

Emergence of *Neisseria meningitidis* W-135 in the context of other rare serogroups

Clin. Invest. (2012) 2(2), 177–188

Neisseria meningitidis can be considered a continually emerging pathogen due to its genetic mutability and dynamic epidemiology. Currently, six serogroups (A, B, C, W-135, X and Y) are important to global disease epidemiology. Until 2000, serogroup W-135 was rare worldwide. Hajj-associated W-135 outbreaks caused by a virulent ST-11 strain in 2000 and 2001 raised concerns about widespread epidemic disease. Serogroup W-135 now circulates worldwide. Serogroup X recently gained health authority attention because of dramatic attack and case fatality rates during recent outbreaks in Africa. Serogroups Z and 29E, in contrast, have remained rare. Some genetic and other mechanisms behind serogroup epidemiology remain poorly understood. Additional surveillance and typing information is necessary to assist these efforts and to inform vaccine policy.

Keywords: epidemiology • meningococcal disease • *Neisseria meningitidis* • serogroup W-135 • serogroup X • serogroup Y • serogroup Z

Since its identification, invasive meningococcal disease (IMD) has been considered of public health importance as a cause of epidemic disease [1–3]. Of the identified meningococcal capsular serogroups, six (A, B, C, W-135, X and Y) are considered to be of current epidemiological importance by the WHO and 29E and Z also cause sporadic disease cases [4,5]. Until 2000, serogroup W-135 caused a small proportion of sporadic cases annually. In that year, outbreaks associated with the annual Hajj pilgrimage resulted in W-135 becoming a globally important pathogenic meningococcal serogroup within a period of weeks. Public health measures, including adjustments to vaccination policies, were implemented to protect Hajj pilgrims, their close contacts and local populations [6–24]. W-135 IMD has also been thrown into contrast by the recent reduction in serogroup A disease following the introduction of MenAfriVac™, a novel, low-cost conjugate vaccine [25–27].

The most common manifestations of IMD are sudden onset, rapidly progressive meningitis and septicemia in otherwise healthy persons. The rapid progression of IMD provides only a narrow window for diagnosis and intervention; thus, permanent sequelae or fatal outcomes occur with some regularity [1–3]. Although IMD occurs worldwide, the annual serogroup A epidemics that affect the African meningitis belt, which extends from Senegal to Ethiopia, represent the single greatest disease burden globally. Serogroup C and W-135 IMD are also of concern in this region [4]; furthermore, since a significant proportion of the population is Muslim, travel to the Hajj is common [4,7,20,21,28]. In the developed world, serogroups B, C and sometimes Y are considered epidemiologically dominant [4].

Serogroup W-135

Serogroup W-135 was first described in 1968, with the first confirmed cases

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approximately a decade later, during a period of dynamic serogroup epidemiology worldwide [29,30]. Thereafter, sporadic serogroup W-135 IMD cases were reported until, in 2000, outbreaks caused by a virulent W-135 ST-11 clone were reported in connection with Hajj pilgrims and their close contacts in 16 countries [10–12]. This outbreak by a previously rare strain was unprecedented; the strain was later found, based on typing of isolates, to have been circulating since at least 1970 [10,31]. The genetic characteristics of this W-135 ST-11 clone strongly suggest that it is a result of capsular switching with a virulent serogroup C strain [21,32–34]. Hajj-associated outbreaks in 2001 raised concerns about the possibility for widespread W-135 epidemics, such as the one reported in [12] Burkina Faso [13,32,33].

Although data are limited, clinical implications of serogroup W-135 disease can be subtly different than those for other serogroups. In the USA from 1997 to 2008, W-135 disease was associated with a higher case fatality rate (16.3%) than other serogroups, possibly because it was also more likely to cause disease in older persons (mean age 53 years) [15]. Serogroup W-135 has caused unusual IMD manifestations such as pericarditis, septic arthritis, pneumonia, peritonitis, neonatal sepsis and chronic meningococemia [35–47].

Serogroup W-135 before 2000

Prior to 2000, few serogroup W-135 IMD cases were reported (Table 1) [8,14,16,20,21,48–66]. The clinical literature shows meningococcal serogroup W-135 cases beginning in the 1970s. These early reports rely on surveillance methods that may differ in scope and focus compared with current methods. For example, reports of disease in New York City prior to 1980 relied on passive surveillance systems that accounted for approximately half of confirmed cases and include

clinical isolates from multiple body sites [48,49]. Scattered reports in European countries, Australia and the USA occurred during the 1970s and 1980s [63–66]. Again, the surveillance methods used and means of obtaining isolates were in many cases quite different compared with current measures.

In the German Democratic Republic, a steady increase in IMD overall after 1977 prompted surveillance efforts that revealed W-135 disease beginning in 1981 [50]. The first case of W-135 disease in France was reported in 1994; during 1995–1999, 3–16 W-135 isolates were collected each year [16]. Of the isolates collected in Sweden in 1978–1987, three carried the Hajj outbreak strain Por A serosubtype compared with eight isolates in the 1990s and six in 2000. All W-135 isolates collected in Sweden in 1998 and following were sulfadiazine resistant, suggesting a genetic shift that predated the Hajj outbreak [51]. Of note sulfonamide-resistant meningococcal strains have been identified since the 1970s [65].

The Kingdom of Saudi Arabia (KSA) had instituted rigorous surveillance and vaccination policies to address serogroup A and C IMD outbreaks during the Hajj and Umrah [8,14,20,51–53], which allowed for systematic identification of pathogenic isolates. Of 483 hospitalized IMD cases during 1987–1997, 31 (6.4%) were caused by serogroup W-135 [53].

The first W-135 case in Africa, reported in Senegal in 1981, was followed by sporadic cases [21,55,56], for example, two cases reported in Nigeria in 1990 [57]. Of note, the small number of pathogenic W-135 isolates collected during serogroup A epidemics in Mali in 1994 and Gambia in 1995 were part of the ET-37/ST-11 clonal group later associated with Hajj outbreaks [9,58].

Serogroup W-135 isolates were only sporadically identified in South America. In Brazil during 1990–2001, 236 W-135 cases were reported, accounting for approximately 2% of cases [59].

Table 1. Cases of serogroup W-135 meningococcal disease before 2000 in the USA and Europe.

Study (year)	Years	Location	No. of years covered	Report (cases)	Approximate no. of cases reported/year	Ref.
Band <i>et al.</i> (1983)	1972–1980	USA	9	66	7	[65]
Fallon <i>et al.</i> (1984)	1973–1982	Scotland	11	56	5	[63]
Galaid <i>et al.</i> (1980)	1973–1978	NY, USA	6	71	12	[48]
De Wals <i>et al.</i> (1984)	1975–1979	Belgium	5	5	1	[64]
Dickinson <i>et al.</i> (1981)	1978–1979	NY, USA	2	3	1.5	[49]
Grahlow <i>et al.</i> (1986)	1981–1984	German Democratic Republic	4	30	7	[50]
Mölling <i>et al.</i> (2001)	1978–1987	Sweden	12	7	2	[51]
Mölling <i>et al.</i> (2001)	1990–1999	Sweden	10	31	3	[51]
Taha <i>et al.</i> (2004)	1994–1999	France	6	49	8	[16]

In China, 11 W-135 isolates were collected during 1975–2005; for reference, 15 isolates each were collected for serogroup X or 29E. No W-135 strain collected in China was associated with ST-11 [60]. In Taiwan, 16 sporadic W-135 infections caused by ST-11 strains were reported in 1996–1999; however, the Hajj outbreak strain was unlikely to have been a cause of disease. Of note, only serogroup W-135 and B strains were isolated in Taiwan during 1996–2000 [61,62].

W-135 during 2000 & 2001

In 2000, concurrent serogroup A and W-135 outbreaks occurred in KSA [14,54]. By May 2000, 241 W-135 cases had been reported in KSA as were 89 cases (WHO 2000), primarily in returning pilgrims and close contacts in 11 other countries [8]. In 2001, 316 W-135 cases were reported in KSA; 82 in Hajj and 25 in Umrah pilgrims [14]. Additional cases were reported in Europe, Africa and Asia [12,201]. Also, the distribution of sporadic W-135 cases in KSA expanded, as did the number of cases in infants and young children. Vaccination against serogroups A, C, W-135 and Y replaced previous recommendations for pilgrims to Mecca [20]. The question of serogroup replacement was raised because some serogroups are not currently vaccine preventable [14]. No observations of serogroup replacement have occurred following national immunization programs using meningococcal conjugate vaccines.

In 2000 and 2001, the Hajj W-135 clone was isolated in African countries including Burkina Faso and Niger in the meningitis belt. The Central African Republic reported three cases of W-135 disease following the 2001 Hajj [9,11,13,59,67,201]. In 2001, annual IMD epidemics in Burkina Faso were nearly 80% attributable to serogroup W-135. In Niger, disease was primarily caused by serogroup A, but W-135 caused a detectable number of cases [21]. In convenience samples from these countries collected at the end of the epidemic, serogroups A and W-135 caused a comparatively similar number of cases [68].

In the USA, fewer Hajj-associated IMD cases were reported in 2001 than in 2000. In a 2001 carriage study at the John F Kennedy airport in New York, zero out of 425 departing Hajj pilgrims tested carried serogroup W-135, although four persons harbored other serogroups. Among 844 returning persons (pilgrims and nonpilgrims) providing samples, 21 carried meningococcus. Of these, ten serogroup W-135 isolates were obtained; nine out of ten were likely the Hajj ST-11 clone [69].

In the 19 weeks following the 2000 Hajj, 90 cases of serogroup W-135 disease and 14 associated deaths were reported in Europe [12], primarily in the UK

and France [18]. Considering the full year following the 2000 Hajj, 51 cases and eight deaths were reported in the UK. In the first 10 weeks after the 2001 Hajj, 33 cases (nine deaths) also were reported in UK. All 84 cases were caused by the Hajj outbreak strain and, as many patients had no known association with pilgrims, it appeared that the strain had begun to circulate [19]. In France in 2000, 55 serogroup W-135 isolates were collected, representing 10.6% of all pathogenic isolates, and an increase was noted in Hajj strain-related isolates [16]. In Sweden, eight W-135 isolates were obtained in 2000; six (four from Hajj pilgrims) shared the Porin A P1.5 serosubtype with the Hajj outbreak strain. As indicated above, all eight W-135 isolates were resistant to sulfadiazine [51].

During a 2001 meningococcal outbreak in Taiwan, 19 out of 43 culture confirmed cases were caused by W-135 ST-11 strains introduced before the Hajj outbreaks. Overall case fatality was 25.6%, but W-135 case fatality was 37.5% [62].

In Singapore, the first 12 cases of W-135 IMD were reported to the Ministry of Health in 2000 and 2001; eight were clearly traceable to the Hajj [12,13,22,23]. In 2001, quadrivalent polysaccharide vaccine was required prior to the Hajj; only four household contacts of pilgrims developed IMD [22]. Of note, recommending groups, such as SAGE, consider the polysaccharide vaccine as effective primarily in protecting the vaccinee from disease [202].

Between 1991 and 2003, during the serogroup B epidemic [70], 1–5% of cases in New Zealand were attributed to serogroup W-135 or Y strains. Prior to 2003, one case of the Hajj-associated W-135 IMD was reported in New Zealand [71].

W-135 after the 2000 & 2001 outbreaks

Since 2000, the Gulf Cooperation Council states, which include the Kingdom of Bahrain, the KSA, Kuwait, the Sultanate of Oman, Qatar and the United Arab Emirates, have observed that W-135 cases have become the most common reported type of IMD in these countries [20]. Current vaccination recommendations reflect this change (Table 2) [20,72].

In the USA and Europe, meningococcal disease caused by serogroup W-135 has become an endemic cause of IMD. The Hajj ST-11 strain caused 14 deaths in Florida in 2008–2009 [73]. A similar W-135 strain caused additional cases in Brazil and Argentina, suggesting spread from South America [74–76]. As observed prior to 2000, W-135 strains likely entered North America by multiple routes.

European epidemiology suggests that genetic variants of W-135 strains are continuously emerging [77]. In France, nine different variants were identified

Table 2. Meningococcal disease in the Gulf Cooperation Council States.

Gulf Cooperation Council State	Dates	No. of cases	Additional information	Serogroups
Kingdom of Bahrain	2002–2009	0		
Kingdom of Saudi Arabia	1995–1999			A, B dominant
	1999–2002	729	39% <2 years of age, 21% 2–5 years of age, 18% 5–14 years of age and 22% ≥15 years of age	W-135 (50%), A (7%), B (2%), C (1%) and unidentified (40%)
	2000	338		W-135
	2001	316		
	2002	55		
	2003	44		
	2004	10		
	2005	18	0.08/100,000 population	
	2006	22		
	2007	13	0.05/100,000 population	
	2008	7	0.03/100,000 population	
	2009	9		
Kuwait	1997–2003	86	0.15/100,000 (1998; low), 1.15/100,000 (2002; high) and 0.64/100,000 (2003; latest)	B (43%), W-135 (22%), A (8%), C (2%), X (2%), Y (2%) and Z (2%)
Sultanate of Oman	2001–2008	45		W-135 (25%), A (21%), C (16%), Y (9%), B (2%) and unidentified (27%)
	2009	0		
Qatar	2008–2010	47		W-135 (38%), A (21%), B (13%) and Y (6%)
United Arab Emirates	2007	51	1.14/100,000 population	

Data taken from [20].

among 43 W-135 isolates in 2001, as were 14 variants among 58 isolates in 2002 [16]. ST-11 W-135 strains accounted for 58 and 34% of isolates in 2001 and 2002, respectively. Twenty different non-ST-11 genotypes were identified in 2002 isolates and seven were found in 2001 [16].

The first W-135 IMD case in Turkey was reported in 2003 and the Hajj outbreak strain was first isolated there in 2004, in four pathogenic and two carriage isolates [78,79]. In 2005/06, 59 out of 138 (42.7%) laboratory-confirmed IMD cases in children in Turkey were serogroup W-135 [80].

Few African countries have active surveillance systems, which affects the quality and quantity of reporting. From 1992–1999, one W-135 IMD case was reported in Mauritius, with four cases, three in close contacts of Hajj pilgrims, reported after 2002 [81]. A serogroup W-135 epidemic in Burkina Faso in 2002 included more than 12,000 cases and 1400 deaths [13,82]. In 2003, 70% of IMD cases in Burkina Faso were serogroup W-135 [21]. A trivalent

polysaccharide vaccine was developed and funded [32] and by 2005, W-135 was a minor cause of IMD in Burkina Faso [83]. Despite international public health community concerns, these epidemics ended relatively quickly, and the relationship of the epidemic strains to the Hajj outbreaks remains equivocal [83,84].

Several western meningitis-belt countries, including Togo and Ghana, have reported more serogroup W-135 IMD cases during the early 21st century than previously [85,86]. In 2006, W-135 outbreaks were reported in Kenya, Sudan and Uganda. By regional standards, these outbreaks were minor [28]. In 2007 and 2008 all endemic IMD isolates in northern Cameroon were serogroup W-135 [87]. Surveillance data following the recent introduction of the low-cost serogroup A conjugate vaccine in Burkina Faso, Niger and Mali indicated a dramatic reduction in serogroup A disease. However, as of June 2011, 128 cases of serogroup X and 479 cases of W-135 disease were confirmed in these countries [25–27]. Data suggest that Niger, in fact, experienced a W-135 outbreak in 2010 [88].

During the 21st century, serogroup W-135 has predominated as a cause of invasive disease in all age groups in South Africa [203]. From 2001–2004, 300–329 cases were reported annually, and the case fatality rate decreased from 14.5 to 8.8% [89], yet in 2007 and 2008, 503 and 456 cases were reported, respectively. The case fatality rate in 2008 was 26%, significantly higher ($p = 0.002$) than that in 2007 or 2006 [203]. In the Gauteng region, IMD incidence increased from 0.8 to 4.0 cases per 100,000 population from 2000–2005 [90], with W-135 causing 75% of cases by 2005. Of 301 W-135 isolates described in a 2008 study, 95% belonged to the same virulent ET-37/ST-11 clone [91]. Concerns about meningococcal disease were raised in connection with the 2010 World Cup because of the virulence of this clone as well as the possibility for disease transmission during international sporting events [92–94].

Recent data suggest that W-135 has not become an important cause of IMD across Asia. In a 2009 study, serogroup W-135 accounted for 31% of IMD in 16 children and adolescents in Taiwan [95]. No W-135 IMD cases have been reported in Singapore since 2003 [22]. In the People's Republic of China [96] during 2006–2008, three cases of serogroup W-135 disease were reported. No genotypic information was available.

In 2003, a new W-135 strain type (W:2a:P1.7–2,4), which carries the same PorA type as the epidemic B strain, caused 12 cases of IMD in New Zealand [71]. No cases of IMD caused by the Hajj outbreak strain have been reported in New Zealand since 2003.

Since 2000, serogroup W-135 has been reported more frequently in certain areas of Brazil and Argentina [76]. In Brazil, 1.5% (396) of laboratory-confirmed cases of meningitis from 1990–2005 were caused by serogroup W-135, with a further 1.5% of cases due to serogroups Y, 29E and Z [76]. In Rio Grande do Sul [74,97] and Rio de Janeiro, the relative proportion of serogroup W-135 isolates belonging to the ET-37/ST-11 strain has increased. In Sao Paulo, more sensitive disease surveillance indicates that pathogenic W-135 isolates are becoming more common as 27 (5.1%) cases were reported in 2007 as were 45 (8.0%) in 2008, which is a marked increase from 1998–2005 [98,99,204], during which 12–24 W-135 cases (2.1–4.9% of all IMD cases) were reported each year [100].

In 2006, serogroups C, W-135 and Y together represented 7% of isolates in Argentina but in 2007 W-135 alone caused 13% of reported cases. In January to May 2008, 27.7% of isolates were serogroup W-135. In the province of Buenos Aires, 89% of isolates were W-135 as were 63% of those from children under 9 years of age [75].

Patterns of emergence for rare meningococcal serogroups

In the early part of the 20th century, the majority of IMD was caused by serogroup A worldwide; however, by 1999, serogroups B and C accounted for the majority of disease in the USA, South America and Europe. The emergence of serogroup Y in the USA between 1991 and 1998 is a typical example of the emergence of a previously rare serogroup [101–103]. In contrast, serogroup W-135 suddenly emerged as a significant cause of outbreak disease worldwide in a matter of weeks, likely because of its association with Hajj, a known vector for meningococcal disease and influenza. A similar pattern is sometimes associated with international sporting events [92–94]. The rapid emergence of W-135 had varied outcomes. In the Americas the introduction of the virulent ET-37/ST-11 W-135 Hajj clone was accompanied by strains from other regions [73–76]. Epidemiology in Europe also suggests a dynamic genetic profile [77–80].

Although serogroup Y has gained importance in some countries and regions, it remains rare in many places. Additional rare meningococcal serogroups are Z, X, and 29E. A typical pattern of disease caused by rare serogroups was observed in the German Democratic Republic during 1979–1984: three out of 515 isolates were serogroup X (0.6%), 16 were serogroup Y (3.1%) and two were serogroup Z (0.4%) [50]. In Brazil from 1990–2001, four serogroup 29E cases, three serogroup X cases and one serogroup Z case were confirmed, representing fewer than 1% of overall isolates [59].

Serogroups Z and 29E have consistently caused very few cases; both have been associated with carriage [48,104]. In fact, serogroup 29E was among the most common carriage strains in studies of German adolescents and college freshmen in the UK [104,105]. In 1971, five serogroup Z cases were reported in infants and toddlers in Scotland; only a single case was noted in a study of disease-causing isolates during a 10-year period at University College Hospital, Galway [106–108]. In the USA, the first confirmed serogroup Z case was reported in 1980, with the next report in 1985 [109,110]. A single 29E isolate was detected in Korea in 2002–2003 [111]. A 2008 study of carriage isolates before and after the Hajj identified one serogroup Z carrier [112]. In 2010, the first case of serogroup Z disease was reported in Slovenia [113]. Unusually, in China, isolates collected from 1975 through to 2005 showed that serogroups 29E and X each accounted for more confirmed cases ($n = 15$ per serogroup), more than either serogroup W-135 (11 isolates) or serogroup Y (four isolates) [60].

Serogroup X has caused small numbers of sporadic cases of IMD cases in Europe, North America

and Asia since the 1960s [29]. In Spain, six cases of serogroup X disease were reported between 1984 and 2000 [114], while individual cases were reported in Turkey and Italy in 2010 [115,116]. The only case in Asia occurred in China in 2007 [110,117]. Reports of disease in Western Kenya and Niger date back to the 1980s [118–124]. Between 1995 and 2000, the 134 reported cases of serogroup X-related meningitis in Niger represented 3.91% of isolates [122]. Although serogroup X had been only a rare cause of sporadic disease, it has recently gained epidemiologic importance and vaccine development has been suggested in the wake of several important outbreaks and epidemics in the meningitis belt, a region primarily affected by serogroups A, C and W-135 [115,123].

During a 2000 IMD outbreak in Ghana, 53 out of 298 samples collected were serogroup X [119]. From January to June 2006, serogroup X caused 51% of the 1139 confirmed IMD cases in Niger, and 90% of cases in the southwestern portion of the country [124]. The first serogroup X outbreak outside the meningitis belt occurred in Kenya in 2005–2006 and was associated with cases in bordering districts of Uganda [118,123]. Recent information confirms the importance of serogroups W-135 and X in Burkina Faso and in association with travel to the Hajj [24,205].

Although it has been suggested that an increased incidence of rare meningococcal serogroups could result from widespread use of vaccines against A, C, W-135 and Y, similar to observations made with the pneumococcus, little evidence supports this assertion in countries with routine immunization against one or more serogroups using currently available conjugate vaccines. For example, although the relative proportion of IMD caused by serogroup B has increased in some countries, such as the UK, the absolute number of cases has remained relatively stable [115,117,119]. Thus, while serogroup X epidemiology should be closely monitored as more widespread serogroup A vaccination is introduced to the African meningitis belt, it seems unlikely that increased incidence due to serogroup replacement will be an ongoing problem. This should be considered separately from the emergence of new disease caused by a new virulent clone, as seen in South Africa for example [118,125].

Meningococcal vaccines

Vaccines against meningococcal serogroups A, C, W-135 and Y have been available since the 1970s as capsular polysaccharide-based formulations. Currently monovalent, bivalent, trivalent and quadrivalent meningococcal conjugate vaccines are in development or clinical use as are combinations of meningococcal serogroup C or serogroups C and Y

with *Haemophilus influenzae* type B. In clinical trials conducted in infants, children adolescents and adults, all licensed polysaccharide and conjugate vaccines against serogroup W-135 have induced protective levels of bactericidal antibodies in a majority of study participants. These vaccines and the results of clinical trials have been recently reviewed [5,126–130]. The most recent epidemiologically significant conjugate is MenAfriVac, which was introduced to control epidemic disease in meningitis-belt countries [25,26]. At present, routine vaccination of infants and young children against meningococcal serogroup C is common in Europe, Canada and other countries. Immunization of adolescents with conjugate ACWY seotype vaccines is recommended in North America, as is the vaccination of Hajj and Umrah pilgrims in regions where such vaccines are available and affordable [20,24,72]. Therefore, although policy measures and funding may be needed, potential vaccine solutions exist for the problem of W-135 IMD without novel technology development.

For currently rare serogroups like X, Z and 29E, vaccine solutions are not so simple. No polysaccharide vaccines against serogroups X, Z or 29E are in development, and given the rarity of these types, such development efforts are unlikely to be cost effective. However, subcapsular component vaccines against serogroup B may offer a partial solution, insofar as they may offer a strong possibility for controlling clonal outbreaks. Since the serogroup B polysaccharide is not immunogenic, investigational vaccines against this pathogen are based on membrane-bound protein antigens and outer membrane vesicles. Furthermore, because meningococcal serogroup and strain epidemiology do not track exactly, it has been observed that many of the same variants and subvariants of the surface proteins found on serogroup B strains also appear on other serogroups [5].

A recent genotypic analysis suggests that certain serogroup X epidemic strains could potentially be covered by existing investigational products, although confirmatory studies would be needed to establish the actual level of clinical protection expected [131]. Furthermore, the outer membrane vesicles approach, which has been employed for serogroup B encapsulated strains that share a PorA serosubtype, is being investigated against serogroups A and W-135 [132]. The potential for cross protection against other serogroups carrying the same PorA serosubtypes should be investigated [133].

Future perspective

As the playwright Eugene Ionesco noted “you can only predict things after they have happened.” Yet

public health interventions often circumvent potential problems. IMD remains a persistent issue despite widespread vaccination campaigns and decreasing incidence in the developed world. Disease caused by serogroup W-135 is of special interest because a formerly rare serogroup came to global public health attention in a matter of weeks. South Africa has experienced a surge in disease caused by highly virulent serogroup W-135 strains while less-virulent strains have emerged in China and New Zealand. The occurrence of serogroup W-135 in epidemics and minor outbreaks in meningitis-belt countries is also of concern because it may represent the most prevalent cause of disease now that a low-cost serogroup A conjugate vaccine has become available for use in the meningitis belt [26,134].

One danger of the emergence of new pathogenic strains is the possibility for epidemic disease. Thus, the potential for future meningococcal ST-2859 or ST-11 epidemics should justify improved assessment and surveillance. The 2000 Hajj outbreak is a frightening example of an unanticipated global public health event that occurred despite the consistent enforcement of vaccination by the KSA, a country that has shown responsible vaccination practice, including subsidies of vaccine for low-income countries, for some decades. Although W-135 disease emerged worldwide within a few weeks, meningococcal pandemics typically disseminate more slowly, as observed for serogroup A. Of interest, serogroups B and C, which were rare in the early 20th century are now globally widespread. Similarly, the emergence of serogroup Y in the USA parallels an increase of that serogroup in Latin America, suggesting a more typical pattern of pandemic emergence. Thus, the possibility that additional meningococcal serogroups could become pandemic also warrants improved surveillance and the consideration of measures for prevention, such as vaccination [134–138]. Serogroups X, Z and 29E may have the potential to spread globally, and could be dangerous if further mutations occur that increase virulence [24].

A common mode of preventing meningococcal disease is vaccination, which can be employed in conjunction with antibiotic prophylaxis, as for Hajj pilgrims from certain regions. Limitations for the possible implementation of routine vaccination include the possibility for funding research, development, and vaccine manufacture and distribution [32]. The financial support of organizations like GAVI Alliance and the The Bill and Melinda Gates Foundation is well known, as observed following the W-135 epidemic in Burkina Faso. The limitations of plain polysaccharide vaccines have been reviewed previously; however,

conjugate vaccines are now more widely available [21,32,128]. We anticipate that with the increased availability of broadly protective conjugate vaccines, more countries may be able to protect their populations. In the case of MenAfriVac, it has been suggested that vaccination policy could be cost saving, even in the developing world [26].

Surveillance will continue to be important as vaccine coverage increases worldwide. Although many countries have excellent surveillance for *Neisseria meningitidis*, further work is needed to fill existing gaps. The European Union Invasive Bacterial Infections Surveillance Network, now under the European Center for Disease Control, and the Latin American SIREVA (Sistema Regional de Vacunas) under the Pan-American Health Organization are two large-scale initiatives that cover specific geographic regions and continue to expand their breadth and scope. In Africa, an initiative has been set up by the WHO. The continued need for adequate surveillance and preparation for emerging diseases cannot be underestimated, especially in the light of disease caused by slowly emerging or potentially emerging pathogens.

Another important consideration in the implementation and continuation of surveillance methods is consistency and adequate granularity of information. The increasing importance of molecular epidemiology has yielded much; however, ongoing changes in nomenclature can highlight other challenges, such as the continued implementation of new typing systems or the ongoing investigation of the structure and function of cellular features like the polysaccharide capsule [139,140]. Consistency of surveillance methods varies. Some countries employ only culture-based methods while others use PCR. Furthermore, although PCR has enabled the detection of many previously unconfirmable cases, the absence of isolates prevents certain kinds of genetic typing. In addition, finotyping methods can provide important information about genetic lineages. The expense of these methods is prohibitive in developing nations [83]. Recent investigations into the virulence associated with the capsular polysaccharide of various serogroups suggests that serogroups W-135 and Y may activate the alternative complement pathway, which was an unanticipated finding given the role of the capsule in protection and evasion of complement [140]. Another area for future investigation is the variable epidemiology of meningococcal carriage. We anticipate that the current worldwide commitment to investigate additional finotyping and genotyping of meningococcal isolates will expand in subsequent years to help make it possible to eliminate meningitis as an important disease worldwide.

Executive summary

Introduction

- Serogroups A, B, C, W-135, X and Y, are epidemiologically important.
- Until 2000, serogroup W-135 was rare globally.

Serogroup W-135

- In 2000, widespread invasive meningococcal disease outbreaks associated with the Hajj pilgrimage were caused by a virulent W-135 ST-11 clone.
- W-135 encapsulated strains that were identical to or genetically closely related to the Hajj outbreak strain were isolated in Europe and Africa before 2000.
- Sulfadiazine-resistant W-135 strains emerged in Sweden in 1998, suggesting a genetic shift.
- An unusual pattern of epidemiology was noted in Taiwan, where W-135 caused a significant proportion of cases before 1999.

W-135 during 2000 & 2001

- In 2000, concurrent serogroup A and W-135 outbreaks occurred in the Kingdom of Saudi Arabia.
- Vaccination against serogroups A, C, W-135 and Y was implemented for Hajj and Umrah pilgrims.

After the 2000 & 2001 outbreaks

- Since 2000, the Gulf Cooperation Council states and South Africa, observed that W-135 cases have become the most common reported type of invasive meningococcal disease.
- Genetic mutability and diversity are noted in W-135 encapsulated strains.

Patterns of emergence for rare meningococcal serogroups

- Rare serogroups can emerge gradually over time, as seen with serogroup Y.
- As seen with serogroup X, another possibility is geographically delimited outbreak and epidemic disease.
- W-135 is the only meningococcal serogroup to emerge as an outbreak strain and spread globally within a few weeks.

Meningococcal vaccines

- Currently monovalent, bivalent, trivalent and quadrivalent meningococcal conjugate vaccines are in development or clinical use as are combinations of meningococcal serogroup C or serogroups C and Y with *Haemophilus influenzae* type B.
- Immunization of adolescents with conjugate ACWY seotype vaccines is recommended in North America, as is the vaccination of Hajj and Umrah pilgrims in regions where such vaccines are available and affordable.

Future perspective

- The potential for future meningococcal ST-2859 or ST-11 epidemics should justify improved assessment and surveillance.
- With the increased availability of broadly protective conjugate vaccines, more countries may be able to protect their populations.
- Surveillance will continue to be important as vaccine coverage increases worldwide.
- The current worldwide commitment to investigate additional finotyping and genotyping of meningococcal isolates may expand in subsequent years to help make it possible to eliminate meningitis as an important disease worldwide.

Acknowledgements

The authors are grateful for review and comments provided by Johanna Pattenier, James Wassil and Michael Broker.

Financial & competing interests disclosure

This work was funded by Novartis Vaccines. All authors participated in writing, critical review and evaluation of the current manuscript. J da Silva initiated a base study of W-135 literature. ZA Memish was the primary author of the paper in which the GCC epidemiology data were first presented. L DeTora and C Malerczyk provided editorial support and guidance for the initial development of the GCC epidemiology manuscript and the current manuscript. Da Silva, DeTora and Malerczyk are, or were, employees of Novartis Vaccines and Diagnostics. The authors

have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial assistance, data checking and a literature review of serogroups X and Z was provided by Sarah Angus of Alpharmaxim.

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