



Surveillance of invasive meningococcal disease in the Tel Aviv District, Israel, 2007–2017



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ABSTRACT

Invasive meningococcal disease (IMD) is one of the leading causes of bacterial meningitis and septicemia in Israel. The purpose of the study was to describe the IMD in the Tel Aviv District and to identify specific populations who could benefit from vaccine introduction.

In the Tel Aviv District, the incidence rates ranged from 0.4 to 1.4 cases per 100,000 population per year during 2007–2017.

During the study period, seventy-nine patients (65%) occurred among children younger than four years of age. Eight deaths occurred (7%), most of them among children under the age of 1 year (5 deaths; 15%). A serogroup was identified in 82 isolates. Most of the isolates (69 cases – 84%) belonged to serogroup B (NmB).

IMD clustered geographically in the city of Bnei Brak, with a predominantly Ultra-Orthodox Jewish population. It is the youngest and most densely populated city in the district. The overall incidence rates of IMD among children in Bnei Brak were more than seven times higher in children up to nine years, compared to the rest of the district. Specifically for NmB, disease rates were 9.08 times higher in children up to the age of four, and 7.74 times higher in children from five to nine years old in Bnei Brak, compared to the rest of the district.

Our findings describe the burden of a vaccine-preventable disease and reinforce the need for routine 4CmenB introduction, especially in groups where the disease clusters.

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1. Introduction

Neisseria meningitidis is one of the leading causes of bacterial meningitis and septicemia in Israel, with an annual incidence ranging between 0.02 and 1.35 cases per 100,000 population between 2005 and 2017 [1]. Most cases in Israel occur among children younger than 5 years of age, with case-fatality rates (CFR) ranging from three to seventeen percent [2] (from 1989 to 2010) and substantial morbidity [3]. While *N. meningitidis* has mainly five pathogenic serogroups, most clinical cases in Israel are caused by serogroup B (NmB) [2,4,5], predominantly among children up to the age of 14 years of the Orthodox Jewish or Arab communities [4], with incidence peaking before one year of age. In 2016, a

meningococcal B vaccine (4CmenB - Bexsero, Novartis) was licensed for use in Israel. Although it was found that 4CmenB introduction might be cost-effective in high incidence groups, the vaccine was not included in the national routine immunization program [6].

The aim of this study is to describe the clinical, epidemiologic and molecular characteristics of invasive meningococcal disease (IMD) in the Tel Aviv District and to determine the extent to which specific groups in the district could benefit from the vaccine introduction.

2. Methods

2.1. Epidemiologic data

Meningococcal disease is notifiable by law in Israel, by clinicians as well as by laboratories, under the 12th Article of the Public

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Health Act, which was established in 1940. It gives legal authority to analyze the recorded data and to report it. All the data regarding IMD patients were anonymized for the purpose of this study. Residents of the Tel Aviv District, Israel, were solely included, based on their address of residence. Cases were collected based on the physician's diagnosis from the cases' hospital records.

For each notified case, the Tel Aviv District conducts an epidemiologic investigation by contacting the case or more commonly a close relative to determine contacts to which post-exposure prophylaxis is to be administered. Demographic and clinical data were collected from the patients' hospital records.

For the purpose of incidence calculations, population data were obtained from the Israeli Central Bureau of statistics [7].

2.2. Molecular data

The bacterial strains were isolated at the clinical laboratories in the hospital where the case-patient was hospitalized. For patients who received antibiotic treatment prior to blood or CSF sample withdrawal, a Polymerase Chain Reaction (PCR) analysis was conducted in order to detect the presence of *N. meningitidis* DNA. *N. meningitidis* isolates were submitted to the National Reference Center for Meningococci for species verification, serogrouping and antimicrobial susceptibility testing [8]. Serogrouping is performed by slide agglutination with the Meningococcus Agglutinating Sera (Remel™) for Groups A, C, D, X, Y, Z and W135 and with the Meningococcus Group B Monoclonal Antibody (Remel™) for Group B. Routine molecular characterization is performed for each isolate at the National Molecular Epidemiology Laboratory since 2007. MLST genotyping is performed according to the standard protocol for *N. meningitidis* [9]. Sequence data analysis is performed with Bionumerics 7.6 (Applied Maths, Belgium) and compared to the PubMLST to determine the allele number, sequence type (ST) and clonal complex (CC). Upon request, selected isolates are analyzed by Pulsed-field gel electrophoresis (PFGE). *NheI* digests of chromosomal DNA are separated on the CHEF-DR III system (BioRad Laboratories, Hercules, CA, USA) and DNA profiles are analyzed using Bionumerics 7.6 (Applied Maths) [10]. The analysis includes comparison to other isolates from the local PFGE profile database and determination of similarities between isolates.

3. Results

3.1. Surveillance and descriptive epidemiology

Between January 1st 2007 and December 31st 2017, 121 cases of IMD were notified to the Tel Aviv District Health Office. During 2007–2017, the average disease rate in the Tel Aviv District was 0.8 cases per 100,000 population (ranging from 0.3 to 1.4 per 100,000 population per year). The average national rate was 0.7 cases per 100,000 population (ranging from 0.4 to 1.2 per 100,000 population per year). The highest disease incidence was observed in the city of Bnei Brak, compared to children of the same age from the rest of the district, where rates ranged between 1.1 and 6.9 cases per 100,000 population per year during 2007–2017 (Fig. 1).

Seventy-eight (65%) cases were male. Seventy-nine (65%) patients were children younger than four years of age, predominantly from the city of Bnei Brak (Table 1). Age stratified rates of meningococcal disease were consistently higher in Bnei Brak compared to the rest of the District, markedly in the younger age categories. Specifically, NmB disease was consistently higher in Bnei Brak with a risk ratio of 9.08 in children up to the age of four years, and 7.74 in children from four to nine years old (Table 2).

Overall, eight deaths occurred (7% CFR), most of them among infants younger than 1 year old (5 deaths; 15% CFR), four of the

infant deaths (4/5) from the city of Bnei Brak. Median duration of hospitalization was 8 days (ranging from one to 33 days). Median time from onset of symptoms to hospitalization was one day (range 0–13 days (the latter in a case of chronic meningococemia)).

Thirty-three (27%) patients reported having suffered from an upper respiratory tract infection up to seven days prior to disease onset. Seventy-six cases (63%) were children attending day-care or school. Twenty-eight (23%) cases were children who were not attending day-care or school. The median number of exposed children in daycare or school classes was 25 (range 1–176 (big yes-hiva)). The median number of household family members was six (range 1–15) and median number of contacts who received antibiotic prophylaxis was 32 (range 2–191).

3.2. Molecular data

The bacterium was detected by PCR or culture in CSF samples alone for 47 cases; in blood samples alone for 40 cases; and in both CSF and blood in 16 cases.

Multilocus sequence typing (MLST) analysis was performed on each *N. meningitidis* isolate in order to describe and to assess genetic similarities among isolates.

A serogroup was assigned for 82 isolates. Overall, 69 (84%) isolates belonged to serogroup B, eight (10%) were serogroup C, three were serogroup W (4%), two (2%) were serogroup Y, and one isolate was nongroupable, based on serology methods (Fig. 2). ST was assigned for 75 cases only. In recent years, as diagnosis by PCR has become more common when bacterial culture isn't possible, further typing was impaired in some specimens. Moreover, in some cases, the central laboratory did not receive the sample from the hospital laboratory and further testing was rendered impossible.

Five out of eight deaths were caused by serogroup B (63%), one death by group C, one death by a nongroupable isolate and one death by an unknown serogroup.

During the studied period, serogroup distribution was stable, with isolates belonging predominantly to serogroup B, notably in the younger age categories (up to 14 years of age) (Figs. 2 and 3).

3.3. Serogroup B

The distribution of the Sequence types (ST) and Clonal Complexes (CC) for serogroup B (2007–2017) in the Tel-Aviv District is presented in Fig. 4. Three CCs, 32, 41/44 and 213 (referred as hyper invasive clonal complexes) were responsible for over half of all the IMD isolates (59%).

The most frequently isolated genotype belonged to the CC-32, with 29 cases. Among them 24 cases were identified as ST-32, five isolates differed by one allele out of the seven used for MLST and one isolate differed by two alleles from the ST-32 sequence type. All the case-patients were children. Two deaths were caused by this genotype. The second most frequent genotype was the CC-41/44 complex with 12 cases. This group was comprised of eight different ST's differing by one or two alleles (Fig. 4). Two case patients were found to be linked epidemiologically (cousins) and molecularly (both with ST-35, CC-35 genotypes). The patients were children (8 months old and 1.7 years old) of Eritrean foreign workers and fell ill three days apart.

As cases clustered geographically in the city of Bnei Brak, the Tel Aviv District Health Office expanded the scope of the epidemiologic investigations to find connections between case-patients. Patients were asked about kindergartens, religious schools where they were studying, possible exposures through their brothers and sisters, synagogues where the fathers prayed and the religious community to which they belonged. In most cases, no connection

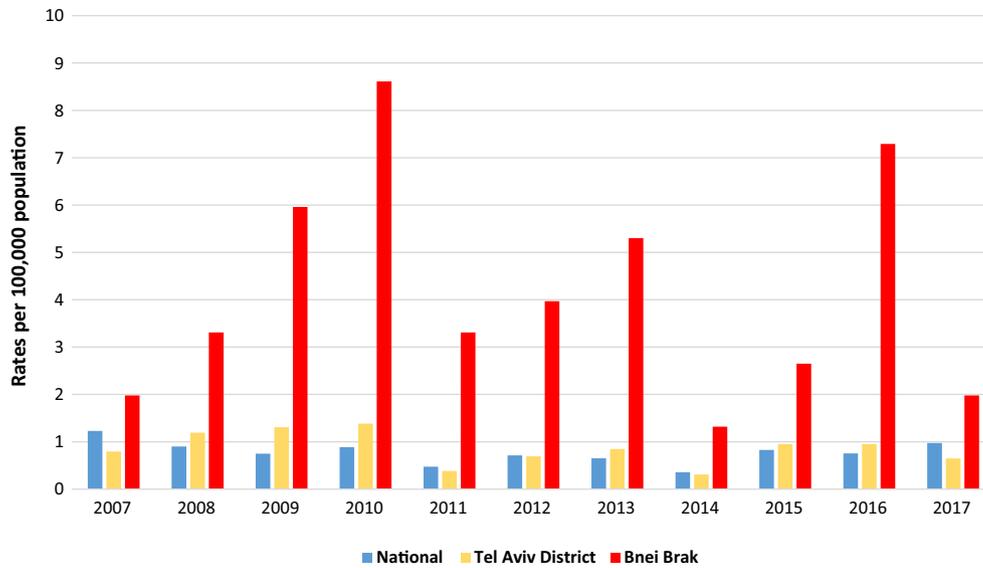


Fig. 1. Meningococcal disease rates per 100,000 population, Israel, 2007–2017.

Table 1

Demographic, clinical and laboratory characteristics of IMD in Bnei Brak and the Tel Aviv District, Israel, 2007–2007.

	Bnei Brak (n = 71)	Tel Aviv District (excluding Bnei Brak) (n = 50)	Tel Aviv District (Total) (n = 121)
Gender (%)			
– Male	44 (62%)	34 (68%)	78 (64%)
– Female	27 (38%)	16 (32%)	43 (36%)
Age Categories (years)			
– 0–4	54 (76%)	25 (50%)	79 (65%)
– 5–9	13 (18%)	6 (12%)	19 (16%)
– 10–14	2 (3%)	3 (6%)	5 (4%)
– 15–84	3 (4%)	16 (32%)	19 (15%)
Clinical presentation			
– Meningitis	31 (44%)	26 (52%)	57 (47%)
– Meningococemia	21 (30%)	15 (30%)	36 (30%)
– Meningitis + meningococemia	19 (27%)	9 (18%)	28 (23%)
Median (range) duration of Hospitalization	8 (1–30)	8 (1–33)	8 (1–33)
Hospitalization in the ICU	53 (75%)	31 (62%)	84 (69%)
Number of deaths (%)	4 (6%)	4 (8%)	8 (7%)
Serogroup			
– B	47 (66%)	22 (44%)	69 (57%)
– C	3 (4%)	5 (10%)	8 (7%)
– Y	1 (1%)	1 (2%)	2 (2%)
– W	2 (3%)	1 (2%)	3 (2%)
– Nongroupable	1 (1%)	0	1 (1%)
– Unknown	17 (24%)	21 (42%)	38 (31%)
Laboratory diagnosis			
– Culture only	53 (75%)	29 (58%)	82 (68%)
– PCR only	10 (14%)	13 (26%)	23 (19%)
– Culture and PCR	1 (1%)	0	1 (1%)
– No laboratory confirmation	7 (10%)	8 (16%)	15 (12%)

was found except for geographic proximity. Two patients attended the same daycare center and were infected by the same genotype (ST-32, CC-32 complex) but fell ill four months apart.

In order to determine whether the geographically related cases were clonal, in addition to MLST of isolates, we further analyzed the ST-32 isolates by Pulse Field Gel Electrophoresis (PFGE). In the pulsograms, none of the isolates from the ST-32 bacteria were identical, including the two cases from the same daycare center.

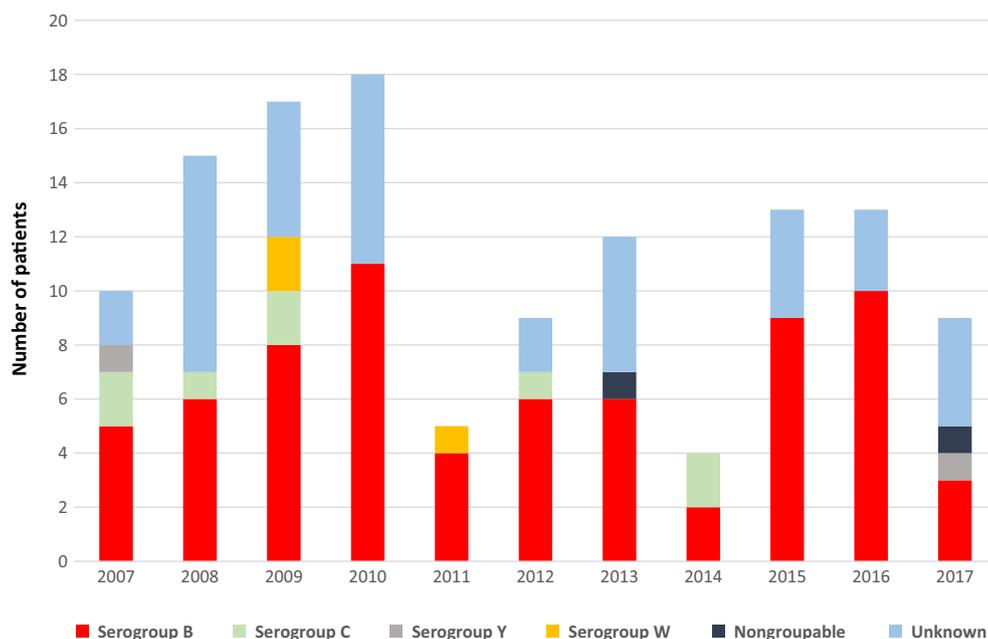
3.4. Serogroup C

Overall, eight cases of serogroup C disease were diagnosed in the Tel Aviv District in the course of 10 years. Six cases were male (75%). Median age was 14 years old (range: 10–36 years old). One death occurred in an otherwise healthy patient who was an MSM (men who have sex with men) (CFR was 13%). This was the only case known to us as an MSM during the study period.

Table 2

Age-stratified incidence rates and risk ratios of IMD in Bnei Brak and the Tel Aviv District, Israel, 2007–2017.

Age categories	Overall meningococcal disease			Serogroup B meningococcal disease		
	Rates per person-years per 100,000 population (cases/person-years)		Risk Ratio	Rates per person-years per 100,000 population (cases/person-years)		Risk Ratio
	Bnei Brak	Tel Aviv District (not including Bnei Brak)		Bnei Brak	Tel Aviv District (not including Bnei Brak)	
0–4 years	18.13 (54/297857.7)	2.58 (25/971006.5)	7.04	13.09 (39/297858)	1.44 (14/971006)	9.08
5–9 years	5.47 (13/237745)	0.76 (6/789041.8)	7.19	2.94 (7/237745.02)	0.38 (3/789041.78)	7.74
10–14 years	0.96 (2/208259.3)	0.44 (3/687663.4)	2.2	0	0	–
15–84 years	0.27 (3/1121047)	0.16 (16/10193540)	1.7	0.09 (1/1121047)	0.04 (4/10193540.04)	2.27

**Fig. 2.** *N. meningitidis* yearly serogroup distribution in the Tel Aviv District, Israel, 2007–2017.

In terms of molecular findings, four cases with STs belonging to CC-11 were identified (two cases with ST-11 and two cases with ST-3375). We did not find an epidemiologic link between any of the cases.

3.5. Serogroup W

Three cases were identified, all among females. Two cases with identical genotypes (ST-1224, CC-22) occurred in 2009 among adults with no identified source of infection or epidemiologic links to each other. In 2011, a five month old born to Eritrean foreign workers was diagnosed with meningococcal meningitis. The genotype identified was ST-11, CC-11. Following this diagnosis, a targeted two-dose vaccination campaign (with a quadrivalent meningococcal polysaccharide vaccine at two and four months of age) was launched among children of African foreign workers. During 2011–2017, a total of 330 infants were vaccinated. Since then no other MenW cases were reported in this group.

3.6. Serogroup Y

In our sample, two isolates were identified as serogroup Y. Both patients were Ultra-Orthodox Jews. One isolate was found to be ST-

6553, CC-23, previously unidentified worldwide and has not been identified since in Israel. The other isolate was part of the ST-23 complex.

4. Discussion

This study describes the epidemiologic and laboratory findings of IMD during 2007–2017 in the Tel Aviv District, Israel.

We found the average disease incidence to be 0.8 per 100,000 population in the Tel Aviv District, which coincides with the incidence rates that are reported in the European Union countries [11].

The IMD activity in the Tel Aviv District caused considerable burden over the study period to the public health, with eight deaths overall (7% CFR), most of which were among infants, and high rates of patients requiring hospitalization in the ICU.

The disease clustered geographically in the city of Bnei Brak, where overall rates in children were as much as seven times higher compared to the rest of the district. The city has a predominantly Ultra-Orthodox Jewish population. It is a notably closed community, where overcrowding might facilitate the circulation of and infection with the bacteria. Bnei Brak is the most densely populated city in the Tel Aviv District (population density of 25709.4 and 8176.8 residents per square kilometer, in Bnei Brak and Tel

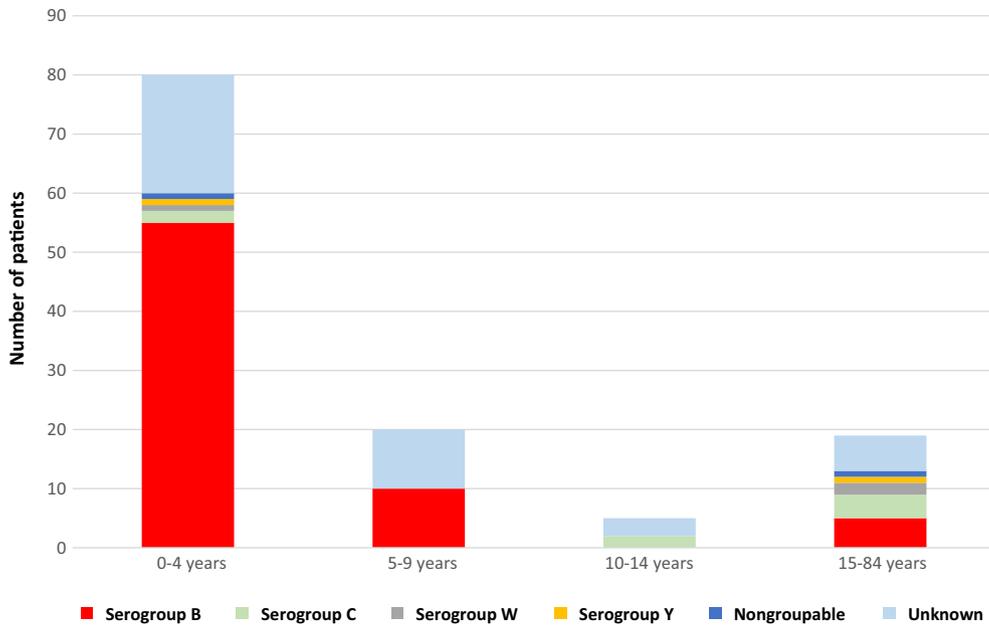


Fig. 3. Meningococcal serogroup isolates by age group in the Tel Aviv District, Israel, 2007–2017.

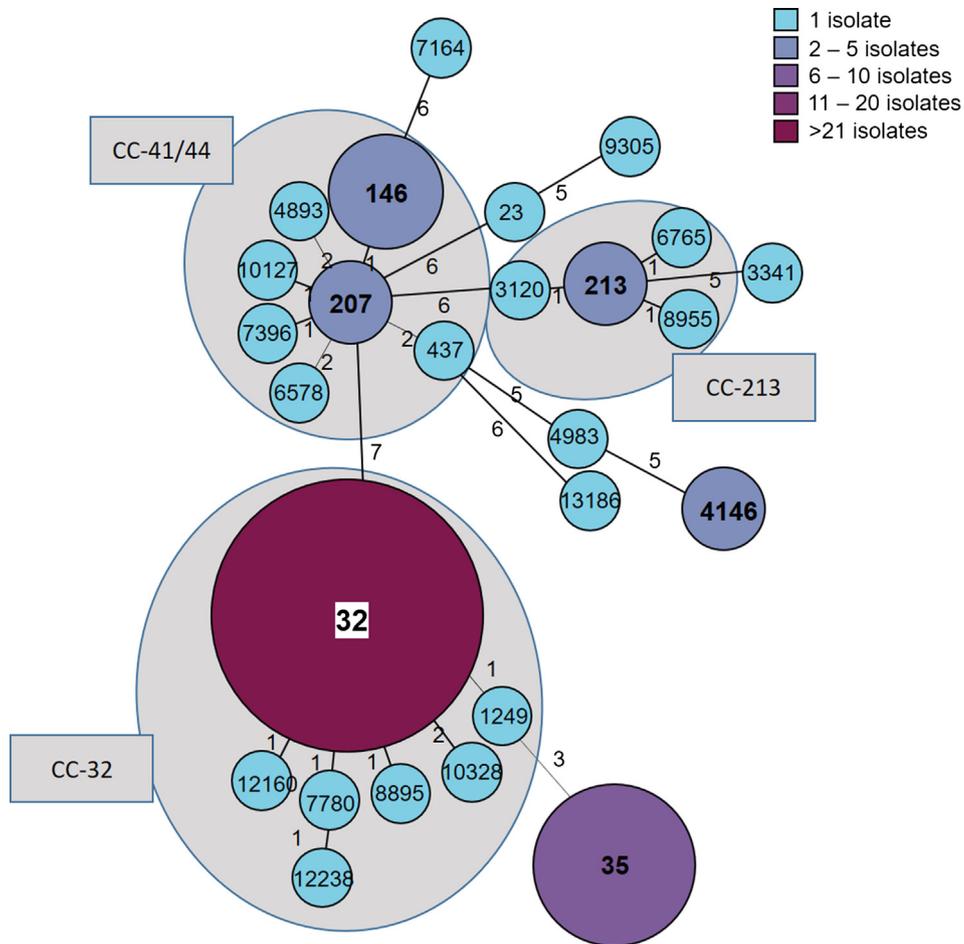


Fig. 4. The Sequence types (ST) and Clonal Complexes (CC), for *N. meningitidis* serogroup B during the years 2007–2017 in the Tel-Aviv District. Minimum spanning tree (MST) of Multilocus Sequence Typing (MLST) data for 76 isolates from blood or CSF. Each circle corresponds to a particular ST, as indicated on the circle (its size proportional to the number of isolates sharing the same ST). The length of the branches corresponds to the allelic distance between STs (1–6 alleles). STs belonging to the same CC are color-shaded and the CC are indicated in boxes.

Aviv District overall, respectively) [12,13]. Also, Bnei Brak has the youngest population in the district, where children under 15 years of age account for 41.5% of its population (Tel Aviv District, 22%) [13,14].

In Bnei Brak, the most frequently isolated bacteria were of serogroup B, especially among the younger age categories (up to 14 years of age). While trying to determine whether the cases were molecularly linked, the Tel Aviv District Health Office requested further analysis of the ST-32 isolates by PFGE. We found that even though we identified clusters of bacteria with identical MLST results, their PFGE profiles were not the same. This suggests the disease was not caused by a single source but rather that in this particular population group the disease incidence is higher, perhaps because of the reasons mentioned above.

During most of the study period, the meningococcal B vaccine had not yet been licensed in Israel and its use was not recommended in Bnei Brak for several reasons. First, as the vaccine was not registered nor available, it would have been possible to request that it be sent specifically under special circumstances, such as an outbreak. However, the disease pattern in Bnei Brak did not fit the meningococcal disease outbreak definition (incidence was lower than 10 cases per 100,000 population in any given three-month period, for all age groups and the isolates were molecularly unlinked) and did not justify such a move. Second, global epidemiologic data was missing concerning the effectiveness of the vaccine, during most of the study period. Moreover, only in 2017 has the Israeli Central Laboratory started to apply Whole Genome Sequencing on the isolates and information was still lacking concerning NmB vaccine antigen distribution.

In 2016, the 4CMenB vaccine was licensed for use in Israel after its introduction showed promising results in England, where it was included in children's routine immunization schedule even before an efficacy trial was completed and with uncertainty regarding its strain coverage [15,16]. The Israeli National Advisory Committee has recently recommended for all children to be routinely vaccinated with the 4CMenB vaccine, based on disease severity, namely hospitalization in the ICU, subsequent morbidity, sequelae, and mortality. The vaccine has currently not yet been included in the national routine immunization schedule, which is publicly funded and under the auspices of the Ministry of Health, for several reasons. First, due to logistic challenges. 4CMenB would need to be given separately due to the high incidence of fever after vaccine administration [17,18] and its need for fever prophylaxis, which is not recommended for the other vaccines routinely administered [19,20]. This would require additional appointments and work force. It would also require the addition of another vaccine to an already busy immunization schedule and might give rise to vaccine selectivity with people choosing to vaccinate with 4CMenB to the detriment of the other recommended vaccines. Second, the vaccine is costly, compared to the vaccines routinely given, and it was not given first priority in the health basket committee. At its current price, the vaccine is above the accepted cost-effectiveness threshold in Israel [6]. The vaccine is currently given in the health funds at a full cost [21] (120.65 USD per dose), and for those with supplementary health insurance it is given at a reduced cost (60.51 USD per dose). As Bnei Brak is one of the cities with the lowest socio-economic status in the country [22], vaccine uptake is inherently at a disadvantage. In this particular group, a targeted routine, publicly funded vaccination campaign among children would be beneficial, in terms of decrease in the overall disease burden. However, it might not be sufficient, as there are close ties between Orthodox Jewish communities living in different cities who also suffer from higher rates of IMD [4]. In addition, nationally there are other com-

munities, notably among the Arab population, where IMD clusters [4].

Our findings describe the severe burden of a vaccine-preventable disease in the Tel Aviv District and reinforce the need for routine 4CMenB introduction, especially in groups where disease clusters.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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