

Review

Global review of meningococcal disease. A shifting etiology

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Accepted 23 March 2009

Despite expansive studies over the past century, the epidemiology of invasive meningococcal disease (IMD) has remained elusive in some of its aspects. The following review attempts to summarize the past and current trends in the etiology of IMD. Data was collected through the analysis of peer-reviewed studies and surveillance data on national, sub-national and regional levels performed using various search engines such as pubmed (www.ncbi.nlm.nih.gov/pubmed/), regional WHO homepages (www.who.int) and department of health websites. Despite the establishment of improved surveillance, the reasons for the differences in IMD epidemiology between endemic and epidemic settings are not fully understood. Factors influence the timing and distribution of epidemics including climatic, socio-economic and cultural factors involving changes in human lifestyle, natural growth of the human population, crowding and increased mobility. These have also strongly affected the global population structure of *Neisseria meningitidis* and are still currently responsible for changing patterns in IMD epidemiology. In recent years, much interest has arisen on the subject due to both the development of conjugate vaccines and to the continuing occurrence of outbreaks, many of them in industrialized countries. With antimicrobial resistance on the rise, effective and affordable vaccines along with continued surveillance are needed to help combat this complex disease.

Key words: *Meningococcal meningitis*, epidemiology, vaccines, antimicrobial resistance, surveillance.

INTRODUCTION

Despite expansive studies over the past century, the epidemiology of invasive meningococcal disease (IMD) has remained elusive in some of its aspects. In recent years much interest has arisen on the subject due to both the development of conjugate vaccines and to the continuing occurrence of outbreaks and epidemics, many of them in industrialized countries, in spite of the availability of these more efficacious vaccines. The following review attempts to summarize the past and current trends in the etiology of IMD.

Data were collected through the analysis of peer-reviewed studies and surveillance data on national, sub-national and regional levels performed using various scientific and non-scientific search engines such as pubmed (www.ncbi.nlm.nih.gov/pubmed/), scielo (www.scielo.org) and scholar google, regional WHO homepages

(www.who.int) and department of health websites. Search vocabulary included terms such as "meningitis", "meningococcal disease", "neisseria meningitidis", "invasive meningococcal disease", "outbreak", "incidence", "serogroups-A, B, C, W135, Y, E29, X", "clonal complexes", "meningococcal vaccines" as well as individual country names. Allowing for differences in surveillance methods and limitations in ascertainment, we contrast major trends of meningococcal disease epidemiology in different regions with a historic perspective.

N. meningitidis, a gram-negative diplococcal bacterium, is a commensal of the human *nasopharynx* and causative agent of *meningococcal meningitis* and *septicemia*. It is one of the most significant human pathogens and is together with *Streptococcus pneumoniae* and *Haemophilus influenzae*, one of the major causes of bacterial meningitis. The disease burden associated with bacterial meningitis is comparable to tropical diseases such as *trypanosomiasis*, Chagas disease, *schistosomiasis*, *leishmaniasis*, *lymphatic filariasis*, *onchocerciasis*, leprosy and

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dengue all combined (Mathers et al., 2002).

Transmitted through droplets of respiratory secretions, *N. meningitidis* carriage rates reach up to 10% of the general population at any point in time (Yazdankhah and Caugant, 2004) whilst invasive disease, developing in a small percentage of carriers is regarded as a medical emergency. Case-fatality rates critically depend on access to health services and despite the availability of antibiotic therapy, 10% of patients die within two days of disease onset whilst *sequelae* such as hearing loss, brain damage and learning disabilities can affect up to 20% of the survivors (Welch and Nadel, 2003). *Meningococcal septicemia*, a complication of the disease, often causes hemorrhagic rashes and rapid circulatory collapse and is associated with higher case-fatality and *sequelae* rates. The annual incidence of meningococcal disease ranges in many industrialized countries from 1 - 5 cases per 100'000 (Greenwood, 2007). Incidence rates (IR) are usually highest during early childhood, in teenagers and young adults, although this also depends on a variety of epidemiological factors. Particularly during epidemics, a broad age spectrum may be observed (Greenwood et al., 1979; Moore, 1992).

Whilst limited outbreaks of disease are often associated with overcrowding, resulting in high transmission of *meningococci* in schools, student dormitories, refugee camps or military facilities, epidemic meningococcal disease claims many lives especially in the so called African *meningitis* belt (Greenwood, 1999). Outbreaks of meningococcal disease in the belt are generally confined to the dry season whilst in Europe, Northern America and other temperate regions, a seasonal increase of meningococcal cases is usually recorded during winter months (Cartwright, 1995; Tikhomirov et al., 1997). Apart from direct case contact and overcrowding, smoking and exposure to smoke (Hodgson et al., 1997; Stanwell-Smith et al., 1994) have also been identified as possible risk factors for infection and invasive disease.

MENINGOCOCCAL CLASSIFICATION AND TYPING

Serological differentiation of meningococcal isolates began in the early 20th century. From a first sub-classification of *meningococci* into main types associated with epidemics, versus rare types associated with endemic disease, four decades were needed to acquire a more comprehensive understanding of antigenic diversity and to develop a standardized serological typing system which was introduced in 1950 (Vedros, 1987). Nowadays, 13 meningococcal serogroups reflecting the chemical structure of the polysaccharide capsule are known (Yazdankhah and Caugant, 2004), of which six (A, B, C, W135, X and Y) are responsible for the vast majority of IMD cases. Historically, epidemics of serogroup, a *meningococci* have caused the highest disease burden worldwide. Currently in many industrialized regions

serogroup B, responsible for endemic disease but also local and intercontinental outbreaks is the most common cause of IMD. Serogroup C has been responsible for causing severe outbreaks in Europe and North America in the past 30 years with a high disease burden in adolescents. Although the remaining meningococcal serogroups are regarded as less virulent and usually only cause symptomless colonization of healthy individuals. serogroups W135 [13-15], Y [16] and X [17-20] have recently also been associated with outbreaks of IMD.

Serotyping and serosubtyping rely on the detection of distinct epitopes present on different classes of outer membrane proteins of *N. meningitidis*. Serotyping epitopes are found on class 2 or class 3 outer membrane proteins (OMP) (P or B) of *N. meningitidis*. Serosubtyping epitopes are present on class 1 OMP (P or A). Although serological typing provides essential information on antigenic diversity in particular for potential OMP-based vaccination strategies, typing reagents are not available for all serotypes or subtypes. Additionally, due to phase variation or loss of the corresponding genes many strains do not react serologically (Claus et al., 2005).

More recently, several molecular methods have been developed which complement serological typing techniques (Caugant, 2008). Multi locus enzyme electrophoresis (MLEE) using the natural variation in electrophoretic mobility of various enzymes has been the standard typing method used until the late 1990s. In the last decade, it was replaced by multilocus sequence typing (MLST) based on the nucleotide sequences of 400 - 500 bp long fragments of seven housekeeping genes (Maiden et al., 1998). For each gene, the sequence variants observed are assigned as distinct alleles which define the sequence type (ST) based on the seven loci of every isolate. Evolutionary developments can be modeled using MLST data in combination with the e-Burst (Based upon related sequence types) application (Feil et al., 2004).

Clonal complexes are defined as closely related groups of isolates in which all STs are linked to a single locus variant of at least one other ST. The clonal complexes differ substantially in their pathogenic potential and only 11 of the 37 so far identified complexes are strongly associated with invasive disease (Caugant, 2008). In particular, serogroup A *meningococci* have a clonal population structure (Olyhoek et al., 1915 and 1983; Morelli et al., 1997; Achtman, 2004) with the majority of isolates in the MLST database assigned to one of three major lineages, the ST-1, ST-4 and ST-5 clonal complexes. The other meningococcal serogroups show a greater genotypic and serologic diversity and clonal complexes commonly include isolates of different capsular serogroups (Yazdankhah et al., 2004) (<http://mlst.net>).

The genetic factors that determine virulence of *N. meningitidis* strains have yet to be clearly identified. Avirulence of unencapsulated strains shows that expression of a polysaccharide capsule is an important factor. Epidemiological data indicate that certain capsule polysacch-

arides such as A, B and C may in particular contribute to resistance against host defense mechanisms. However, recent outbreaks caused by strains belonging to serogroups W135, X or Y demonstrate that strains expressing other capsules also present epidemic potential. It is mostly assumed that complex constellations of genetic factors determine virulence (Caugant, 2008).

FIRST REPORTS OF MENINGOCOCCAL DISEASE IN THE 19TH CENTURY

Whilst accounts of "epidemic convulsions" in China date back a thousand years (Zhen, 1987), the first reliable records of epidemic meningococcal disease originate from the early 19th century, specifically from Geneva (Switzerland) in 1805 (Vieusseux, 1805) and Massachusetts (U.S.A) in 1806 (Harrison and Broome, 1987). The causative agent was not identified until 1884 (Marchiafava and Celli, 1884) and *N. meningitidis* was cultivated for the first time by Weichselbaum in Vienna in 1887 who named it *Diplococcus meningitidis intracellularis* (Weichselbaum, 1887). Early accounts and reports of the disease were compiled by Hirsch in his "Handbook of geographical and historical pathology" which appeared in 1886. Hirsch distinguished three periods of IMD spread in Europe and Northern America, prior to the emergence of *N. meningitidis* as a globally distributed pathogen in the 1880s (Hirsch, 1886). First outbreaks were seen in various regions of the USA and Canada in the years 1805 - 1816 and in Europe, particular in France and southern Italy from 1805 - 1830.

During the second period between 1837 - 1850 outbreaks were reported from France, Italy, Denmark, Spain, Ireland and Germany. In the USA, meningitis outbreaks mostly affected several eastern states during that period (1842 - 1850) (Hirsch, 1886). During the third period between 1854 - 1875, IMD became widely distributed in the USA and in Europe with severe outbreaks in Sweden and Germany. Hirsch described many characteristic features of IMD such as the strong seasonality, the role of overcrowding as risk factor, the age distribution of cases and age shifts in certain epidemic situations (Hirsch, 1886). In response to the emergence of epidemic meningitis in Europe, the first notification system for meningococcal disease was implemented in 1875 in Sweden, even before the causative agent was described (Jones and Abbott, 1987; Peltola, 1987; Cartwright, 1995).

On the African continent, first outbreaks were seen, most likely imported by French soldiers among soldiers in Algiers around 1840 (Hirsch, 1886) and in South Africa by 1888 (Greenwood, 1999). First accounts from the near east comes from Jerusalem in 1872 and Persia 1874/75 (Hirsch, 1886). In South America, the disease was first reported amongst Portuguese immigrants in Sao Paolo in 1906 (de Moraes and Barata, 2005). Other early reports dated back to 1879 in the Indian subcontinents, 1897-98 in China, Hong Kong and the Yangtze Valley and 1900 in

Australia and New Zealand (Hansman, 1987).

1900 - 1950: Large serogroup A epidemics associated with the world wars

In the early 20th century, several larger outbreaks were recorded in Europe and Northern America including Germany where the industrial and mining regions were severely affected with over 10'000 cases being reported between 1904 and 1907. Similarly, Norway, Sweden and Scotland experienced serious outbreaks in the period preceding the first world war (Jones and Abbott, 1987; Peltola, 1987; Peltola, 1983; Kuzemenska and Kriz, 1987). During the first world war, England was heavily affected with altogether more than 10,000 cases in civilian and military populations (1915 - 1919) but also Italy reported an epidemic wave of IMD from 1915 - 1918 (Ballada et al., 1990). In the USA, major outbreaks of IMD were seen in the early 20th century in particular during the recruitment and mobilization of military forces. This included outbreaks associated with the occupation of Cuba which began in 1899 as well as in Mexico in 1914. The first large epidemic with over 5,000 cases occurred during the winter of 1916 - 1917. Additionally, US Army camps located in France and Britain during the first world war reported over 5,000 cases with a case fatality rate of 39%. Post-war, further outbreaks were reported in 1928 - 1929 and 1936 - 1937, affecting US Army personnel as well as spilling over into the civilian population (Harrison and Broome, 1987; Brundage and Zollinger, 1987). In Canada, two outbreaks were reported in 1929 and 1941 with overall IRs of 3.1 and 12.8 /100,000 respectively (Varughese and Acres, 1987).

The most extended outbreaks in Europe occurred during the second world war throughout the continent, primarily affecting the countries directly involved in the war.

Between 1940 and 1942, England reported 30'000, Germany 15,000 and Italy nearly 9,000 cases. Outbreaks were also reported from Austria, France, Portugal, Spain, Bulgaria, Romania and Greece (WHO, 1945). In Scandinavia, meningococcal outbreaks were introduced by occupying troops and IRs peaked in 1941 (Norway, Iceland) and 1944 (Denmark). Whilst Finland, occupied by the Russians, experienced a small outbreak, meningococcal meningitis epidemics were absent from Sweden in the 1940s (Peltola, 1987). Yugoslavia and Hungary each reported epidemics of greater than 3'000 cases in 1940 before entering the war in 1941 (WHO, 1945). In the USA, an epidemic occurred during the mobilization for the second world war in the winter of 1942 - 1943 with more than 13'000 cases being reported in army training camps mostly affecting fresh recruits (Brundage and Zollinger, 1987).

Comparable to Europe and Northern America, serogroup A epidemics occurred in Australia on a continent-wide basis during the two world wars. Overall IRs peaked at 30 - 35/100'000. Relatively high notification rates of

IMD attributed to extensive population movements and immigrations (Patel, 2007) were also recorded in several states in the 1950's with IRs of up to 7/100'000 in western Australia and Victoria.

In Asia, following outbreak reports as early as 1879 in British-occupied India, larger incidents were recorded in prisons located in Shikarpur and Alipore as well as in China and Hong Kong where local outbreaks were described in 1917/1918 (Hong Kong), 1919 - 1920 (Anhui), 1923 (Taiwan), 1932 (Guangzhou), Macao (1932) and 1934/1935 (Hunan). First nationwide epidemics occurred in 1938 and 1949 (Zhen, 1987; Cadbury, 1934). In Russia two serogroup A epidemics occurred in 1931 and 1940 (Achtman et al., 1969 – 1997).

In South America, cases of IMD were reported in Sao Paulo since 1906 and a first epidemic started in 1920 with the majority of cases being attributed to serogroup A and about 25% to serogroup C (de Moraes and Barata, 2005). After the peak in 1923 with IRs of circa 12/100'000, the rate returned to endemic levels of 1.3 - 4.1/100'000 by 1926. During the second world war, the region was again seriously affected by epidemics followed by a large outbreak in Sao Paulo in 1947. During this period, outbreaks were also noted in Chile (1941 - 1942) (Cruz et al., 1990) and Mexico (1945-1949) (Almeida-Gonzalez et al., 2004).

Already in 1963, Lapeyssonnie defined the so called 'African Meningitis Belt' a region south of the Sahara and north of the tropical rain forest within the 300 – 1100 mm mean annual rainfall isohyets and stretching from the Gambia to Ethiopia and Sudan. He reported that endemic and epidemic IMD occurs in this area on a strictly seasonal basis during the dry and hot season of the year (December - May) and rapidly declines with the onset of the rains (Moore, 1992). These large epidemics were characterized as occurring within 8 - 14 year cycles and having IRs of up to 1% of the general population (Lapeyssonnie, 1963). The first epidemics in West Africa occurred in Nigeria in 1905 (McGahey, 1905) and in Ghana between 1906 - 1908. The *meningococci* causing the 1906 - 1908 outbreak were possibly introduced by pilgrims returning from Mecca and were also implicated in an epidemic in Sudan a few years earlier (Greenwood, 1999). Subsequently, three epidemic waves set off in 1934, 1942 and 1949. The latter causing over 50'000 cases in 1950 and 1951 respectively in Sudan and Nigeria and 16'000 cases in Burkina Faso in 1957. Virtually all bacterial isolates obtained in the first decades of the 20th century showed serogroup A capsule agglutination except for a few isolates from Sudan where serogroup B was seen or the capsule could not be determined with the available antisera (Lapeyssonnie, 1963).

1950 - 1990: Changes in serogroup distribution

After the end of the second world war, stabilizing social

and economic conditions were associated with a decrease in large serogroup A outbreaks previously reported in the industrialized countries (Schwartz et al., 1989). The introduction of both capsule carbohydrate vaccines and chemoprophylactic measures contributed further to a decrease in IRs (Harrison and Broome, 1987; Brundage and Zollinger, 1987). Although epidemics became rarer in these regions. Certain foci, such as northern parts of Europe and the USA remained hotspots for IMD. During 1973 - 1976, a serogroup A epidemic occurred in Finland accounting for over 1'500 cases (Peltola, 1978), whilst a serogroup B outbreak in Iceland and Norway (1976 - 1986) claimed 3'000 cases in Norway alone with high case-fatality rates associated with elevated rates of septicemia (Peltola, 1983; Caugant et al., 1986; Bovre and Gedde-Dahl, 1980). In the USA, a serogroup A outbreak in skid row populations in Alaska, Seattle and Portland was recorded in 1975 (Filice et al., 1984). In Canada, case clusters of serogroup A followed by serogroup C caused elevated IRs in the early 1970s (Varughese and Acres, 1987).

In Australia, epidemics of serogroup A also subsided after the second world war with the exceptions of two localized outbreaks among the Aboriginal population in Alice Springs in 1971 - 1973 (Creasey, 1991) and 1987 - 1991 (Patel et al., 1993). In Canberra a sharp increase in the proportion of serogroup C disease appeared in the 1980s, preceded by clusters of serogroup C disease in 1968 (Hansman, 1987). Rising IRs in the 1980s was attributed to both serogroups B and C.

Serogroup A outbreaks were also reported from New Zealand in the Maori population between 1985 - 1987 representing one of many examples that distinct ethnic groups may be affected differently. In New Zealand IRs of 68/100'000 and 17/100'000 were recorded in 1968 in Maori tribes and non-Maori populations respectively (Knights, 1972). Apart from these serogroup A outbreaks, IRs generally dropped continuously during the 1960s and 1970s to <0.5/100'000 in 1981 with a dominance of serogroup B.

Although the quality of surveillance data is poor for many regions in Asia, certain trends in incidence and serogroup distribution can be deduced. In China the IR of IMD increased in the early 1950s continuously until the end of the 1980s to hyperendemic levels between 8.7 in low and >25/100'000 in high incidence regions. In addition, nationwide epidemic waves peaked in 1957/1958, 1967, 1977 and 1985 (Wang et al., 1992). In Russia, an epidemic introduced by Vietnamese factory workers entering through China, started in 1968 and peaked in Moscow in 1970 (Wang et al., 1992). In India, various outbreaks of meningococcal meningitis occurred in particular in Delhi and its surrounding in 1966 and in 1985 as well as in other regions such as Surat and Gujarat in 1985 - 1987 (Manchanda et al., 2006). Mongolia suffered from IMD outbreaks in 1974 - 1975 (Ebright et al., 2003). In Viet-nam, an epidemic occurred in Ho Chi Minh city in

1972 - 1973 and a serogroup C outbreak associated with a high case fatality rate was reported in 1977 - 1978 from the southern provinces (Oberti et al., 1981). In Bhutan 250 cases were notified in 1985 - 1986 (Manchanda et al., 2006), and in Nepal a severe serogroup A epidemic in the Kathmandu valley in 1982 - 1984 (Manchanda et al., 2006; Cochi et al., 1987). In contrast, in Japan (Takahashi et al., 2004) and Taiwan (Hsueh et al., 2004), IMD IRs have been comparably low during the past 50 years, although more than 4'000 annual cases were reported in pre-world war II Japan whereby serogroups B (57%) and Y (21%) have dominated strain collections in the past 30 years (Takahashi et al., 2004).

In the near and middle east, three major serogroup A epidemics were reported between 1967 - 1989 with a seasonal pattern similar to the African meningitis belt. However, IRs have never reached comparable dimensions as in the Belt (Girgis et al., 1993; Sippel and Girgis, 1987) whilst reports from Israel indicate a major contribution of serogroup B in the general population. Serogroup A has been isolated at a higher frequency in the Arab community. Compared to the national average, IRs were higher in communities with lower socio-economic status and in Jerusalem (2.45 vs. 1.13 /100'000) (Block et al., 1993; Stein-Zamir et al., 2007).

In South America, low endemic levels (IRs of 0.3 - 0.6/100'000) of IMD were reported from Chile and Brazil (Cruz et al., 1990) and many other countries (WHO, 1977) throughout the 1950s and 1960s.

In Sao Paulo, a serogroup C epidemic starting in 1971 was replaced by a second wave caused by serogroup A. IRs exceeded 100/100'000 (Souza et al., 1974) with 20'000 cases being reported in that year alone (WHO, 1977). In Argentina, an outbreak with a national IR of 8.3/100'000 and 2,144 notified cases occurred in 1974 with a dominance of serogroup C (82%) and some contribution of serogroup A (18%) (WHO, 1975). Similarly, an outbreak reported in southern Chile in 1978 - 1979 saw a serogroup shift from C to A associated with increasing case fatality rates. Since 1988, hyperendemic IRs of IMD have been notified in Sao Paulo (Santos and Ruffino-Netto, 2005), along with an increase in serogroup B disease. The most prominent serogroup B outbreaks occurred in Cuba in the early 1980s (Caugant et al., 1986; Rico et al., 1996) with a peak IR of 14/100'000 and in Iquique, Chile with an IR of >20/100'000 between 1983 - 1987, rated 20 times higher than in the rest of the country (Cruz et al., 1990). In Mexico, IMD has been rare since an outbreak in the 1940s (Almeida-Gonzalez et al., 2004).

Epidemic meningococcal disease on the African continent continued to threaten countries in the meningitis belt in particular, occurring in frequent intervals (Figure 1).

Virtually all epidemics were caused by serogroup A until the 1990s with the exception of some reported serogroup C outbreaks in the 1970s (Broome et al., 1983; Whittle et

al., 1975). Data from outside the meningitis belt are rare. Some hospital based studies indicate that in many regions *S. pneumoniae* and *H. influenzae* meningitis (particular in children) are of higher significance than IMD (Cadoz et al., 1981; Muhe and Klugman, 1999; Gordon et al., 2000; Peltola, 2001). Longitudinal data from South Africa show a decrease of IRs from 5 - 10/100'000 to < 2/100'000 since 1945 with hyperendemic waves (Coulson et al., 2007).

Since 1990: Improved surveillance and the introduction of conjugate vaccines

Since 1990, several regional surveillance networks have been established including the EU-IBIS network in Europe (<http://euibis.org>), the SIREVA network in South America, the WHO-EMRO network in the countries of North Africa and the near and Middle East, including national surveillance centers distributed throughout the world such as the active bacterial core surveillance and the center for disease control (CDC) in the United States (<http://www.cdc.gov/ncidod/DBMD/abcs/>). Even though this has substantially increased the ascertainment of meningococcal disease in these areas, many factors for example different surveillance methods or case definitions still limit the comparability of epidemiological datasets for different regions (Trotter et al., 2005).

In Europe about 90% of IMD is currently caused by serogroups B and C, yet the exact distribution of serogroups and the relative importance of different clonal complexes vary significantly between countries. Interestingly, Sweden has a relatively high proportion of serogroup W135 and Y isolates (EU-IBIS Network, 2003/2004). Although it has largely disappeared from Europe since the 1950s, serogroup A IMD is still sporadically reported. With an exception of the finish outbreak in the 1970s, most of these cases are imported cases from endemic areas and not associated with major spread into the general population (Zhu et al., 2001). However, in Eastern Europe and Russia, serogroup A seems to persist and has been responsible for more than 30% of all analyzed IMD cases in two Romanian districts between 2000 and 2002 (Luca et al., 2004).

Overall IRs in the USA has stabilized at about 1/100'000 per year, although there is some spatial and temporal variation between states and regions (Harrison and Broome, 1987). The contribution of serogroup Y increased from 2% during 1989 - 1991 to 37% during 1997 - 2002 (Bilukha and Rosenstein, 2005). Hyperendemic rates of serogroup B disease are found in the state of Oregon since 1987 (Bilukha and Rosenstein, 2005).

In Canada, the overall IR has remained between 0.5 and 2 cases /100'000 since the early 1940s (Varughese and Acres, 1987; Pollard and Scheifele, 2001). Recent trends include two waves of increased serogroup C meningitis in several provinces in the early 1990s and 2001 (De Wals, 2004) and a cluster of serogroup B

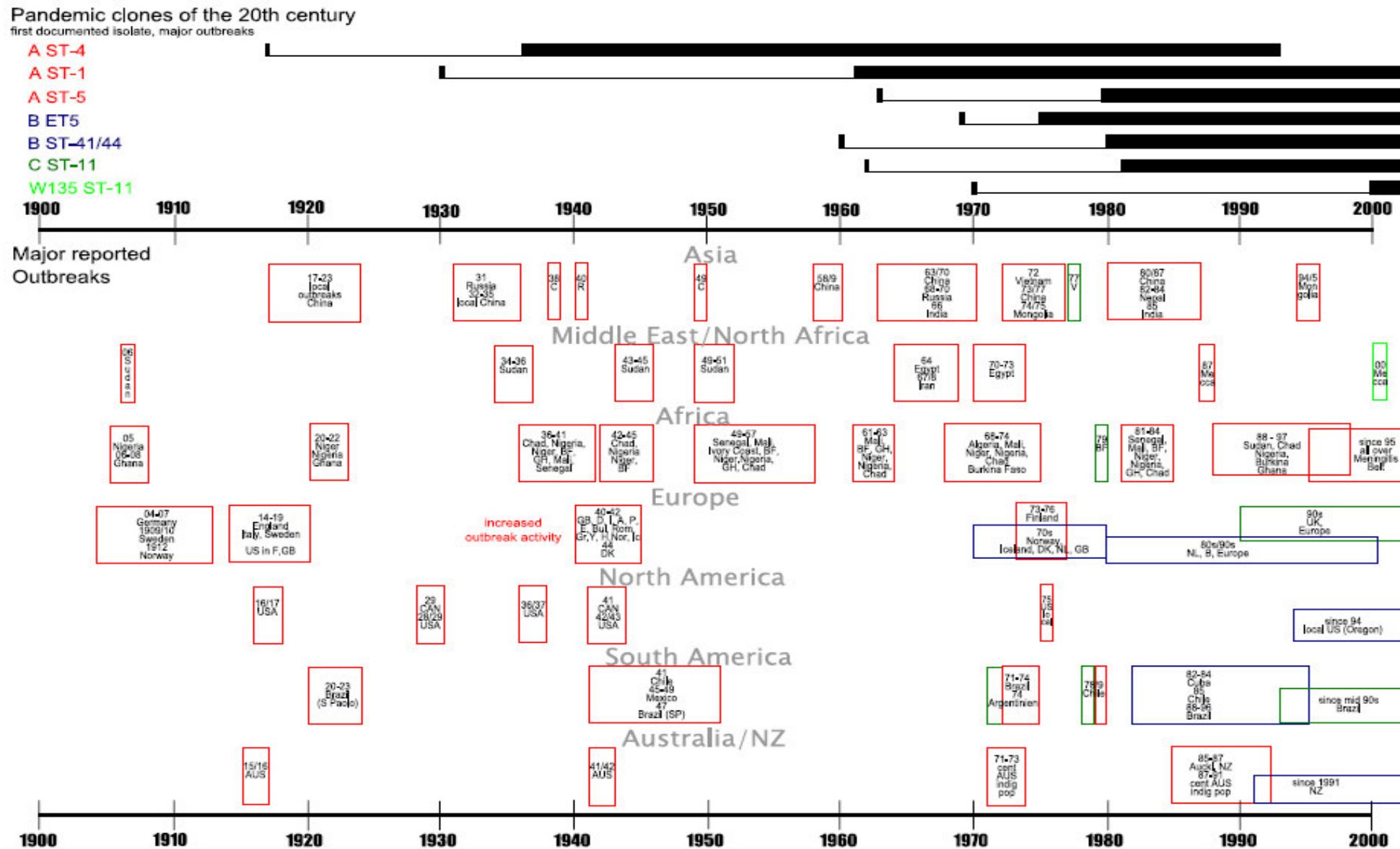


Figure 1. Large meningococcal meningitis outbreaks of the 20th century. Pandemic meningococcal clones with their period of isolation and most important reported outbreaks of the 20th century. (Abbreviations; BF= Burkina Faso/Obervolta, C=China, F=France, GB= Great Britain, GH= Ghana/Goldcoast, R=Russia, V=Vietnam).

meningococcal cases in 2003 (Law et al., 2006). Invasive meningococcal disease in Australia and New Zealand has persisted at a hyperendemic level since the 1990s. In Australia, serogroup B meningococci dominate, although serogroup C meningococci have also caused outbreaks in several regions motivating the introduction of the serogroup C conjugate vaccine (Patel, 2007). In New Zealand, an extended serogroup B epidemic started in the early 1990s and reached its peak between 1996 - 2000 with IRs of 13.9/100'000. A strain-specific OMP- based vaccine was used to control the epidemic (Kelly et al., 2007).

In the larger countries of Asia such as India, China and Russia serogroup A IMD is still very important with outbreaks reported in Mongolia in 1994/1995 (WHO, 1995), Moscow in 2003 (Communicable Disease and Health Protection Quarterly Review, 2003) and Delhi in 2005 (Manchanda et al., 2006). In China, the strong decrease of the annual national IR to $\sim 0.2/100'000$ was attributed to regular vaccination campaigns introduced in the 1980s (Zhang et al., 2007). Recently however, reports of serogroup C outbreaks together with rising IR in certain regions have been published (Zhang et al., 2007; Shao et al., 2006) suggesting a gradual replacement of serogroup A by serogroup C (Ni et al., 2008). In Japan and Taiwan serogroups B and Y have dominated for a long period of time (Takahashi et al., 2004). Since 2001 an increasing number of cases caused by imported serogroup A, C and W135 strains have contributed to an increase in national IRs (Hsueh et al., 2004; Yang et al., 2006; Chiou et al., 2006).

In Morocco and Tunisia, serogroup A has lost its significance in particular since the introduction of vaccination for the Hajj in Mecca and serogroup B has dominated since the 1990s (Zerouali et al., 2002; Maalej et al., 2006). Reports from Saudi Arabia have indicated a predominance of serogroup A between 1995 and 1999 while serogroup W135 caused 13% of IMD cases (Lingappa et al., 2000). The overall national IR is low during endemic periods (Mahmoud et al., 2002; Almuneef et al., 1998) but during a W135 outbreak in 2000, it rose to 2.5/100'000. For Pakistan, IRs of >4 cases/100'000 have been reported in the 1990s (<http://gis.emro.who.int/HealthSystemObservatory/Database/Forms.aspx>).

In South America, after a long period of low IR in the 1970s and 80s, increasing IR and outbreak activities were reported since the late 1980s. In Brazil, a serogroup B outbreak, starting in 1988 and peaking in 1996 was mainly observed in the large cities, for example, Sao Paulo and Rio de Janeiro. Furthermore, serogroup C caused severe outbreaks in different parts of the country as seen in Rio de Janeiro between 1993 and 95 (Barroso and Rebelo, 2007) and in Sao Paulo since 2002 (de Lemos et al., 2007) as well as other parts of the country (Baethgen et al., 2008). The recent emergence of serogroup W135 IMD has also been observed (Barroso and Rebelo, 2007; Baethgen et al., 2008). In Argentina in contrast, IR levels decreased from 2.6 to 0.6/100'000

between 1993 and 2005. The dominance of serogroup B meningococcal disease was interrupted by an intermediate peak of serogroup C between 1996 and 2000. Furthermore, an increase of serogroups Y and W135 has been observed (Chiavetta et al., 1993-2005). In Uruguay a local serogroup B outbreak threat the city of Santa Lucia in 2001, but was answered with immediate vaccination campaign (Pérez et al., 2004). Even from Mexico, increasing numbers of serogroup C have been reported (Almeida-Gonzalez et al., 2004).

The meningitis belt of Africa still carries the heaviest meningococcal disease burden, although changes in the epidemiology have recently been observed. Serogroup A continues to play a major role but substantial outbreaks have also been caused by W135 meningococci. There seems to be an extension of the meningitis belt to the east and the south which may be associated with climate change (Savory et al., 2006; Molesworth et al., 2002). Outbreaks of serogroup W135 (Taha et al., 2000; Fonkoua et al., 2002; Traore et al., 2006) and serogroup X (Djibo et al., 1995-2000; Gagneux et al., 2002; Boisier et al., 2007) are of concern for control strategies based on monovalent serogroup A conjugate vaccines. In South Africa, IR of 0.64/100'000 were reported in 2002 whereby 41% of the cases were attributed to serogroup B, 23% to serogroup A, 21% to serogroup Y, 8% serogroup C and 5% serogroup W135 (Coulson et al., 2007). Similarly to above mentioned areas, a highly lethal serogroup W135 clone caused increasing IR particularly in the Gauteng Province (von Gottberg et al., 2008). Together with serogroup C (Faye-Kette et al., 2003; Newman, 2004), serogroup B seems to play a major role in African countries outside of the meningitis belt such as Cameroon, Uganda, Madagascar (<http://www.mlst.nt>) and Angola (Gaspar et al., 2001).

Global spread of hypervirulent clones

With improved surveillance systems in place, growing strain collections from laboratories worldwide and advances made in molecular epidemiology, global trends in IMD can more readily be attributed to the spread of hypervirulent clones (Figure 1). Three pandemic waves caused by serogroup A meningococci are well documented. The first involved North Africa and the Mediterranean in 1967 and has mainly been associated with the ST1 clonal complex. In addition, clonally related non-epidemic isolates are available from Pakistan, the Philippines, the USA, South Africa, several European countries, Russia and Australia (Olyhoek et al., 1915 and 1983; WHO, 1977). The ST5 clonal complex caused the highest serogroup A disease burden in the second half of the 20th century and was responsible for the second and third pandemic waves. The second pandemic started in the early 1980s in China and Nepal and spread to many countries throughout the world facilitated by pilgrims returning from Mecca where an outbreak occurred in 1987

and extended to epidemics in the African meningitis belt between 1988 - 1995. A third wave began in Asia in the early 1990s and continued in Africa since 1995. While the second pandemic was mainly associated with ST5 bacteria, the third was caused by ST7 (a single locus variant of ST5) meningococci (Zhu et al., 2001; Achtman, 1997; Caugant and Nicolas, 2007). Recently, outbreak strains belonging to a new serogroup A clone associated with ST 2859 (a single locus variant of ST7) have been isolated in Burkina Faso, Ghana and Sudan (Sie et al., 2008).

The few serogroup A meningococcal strains available from world war I and II associated epidemics in Europe and the USA belong to the ST4 clonal complex. Since bacterial isolates from earlier serogroup A outbreaks in South America, Australia and China are not available, the extent of the spread of the ST4 meningococci is not known. However, ST4 complex bacteria have been isolated in the African meningitis belt for over 20 years from epidemic waves in 1960 -1963, 1968 -1974 and 1981 - 1983 as well as from the inter-epidemic periods (Crowe et al., 1987). ST4 complex isolates are very homogenous by MLST and belong almost exclusively to one single sequence type, ST4. The latest ST4 complex isolates in the MLST database dated from 1992, suggesting a loss of significance of this subgroup since then. In contrast, ST1 complex bacteria have continuously been isolated as seen for example during recent outbreaks in Moscow (www.mlst.net).

Apart from the dramatic serogroup A pandemics, serogroup B, C and W135 have also contributed substantially to the global burden of IMD. While one has to take into account that the MLST database is highly biased in terms of geographical coverage of the isolates, the entered datasets nevertheless shows that the most important non-serogroup A clonal complexes of the 2nd half of the 20th century are the ST32, ST11 and ST44/41 clonal complexes. The ST32 (ET 5) clonal complex emerged in Norway in 1975 causing a serogroup B epidemic with an IR of 24/100'000. Subsequent outbreaks were recorded in Iceland, Denmark, the Netherlands and Great Britain (Poolman et al., 1986).

Intercontinental spread of this clone was responsible for outbreaks in Cuba, Chile and Brazil (Cruz et al., 1990; Schwartz et al., 1989; Caugant et al., 1986). The first extended serogroup B outbreak in the US in the 1990s has also been attributed to this clonal complex (Diermayer et al., 1999).

The ST11 (ET-37) clonal complex is associated with serogroups B, C, W135 and Y. Most serogroup C outbreaks described have been caused by strains belonging to this complex. The first isolates date back to 1917 and the first outbreak were reported in the 1960s among US army personnel. It has also been attributed to the 1971 outbreak in Brazil (Caugant, 1998). Since the 1980s, the ET15 clone of the ST11 complex emerged with increasing contributions to IMD in Europe and North America in particular in adolescents and young adults encouraging

the implementation of serogroup C polysaccharide conjugate vaccines (Hubert and Caugant, 1997; Jelfs et al., 2000). Interestingly, the W135 meningococci responsible for the outbreaks in Mecca and the African meningitis belt since the year 2000 also belong to the ST11 clonal complex. Causing sporadic IMD all over the world including the African meningitis belt since the 1970s, a hypervirulent clone of this serogroup has caused serious outbreaks in different geographic regions after the outbreak in Mecca in 2000 (Aguilera et al., 2000; Traore et al., 2006; Kwara et al., 1998; Mayer et al., 2000).

With over 1,000 associated STs, the ST44/41 clonal complex (Lineage III) dominated by serogroup B is according to the MLST database the most diverse meningococcal clonal complex. In contrast to the other complexes, it is also frequently isolated from healthy carriers. First isolates of a particular lineage III clone were found in the 1960s followed by a strong increase in the frequency of observed cases in the Netherlands around 1980s and developed into one of the most important meningococcal groups in the 1990s (Scholten et al., 1994). Later, closely related meningococci caused increasing IMD case numbers in Belgium (Van Looveren et al., 1998) and have been responsible for an extended outbreak in New Zealand since 1991 (Dyet and Martin, 2006). Currently in Europe, the ST41/44 is the most dominant clonal complex causing IMD in Ireland, Netherlands, Belgium, and Italy (EU-IBIS Network, 2003/2004).

Furthermore, the ST8 (cluster A4) clonal complex seen worldwide since 1960 and the ST18 clonal complex mostly isolated in Eastern Europe and Russia since the 1970 have been described (Caugant, 1998; Caugant et al., 1987). Since the introduction of MLST, four additional hypervirulent clonal complexes have been identified, the ST174 complex mostly associated with serogroup W135 disease, the ST269 complex, an important cause of IMD in the UK and recently associated with serogroup B outbreaks in Canada (Law et al., 2006), the ST334 clonal complex and the ST461 clonal complex (Caugant, 2008).

Antimicrobial resistance

As with many other pathogens, *N. meningitidis* has developed resistance mechanisms against a wide range of antimicrobials (Manchanda et al., 2006; Jorgensen et al., 2005). Although most reported resistance has been linked to serogroups B and C, antibiotic resistant serogroup A isolates have also been described. Tetracycline, sulfisoxazole and trimethoprim-sulfamethoxazole resistance has been observed in Africa, Asia, and the USA with tetracycline resistance being attributed to the drug efflux mechanism encoded by *tet(B)* (Crawford et al., 2005). Resistance of serogroup B strains to chloramphenicol, streptomycin and sulphonamides in isolates from Vietnam and France (Galimand et al., 1998) were caused by internal deletions affecting the *catP* gene and directly influencing the production of the enzyme chloram-

phenicol acetyltransferase. In strains from Portugal and several other European countries, penicillin and sulphadiazine resistance caused by a reduced affinity to penicillin binding protein type 2 has been described (Ferreira et al., 2001-2002).

Impact of meningococcal meningitis vaccination

Attempts to prevent IMD through vaccination started as early as 1912, yet the first polysaccharide-based vaccines against serogroups A and C were developed in the 1960s (Gotschlich et al., 1969) and proved effective in military recruits (Artenstein et al., 1970) as well as against epidemic serogroup A meningitis in Africa (Erwa et al., 1973; Etori et al., 1977) and Europe (Makela et al., 1977). Until the 1990s, only pure polysaccharide-based vaccines were available against serogroups A, C, Y and W135. In spite of a vaccine efficacy of 95% against serogroup A disease in older children and adults in the first year after immunization (Patel and Lee, 2005), the polysaccharide antigens do not induce long lasting antibody responses nor immunological memory. Furthermore, immune responses in infants are poor (Jodar et al., 2002) and only serogroup A polysaccharide vaccines elicit a limited and short lived immunity in infants below 2 years of age (MacLennan et al., 1999; Reingold et al., 1985). Due to these limitations, polysaccharide vaccines have mainly been applied in response to outbreaks and epidemics (Cochi et al., 1987; Jamba et al., 1979; Peltola et al., 1976; Lennon et al., 1992). It was often criticized that particularly in the African meningitis belt, vaccination campaigns were often carried out too late to prevent the majority of cases (Robbins et al., 2003). Additionally, the effect of preventive immunization in Africa has also raised some controversy (Hassan et al., 1998; Lengeler et al., 1995; WHO, 2003). Only few countries have adopted polysaccharide vaccine routine immunization schemes for the control of epidemic IMD. In Egypt, a measurable reduction in the serogroup A meningococcal disease after the introduction of a school-based immunization program has been reported (Nakhla et al., 2005). In China, large scale preventive immunization programs were carried out in order to prevent serogroup A epidemics (Zhen, 1987). In Brazil a mass immunization was performed in response to the severe A and C epidemics in the early 1970s.

For a better immunogenicity and immunological memory as well as satisfactory effectiveness in infants, polysaccharide-protein conjugate vaccines against serogroups A, C, Y and W135 have been developed. The first meningococcal conjugate vaccine against serogroup C was introduced into routine immunization in the UK in 1999 (Jodar et al., 2002), resulting in an overall decrease in serogroup C invasive disease by over 85% between 1999 and 2001 in the targeted age groups (Balmer et al., 2002). It was shown that in contrast to pure polysaccharide vaccines, capsule conjugate vaccines also

affected carriage and transmission (Maiden and Stuart, 2002) and might therefore contribute to the development of herd immunity in the non-vaccinated population. Yet the limited data available indicates that this effect is restricted to the vaccine serogroup and has only little impact on the overall meningococcal colonization (Maiden and Stuart, 2002; Trotter et al., 2005). Thereafter, the meningococcal C conjugate vaccine was also introduced into the national immunization scheme of other European countries. Additionally, a quadrivalent conjugate vaccine (A,C,Y,W135) for targeted use in populations was licensed in the USA and Canada in 2005 and 2006 respectively (Vu et al., 2006). A serogroup A polysaccharide conjugate vaccine for use in mass vaccination campaigns in Africa is currently being developed (www.meningvax.org). Since the poly-sialic acid capsule of serogroup B meningococci is not suitable for the design of a polysaccharide-based vaccine, vaccines targeting OMPs are currently being investigated but are strongly restricted by the high diversity of OMPs. However, strain-specific outer membrane vesicle (OMV)-based vaccines already developed to combat epidemics in Norway (Bjune et al., 1991) and Cuba (Sierra et al., 1991), showed limited efficacy. The Cuban vaccine was used further to control outbreaks in Chile, Brazil (de Moraes et al., 1992) and Uruguay (Pérez et al., 2004). The most recent example of a "tailor made" strain-specific OMV vaccine was used in the New Zealand epidemic and has been shown to be effective in reducing the incidence of IMD during a serogroup B epidemic (Kelly et al., 2007).

DISCUSSION

Despite the establishment of improved surveillance in many parts of the world, the reasons for the differences in IMD epidemiology between endemic and epidemic settings are not fully understood rendering it difficult to predict the emergence of epidemics. Several factors influence the timing and distribution of epidemics including climatic, socio-economic and cultural factors involving changes in human lifestyle, natural growth of the human population, crowding and increased mobility. These have also strongly affected the global population structure of *N. meningitidis* and are still currently responsible for changing patterns in IMD epidemiology. It will be crucial to analyse meningococcal colonization patterns in greater detail, in particular after the introduction of new capsule conjugate and OMV vaccines in order to understand the consequences of these interventions. Traditionally in Northern America, IMD during endemic periods was primarily caused by serogroup B and C, whereas serogroup A dominated during epidemics (Branham, 1956). This suggests that low level endemic IMD may have existed even before the emergence of serogroup A associated epidemic disease in the beginning of the 19th century. During the last sixty years serogroup A epidemics

have largely disappeared from many developed regions and only endemic IMD primarily caused by sero-group B and C meningococci is found. However, the recent emergence or detection due to altered surveillance performances of new or previously unrecognized threats such as epidemics caused by serogroup W135 and X in Africa, the increasing significance of serogroup Y in Northern America and of serogroup C in China indicate that prevention and control of IMD will remain a challenge. With antimicrobial resistance on the rise, effective and affordable vaccines along with continued surveillance are needed to help combat this complex disease.

ACKNOWLEDGEMENTS

This publication made use of the *Neisseria* multi locus sequence typing website (<http://pubmlst.org/neisseria/>) developed by Keith Jolley and Man-Suen Chan and sited at the University of Oxford (Branham, 1956). The development of this site has been funded by the Wellcome trust and the European Union.

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