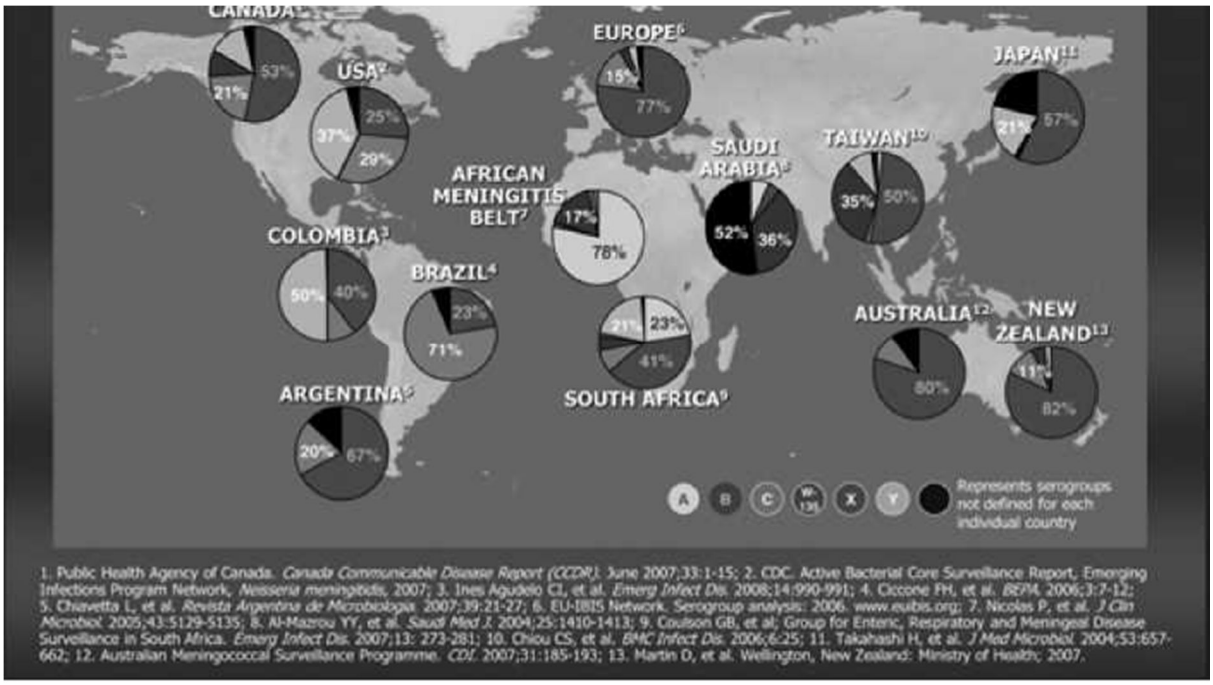
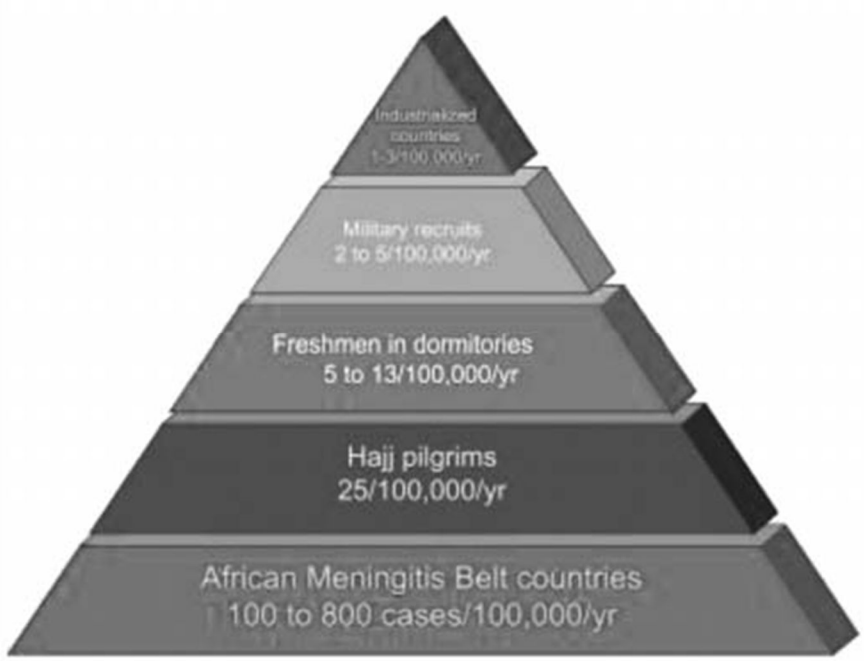



**Figure 2**
***The "meningitis Belt of Africa" Reference:***
http://wwwnc.cdc.gov/travel/yellowbook/2010/ch apter-2/meningococcal-disease.aspx accessed 16 August 2010

*CDC Map 2-6 Areas with frequent epidemics of meningococcal meningitis*

with high morbidity and mortality. Even with appropriate treat ment, mortality is around 10% with 11-19% of the survivors being left with permanent neurological sequaelae.[5] Travellers most at risk are those who come in direct contact with the local populations, particu-larly healthcare workers, VFRs (visiting friends and relatives), backpackers, and long-term travellers

**Figure 3**
***Risk of meningococcal disease in various settings.***
*Reference:*
*Annelies Wilder-Smith. Meningococcal disease: Risk for international travellers and vaccine strategies. Travel Medicine and Infectious Disease 2008;6:182-186 (with permission)*




**Risk assessment and prevention**

Travellers at risk of meningococcal infection are those travelling particularly to endemic areas during the dry season. it is important to take a good history as regards to duration of stay and planned activities. Staying or working closely with locals, having pro-longed direct contact with the local population increases the risk of the traveller contracting the dis-ease. Coming in contact with large numbers of people, as in the case of religious pilgrimages, increases the risk considerably. Travellers should know that coming in close prolonged contact with a known case of meningococcal disease requires them to seek urgent medical advice and immediate antibiotic prophylaxis. The risk is greatest during epidemics. in comparison with the low incidence in the UK (1-3 per 100,000), during epidemics in sub-Saharan Africa as many as 1,000 per 100,000 population may be affected.[6] Figure 3 shows the risk of meningococcal disease in various settings. Travellers are well advised to avoid, where possible, overcrowded conditions.

**Immunisation for Travellers**

As a result of the introduction of the conjugate meningococcal C (Men C)_ vaccine in the UK in 1999 (the first country to do so in the world), herd immunity was created and nasal carriage rate was reduced significantly. Compared to 1999, 2001 saw a reduction in carriage rate of the magnitude of 81%.[7]

Travellers at risk need a broader protection against meningococcal serogroups that are more prevalent abroad, namely A, C, W, and Y. Two such quadrivalent vaccines are licensed in the UK.

*The polysaccharide meningococcal vaccine ACWY vax*® has been available in the UK since 2002. As a polysac-charide vaccine, it is poorly immunogenic in subjects under 24 months of age. it is best given to children age 5 years and above. A protective antibody level against all four serogroups is achieved within 10-14 days after vaccination. it is administered by deep subcutaneous injection, one single dose. The protection it offers is in the order of 90-95%.[8] Immunity is expected to last at least for 3 years.[9] Long-term protection is not achieved as it

does not induce immunological memory, nor does it significantly reduce colonisation, therefore, it does not provide herd immunity. It can be given following MenC vaccine after an interval of at least 2 weeks.

Year 2010 saw the introduction in the UK of the *conjugate meningococcal ACWY vaccine (MenACWY) Menveo®*. Conjugating the polysaccharide vaccine to a protein enhances its immunogenicity, particularly as regards to young children and the elderly. Other benefits of such conjugation are long-term protection after vaccination and reduction in nasopharyngeal carriage. The response to serogroup C is comparable with that seen with the monovalent MenC conjugate vaccine. This vaccine is not licensed for children under the age of 11 years as yet. Nonetheless, the *Green Book* recommendation is that, based on the experience with other conjugate vaccines, immunity is expected to be higher, longer-lasting and confer less risk of immunological tolerance than the plain polysaccha-ride vaccine. For this reason, this conjugate vaccine is recommended in preference to polysaccharide vaccine in children under five years of age.[2] The *Green Book* recommends the use of the conjugate vaccine (MenACWY) outside its licence for children travelling to endemic areas and at risk, aged 2 months and over. As yet, the need for a booster has not been determined.

Table 2 summarises the current recommendations for the administration of the ACWY vaccines. Although the MenACWY (Menveo®) vaccine is licensed for individuals aged 11 years and over, the Green Book overrides the current licence of the vaccine and recommends its use in all ages and, therefore, off-label for the ages of 2 months to 11 years.

In the case of ***asplenia or splenic dysfunction,*** the *Green Book*[2] recommendations are as follows:
• Children under 1 year of age:
| at 2 and 3 months administer the MenACWY
(Menveo®) vaccine (two doses one month apart)
instead of MenC; | at 12 months administer Hib/MenC vaccine
(Menitorix®); • at 14 months (or two months later) one dose of
MenACWY (Menveo®) vaccine
• Children over 1 year of age and Adults: one dose of Hib/MenC vaccine (Menitorix®) followed by single dose of MenACWY (Menveo®) two months later
• Children and adults, who have been fully immunised with MenC vaccine as part of the routine programme, but who then develop splenic dysfunction: administer an additional dose of the combined Hib/MenC (Menitorix®) vaccine, followed by a single dose of MenACWY (Menveo®) vaccine two months later

**Hajj - meningococcal vaccine requirements**
Hajj, the Muslim pilgrimage to Mecca, is the largest annual gathering of its kind in the world. This pil-grimage is a religious obligation to be performed at least once by all adult Muslims whose health and financial means permit it. Each year, over 2 million Muslims from around the world gather in Mecca. The Hajj takes place between the 8th and 13th day of the last month of the Islamic lunar calendar (355 days) and, therefore, falls at different dates each year.
When applying for a visa to Saudi Arabia, all pil-grims are required to submit proof of vaccination (mandatory) with the quadrivalent ACWY vaccine. The vaccine should have been received no more than 3 years and not less than 10 days before travel to Saudi Arabia. The vaccination certificate should show the ;e Prevention... *continued*

traveller's full name. Children over 3 months and under 2 years of age may not be adequately protected by a single dose of ACWY Vax® vaccine, therefore, they are required to have received (off-label) two doses of the vaccine with an interval of three months. The *Green Book* now suggests off-label use of the con-jugate MenACWY vaccine Menveo®.

**Table 2**
***The ACWY vaccines available in the UK -administration.***

| **Meningococcal ACWY vaccines Vaccine Dose** | | **Age** | **Booster** |
|---|---|---|---|
| ACWY Vax<br><br>_(polysaccharide) | Single dose (SC) | 2 years & Adults<br>3 m to 2 years for pilgrims to Hajj or Umrah only, two doses, 3 months apart - **"off-label"** | 3-5 years |
| Menveo<br><br>(conjugate)<br><br>*Green Book* **"off-label"** recommendations: | Single dose (IM) 0.5 ml<br><br>Two doses* 1 month apart<br>Single dose 0.5 ml | 11 years & over and adults<br><br>Infants under 1 year<br>1 to 1**1** years | The need for, and timing of, a booster dose has not yet been determined |

*Replace the MenC vaccine with MenACWY conjugate vaccine if the infant requires MenACWY conjugate vaccine at the same time as the routine MenC vaccinations. If the infant has already had two MenC vaccinations then two MenACWY conjugate vaccines should also be given.*

**Summary**
*Neisseria meningitidis,* is the leading cause of bacterial meningitis worldwide. Meningococcal dis-ease has spread around the globe. UK travellers abroad, particularly to pilgrimages such as The Hajj, and to endemic areas such as the "meningitis belt of Africa", are at particular risk of contracting the dis-ease. The introduction of a conjugate meningococcal vaccine for the five main serogroups of *Neisseria meningitidis,* offers a real advantage over the previous-ly introduced polysaccharide vaccine. It is more immunogenic in young children and elderly, reduces nasopharyngeal carriage, compares well to the response elicitated by the conjugate vaccine MenC, and offers long-term protection. For these reasons, the *Green Book* recommends the conjugate MenACWY vaccine in all ages.

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References:

1 Williams & Burnie (1987) *Bacterial Meningitis*, pp. 93-115. Academic Press, London.
2 The "Green Book": http://www.dh.gov.uk/prod_consum_dh/groups/dh_ digitalassets/@dh/@en/documents/digitalasset/dh_ 121552.pdf - accessed 7th December.
3 Stephens DS, Greenwood B, Brandzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis. Lancet.* 2007;369:2196-2210.
4 WHO:
http://www.who.int/csr/disease/meningococcal/impact/ en/index.html - accessed 7th December.
5 Rosenstein NE, at al. Meningococcal disease. *N Engl J Med* 2001;344(18):1378-88.
6 Pollard AJ. Global epidemiology of meningococcal disease and vaccine efficacy. *Pediatr Infect Dis J* 2004;23(12 Suppl):S274-9.
7 Maiden MCJ et al. Impact of meningococcal serogroup C conjugate vaccines on carriage and herd immunity. *Journal of Infectious Diseases* 2008;197:737-743.
8 Annelies Wilder-Smith. Meningococcal disease: Risk for international travellers and vaccine strategies. *Travel Medicine and Infectious Disease* 2008;6:182-186.
9 ACWY vax® summary of product characteristics (SPC) :
http://www.medicines.org.uk/EMC/medicine/4204/SPC/
ACWY+Vax+Vaccine/#POSOLOGY - accessed 7th December.
10 Southern J, Borrow R, Andrews N et al. Immunogenicity of a reduced schedule of meningococcal group C conjugate vaccine given concomitantly with a 7-valent pneumococcal conjugate vaccine and a combination DTaP5/Hib/IPV vaccine in healthy UK infants. *Clin Vaccine Immunol* 2009;16(2):194-199.