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REVIEW ARTICLE

Protection of travellers against meningococcal disease: tetravalent conjugate vaccines offer new options*

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INTRODUCTION

Over the last 200 years, outbreaks and epidemics have occurred in many regions of the world (1). The epidemiology of invasive meningococcal epidemiology varies considerably geographically and in time and the risk to acquire meningococcal disease is influenced by living conditions and behaviour. Of the 12 *Neisseria meningitidis* serogroups which have been described (2), serogroups A, B, C; W-135 and Y are the most important cause for disease. Invasive meningococcal infections mostly occur as sporadic cases, however, these infections are regularly epidemic within the African meningitis belt spanning sub-Saharan Africa from Senegal in the west to Ethiopia in the east.

International travel and tourism are continuing to grow at an astonishing rate. In 2007, the three regions that recorded the greatest increases in such growth were the Near East, the Asian Pacific and Africa, with growth rates of 13%, 10% and 8%, respectively (3). With tourism expanding to traditionally less-often visited areas, there is a growing need to develop an awareness of the risks of contracting infectious diseases, and of possible vaccinations over and above those that are routinely offered in the traveller's home country.

The risk for travellers, including tourists

One such infectious disease that is commonly underestimated is meningococcal infection. Among the various reasons for this is the fact that the incidence of meningococcal disease in travellers is appreciably below that of other diseases preventable by vaccination (for example hepatitis A, influenza, typhoid fever). Globally, invasive meningococcal infections annually account for some 500,000 cases with a fatal outcome in 50,000 (4). In this connection, an easily overlooked fact is that in the event of an outbreak, tourists, too, may be affected. In view of the severity of the disease (mortality rate approximately 10% and lasting pathological sequelae up to 20%) the risk of a traveller contracting a serious meningococcal infection should not be underestimated. The time lapse between infection and manifestation of the disease may be extremely brief and a fatal outcome may result within 24 hours. The time window for establishing the clinical diagnosis and initiating treatment is very narrow. In the case of travellers to far removed regions or poor countries, however, a correct diagnosis and rapid commencement of therapeutic measures, is often fraught with difficulties.

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The regions comprising the Middle East and Africa, which belong among those experiencing the greatest increase in international travel, are also those with the highest incidence of meningococcal diseases. One of the most severe epidemics occurred in 1996 and was triggered by serogroup A. During its course in excess of 250,000 people became infected, and more than 25,000 deaths were recorded (1).

The spread of such infections in both geographical and temporal terms is virtually impossible to predict.

The epidemiology of the meningococci is both dynamic and unpredictable, both in terms of geographical distribution and appearance in time. International travel can accelerate the intercontinental spread of the various serogroups.

While, originally, serogroup A (and to a lesser extent, serogroup C) was responsible for the majority of epidemics (mainly in Africa) recent years have witnessed the emergence of the serogroup W-135 (e.g. in Saudi Arabia, Turkey, West Africa). In a number of countries (e.g. USA, Columbia) serogroup Y is becoming increasingly evident. Recently, serogroup X, which previously had occurred only rarely, caused an outbreak in Niger (4,5). Since the epidemiological situation is constantly changing, the data intended to provide travellers with information on the global distribution of serogroups (worldwide), must be regularly updated.

Depending upon the epidemiological situation, the risk of a traveller´s contracting invasive meningococcal disease while on a journey abroad varies, and a multiplicity of factors may be involved. Since disease transmission is effected via airborne droplets, the danger of becoming infected increases in the presence of certain circumstances. Overcrowded rooms, dry air, duration of exposure to infected or asymptomatic carriers of meningococci, and close contact with, or close proximity to, the local population with (at least in part) a high level of nasopharyngeal carriage, are all factors that increase the overall risk of acquiring the disease. Furthermore, travellers may also be asymptomatic carriers, and thus potential transmitter of meningococci. Consequently, they may import meningococcal serogroups into their home countries, where such serogroups are unusual or rare.

While the incidence of meningococcal infections during the Hajj pilgrimage to Saudi Arabia may be as high as 200/100,000 inhabitants, the estimated risk for travellers to countries characterised by a low incidence is a very small 0.04/100,000 population per month (6,7). Nevertheless, even in the case of a relatively low risk of infection, the extent of the disease and its consequences can be substantial. Invasive meningococcal disease has a case fatality rate of about 10%, but can be much higher in certain age groups and depending on the serogroup, e.g. in the province Gauteng in South Africa, where serogroup W-135 predominates, the case fatality rate was reported to exceed 20% during the last years (8). In addition, in remote areas, it can be difficult to obtain quick and adequate medical care.

Distribution of serogroups in various countries

Africa

Most of the epidemics in Africa are caused by serogroup A, with serogroup W-135 in second place. The risk of contracting an infection is highest in the so-called meningitis belt, a region that extends from Ethiopia in the east to Senegal in the west (figure 1). At intervals of 10-15 years, epidemics giving rise to incidences of up to 800/100.000 inhabitants occur there (1,5). It would appear that the meningitis belt is currently in the process of expanding (9). Other regions outside the belt have also been scourged by epidemics (Burundi, Ruanda, Tansania, Niger, Camaroon). At the beginning of 2009, the north of Nigeria experienced a meningococcal epidemic, and by the end of April 2009, more than 50,000 cases

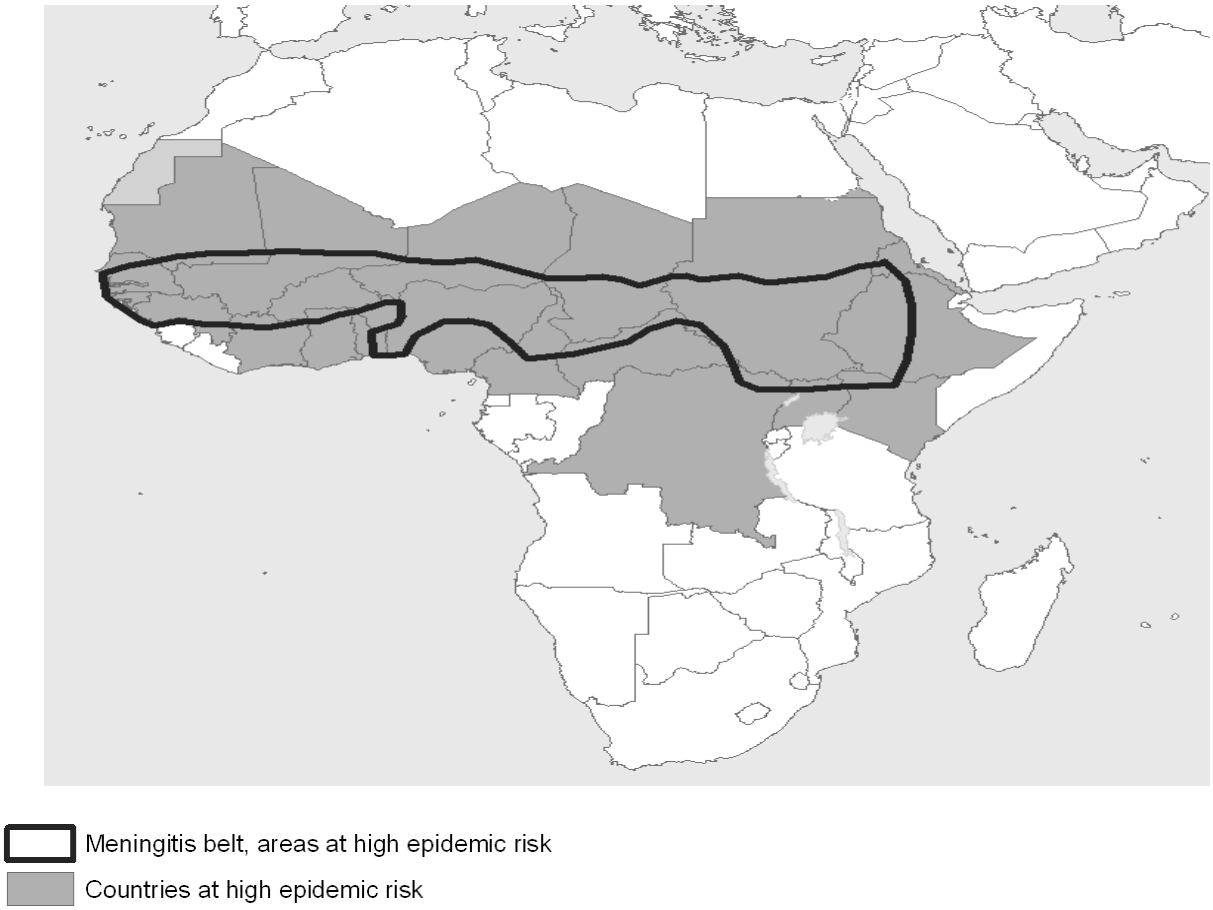

Figure 1. The African meningitis belt is expanding: Neighbouring countries with a risk for meningococcal disease. Figure and data from WHO (9)

resulting in 1900 deaths had been reported (10). A more recent occurrence underscores the unpredictability of meningococcal epidemiology: in the spring of 2009 serogroup W-135, which had occurred only sporadically in West and Central Africa and had last been observed in Tschad ten years previously, caused an epidemic that resulted in more than 100 deaths in the first half of 2009, while in the first quarter of 2010, some areas experienced mixed epidemics with serogroup A and W-135 (11).

International efforts made by the WHO and Program for Appropriate Technology in Health (PATH) recently allowed a low-price conjugate vaccine to be developed against serogroup A (MenAfriVac®). Anticapsular conjugate vaccines against additional serogroups (in particular W-135 and X) should hence be explored with the possible combination of these serogroups and the serogroup A conjugate vaccine, which is in development (12).

South Africa

As epidemiological studies show, most of the cases that were recorded in the period between 1992 and 1997 in South Africa were caused by serogroup A. In the years between 2000 and 2005, serogroup W-135 emerged strongly, with the percentage of cases it caused increasing from 5% in 2000 to 62% in 2005. Its incidence per 100,000 inhabitants increased from 0.54 in 2000 to 1.6 in 2005. At the same time, the incidence of serogroup A involvement decreased, while that of serogroup B and Y remained relatively unchanged (13). The

annual report 2009 of the National Institute for Communicable Diseases of the National Health Laboratory Service in Johannesburg indicates that W-135 continues to be the predominant serogroup with 59% (8).

The Middle East and Saudi Arabia

In these two regions, serogroups A, C and W-135 predominate. A high risk is associated with a pilgrimage (Hajj, Umrah). In Mecca, extremely large numbers of people (more than 2 million pilgrims from more than 140 different countries) crowd together in a limited area, which increases the risk of infection enormously. The nasopharyngeal carriage within the area in the vicinity of the holy mosque may be as high as 80% (14).

In the year 1997, serogroup A, and in the years 2000 and 2001, serogroup W-135 were responsible for outbreaks, In 2000, serogroup W-135 caused more than 400 meningococcal infections among Hajj pilgrims and/or their contacts from 16 countries, and was the largest W-135-associated outbreak worldwide. The W-135 outbreak in 2001 resulted in 200 infections, and a total of 55 people died during the two outbreaks (4). Since 2002, the Saudi Arabian authorities have required all those visiting their country during the Hajj to have been vaccinated with a tetravalent meningococcal vaccine replacing the bivalent A/C vaccine.

Asia

Here, the predominant serogroups are A and C. Between 1982 and 1984, Nepal experienced an outbreak caused by serogroup A meningococci with more than 4500 cases. Six travellers became infected, 2 of whom died. Those affected had been tourists who had had close contact with the local population. Further outbreaks occurred in India (1985), in Mongolia (mid-1990), in the Philippines (2004/2005) and again in India in 2005 (4).

In the years 2003/04 and 2004/05, China experienced several local meningococcal C outbreaks. Vaccination countermeasures appreciably reduced the number of those affected (15). In Korea, the incidence of meningococcal disease is generally very low, with serogroup Y apparently predominating (16).

USA

For many years, the incidence of meningococcal disease remained at 1.0-1.5/100,000 inhabitants/ year, and over the past few years it has been declining and was 0.33 cases per 100,000 population in 2007 (17). The predominant serogroups are B, C and Y, with serogroup Y gaining in importance. Since the middle of 1990, the number of cases caused by serogroup Y has increased dramatically, and in 2008 accounted for almost 40%. In the USA, vaccination with tetravalent conjugate meningococcal vaccine is recommended for youngsters aged 11-18 years, and for persons in the age range 2-55 years who are at an increased risk (18).

The unpredictability of meningococcal epidemiology is exemplified by the 14 cases caused by serogroup W-135 in the south of Florida in the period between December 2008 and April 2009. Four of the 14 cases proved fatal and included a 26-year-old British male tourist (19).

Latin America

Epidemiology of meningococal disease in Latin America is characterized by marked differences from country to country. The overall incidence of meningococcal disease per year varied from less than 0.1 cases per 100,000 inhabitants in countries like Mexico to two per 100,000 inhabitants in Brazil. In Brazil, the percentage of invasive meningococcal infections triggered by serogroup C was 36% in the years 1999 to 2002, but increased to 65% in the period 2003-2005 (20). The case fatality rates in Brazil are still very high, reaching 20% in recent years (21).

In the period between 1994 and 2006, some 78% of the cases seen in Columbia were caused by serogroup B, with serogroups C and Y each responsible for roughly 10%, and serogroup W-135

for 0.5% of the cases. Unexpectedly, serogroup Y involvement increased from 0 in 1994 to 50% in 2006 (22). So far, Brazil is the only country in the region that has already decided to add meningococcal C conjugate vaccine to the routine childhood immunization schedule, anticipating that, from October 2010 on, the vaccine will be available for all children under two years of age (21).

Europe

In Europe, serogroups B and C predominate, with the serogroups A and W-135 gaining ground in a number of countries. Outside of epidemics, the incidence of infection is some 1-3/100,000 inhabitants/year (23), with serogroup B responsible for the majority of cases, and serogroup C in second place. In the last decades, Finland, Norway, Great Britain and Ireland have all experienced epidemic outbreaks (Norway: serogroup B; Great Britain serogroup C). In Great Britain and Ireland, the incidence decreased dramatically following the introduction of meningococcal C conjugate vaccination into the infants' vaccination schedule and the implementation of vaccination campaigns. Different vaccination strategies were applied to combat against serogroup C disease in various countries and in general all these vaccination strategies have been successful (24).

Within the period 1999-2003, serogroup A was in second place in Greece (19%), followed by serogroup W-135 (11%) (25). Epidemiological studies carried out in Turkey in 2005 and 2006 revealed a relative involvement of 42.7% for serogroup W-135, of 31.1% for serogroup B, 2.2% for serogroup Y, and of 0.7% for serogroup A (26).

The unpredictability of meningococcal infections and outbreaks was recently illustrated in Italy, a country with one of the lowest incidences of such diseases in Europe. In 2007 and 2008, two clusters of meningococcal disease (caused by serogroup C) resulting in 6 deaths among the 10 persons affected were reported (27).

New Zealand

Here, serogroup B is the predominant strain and causes a serious epidemic that lasted for more than a decade. With the aid of a vaccine specially developed for this strain, the epidemic was successfully brought under control (28).

Vaccination providing protection at home is not necessarily adequate in other countries.

The vaccinations recommended for a traveller´s home country do not necessarily provide protection from meningococcal infection abroad. Since the immune response is strictly serogroup-specific, the routine meningococcal C conjugate vaccine recommended e.g. for children in the German-speaking countries (Germany, Austria, Switzerland) offers no protection against other serogroups. For this reason, travellers should in good time seek expert advice about possible and necessary vaccination and the vaccines available. Such vaccinations are capable not only of reducing the risk of the individual traveller of contracting an infection, but can potentially also help limit the global spread of the bacteria involved.

For travellers to Saudi Arabia during the pilgrimage season, the authorities require vaccination with a tetravalent meningococcal vaccine. In most countries the tetravalent polysaccharide vaccine is available to travellers. However, a vaccine containing a free polysaccharide, provides only limited protection: i) protection persists for only 3–5 years and ii) revaccination can induce hyporesponsiveness (reduced immunogenicity), iii) in children younger than 2 years the vaccine is not immunogenic. As a T cell independent antigen, iv) it cannot induce immunological memory and is not boostable and v) it cannot reduce nasopharyngeal carriage (table 1) (18). This means that a polysaccharide vaccine cannot prevent the importation of meningococci into the home country by asymptomatic travellers.

If possible, a tetravalent conjugate vaccine should be given. Having a similar tolerability

profile, the conjugate vaccine induces a greater immune response, is immunogenic in children younger than 2 years (18, 29, 30), does not result in a reduced immune response (hyporesponsiveness) on repeated administration (30). Furthermore, the conjugate vaccine can induce immunological memory and a booster response, and can potentially reduce nasopharyngeal carriage (table 1); thus its widespread use can in principle, build up herd immunity (18).

Table 1. Advantages and disadvantages of polysaccharide and polysaccharide conjugate vaccines

Properties	Polysaccharide vaccines	Conjugate-vaccines
Effective in infants and young children	no	yes
Development of an immune memory	no	yes
Prolonged protection	no	yes
Immune response boostable	no	yes
Reduction of nasopharyngeal carriage	no	yes
Herd immunity	no	yes
'Hyporesponsiveness' (reduced immune response on repeated vaccination)	yes	no

New tetravalent conjugate vaccines available

In North America, two tetravalent meningococcal ACWY conjugate vaccines are registered. In one of these vaccines, the polysaccharide is conjugated to the carrier protein diphtheria toxoid (Menactra®; Men ACWY-D). The other conjugate vaccine that employs the CRM197 ("cross-reactive material" – a non-toxic mutant of the diphtheria toxoid) as carrier protein (Menveo®, MenACWY-CRM197) was registered in North America and in the European Unit at the beginning of 2010. In Europe, only the CRM197 based conjugate vaccine has been registered so far. For travellers, the tetravalent conjugate vaccine, with its advantages vis-à-vis the free polysaccharide vaccine will in most cases be preferred (18).

The risk to acquire meningococcal disease of international flights

The overall risk of meningococcal transmission during a flight is very low. The health authorities in the USA (Centres for Disease Control and Prevention, CDC) reported 21 cases of meningococcal disease acquired by passengers during a flight in the period between February 1999 and May 2001 (31) (definition of the CDC: meningococcal infection manifesting within two weeks after a flight of at least 8 hours).

Case reports

In the year 2000, a 20-year-old male student flying from Tel Aviv in Israel to New Jersey (USA) became ill on board. He died 2 hours after admission to hospital and the diagnosis was meningococcal meningitis and sepsis (32). In 2005, two passengers on the same international flight were taken ill with a meningococcal B infection. The bacterial isolates were genetically identical. All contact persons were given chemoprophylactic treatment. The possible transmission pathways in the aircraft might have been from one infected person to the others, or from an asymptomatic carrier passenger to both persons (33).

Another case of an in-flight meningococcal B infection occurred in 2005 when a member of the military contracted a meningococcal-B infection on a transatlantic flight from the southeast of the United States to Kuwait with a stopover in Germany. More than 200 passengers (US military and civilian personnel) were on board the aircraft. With the aim of preventing further infections and providing prophylactic antibiotic treatment to all contact persons, rapid international cooperation was needed. Since the illness was first diagnosed only several days after the flight, the identification and tracking of all possible contacts required a

considerable international effort. Thanks to the cooperation of the health authorities in a number of countries, all the contacts were identified within a short period of time, and received chemoprophylaxis (34).

Meningococcal diseases in aircraft; the occupational medical view

A special case is the situation of people on business trips, in particular when they travel to countries with a relatively high incidence of meningococcal diseases and come into close contact with other travellers or the local population. Meningococcal diseases on board an aircraft represent an extremely difficult medical problem. Recently, Rao et al. have proposed a plan of action involving both preventive and therapeutic measures (35). A major aspect of this is the storage on board of suitable antibiotics (penicillin G, cephalosporins of the third generation) and appropriate training of the cabin crew.

As soon as tetravalent meningococcal conjugate vaccines are widely available, consideration should be given to the vaccination of the cabin crew (36). These are the people who will be the first line of care for the sick person and are themselves at a high risk from aerosol infection. A general recommendation for vaccination with a polysaccharide vaccine is not currently in force, and would also appear to make little sense, since it provides protection for only a relatively short period, and repeated vaccinations may lead to a weakening of the immune response.

These disadvantages are not to be found with the novel conjugate vaccines. On the basis of experience with the monovalent serogroup C conjugate vaccine they have the potential not only of protecting the individual vaccine against a meningococcal infection, but also of preventing colonisation of the nasopharynx by the four meningococcal serogroups against which the vaccine provides protection. This would ensure that vaccinated cabin crew have individual protection, and the potential spread of the meningococci by asymptomatic carriers could be reduced.

In view of the lack of relevant data, the occupational-medical significance of meningococcal disease cannot be estimated with any degree of certainty. Nevertheless, the STIKO (Standing Vaccination Committee at the Robert-Koch Institute in Berlin) has classified the risk of such infections in laboratory personnel exposed to possible contact with aerosols as highly probable (37). According to Hofmann, occupations involving close contact with the public should (as in the case, for example, of influenza) be considered high-risk activities (38).

For the cabin crew, travelling is an occupational activity, and vaccination against meningococci would thus represent occupational-medical prophylaxis. A similar situation is to be found among personnel employed on cruise liners and long-distance tour buses. Consideration should be given to the question as to whether persons in such occupations also need to be offered vaccination with a tetravalent meningococcal conjugate vaccine.

Mass meetings and events

In our modern world, public events attended by large crowds of people are commonplace, and international air travel at moderate financial cost to the traveler has resulted in an enormous increase in the movement of people around the entire world. Reasons for such mass events vary widely; they may be of a religious nature – for example the Hajj pilgrimage with a regular participation of more than 2 million people, or the Catholic Youth Rally (in 2008 attended by several hundred thousand persons from more than 70 countries); or sporting events such as, for example, the World Athletics Championships held in Berlin in 2009, the Winter Olympic Games in Vancouver, and the World Football Championship in South Africa, both in 2010. Alternatively, they may have an economic background, as in the case of Expo 2010.

Whenever large numbers of people are expected to congregate together for such events, it is worth considering whether additional prophylactic vaccination should be offered to the tourists (39). Experience has shown that people gathered in close proximity in a confined space have an elevated risk of contracting meningococcal disease. This applies, for example to students sleeping in dormitories, military recruits and, as meningococcal outbreaks in 2001 and 2002 showed, also to the Hajj. A major feature of meningococcal epidemiology is the unpredictability of the bacteria. Organisers of such mass events should perhaps be advised to draw attention to meningococcal diseases and the protection provided by meningococcal conjugate vaccines.

The following items may be concluded:

- Meningococcal diseases in travellers are rare.
- However, the associated high mortality rate and the severity of the sequelae identify them as a serious medical problem
- The epidemiology of the meningococci is constantly changing
- Polysaccharide vaccines can help protect travellers against meningococcal infection
- Newly developed polysaccharide conjugate vaccines should be the preferred choice for travellers to areas with an elevated risk for meningococcal diseases
- In the view of occupational medical experts, the novel tetravalent meningococcal ACWY conjugate vaccine would appear ideal for those travellers whose business trips abroad expose them to an elevated risk of infection.

Conflict of interest: M.B. is full-time employee of Novartis Vaccines and Diagnostics GmbH, a pharmaceutical company producing meningococcal vaccines.

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