# Trends of Bacterial Meningitis Incidence Rate over 20 Years (2000 to 2019): The Israel Experience

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**ABSTRACT** **Background:** Bacterial meningitis (BM) remains a considerable cause of morbidity.

**Objectives:** To evaluate BM incidence rate trends in diverse age groups.

**Methods:** We conducted a retrospective cohort study based on the Israeli national registry. Inclusion criteria were acute admissions 2000 to 2019 with primary diagnosis of BM. Predefined age groups were neonates (⩽ 30 days), infants (31 days to 1 year), younger children (1 ≤ 5 years), older children (5 ≤ 18 years), and adults (⩾ 18 years). Average annual incidence rates per 100,000/year were calculated for the entire period and by decade. Incidence rates for neonates and infants were calculated per 100,000 live births (LB).

**Results:** There were 3039 BM cases over 2 decades, 60% were adults. The overall BM incidence rate was 2.0/100,000/year, neonates, 5.4/100,000/year LB, infants 17.6/100,000/year LB. First year of life incidence rate (neonates and infants combined) was 23.0/100,000/year, younger children 1.5/100,000/year, older children 0.9/100,000/year, and adults 1.8/100,000/year. All age groups presented a decrease in incidence rate (last decade vs. previous) except neonates, which increased by 34%. Younger and older children presented the most considerable decrease: 48% and 37% (last decade vs. previous).

**Conclusions:** Adults showed the highest number of BM cases. The incidence rate was highest during the first year of life (neonates and infants combined). All age groups, except neonates, showed a decreasing trend. Younger and older children presented the most considerable decrease, most likely attributable to vaccination. The observed increase in BM incidence rate in neonates may influence whether preventive strategy is considered.

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**KEY WORDS:** adults, bacterial meningitis, incidence rate, neonates, pediatric

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Bacterial meningitis (BM) remains a significant cause of morbidity, mortality, and hospitalization for pediatric and adult populations [1-3]. The main pathogens of bacterial meningitis differ by age, era, and geographic area. Group B Streptococcus (GBS), *Escherichia coli* (*E. coli*), and Listeria monocytogenes are the most common causative organisms of neonatal bacterial meningitis in Western countries [4], which is different than other regions such as Asia, Africa, and the Middle East.

In China and Taiwan, as in Western countries, GBS and *E. coli* were the most common organism causing BM in neonates [5,6]. A meta-analysis published in 2018 by Oordt-Speets found that *E. coli* and *Streptococcus pneumoniae* were the most common pathogens causing BM in neonates in Africa [7]. Data from the Middle East are limited. In Turkey *Staphylococcus epidermidis* was the most common organism causing neonatal BM followed by Serratia and *klebsiella spp* [8]. In Iran, *Klebsiella pneumoniae* and *Enterobacter spp* dominate in neonatal BM [9].

Hemophilus influenzae type B (Hib), *S. pneumoniae*, and *Neisseria meningitidis* were considered the three most common pathogens for childhood and adulthood bacterial meningitis in most countries prior to the introduction of pathogen specific vaccines [7,10,11].

The introduction of a pathogen-specific vaccine Hib conjugate vaccine, the pneumococcal conjugate vaccine (PCV), and a *Neisseria meningitides* group B vaccine has changed the epidemiology of BM incidence rates and the underlying pathogens [12,13].

The effect of vaccination on morbidity was evaluated in both developed and developing countries. The incidence rate of bacterial meningitis in the United States declined by 55% (1998) and then by 31% (2007), largely due to the use of the Hib conjugate vaccine for infants, which was introduced in 1990 [14]. In France, 15 years after the introduction of vaccination the invasive Hib disease in children aged < 5 years declined by 96% [15]. In Senegal from 1986 until 1995, near elimination of Hib meningitis occurred after the Hib conjugate vaccine was added to their routine infant immunization program [16]. PCV for infants also resulted in decreasing rates of pneumococcal meningitis [17,18].

Despite significant decline in the incidence rate of pediatric bacterial meningitis due to vaccination policy, it was not expected to affect neonates as *E. coli* and GBS remained the most common causes of bacterial meningitis in Western countries during the first 90 days of life [19]. Screening for GBS and intrapartum antibiotic prophylaxis is common practice in many countries [20] to reduce the risk of early-onset infection. Such

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measures may have no effect on the risk of late-onset disease [21]. The Israeli obstetrics association has not recommended routine screening for GBS in pregnant women.

The trends of bacterial meningitis among adults are relatively stable. Given the decrease in pediatric BM, it is considered a disease of adults [14,22,23]. Research in the U.K. showed only a 0.6% decrease in incidence rate of BM between 2004 and 2011. Pediatric vaccination against frequent BM pathogens, initiated during the 1990s, only partially affected the incidence rate of BM in adults [13,23]. Furthermore, implementation of PCV7 in 2006 did not affect overall pneumococcal meningitis incidence rates. Replacement with PCV13 in 2010, however, led to a 48% reduction in pneumococcal meningitis incidence rate by 2015–2016, mainly in children [24].

The vaccination policy for Israeli children against BM was initiated in 1994 with Hib and PCV7 in July 2009, which changed to PCV13 in November 2010. As compliance with the vaccination plan gradually increased, a stronger influence of Hib conjugated vaccination on prevention of childhood BM compared to the PCV13 vaccination, which started only at the beginning of last decade. In adults older than 65 years of age, vaccination policies against *S. pneumoniae* with polysaccharide vaccine (PPSV23) started in the 1990s.

The epidemiological challenge we face is to determine whether BM is still a considerable morbidity. We evaluated age-group-specific incidence rate trends of bacterial meningitis in Israel from 2000 until 2019 during which vaccination policy was adopted but not GBS screening policy.

## PATIENTS AND METHODS

We conducted retrospective cohort study, based on Israel's National Hospital Discharges Database (NHDD). NHDD is compulsory reporting system that captures structured data on hospitalization from all acute care hospitals. Coded discharge diagnoses are determined by professional coding personnel in medical record units of each hospital, under the instructions and inspections conducted by the Ministry of Health. Inclusion criteria were acute hospitals admission rates of all ages from 1 January 2000 to 31 December 2019 with documented primary discharge diagnosis of bacterial meningitis.

The retrieved data included patient age, sex, admission date, admission type, coded diagnosis, diagnosis order, discharge date, discharge type, and length of stay. The study was approved by the Ministry of Health institutional review board. Signed consent was waved.

The following age groups were predefined for the purpose of this study:

Neonate: ≤ 30 days
Infants: 31 days < 1 year
Younger children: 1 year < 5 years
Older children: 5 years < 18 years
Adults: ≥ 18 years

BM was defined as coded discharge diagnosis codes 320* according to international classification of diseases (ICD-9).

The research focused on BM incidence rate trends during 2000-2019.

Incidence rate computed as cases per 100,000/years of the respective populations in the entire groups, excluding neonates and infants in which incidence rates were calculated as cases per 100,000/live births (LB) (neonates contributed 30 days and infants 335 days in the first year of life). However incidence rate in first year of life (neonates and infants combined) cases per 100,000/LB is identical to incidence rate per 100,000/year (as neonates and infants combined contributed a full year in the first year of life).

We calculated BM incidence rates for each decade as the overall sum of cases during the respective period divided by the sum of the annual population size in each year during the respective period divided by number of years. Population data were derived from the Israel national bureau of statistics.

Incidence rate comparison between the two decades was determined by incidence rates ratio (IRR) calculated as incidence rate in last decade (2010–2019) divided by the respective incidence rate in the previous decade (2000–2009). IRR < 1 indicates a decrease in the last decade compared with previous decade. IRR > 1 indicates an increase in the last decade incidence compared to previous decade.

We evaluated individual year incidence rate as the annual number of cases divided by the respective year population size. Incidence rate trends over 20 years were evaluated through a linear regression model.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Differences in incidence rate were determined using Fisher's exact test. $p < 0.05$ was considered statistically significant.

## RESULTS

### INCIDENCE RATE

There was an overall total of 3039 BM cases, 1374 females and 1665 males (male predominance of 55%). The 20 years reveal sum of 151.9 × 106 population years. The average incidence rate of the entire BM cases over 20 years was 2.0/100,000/year.

Adults contributed 59.6% of all BM cases (1810). There were 1229 pediatric cases (40.4% of the entire BM cases). The pediatric population under 5 years of age (neonates, infants, and young children) contributed 923 (75%) of the pediatric BM cases, and older children included 306 (25%) of all pediatric BM cases.

Average incidence rate in neonates was 5.4/100,000 LB and in infants 17.6/100,000 LB. The overall first year of life incidence rate was 23.0/100,000/year. The incidence rates of all other pediatric subpopulations were much lower: 0.9–1.5/100,000/year. The annual average incidence rate for adults was 1.8/100,000/year. Males had a considerably higher average incidence rate than females in each of the age groups, except first year of life (neonates and infants).

### LAST VERSUS PREVIOUS DECADE

Table 1 shows the population size, number of cases, and incidence rates over the entire 20-year period and in each decade.

The Israeli annual midyear population size grew from 6.29 × $10^6$ in 2000 to 9.05 × $10^6$ in 2019. As derived by IRR there was a decrease of 14% in the overall incidence rate. The incidence rate of newborns increased by 34%, while all other age groups decreased The incidence rate for infants decreased by 12%, in younger children by 48%, and in older children by 37%. The incidence rate for adults decreased by 9%. IRR confidence intervals were narrow (due to the size of the populations) and informative as it had not crossed IRR=1 (statistically significant).

### ANNUAL PATTERNS

Figure 1 shows the fluctuation of the annual BM incidence rate patterns of neonates and infants per 100,000 LB and first year of life incidence rate (neonates and infants combined). Neonates showed a mild increasing trend in incidence rate (+0.059/100,000/LB/year). Infants showed a decreasing trend (-0.26/100,000LB/year), first year of life (neonates and infants combine) showed a decreasing trend (-0.20/100,000LB/year. The first of life incidence rate (neonates and infants combined) in terms of /100,000LB is entirely identical to incident rate in terms of /100,000/year (first year of life).

**Table 1.** Bacterial meningitis incidence rates in the last decade vs. the previous decade

| Previous decade (2000–2009) incidences | | | | | Last decade (2010–2019) incidences | | | | | Incidence rate ratio (last / previous decade) | Incidence rate ratio, 95% confidence interval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cumulative live births (millions) | Cumulative population, years (millions)* | Cases | Incidence rate /$10^5$, live births | Incidence rate/$10^5$/ year | Cumulative live births (millions) | Cumulative population, years (millions)* | Cases | Incidence rate/$10^5$/ live births | Incidence rate/$10^5$/ year | | |
| | 68.755 | 1489 | | 2.2 | | 83.151 | 1550 | | 1.9 | 0.86 | 0.86074–0.86075 |
| 1.442 | | 66 | 4.6 | | 1.746 | | 107 | 6.1 | | 1.34 | 1.27–1.41 |
| 1.442 | | 270 | 18.7 | | 1.746 | | 289 | 16.6 | | 0.88 | 0.84–0.93 |
| | 1.442 | 336 | | 23.3 | | 1.746 | 396 | | 22.7 | 0.97 | 0.9733–0.9734 |
| | 5.582 | 117 | | 2.1 | | 6.775 | 74 | | 1.1 | 0.52 | 0.52109–0.52112 |
| | 15.905 | 175 | | 1.1 | | 18.880 | 131 | | 0.7 | 0.63 | 0.630606–.630626 |
| | 45.826 | 861 | | 1.9 | | 55.751 | 949 | | 1.7 | 0.91 | 0.905979–0.905996 |

**Figure 1.** Bacterial meningitis annual incidence rates, in first year of life /100,000 live births First year of life incidence rate is neonate and infant rates combined

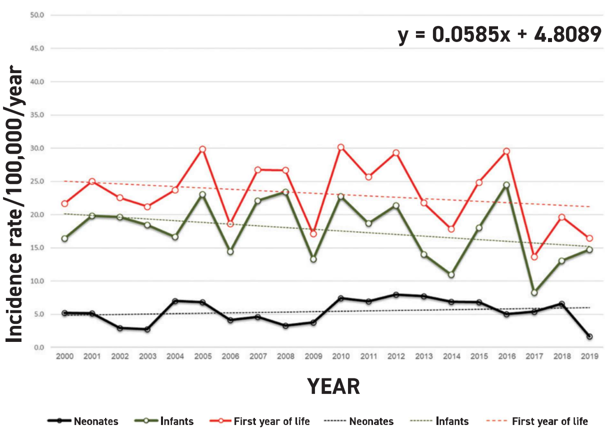


**Figure 2.** Annual incidence rates of bacterial meningitis, ages 1 year and older /100,000/year

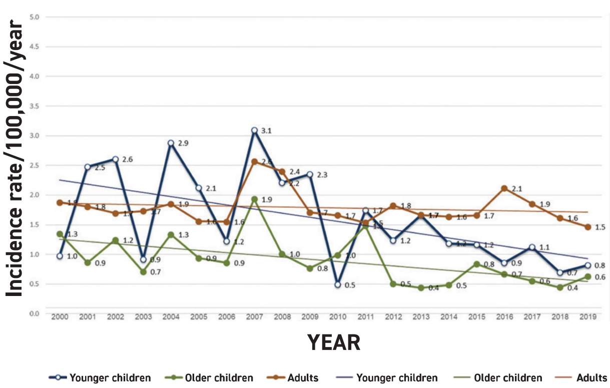

Figure 2 displays the fluctuation of annual BM incidence rate patterns by age groups (excluding first year of life that demonstrated in Figure 1). For the Y-axis in Figure 2, the range is 0–5/100,000/year while the range for the Y-axis in Figure 1 is 0–50/100,000/year. Younger and older children showed considerable decrease patterns (younger children -0.07/100,000/year, older children -0.037/100,000/year). Adults showed a minor decrease trend (-0.008/100,000/year). That fluctuations were moderated with time.

The annual trend of each age-specific annual incidence rate complies with the trends between the two decades (last decade 2010–2019 vs. previous decade 2000–2009) as demonstrated in Table 1.

## DISCUSSION

The aim of our study was to evaluate age-group and sex specific incidence rate trends of BM in Israel during 2000–2019 to determine whether BM still contributed to morbidity during the vaccination and GBS prophylaxis era.

The results indicated an overall mild decrease in incidence rates in the last decade versus the previous decade (by 14%). The incidence rates of neonates mildly increased while in all other age groups the incidence rate decreased. Younger and older children showed the most considerable decrease by 48% and 37%, respectively.

Linear regression models of BM for 20 years 2000–2019 revealed a mild increasing trend in neonates in contrast to the decreasing trend in infants, which affected the entire first year of life pattern. Younger children presented a considerable decreasing trend, and to slightly lesser extent older children. Adults presented a very mild decreasing trend (nearly stable).

As vaccination schedules against BM start at 2 months of age and *E. coli* and GBS remained the most common causes of bacterial meningitis in neonates [19], vaccination was not expected to benefit neonates. However, the observed increase of incidence rates for neonates in our study was entirely unexpected, still it is a real concern as immune systems and complement systems are not yet developed, which make them more vulnerable.[25]

BM in neonates is mostly acquired during passage in the birth canal; hence, the focus should be the prevention of GBS through screening. Should all pregnant women be offered testing for group B streptococcus? Screening is simple, inexpensive, painless, and potentially beneficial in reducing early onset infection. However, it may increase the number of women taking antibiotics during labor. Better hand hygiene can be a complementary measure.

Infants showed a mild decreasing pattern that may reflect partial effect of vaccination (as expected) given vaccination starts at 2 months age and provides partial immune coverage during the first months of life.

The most considerable decrease in incidence rate was in young children (by 48% between the first and second decade of our study). The decrease in older children (by 37%) was most probably due to vaccination. The lower decrease in older children compared to younger children can be explained by their being beyond the age of vaccination, at least PCV13 vaccine, or gradual increase of compliance with vaccination policy implementation. Another explanation may be the decline in immunization over time. This situation should be evaluated in the future to consider vaccination boost.

The effect of vaccination in adults was not expected or, more precisely, should be expected only after vaccinated children reach adulthood. Incidence rates in adults mildly decreased (by 9% between last to previous decade), which is encouraging given that adults contributed most of BM cases. Vaccination policy against pneumococcal infection for people 65 years of age and older may contributed to these results.

This study was based on an existing registry database and provides an epidemiological insight on BM incidence rate in all age groups. Our results suggest that BM is still a considerable concern despite decrease pattern in BM incidence rate.

Most BM cases were in adults (even though their incidence rate was relatively low), which conform to the international findings that BM is a morbidity of adults. BM remains considerable in the first year of life given the high incidence rates. Moreover, neonates showed unexpected increase in incidence rate that raise two questions: first, is this a universal phenomena? Second, what may explain this? The answer to the first question is to evaluate neonate BM incidence patterns in other countries. The answer to the second question can only speculated. On one hand, it may be resulted by better awareness detection and diagnosis of neonates BM, on the other, it may be the result of contamination due to insufficient hygiene due to crowded wards and incompliance with the recommendation to isolate neonates and infants.

We conclude that new strategies should initiate and evaluate to reduce morbidity in neonates and infants. The focus should be the prevention of GBS through screening. Hygiene, especially hand hygiene, should be strictly preserved in the presence of neonates from birth. The policy to isolate and not to expose neonates and infants to others should be strictly implemented.

The considerable decrease in BM incidence rate in both younger and older children suggests effective vaccination. Better compliance with the current vaccination policy and implementation of new vaccine against other pathogens such as *Neisseria meningitides* and other strains of *S. pneumonia* may even improve these results.

Adult morbidity should be targeted for prevention given that they contributed the highest number of cases.

The study strength is the data source of a comprehensive, reliable registry of all Israeli hospitals reporting to the Ministry of Health. The existing registry may reveal epidemiological insights to provide policy makers the basis for policy and outcome evaluation. Nevertheless, a registry carries several limitations. The data collected from different hospitals may be prone to different degrees of precision. The study was based on administrative rather than clinical data. Specific pathogens and specific patient vaccination state could not be evaluated.

## CONCLUSIONS

New strategies should target the first year of life (neonates and infants) because they carry the highest incidence rates. We recommend reevaluation, discussion, and reconsideration of the current guidelines regarding GBS screening. Vaccination seems to be an effective measure to prevent BM among children, and compliance is recommended. New vaccines may improve the results in younger and older children. Adult prevention measures should be considered.


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**It takes a lot of time to be a genius; you have to sit around so much doing nothing, really doing nothing.**

Gertrude Stein (1874–1946), American novelist, poet, and playwright

**The ideals which have lighted my way, and time after time have given me new courage to face life cheerfully, have been Kindness, Beauty, and Truth.**

Albert Einstein (1879–1955), German-born theoretical physicist who developed the theory of relativity, one of the two pillars of modern physics (alongside quantum mechanics)