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CLINICAL AND EPIDEMIOLOGICAL STUDY

Dynamics of childhood invasive meningococcal disease in Israel during a 22-year period (1989–2010)

S. Ben-Shimol · R. Dagan · Y. Schonmann · N. Givon-Lavi · N. Keller · C. Block · I. Kassis · M. Ephros · D. Greenberg

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Abstract
Aim To describe the dynamics in the incidence of childhood invasive meningococcal disease (IMD) in Israel during a 22-year period (1989–2010).
Methods A longitudinal prospective surveillance in all 27 medical centers with pediatric services in Israel. All cases of children <15 years old with positive blood/cerebrospinal fluid (CSF) culture for *Neisseria meningitidis* were reported. Demographic, clinical, and bacteriological data were recorded. Meningococcal vaccine was not routinely given to Israeli children during the study period.
Results The mean age ± standard deviation (SD) among the 743 cases was 40.7 ± 40.2 months. The mean yearly incidence/100,000 was 2.0 ± 0.8. Age-specific incidences were 8.7 ± 2.8, 2.9 ± 1.5, and 0.8 ± 0.5 for children <1, 1–4, and >4 years old, respectively. The overall incidence decreased significantly from 3.7 in 1989 to 1.5 in 2010. Meningitis constituted 69.2 % of all cases. The most common serogroups were: B (76.9 %), C (10.9 %), Y (8.0 %), and W_{135} (2.9 %). 78.6 % of all serogroup B isolates were from children <5 years old ($p < 0.01$). Serogroup C was found mainly in children ≥5 years old (63.4 %). The case fatality rates (CFRs) for children <1, 1–4, >4 years old, and the total study population were 9.2, 12.3, 7.7, and 9.9 %, respectively. CFRs were higher for children without meningitis (14.9 %) compared to children with meningitis (7.9 %) ($p < 0.01$).
Conclusions Overall, and for serogroups B and W_{135}, childhood IMD rates decreased significantly in Israel during the study period, without routine vaccine usage. The most common serogroup in all age groups was B, which was most prevalent in children <5 years old. No change in the trend of the overall CFR was noted during the study period.

Keywords Dynamics · Children · Meningococcal disease

On behalf of the Israeli Pediatric Bacteremia and Meningitis Group (IPBMG).

Members of the Israeli Pediatric Bacteremia and Meningitis Group (IPBMG) are given in the Appendix.

S. Ben-Shimol · R. Dagan · Y. Schonmann · N. Givon-Lavi · D. Greenberg
Ben-Gurion University of the Negev, Beer-Sheva, Israel

S. Ben-Shimol · R. Dagan · Y. Schonmann · N. Givon-Lavi · D. Greenberg (✉)
Pediatric Infectious Disease Unit,
Soroka University Medical Center, Beer-Sheva, Israel
e-mail: dudi@bgu.ac.il

N. Keller
National Center for Meningococcal Diagnosis,
Chaim Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel

C. Block
Hadassah Hebrew University Medical Center, Jerusalem, Israel

I. Kassis
Rambam Medical Center, Haifa, Israel

M. Ephros
Carmel Medical Center, Haifa, Israel

Introduction

Neisseria meningitidis (Mnc) remains an important pathogen in many industrialized countries. Invasive meningococcal disease (IMD) occurs as endemic sporadic cases in developed countries (incidence ~1–5/100,000/year) or as epidemics in developing countries. In the "meningitis belt" in sub-Saharan Africa, IMD is highly endemic, with annual

incidence during serogroup A epidemics of up to and even exceeding 500 cases per 100,000 population [1–5].

Serogroup B, and, less so, serogroups C and Y, are most common in Europe, North America, New Zealand, and Australia, while serogroup A is most prevalent in Africa and Asia, [1, 3–6], although serogroups C, Y, and W_{135} have been increasingly identified in IMD [7]. The worldwide emergence of serogroup W_{135} has been linked to the Hajj pilgrimage [1, 8].

Current vaccines are based on the capsular polysaccharides (PS) of serogroups A, C, Y, and W_{135}, but are poorly immunogenic in infants [2, 4, 9]. A monovalent meningococcal conjugate vaccine (MCV) vaccine against serogroup C was developed and successfully utilized in several industrialized countries [3, 4, 10]. A quadrivalent MCV, containing serogroups A, C, Y, and W_{135}, was licensed in the US in 2005 [2] and other conjugate vaccines are under development [9], including the recently licensed serogroup A vaccine (MenAfriVac) [11].

Despite the availability of several effective vaccines, only a few countries have implemented a routine vaccination schedule against Mnc, mainly because, currently, no vaccine exists against serogroup B, which is responsible for most sporadic cases in infants and children younger than 5 years of age [9, 12, 13]. Recently, vaccines active against group B Mnc (e.g., the 4CMenB vaccine), containing common protein and other components, have been studied [14–16]. In November 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended the granting of a marketing authorization for the 4CMenB vaccine.

In 2010, the population in Israel was 7.2 million (80 % Jewish; most non-Jews were Moslem-Arabs) [17]. In general, the non-Jewish population lives under lower socioeconomic conditions than the Jewish population, with more crowded living conditions, a greater proportion of children <15 years old, a smaller proportion of elderly persons, and a more rapid rate of population growth. Crowding may be an important risk factor for IMD in the non-Jewish population. A previous report from Israel observed that the annual IMD incidence in Jerusalem was higher than the national mean incidence (2.5 vs. 1.1 per 100,000) [18]. This was probably due, in part, to the high proportion of Arabs and ultra-orthodox Jews living in the city, the two most crowded Israeli sub-populations. To date, no routine immunization with any Mnc vaccine has been implemented in Israel. In rare, special circumstances (e.g., complement deficiency), children receive a quadrivalent polysaccharide vaccine. Conjugate meningococcal vaccines were not available in Israel during the entire study period.

The objectives of this study were: (1) to describe the overall and serogroup-specific dynamics of childhood IMD in Israel during a 22-year period (1989–2010); (2) to compare the overall age-specific and serogroup-specific IMD incidence dynamics; (3) to calculate the IMD case fatality rate (CFR) dynamics in Israel over this 22-year period.

Patients and methods

Study design

An ongoing, nationwide, prospective, population-based surveillance was initiated in 1989. Data are presented for 22 years of surveillance (January 1989 through December 2010). Data collection was conducted in 27 medical centers routinely obtaining blood cultures from children: all 26 hospitals admitting children and one major outpatient health maintenance organization's (HMO, Maccabi Healthcare Services) central laboratory. Less than 1 % of blood cultures from patients of all ages and no cerebrospinal fluid (CSF) cultures are obtained outside of these centers. This allowed for the identification of practically all culture-confirmed pediatric IMD cases in Israel. There are no financial or other barriers to health-care service use in Israel.

A local investigator in each center reported monthly to the central headquarters at the Pediatric Infectious Diseases Unit of the Soroka University Medical Center. This network constituted the Israeli Pediatric Bacteremia and Meningitis Group (IPBMG).

This study was approved by the Human Ethics Committee of the Soroka University Medical Center.

Case definition

IMD episode

An illness episode during which *N. meningitidis* was isolated from blood or CSF. A meningitis episode was defined as an illness with either positive CSF culture for *N. meningitidis* or positive blood culture for *N. meningitidis* with CSF findings of meningitis (i.e., pleocytosis). Any non-culture diagnosis [polymerase chain reaction (PCR), antigen tests, or clinical diagnosis] was excluded. Positive cultures from sites other than blood and CSF were also excluded.

Study population

All children <15 years of age in Israel.

Data collection

Investigators in each center responded monthly to a questionnaire distributed by the principal investigator, located at the Pediatric Infectious Diseases Unit of the Soroka University Medical Center (SUMC; the study headquarters). Each investigator completed a report which included

the following data: isolates' source (blood/CSF), culture date, birth date, gender, ethnicity (Jewish/non-Jewish), main diagnoses including complications, outcome (mortality), and duration of hospitalization.

IMD is a reportable disease in Israel by law; this applies both to physicians and to microbiological laboratories. High reporting rates are achieved compared with other invasive infections because the Ministry of Health (MoH) is responsible for administering chemoprophylaxis. Positive Mnc isolates from blood and CSF were further evaluated by the National Center for Meningococcal Diagnosis at the Chaim Sheba Medical Center, Tel Hashomer.

IMD cases reported by investigators at each site were constantly compared to the list of isolates sent to the reference laboratory at the National Center for Meningococcal Diagnosis. Less than 10 % of episodes were not reported by site investigators. Those cases were included following their identification.

Bacteriology

N. meningitidis isolates from blood or CSF were identified according to standard procedures and serogrouped, as previously described [19, 20]. Antibiotic susceptibility was determined at each center and retested at the National Center for Meningococcal Diagnosis, using Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints [21].

Statistical analysis

Data were recorded using the Microsoft Access software package. Statistical analysis was performed using SPSS 15.0. Contingency table analysis for comparing rates between unmatched samples was performed using χ^2 tests or Fisher's exact test, as appropriate. Annual IMD incidence rates were calculated for ethnic groups per 100,000 children for children aged <15 years. The age-specific population at risk was estimated according to the Israeli Central Bureau of Statistics reports. During the study period, the population of children <1, 1–4, and <15 years old increased from 100,800, 377,600, and 1,336,000, respectively, in 1989 to 165,300, 617,800, and 2,112,000, respectively, in 2010.

Trends in total IMD and for specific serogroup incidence rates were calculated using χ^2 for linear trends in proportions. Differences were considered to be significant at the level of $p < 0.05$.

Results

During the study period, a total of 743 IMD cases were recorded; 514 (69.2 %) cases with meningitis and 229 (30.8 %) cases without meningitis. The mean age [± standard deviation (SD)] of the patients was 40.7 ± 40.2 months (median, 25 months). Of all the cases, 423 (56.9 %) were males.

Dynamics of IMD

The mean yearly incidence (per 100,000) was 2.0 ± 0.8. The mean age-specific incidences for children <1, 1–4, and >4 years old during the entire period were 8.7 ± 2.8, 2.9 ± 1.5, and 0.8 ± 0.5, respectively. The overall IMD incidence decreased significantly from 3.7 in 1989 to 1.5 in 2010 ($p < 0.01$, $r - 0.75$) (Fig. 1).

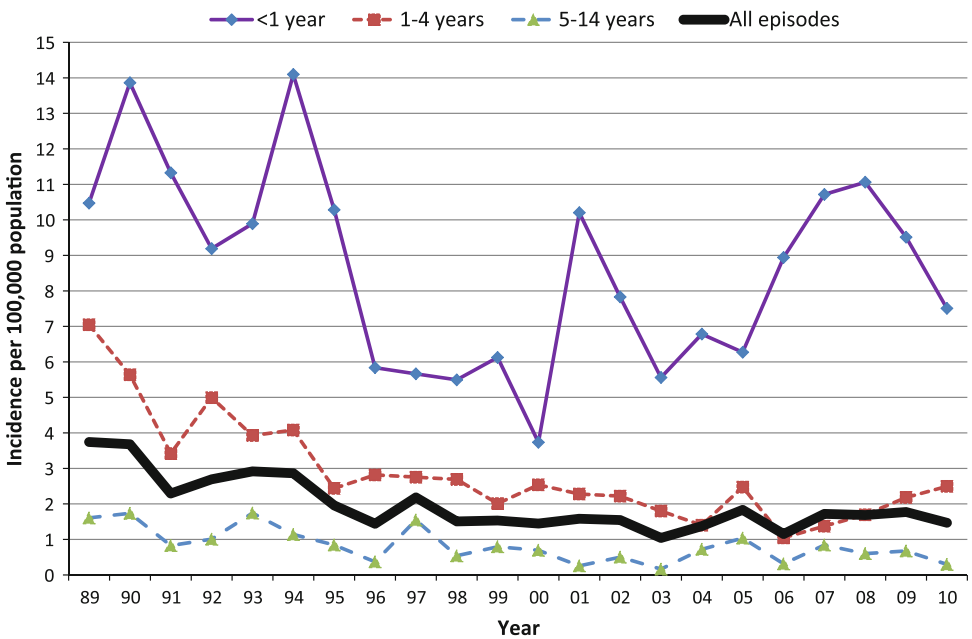

Fig. 1 Age-specific and overall invasive meningococcal disease (IMD) incidence in children in Israel from 1989 to 2010

Table 1 Serogroup prevalence by age in children <15 years old in Israel, 1989–2010

Serogroup *N* (%)	A, $n = 8$ (1.2 %)[a]	B, $n = 500$ (76.9 %)[a]	C, $n = 71$ (10.9 %)[a]	W_{135}, $n = 19$ (2.9 %)[a]	Y, $n = 52$ (8.0 %)[a]	ND, $n = 93$ (12.5 %)	Total, $n = 743$	$p < 0.05$
Age <5 years								
Age <1 year, no. (%)	1 (0.5)	180 (87.4)	6 (2.9)	7 (3.4)	12 (5.8)	38	244 (32.8)	α, β, γ
Age 1–4 years, no. (%)	4 (1.5)	213 (80.1)	20 (7.5)	7 (2.6)	22 (8.3)	33	299 (40.2)	α, β, ε
Total <5 years, no. (%)	5 (1.1)	393 (83.3)	26 (5.5)	14 (3.0)	34 (7.2)	71	543 (73.1)	α, β, γ
Age ≥5 years, no. (%)	3 (1.7)	107 (60.1)	45 (25.3)	5 (2.8)	18 (10.1)	22	200 (26.9)	α, β, γ, ε

α B vs. C, β C vs. W_{135}, γ C vs. Y, δ B vs. W_{135}, ε B vs. Y, μ Y vs. W_{135}

ND not determined

[a] Percentage calculated from known serogroups

IMD incidence decreased significantly in all age groups between 1989 and 2010 ($p < 0.01$). Since 2001, however, in children <1 year old, a trend toward increased disease incidence compared with the 5 years between 1996 and 2000 has been observed.

Serogroup distribution

Of all 743 isolates, 650 (87.5 %) were serogrouped. The most common serogroup was B (76.9 %), followed by C (10.9 %), Y (8.0 %), W_{135} (2.9 %), and A (1.2 %) (Table 1). Serogroup B was the most prevalent serogroup in all age groups. Serogroup C was found mainly in older children (6 vs. 25 % of all IMD cases in children <5 years and 5–14 years old, respectively, $p < 0.01$).

In 93 IMD cases (12.5 %), the serogroup was not determined. The mean number of non-serogrouped isolates per year was 4.2 ± 3.0, with a median of 4 cases (range 0–13, 0–37.1 % of cases/year).

During the study period, the incidences (per 100,000) of serogroups B and W_{135} decreased significantly from 3.0 to 1.1 and from 0.2 to 0, respectively ($p < 0.01$) (Fig. 2).

Comparison of IMD dynamics between Jewish and non-Jewish children

The mean overall IMD incidence rates in Jewish and non-Jewish children were 1.8 ± 0.8 and 2.1 ± 0.8 ($p = 0.14$), respectively.

The mean incidences of serogroups B, C, and W_{135} IMD were similar in Jewish and non-Jewish children: 1.28 ± 0.65 vs. 1.56 ± 0.73, 0.22 ± 0.17 vs. 0.18 ± 0.26, and 0.06 ± 0.10 vs. 0.07 ± 0.13, respectively. However, the serogroup Y disease rates were significantly higher (mean 0.25 ± 0.23) in non-Jewish children compared with Jewish children (mean 0.09 ± 0.08, $p = 0.01$) (Fig. 2).

Case fatality rate

The yearly mean CFR was 9.9 % ± 4.1, and the mean mortality incidence was 0.2 ± 0.1 cases per 100,000 children. Considerable fluctuations in the annual CFRs were noted. The lowest CFR was noted in 1995 (1/32, 3.1 %) and the highest CFR was noted in 2007 (6/35, 17.1 %) (Fig. 3). The CFR for children <1, 1–4, >4 years old, and for the total study population were 9.2, 12.3, 7.7, and 9.9 %, respectively. The CFRs were similar in Jewish and non-Jewish children. Higher mortality rates were observed in children without meningitis compared with children with meningitis (14.9 vs. 7.9 %, respectively, $p < 0.01$).

Discussion

Incidence

This study presents the results of a prospective, 22-year, nationwide surveillance of IMD in the pediatric population of Israel. The mean annual incidence (per 100,000) was 2.0. This rate is similar to the IMD incidences reported from other developed countries [2, 22–26]. In developing countries, incidences are as high as 100–500 cases per 100,000 population, especially in the region of sub-Saharan Africa, called the "meningitis belt" [26]. A positive association has been observed between social deprivation and the risk of meningococcal disease in several studies [26–29]. A previous Israeli study (1999–2005) reported that the average annual incidence rates in children aged 0–14 years among the Arab and Jewish ultra-orthodox groups differed significantly from those of the Jewish traditional/secular group (8.95, 8.63, and 2.41/100,000, respectively) [18].

We did not find significant differences in the overall disease rates between Jewish and non-Jewish children, though

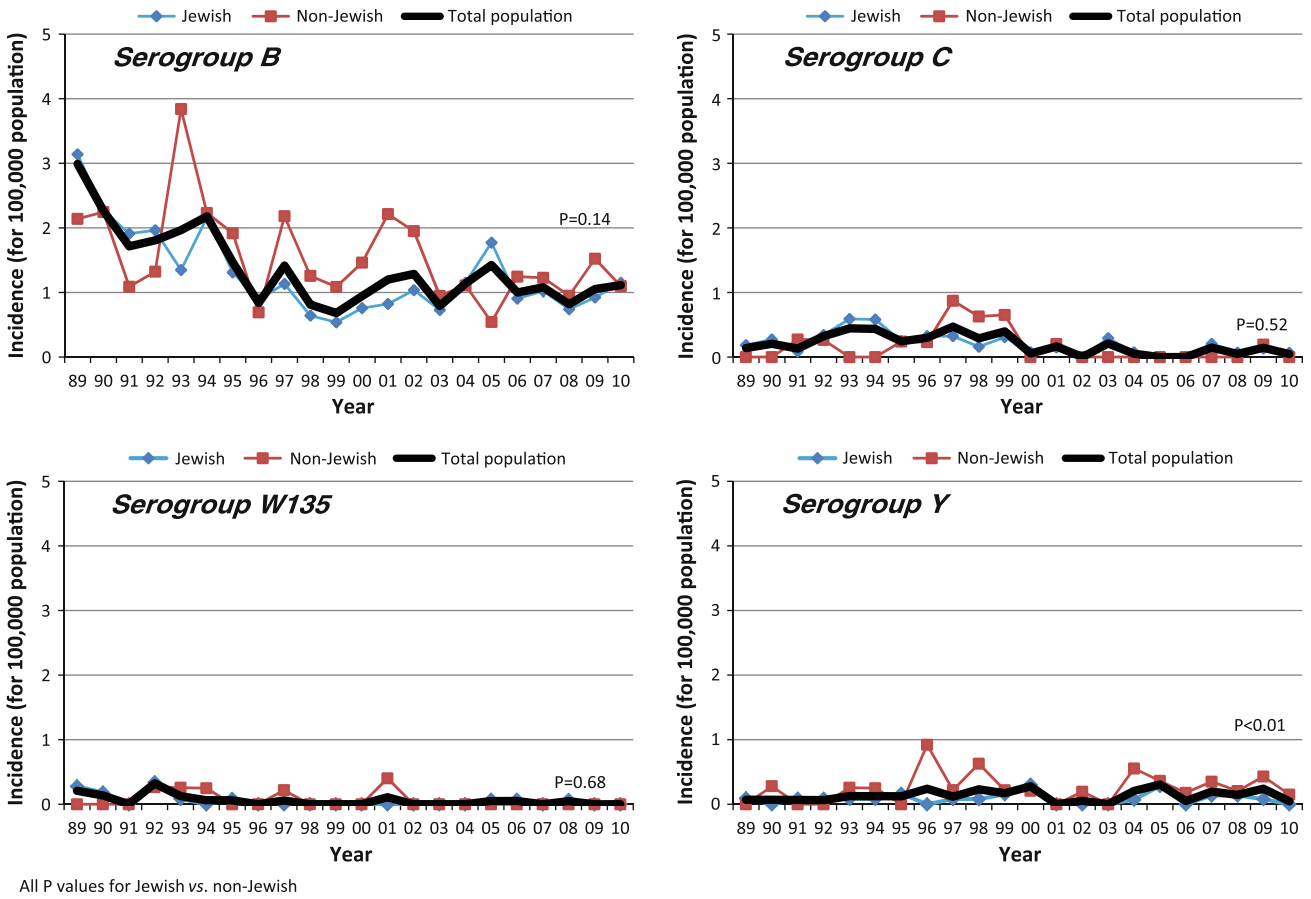

Fig. 2 Serotype-specific dynamics of IMD incidences in children in Israel from 1989 to 2010: Jewish children vs. non-Jewish children

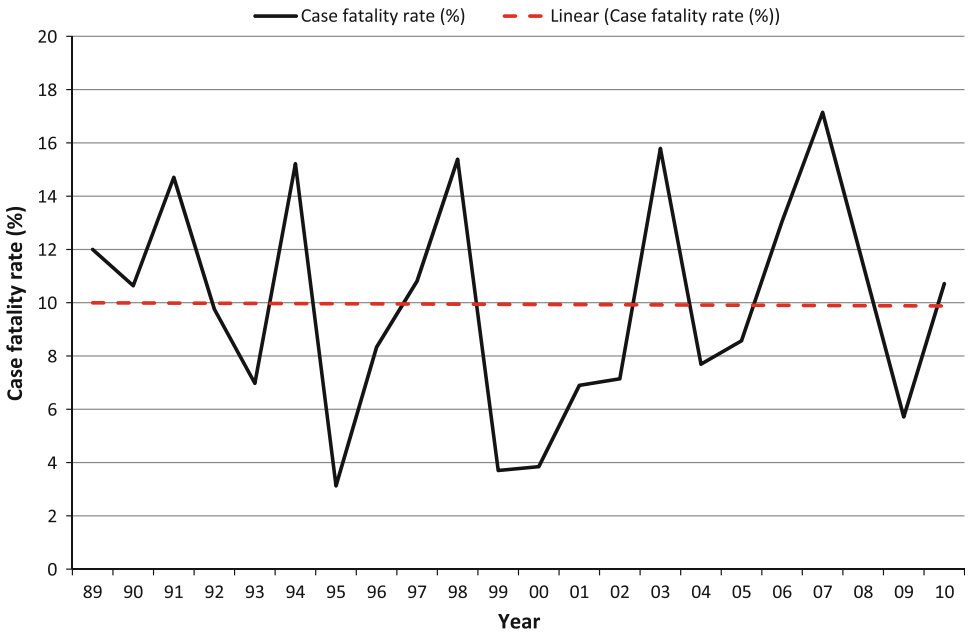

Fig. 3 Total case fatality rate (CFR) in children <15 years old with IMD, 1989–2010

there was a trend toward higher disease rates in non-Jewish children and a significantly higher serogroup Y disease rate. This possibly reflects the socio-economic or imported sources differences between the two sub-populations.

The incidence of IMD in pediatric patients usually has two peaks. The highest incidence of meningococcal disease is in infants younger than 1 year old, but a second, lower peak occurs during adolescence [2]. A second peak of

overall IMD incidence in older children was not identified, although higher serogroup C IMD rates were noticed in children 5–14 years old compared with children <5 years old (data not shown). The lack of a peak in IMD rates in older children is potentially attributable to the fact that our data were limited to children <15 years of age, and the great majority of our cases were caused sporadically by serogroup B, which is mainly a serogroup affecting infants and toddlers.

The overall incidence of serogroups B and W_{135} IMD during childhood decreased significantly in Israel during the study period, without any vaccine usage. This decrease was noted in all age groups. However, the decrease was less apparent in infants <1 year of age. A similar trend was observed in other developed countries, as the IMD annual incidence in the US decreased between 1998 and 2007 by 64.1 % (from 0.92 to 0.33 per 100,000) [30].

A combination of environmental, pathogen, and host factors could be responsible for this decrease in the incidence of IMD. Since meningococcal vaccines were not given routinely in Israel during the study period, the decline in IMD could be attributed to improved socioeconomic status and reduction of environmental risk factors, such as smoking and crowding. However, unexplained secular trends most probably play an important role and, thus, possible future increases in rates of IMD cannot be ruled out.

Serogroup distribution and possible vaccine strategies

The most common serogroup in this study was serogroup B, which was responsible for 76.9 % of all IMD cases. The other important serogroups were: C (10.9 %), Y (8.0 %), W_{135} (2.9 %), and A (1.2 %). This represents a relatively low proportion of serogroup C compared to many developed countries, such as the UK, Canada, or the USA, but a similar proportion to New Zealand, where high rates (87 %) of serogroup B IMD were recorded in the late 1990s as part of an epidemic [26, 31].

Currently licensed meningococcal vaccines (either capsular polysaccharide or conjugate vaccines) are active against serogroups A, C, W_{135}, and Y. No universal vaccines are licensed (for any age) for the prevention of disease caused by serogroup B [32], outside local provisional licensed vaccines for specific strains, used during epidemics (e.g., in New Zealand) [33]. The successful introduction of a monovalent serogroup C vaccine into the UK infant immunization schedule has eliminated virtually all childhood group C disease [34], likely by a combination of individual and herd immunity following reduced nasopharyngeal carriage rate [26].

In our study, Mnc C was isolated in 10.9 % of all Mnc isolates over a period of 22 years. Thus, the routine immunization of all children could prevent (on average) ~3 pediatric cases of Mnc C invasive disease annually. Serogroup C was mainly found in children 5–14 years old, although it caused only a quarter of the IMD cases in that age group. Therefore, vaccinating children aged 5–14 years (and possibly adolescents >15 years of age) could lead to a reduction of IMD burden, or even to the elimination of group C disease, as was observed in the UK [34, 35].

The focus of meningococcal vaccination policies targeting adolescents is only a partial solution. If the basic public health goal is to reduce mortality in the affected population groups, the universal vaccination of infants, especially with an effective Mnc B vaccine included in the vaccine's composition, represents a logical strategy for the control of IMD (just as it was for *Haemophilus influenzae* type B and the pneumococcus). Thus, the development of meningococcal vaccines for use in infants (particularly those <1 year of age) is essential [32]. In this regard, the development of a broadly protective serogroup B vaccine that is safe and immunogenic in young infants during recent years and the anticipated licensure of this vaccine means that, for the first time, vaccines to prevent all five of the serogroups causing the most meningococcal disease worldwide will be available [36].

Case fatality rate

The yearly mean CFR was 9.9 % and the mean mortality rate was 0.2 cases per 100,000 children. Although considerable fluctuations in the annual total CFR were noted, no change in the trend of the overall CFR was noted during the study period. In an Israeli study conducted in the Jerusalem region, the overall CFR for children <15 years old was 8.9 % [18].

The incidence of IMD and the CFRs in Israel are similar to those in other industrialized countries [2, 22]. Despite continuous improvement in medical services over the last several decades, the rate of CFR attributed to IMD has not changed significantly. It seems that preventive rather than therapeutic strategies are the key to the elimination of the grave IMD-attributable morbidity and mortality.

Limitations of the study

We included only blood and CSF culture-positive cases. Since PCR was not performed routinely in Israel during the whole study period, no cases based solely on PCR diagnosis were available. Thus, our figures likely represent only minimal incidence; the true incidence is probably significantly higher. Still, the consistent method of IMD reporting during the entire study period allows for a comparison of annual incidences and recognition of trends in disease rates.

Furthermore, since most hospitals in Israel are not located at a significant distance from the majority of the population, we speculate that antibiotic usage before admission, which might mask positive Mnc cultures, was relatively low.

Another limitation of our study lies in the rate (12.5 %) of non-serogrouped isolates. However, we did not observe significant changes in the proportion of serogroup B (the most common serogroup) disease over the study years, suggesting a good approximation of the serogroups distribution during the entire study period.

Conclusions

Overall, and for serogroups B and W_{135}, the childhood invasive meningococcal disease (IMD) rates decreased significantly in Israel during the study period, without routine vaccine usage. The most common serogroup in all age groups was B, and it was the most prevalent in children <5 years old. Serogroup C was found mainly in children ≥ 5 years old. No change in the trend of the total case fatality rate (CFR) was noted during the study period.

Conflict of interest None.

The Israeli Pediatric Bacteremia and Meningitis Group (IPBMG)

Principal investigator: Ron Dagan.

Investigators: Jacob Amir, Petah Tikva; Galia Barkai, Tel Hashomer; Diana Averbuch, Jerusalem; Shraga Aviner, Ashkelon; Ahuva Bachinski, Hadera; Maskit Bar-Meir, Jerusalem; Avihu Bar-Yochai, Zerifin; Ilana Benedikt, Jerusalem; Rita Bernstein, Rehovot; Nael Elias, Nazareth; Dan Engelhard, Jerusalem; Moshe Ephros, Haifa; Daniel Glikman, Nahariya; Giora Gottesman, Kfar Saba; Galia Grisaru-Soen, Tel Aviv; Alex Guri, Rehovot; Imad Kassis, Haifa; Nathan Keller, Tel Hashomer; Orli Megged, Jerusalem; Dan Miron, Afula; Meirav Mor, Petah Tikva; Hana Ofir-Mintzer, Bnei Brak; Avi Peretz, Tiberias; Uri Rubinstein, Netanya; Yechiel Schlesinger, Jerusalem; David Schwartz, Tel Aviv; Itamar Shalit, Petah Tikva; Eli Somekh, Holon; Isaac Srugo, Haifa; Alvira Zbriger, Hadera; Miriam Zucker, Zfat.

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