Trends and variations in the epidemiology of meningococcal disease in Kuwait 1987–2013

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Received 23 September 2014; received in revised form 23 December 2014; accepted 23 January 2015

KEYWORDS
Neisseria meningitidis; Kuwait; Meningococcal conjugate vaccine; Meningococcal polysaccharide vaccine

Summary The introduction of Haemophilus influenzae type b (Hib) conjugate vaccine and conjugate pneumococcal vaccine into routine childhood vaccination in Kuwait has resulted in the emergence of Neisseria meningitidis as the leading cause of invasive bacterial infection in children. Currently, a quadrivalentACYW-135 meningococcal polysaccharide vaccine is administered as part of routine childhood vaccination in Kuwait at the age of 2 years. Conjugate meningococcal vaccines have been shown to be more effective in preventing meningococcal infection in young children. The objective of this study was to describe the epidemiology of meningococcal disease (MD) in Kuwait and evaluate the need for conjugate vaccine in routine childhood immunization. We have reviewed the MD surveillance data from the communicable disease unit, Ministry of Health, Kuwait during the period from 1987 to 2013. The analysis included microbiologically confirmed cases of N. meningitidis in the blood and cerebrospinal fluid. There were 293 cases of confirmed MD during the study period. Two hundred and four cases (70%) were in children ≤14 years of age. The mean incidence rate was 0.5/100,000 persons. The dominant serogroups were W-135 and B, accounting for 80 cases (32%) each. Serogroup B accounted for 69/204 (34%) of all cases in children ≤14 years and serogroup A accounted for 36/89 (40%) of all adult cases. There were three outbreaks: 1987 (caused by serogroup A), 1989 (caused by serogroup W-135) and 2002 (caused by serogroup B). The mean case fatality rate was 13.5%. In conclusion, despite childhood routine vaccination with...
Introduction

After the introduction of *Haemophilus influenzae* type b (Hib) conjugate vaccine and pneumococcal conjugate vaccine (PCV) into routine childhood vaccination programs, *Neisseria meningitidis* has become the leading bacterial cause of meningitis and sepsis in children [1]. It has been estimated that it causes 500,000 cases and 50,000 deaths annually in children less than 5 years of age worldwide [2].

Kuwait is situated in the northern edge of Eastern Arabia at the tip of the Persian Gulf. Its size is 17,820 km² with a population of 4 million as of 2013. The Ministry of Health is the major provider of health care through six regional health care districts. The private health sector has emerged as a contributor to health care in the last 10 years.

The Hib vaccine was introduced in Kuwait in 1996 and PCV in 2006. Additionally, the current vaccination schedule includes the routine administration of a quadrivalent ACYW-135 polysaccharide meningococcal vaccine at the age of 2 years. We have previously reported that *N. meningitidis* is the most common cause for bacterial meningitis in children in Kuwait [3].

Meningococcal vaccination recommendations in Kuwait have changed over the years based on the changing epidemiology of meningococcal infection in the country. In 1987, an outbreak of *N. meningitidis* serogroup A led to a recommendation for the use of a bivalent AC meningococcal polysaccharide vaccine in the expanded program on immunization (EPI) for children 4 years of age. Additionally, the vaccination program of pilgrims going to Hajj in Saudi Arabia was started in the same year. In 1997, following the emergence of serogroup W-135 in the country, the quadrivalent ACYW-135 meningococcal polysaccharide vaccine replaced the bivalent AC polysaccharide vaccine in the EPI schedule for children at 4 years of age. In 2008, the quadrivalent ACYW-135 polysaccharide vaccine was introduced at 2 years of age instead of 4 years as part of the EPI schedule.

In addition to routine vaccination with the quadrivalent ACYW-135 meningococcal polysaccharide vaccine in all children at the age of 2 years, the current efforts to reduce meningococcal infection in Kuwait include the following recommendations: vaccination of all contacts of cases with meningococcal disease including medical and paramedical personnel, students in police and military colleges and pilgrims going to Hajj and Umrah with quadrivalent ACYW-135 meningococcal polysaccharide vaccine [4]. In addition, a bivalent AC meningococcal polysaccharide vaccine is given to all expatriate laborers and housemaids [4]. No conjugate vaccine is routinely administered to any of the groups above.

The objective of this study was to describe the epidemiology of meningococcal disease (MD) in Kuwait from 1987 to 2013 and to evaluate the need to introduce a conjugate meningococcal vaccination in the routine vaccination schedule.

Methods

Surveillance

Population-based surveillance for MD is a national active surveillance in Kuwait that was started in 1987 by the Ministry of Health (MOH). Positive cases with *N. meningitidis* are instantly reported to the Preventive Medicine Department in each hospital. The report is forwarded from all six general hospitals and other subspecialty hospitals in Kuwait to the Department of Communicable Diseases Control Unit at Ministry of Health within 24 h of identification. MD is defined as the isolation of *N. meningitidis* from the blood or cerebrospinal fluid. After confirmation of the case, a notification form includes patients’ demographic data including name, age, nationality, contact tracing information and outcome. This notification form is completed
by the preventive medicine doctors at the hospital and is forwarded to the Department of Communicable Diseases Control Unit. We excluded cases of meningococcal disease based on clinical suspicion without microbiological evidence of *N. meningitidis*. We retrospectively collected all available data on this active surveillance from 1987 to 2013 for further analysis. There were no reports from the period from August 1990 to February 1991, as the country was under the Iraqi invasion.

**Laboratory methods**

All suspected or confirmed *N. meningitidis* isolates were transported from the microbiology laboratory of the hospital to the central public health laboratory on chocolate agar media labeled with the patient’s name and identification number. The isolate was re-cultured and subjected to biochemical testing for confirmation. Serogrouping was confirmed using Bacto® *N. Meningitidis* antisera [5]. Isolates were classified into one of five serogroups: A, B, C, X/Z, Y and W-135. Some isolates were only identified by a gram stain as gram-negative diplococci, but the culture was negative. As a result, the isolate serogroup was labeled as ‘undefined’. The serogroup was reported to the Department of Communicable Diseases Control Unit to be added to the notification form. Currently, there is no polymerase chain reaction (PCR) testing for identification or serogrouping of *N. meningitidis* in Kuwait.

**Statistical analysis**

Age group, monthly distribution of cases, meningococcal serogroups, crude annual disease incidences and case fatality rate were calculated for all MD cases among the population in Kuwait (citizens and residents). The reported ages were as follows: <1 year, 1–4 years, 5–9 years, 10–14 years, 15–19 years, 20–24 years, 25–34 years, 35–44 years and >45 years.

All data were expressed in numbers and proportions. Surveillance data were computerized using Excel program (Microsoft, USA).

**Results**

A total of 293 cases of meningococcal disease were reported from 1987 to 2013, excluding August 1990–February 1991. The annual frequency and incidence of meningococcal disease in Kuwait per 100,000 populations is shown in Fig. 1. The mean annual incidence is 0.5/100,000 populations. The peaks in the graph correspond to three outbreaks in 1987, 1989 and 2002. The disease incidence was the lowest and most steady in the last four years of surveillance (2010–2013) of 0.10–0.13/100,000 population. The highest proportion of cases occurred between the months of December and April in 210 cases (71%). The reported ages were as follows: <1 year 61 (21%), 1–4 years 79 (27%), 5–9 years 48 (16%), 10–14 years 17 (6%), 15–19 years 10 (3%), 20–24 years 20 (7%), 25–34 years 30 (10%), 35–44 years 18 (6%), >45 years 10 (3%).

We excluded 41 isolates that were undefined in the subsequent serogroup analysis. Out of 252 identified isolates, there were 80 isolates (32%) for both serogroup B and serogroup W-135. Serogroup A accounted for 74 isolates (29%), Y 10 isolates (4%), C 7 isolates (3%) and X/Z 1 isolate (0.4%).

The dynamic variation of serogroup distribution over the period of the study is shown in Fig. 2. Out of the 293 isolates, there were 204 (70%) isolates from children ≤14 years of age and 89 isolates (30%) in adults (>14 years of age). Fig. 3 shows the serogroup distribution in relation to age. During the surveillance period, there were three outbreaks of MD in 1987, 1989 and 2002. Table 1 shows the serotype distribution during the three outbreaks. The mean case fatality rate (CFR) during the observation period was 13.5%, ranging from 0% during 1996–1997, 2003–2004, 2007, 2010 and 2013 to 33% in 1991 and 1998.

To evaluate the trends and changes in the epidemiology of MD in relation to different vaccination programs in Kuwait, we divided the interval of the study into three periods: Period (1), in which the bivalent AC polysaccharide vaccine was administered at the age of 4 years (1987–1997); period (2), in which the quadrivalent ACYW-135 polysaccharide vaccine was administered at the age of 4 years (1998–2008); and period (3), in which the
quadrivalent ACYW-135 polysaccharide vaccine was administered at the age of 2 years (2009—2013). The number of cases of MD was 133 in period (1), 139 in period (2) and 21 in period (3). The mean incidence rate/100,000 persons were 0.74 (range 0.3—1.4) for period (1), 0.5 (0.2—1.1) for period (2) and 0.13 (0.1—0.2) for period (3). The decrease of the population incidence of MD after the switch to the quadrivalent ACYW-135 was associated with a $P$ value of <0.01. There was an 82% reduction in the incidence of MD in period (3) compared to period (1). Children up to 14 years of age were dominant in periods 1 and 2 with 89 cases (67%) and 106 cases (76%), while adults were more dominant in period 3 with 12 cases (57%). Serogroup epidemiology varied as follows: serogroup A was dominant in

![Figure 2](image2.png)

**Figure 2** Meningococcal serogroup distribution during 1987—2013.

![Figure 3](image3.png)

**Figure 3** Serogroup distribution in relation to age.

<table>
<thead>
<tr>
<th>Year</th>
<th>A (%)</th>
<th>B (%)</th>
<th>C (%)</th>
<th>W-135 (%)</th>
<th>Ungrouped (%)</th>
<th>Total #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>23 (88)$^a$</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>2 (8)</td>
<td>26</td>
</tr>
<tr>
<td>1989</td>
<td>7 (26)</td>
<td>4 (15)</td>
<td>2 (7)</td>
<td>12 (45)$^a$</td>
<td>2 (7)</td>
<td>27</td>
</tr>
<tr>
<td>2002</td>
<td>2 (8)</td>
<td>17 (65)$^a$</td>
<td>0</td>
<td>5 (19)</td>
<td>2 (8)</td>
<td>26</td>
</tr>
</tbody>
</table>

$^a$ Denotes the serogroup responsible for the outbreak.

| Table 1 | Neisseria meningitidis serogroup distribution during the three outbreaks in Kuwait. |
period (1), serogroup B in period (2) and serogroup W-135 in period (3). The mean CFR was 17.5% for period (1), 11.3% for period (2) and 12% for period (3).

Discussion

This study is the first to present this comprehensive data on the changing epidemiology of MD in Kuwait since the establishment of the active surveillance 27 years ago. Ceyhan et al. reported on the serogroups and CFR in Kuwait as part of their report of meningococcal disease in the Middle East and North Africa [6]. Memish and Shibl had previously published part of this surveillance of 157 cases during the period of 1997–2009 [4].

There was an 82% reduction in the incidence rate of MD in Kuwait over the last 27 years. Similar reductions in the number of cases have been reported from neighboring Saudi Arabia from 338 cases in 2000 to 6 cases in 2009 [4]. Other near Gulf countries such as Oman, Qatar and Bahrain have reported a low incidence of <2/100,000 population [4]. This reduction in Kuwait can be explained by many factors: strenuous effort by the Ministry of Health to prevent the importation of N. meningitidis into the country by the implementing routine vaccination in children and vaccinating pilgrims and laborers. Though vaccination seems to have played a major effect in reducing MD, the reduction could also be attributed to the secular trend of infection because the reduction was similar among all major serogroups [6]. Another factor that might explain this reported drop in the incidence of MD especially in the last four years of the surveillance is the liberal use of oral and parenteral antibiotics by doctors before appropriate cultures are obtained.

Despite the variation in serogroup distribution during the three periods of the study, serogroups B and W-135 together accounted for two-thirds of all isolates. This dominance differs from other Gulf countries where serogroup W-135 remains the dominant serogroup in Saudi Arabia, Oman and Qatar [4]. It is interesting to note that the appearance of W-135 in Kuwait was first noted during the outbreak of 1989, which was before the outbreak in Saudi Arabia in the year 2000 [7]. As a result of the 1989 outbreak and the persistence of serogroup W-135 in the subsequent years, the Ministry of Health in Kuwait introduced the quadrivalent ACYW-135 polysaccharide vaccine in 1997. It seems that this early introduction of the quadrivalent ACYW-135 polysaccharide vaccine prevented a similar severe W-135 outbreak reported from Saudi Arabia in 2000.

As previously discussed, while the routine use of the quadrivalent ACYW-135 polysaccharide vaccine was successful in reducing the serogroup-related burden of MD in Kuwait, serogroup B has emerged as a major cause of MD. Serogroup B was responsible for the following in Kuwait: MD outbreak in 2002 accounted for 30% of all cases of MD and is the main cause of MD in children up to 14 years (39%). A similar emergence of serogroup B was reported in Saudi Arabia by Khalil and Borrow where it constituted 60% of the isolates in 1998 [8]. Epidemics of serogroup B have been reported in other countries such as the United States, Canada and New Zealand [9–11]. Serogroup B dominance in Kuwait might be related to routine vaccination with the quadrivalent polysaccharide vaccine that does not contain serogroup B. With reduction of the serogroups A, C, W-135 and Y, the relative proportion of serogroup B may have increased. A similar explanation was given when the number of serogroup B cases increased playing a significant role in children <4 years of age in Saudi Arabia [12]. Many studies have demonstrated capsular switching of N. meningitidis or replacement of the serogroups in the nasopharynx following elimination of other serogroups, which may play a role [13,14].

Consistent with earlier studies, infants and young children represent the highest risk group for MD. In the United States, the reported incidence of meningococcal disease in children less than one year was 17% between years 1992 and 1997 with the peak incidence in infants 4–5 months of age [15]. In our population, 21% of MD cases were in children <1 year of age. Although the vaccination strategies have changed, children constituted 67%, 76% and 43% for periods 1, 2 and 3, respectively, of all cases of MD. This high proportion of MD in children suggests that the current vaccination strategy with the quadrivalent ACYW-135 polysaccharide vaccine is not effective in preventing MD in young children.

A more effective vaccination strategy using conjugate vaccine in the routine vaccination schedule is needed in Kuwait. It is well known that conjugate vaccines in children less than 2 years of age are highly immunogenic and induce substantial B-cell memory in young infants, which make them more efficacious than polysaccharide vaccines [16]. Studies have shown that a quadrivalent meningococcal conjugate vaccine MenACWY-CRM used in infants and toddlers was immunogenic and well tolerated [17,18]. The UK experience with the conjugate meningococcal serogroup C vaccine resulted in decreased hospital admissions with meningococcal diseases in children from 34.5/100,000 in 1999 to 12.4/100,000 in 2011 [19]. In their position
paper in 2011, the WHO preferred the use of conjugate vaccine over polysaccharide vaccines due to their increased immunogenicity, particularly in children <2 years and their potential herd immunity [20].

Regardless the significant reduction in the incidence rate, the observed case fatality rate did not change significantly. The mean case fatality rate of 13.5% (11.3–17.5% for the different periods) is in the range of what has been reported elsewhere with invasive meningococcal disease. Bilukha and Rosenstein reported a case fatality rate in the US of 10–14% [21].

Despite the various insights this study provided about MD in Kuwait, several limitations do exist. The main limitation is its retrospective nature. The available data lacks the collection of specific demographic data such as specific ages rather than the age group, the type of infection and relation of mortality to serogroup. We do not have data on vaccinated vs. unvaccinated individuals and the type of vaccine to evaluate vaccine efficacy.

## Conclusion

In conclusion, MD surveillance data in Kuwait provide valuable information about the different trends of MD. There has been a dramatic reduction in the incidence of MD over recent years. Infants and young children remain at the highest risk, which calls for the administration of a conjugate vaccine. There is a need for continuous and informative surveillance and monitoring of MD to help in further public health measures and interventions.

## Conflicts of interest

All authors declare that there is no conflict of interest.

## Acknowledgments

We wish to acknowledge Dr. Claudius Malerczyk for his contributions in critically reviewing and editing the manuscript.

## References

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