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Bacterial meningitis in Finland, 1995-2014:

a population-based observational study

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ABSTRACT

Objectives: Bacterial meningitis remains an important cause of morbidity and mortality worldwide. Its epidemiologic characteristics, however, are changing due to new vaccines and secular trends. Conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (10-valent) were introduced in 1986 and 2010 in Finland. We assessed the disease burden and long-term trends of five common causes of bacterial meningitis in a population-based observational study.

Methods: A case was defined as isolation of *S. pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Listeria monocytogenes* or *H. influenzae* from cerebrospinal fluid and reported to national, population-based laboratory surveillance system during 1995-2014. We evaluated changes in incidence rates (Poisson or negative binomial regression), case-fatality proportions (chi-square) and age distribution of cases (Wilcoxon rank-sum).

Results: During 1995-2014, *S. pneumoniae* and *N. meningitidis* accounted for 78% of the total 1361 reported bacterial meningitis cases. *H. influenzae* accounted for 4% of cases (92% of isolates were non-type b). During the study period, the overall rate of bacterial meningitis per 100, 000 population decreased from 1.88 cases in 1995 to 0.70 cases in 2014 (4% annual decline (95% Confidence Interval (CI) 3-5%). This was primarily due to a 9% annual reduction in rates of *N. meningitidis* (95% CI: 7-10%) and 2% decrease in *S. pneumoniae* (95% CI: 1-4%). The median age of cases increased from 31 years in 1995-2004 to 43 years in 2005-2014 (P=0.0004). Overall case-fatality proportion (10%) did not change from 2004-2009 to 2010-2014 (P=0.22).

Conclusions: Substantial decreases in bacterial meningitis were associated with infant conjugate vaccination against pneumococcal meningitis and secular trends in meningococcal meningitis in the absence of vaccination program. The documentation of changes in causative organisms and age distribution for meningitis cases are important for re-evaluating clinical guidelines for empiric antibiotic therapy.

Strengths and limitations of this study:

- This study describes the epidemiologic characteristic of >1300 cases of bacterial meningitis reported to national surveillance during 20 years in Finland.
- The study provides clinically important information on the changing distribution of pathogens and age of cases.
- The study documents the population level impact of infant *Haemophilus influenzae* type b and *Streptococcus pneumoniae* conjugate vaccination on reducing the burden of bacterial meningitis as well as secular changes in rates of meningococcal meningitis.
- As the data were from laboratory-based surveillance system, clinical information such as severity or treatment was not available.
- Incidence rate of bacterial meningitis may be underestimate since cases diagnosed by PCR or antigen detection and culture-negative meningitis cases diagnosed based on clinical symptoms and findings were not included in the analysis dataset.

INTRODUCTION

Despite the availability of vaccines, antibiotics and advances in intensive care, bacterial meningitis remains an important cause of morbidity and mortality worldwide. Persistent neurological sequelae including hearing loss, neuropsychological impairment or seizures are reported in 10-30% of survivors [1]. The case fatality proportion ranges from 5% to 30% for different bacteria [2-3].

Globally, *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* are the most important causes of bacterial meningitis, particularly in young children [4-5]. Among neonates the most common cause of bacterial meningitis is *Streptococcus agalactiae* [2, 6], while *Listeria monocytogenes* is important in newborns and elderly persons with comorbidities [7]. However, the leading organisms causing bacterial meningitis vary by age of the patient, time and geographical location [5]. As the choice of empiric antimicrobial treatment for bacterial meningitis should be based on local epidemiology, patient's age, presence of risk factors and regional resistance patterns [8-12], population-based surveillance data are important to help in formulating clinical guidelines.

The introduction of effective protein conjugate vaccines against *H. influenzae* type b (Hib), *S. pneumoniae* and *N. meningitidis* has changed the epidemiology of bacterial meningitis in many countries [13-14]. In Finland, universal vaccination against Hib since 1986 resulted in rapid elimination of the disease [15] and introduction of the ten-valent pneumococcal conjugate vaccine (PCV10) in September 2010 has resulted in substantial reduction in vaccine-type invasive disease [16-17]. Meningococcal conjugate vaccines have not been introduced into Finnish National Vaccination Programme (NVP). However, meningococcal polysaccharide vaccine has been offered to military conscripts since 1982.

To provide information for developing future prevention strategies and to help in formulating clinical guidelines, we conducted a population-based observational study to determine the contribution of specific pathogens to the total bacterial meningitis disease burden and to assess long-term trends in the incidence of common etiologies in Finland during 1995-2014.

MATERIALS AND METHODS

Data sources

Since 1995, all clinical microbiology laboratories in Finland have had legal obligation to report microbial isolations from blood and/or cerebrospinal fluid (CSF) to the National Infectious Diseases Register (NIDR) - a population-based, electronic laboratory surveillance system maintained by the National Institute for Health and Welfare (THL). Routinely collected information include: the microbe, specimen date, date of birth, sex, place of residence and unique Personal Identity Code (PIC). For blood or CSF findings concerning *S. pneumoniae*, *S. agalactiae*, *N. meningitidis*, *L. monocytogenes*, or *H. influenzae*, multiple notifications with the same PIC and microbe are merged into one case if they occurred within 3 months of the first notification. Since 2004, information on vital status after episode is routinely obtained from the Population Information System. All clinical microbiology laboratories also submit isolates from reported cases to THL reference laboratories for species verification and characterization of the isolates including serotyping or serogrouping. Since 2004, serotyping results are linked to NIDR notifications by using the PIC.

Case definitions

We defined a case of bacterial meningitis as isolation of *S. pneumoniae*, *S. agalactiae*, *N. meningitidis*, *L. monocytogenes* or *H. influenzae* from CSF and notified to NIDR from 1995 through 2014.

For cases reported during 2004-2014, we calculated the pathogen-specific case fatality proportion (CFP) as number of cases resulting to death within 30 days from the first positive CSF culture, divided by all cases.

We calculated the proportions of *S. pneumoniae*, *N. meningitidis* and *H. influenzae* cases due to vaccine-preventable serotypes/serogroups during 2004-2014. Serotypes covered in PCV10 are: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F; the 13-valent pneumococcal conjugate vaccine (PCV13) adds serotypes 3, 6A, and 19A. Vaccine-preventable meningococcal serogroups include those in the quadrivalent meningococcal conjugate vaccine (MCV-4, A, C, W, and Y) and serogroup B isolates targeted by novel protein-based vaccines (MenB). For *H. influenzae*, type b was considered vaccine preventable.

Statistical analysis

By using data from the Population Information System as denominators, we calculated pathogen- and age-specific annual incidence rates. Poisson regression was used to test for log-linear trend in rates of bacterial meningitis during 1995-2014. Incidence rate ratios (IRR), their 95% confidence intervals (CI) and p-values for yearly changes were calculated using time (year) as a continuous explanatory variable in the Poisson model. When appropriate, we used negative binomial regression to correct for overdispersion of data. To compare age distribution of cases across years we used Wilcoxon rank-sum test. To assess changes in case fatality proportion we used chi-square analyses; p-value <0.05 was considered statistically significant. All analyses were done with STATA version 13 (STATA Corp., Texas, USA) and Microsoft Excel 2013.

Ethical considerations

Data used in the analysis were collected as a part of surveillance and infection control activities which falls under the existing mandate of THL. Identification data (personal identity numbers, names, addresses) were removed after matching with vital status.

RESULTS

Overall incidence rates of bacterial meningitis

From 1995 to 2014, 1361 cases of bacterial meningitis caused by *S. pneumoniae*, *N. meningitidis*, *S. agalactiae*, *L. monocytogenes* or *H. influenzae* were reported (mean annual incidence rate, 1.29 cases/100000 population) (Table 1). *S. pneumoniae* and *N. meningitidis* were the most common etiologies accounting for 78% of cases (Table 2). The median age increased from 31 years in 1995-2004 to 43 years in 2005-2014 ($p<0.05$). Rates were higher in men than women (1.52 vs 1.07 cases/100000 population; IRR 1.42) (Table 2).

The annual rates of all bacterial meningitis ranged from 1.97 in 1996 to 0.7 cases/100000 population in 2014, with an annual decrease of 4% (95% CI: -3%; -5%) (Table 3). During 2004-2014, 65 patients died within 30 days from culture (CFP, 10%). There was no change in CFP from 2004-2009 (10.6%) to 2010-2014 (9.6%), p=0.22.

Characteristic of bacterial meningitis by age group

Children <2 years of age accounted for 20% of cases (268) and had the highest incidence rate (11.38 cases/100000 population) (Table 2). The most common pathogens in this age group were *S. agalactiae* (4.50 cases/100000 population) and *S. pneumoniae* (3.52 cases/100000 population) (Figure 1). From 1995 to 2014, the rate of bacterial meningitis in this age group decreased by 2% annually (95% CI: -4%; -1%) (Table 3). The average CFP in 2004-2014 was 2.1% (3 deaths). In children 2-4 years of age, 70 cases (5%) of bacterial meningitis were reported during 1995 to 2014; (1.94 cases/100000 population). The most common pathogens in this age group were *N. meningitidis* (1.33 cases/100000 population) and *S. pneumoniae* (0.5 cases/100000 population) (Table 2). During the study period, the rate of all meningitis did not change significantly (Table 3). The CFP in 2004-2014 was 14.2%; all 4 deaths were due to *N. meningitidis.*

Table 1. Annual incidence rates per 100000 population and number of cases of bacterial meningitis in Finland, 1995-2014

	1995	***1996***	***1997***	***1998***	***1999***	***2000***	***2001***	***2002***	***2003***	***2004***	***2005***	***2006***	***2007***	***2008***	***2009***	***2010***	***2011***	***2012***	***2013***	***2014***	***Mean 1995-2014***
S. pneumoniae	0.70	0.64	0.58	0.68	0.70	0.52	0.62	0.52	0.90	0.67	0.53	0.63	0.49	0.71	0.67	0.48	0.46	0.44	0.42	0.26	0.58
	(36)	(33)	(30)	(35)	(36)	(27)	(32)	(27)	(47)	(35)	(28)	(33)	(27)	(37)	(36)	(26)	(25)	(24)	(23)	(14)	(611)
N. meningitidis	0.88	0.95	0.60	0.72	0.60	0.46	0.42	0.52	0.40	0.38	0.42	0.55	0.45	0.17	0.24	0.22	0.20	0.22	0.13	0.07	0.43
	(45)	(49)	(31)	(37)	(31)	(24)	(22)	(27)	(21)	(20)	(22)	(29)	(24)	(9)	(13)	(12)	(11)	(12)	(7)	(4)	(450)
S. agalactiae	0.06	0.23	0.04	0.17	0.12	0.15	0.10	0.15	0.04	0.23	0.13	0.17	0.25	0.09	0.13	0.24	0.06	0.09	0.06	0.17	0.13
	(3)	(12)	(2)	(9)	(6)	(8)	(5)	(8)	(2)	(12)	(7)	(9)	(13)	(5)	(7)	(13)	(3)	(5)	(3)	(9)	(141)
L. monocytogenes	0.18	0.10	0.14	0.21	0.06	0.08	0.08	0.04	0.11	0.06	0.08	0.09	0.06	0.06	0.07	0.13	0.09	0.09	0.09	0.11	0.10
	(9)	(5)	(7)	(11)	(3)	(4)	(4)	(2)	(6)	(3)	(4)	(5)	(3)	(3)	(4)	(7)	(5)	(5)	(5)	(6)	(101)
H. influenzae	0.06	0.04	0.06	0.12	0.08	0.06	0.12	0.04	0.06	0.02	0.04	0.04	0.04	0.08	0.06	0.00	0.07	0.02	0.04	0.09	0.06
	(3)	(2)	(3)	(6)	(4)	(3)	(6)	(2)	(3)	(1)	(2)	(2)	(2)	(4)	(3)	(0)	(4)	(1)	(2)	(5)	(58)
Total rate	1.88	1.97	1.42	1.90	1.55	1.27	1.33	1.27	1.51	1.36	1.20	1.48	1.28	1.11	1.18	1.08	0.89	0.87	0.73	0.70	1.29
Total number	(96)	(101)	(73)	(98)	(80)	(66)	(69)	(66)	(79)	(71)	(63)	(78)	(69)	(58)	(63)	(58)	(48)	(47)	(40)	(38)	(1361)

Table 2. Characteristics of bacterial meningitis cases in Finland, 1995-2014

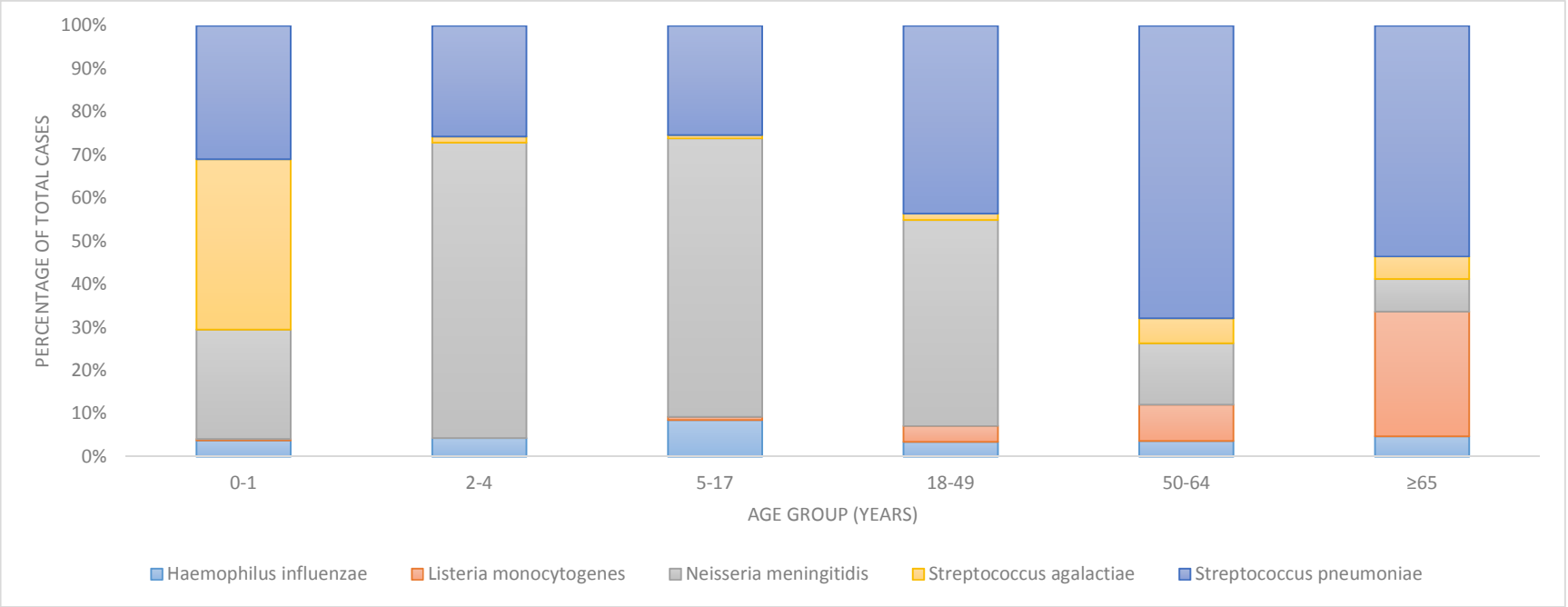
Characteristic	***S. pneumoniae***	***N. meningitidis***	***S. agalactiae***	***L. monocytogenes***	***H. influenzae***	**Total bacteria**
Number of cases (% of total)	611 (45)	450 (33)	141 (10)	101 (8)	58 (4)	1361 (100)
Mean annual incidence rate (per 100000 population)						
<2 years	3.52	2.89	4.50	0.04	0.42	11.38
2-4 years	0.50	1.33	0.03	0.00	0.08	1.94
5-17 years	0.20	0.52	0.01	0.01	0.07	0.80
18-49 years	0.40	0.43	0.01	0.03	0.03	0.91
50-64 years	0.88	0.18	0.08	0.11	0.05	1.30
≥65 years	0.66	0.09	0.06	0.35	0.06	1.23
Overall	0.58	0.43	0.13	0.10	0.06	1.29
Gender Number of cases (% of total)						
Male	347 (57)	268 (60)	70 (50)	71 (70)	28 (48)	784 (58)
Female	264 (43)	182 (40)	71 (50)	30 (30)	30 (52)	577 (42)
Age						
IQR	28-62	4-35	0	56-74	6-54	5-58
Mean	43	22	15	64	32	34
Median	48	18	0	68	29	36
Case fatality*						
No of deaths (No of cases)	38 (308)	14 (163)	2 (86)	11 (50)	0 (26)	65 (633)
Case fatality proportion (%)	12.3	8.6	2.3	22	0	10.3

*Data are for cases reported during 2004-2014

Table 3. Relative change in mean incidence (95% CI) of bacterial meningitis in Finland, 1995-2014

	Slope (95% CI)	p value
Age group (years)		
<2	-2 (-4; -1)	0.022
2-4	-5 (-10; 0)	0.054
5-17	-8 (-12; -4)	0.000
18-49	-7 (-8; -5)	0.000
50-64	-4 (-6; -2)	0.001
≥65	-1 (-4; 1)	0.324
Overall	-4 (-3; -5)	0.000
Pathogen		
S. pneumoniae	-2 (-4; -1)	0.001
S. agalactiae	0 (-3; 3)	0.975
H. influenzae	-2 (-7; 2)	0.299
N. meningitidis	-9 (-10; -7)	0.000
L. monocytogenes	-2 (-5; 1)	0.201

Figure 1. Proportions of bacterial meningitis cases caused by each pathogen according to age group in Finland. 1995-2014



Children 5-17 years of age accounted for 130 cases (9%) of bacterial meningitis and had the lowest rate (0.8 cases/100000 population) (Table 2). *N. meningitidis* and *S. pneumoniae* were the main causes (0.52 and 0.20 cases/100000 population, respectively) (Figure 1). From 1995 to 2014 the rate of bacterial meningitis decreased by 8% annually (95% CI: -12%; -4%) (Table 3). The CFP was 6.7%; all 3 fatal cases were due to *N. meningitidis*.

Adults 18-49 years of age accounted for 408 cases (30%) of bacterial meningitis (0.91 cases/100000 population) (Table 2). *N. meningitidis* and *S. pneumoniae* caused most of the cases (Figure 1); incidence rates, 0.43 and 0.40 cases/100000 population, respectively. During 1995-2014, the overall rate decreased by 7% annually (95% CI: -8%; -5%) (Table 3). The CFP was 8.5% (13 deaths), with 9 deaths due to *S. pneumoniae* infection.

Among persons 50-64 years of age there were 274 cases (20%) of bacterial meningitis (1.30 cases/100000 population) (Table 2), of which 186 cases (68%) were caused by *S. pneumoniae* (0.88 cases/100000 population) (Figure 1). During the study period, the overall rate decreased by 4% annually (95% CI: -6%; -2%) (Table 3). The CFP was 12.6% (18 deaths), with most fatal cases attributable to *S. pneumoniae* (16 deaths).

In adults ≥65 years of age, there were 211 cases (15%) of bacterial meningitis (1.23 cases/100000 population) (Table 2). *S. pneumoniae* caused 53% (113) of the cases (0.66 cases/100000 population), followed by *L. monocytogenes*. There was no significant change in the overall rate during 1995-2014 (Table 3). This age group had the highest CFP (19.2%, 24 deaths). Half of the fatal cases were due to *S. pneumoniae* (12 deaths); *L. monocytogenes* caused 10 deaths.

Causes of bacterial meningitis

Streptococcus pneumoniae

From 1995 to 2014, 611 cases of pneumococcal meningitis were reported. Median age was 48 years; 57% of cases were male (male-to-female IRR, 1.4) (Table 2). The overall annual rate per 100000 population

decreased from 0.70 in 1995 to 0.26 in 2014 (Figure 2), a 2% annual decrease (95% CI: -4%; -1%) (Table 3). The incidence of pneumococcal meningitis decreased annually by 4% (95% CI: -7%; 0%), 7% (95% CI: -13%; -1%) and 4% (95% CI: -6%; -1%) in age groups <2 years, 5-17 years and 18-49 years, respectively. During 2004-2014, *S. pneumoniae* accounted for 58% of fatal cases; (CFP 12.3%).

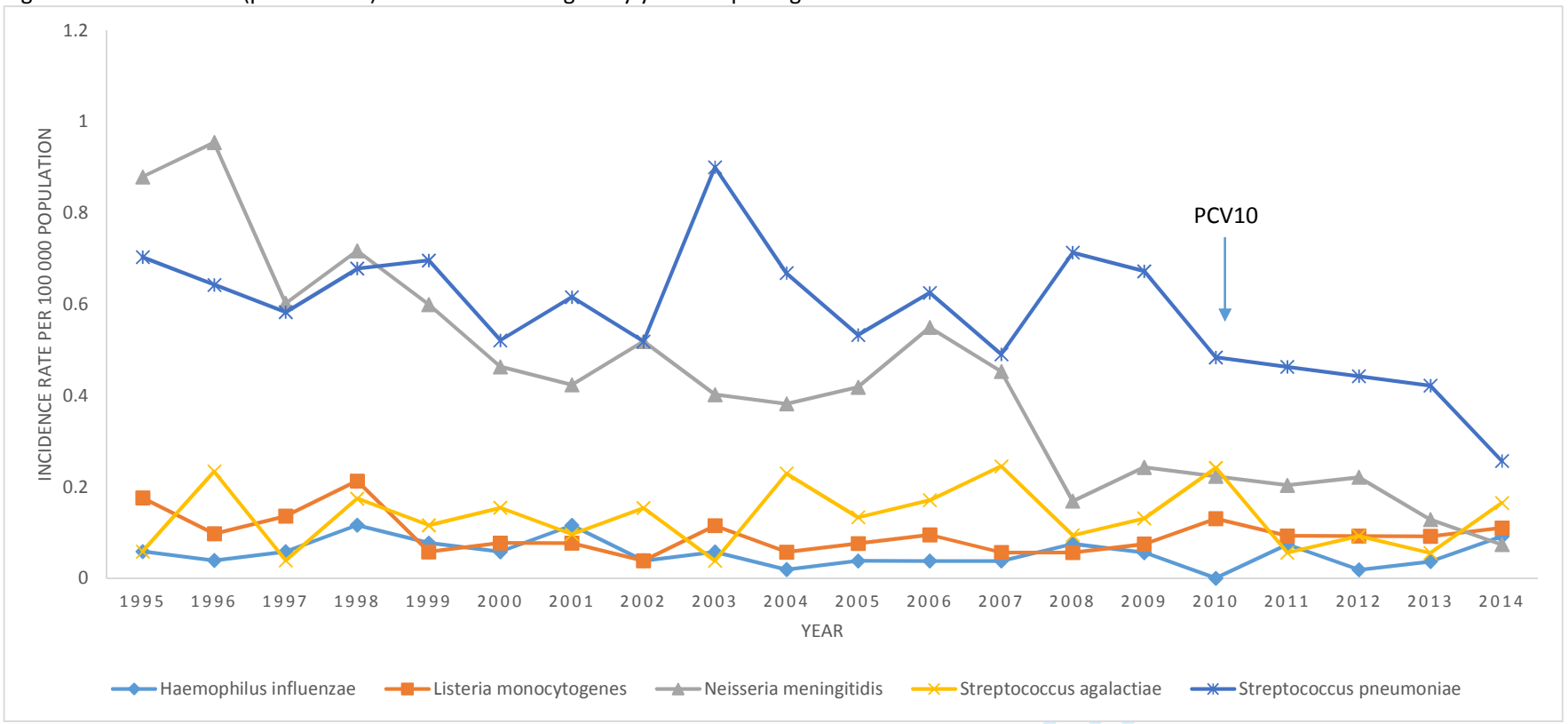
Of the 308 pneumococcal meningitis cases reported during 2004-2014, information on serotype was available for 296 (96%). The proportion of cases caused by PCV10 serotypes decreased from 61% (35/57) in 2004-2005 to 15% (9/36) in 2013-2014. PCV13 serotypes accounted for 70% (40/57) cases in 2004-2005 and 44% (16/36) in 2013-2014. In children less than 2 years, proportion of meningitis cases caused by PCV10 serotypes decreased from 75% (9/12) in 2004-2005 to 20% (1/5) in 2013-2014. In 2014, no meningitis cases were caused by PCV10 serotypes.

Neisseria meningitidis

During the study period, meningococcal meningitis accounted for 450 cases (0.43 cases/100000 population) (Table 1). Median age was 18 years and 60% of cases were male (male-to-female IRR 1.5) (Table 2). The overall annual incidence per 100000 decreased from 0.88 in 1995 to 0.07 in 2014; the annual decrease was -9% (95% CI: -7%; -10%) (Table 3). The decline occurred in all age-groups except in <2 years and ≥65 years of age. The incidence decreased annually by 6% (95%CI: -1%; -10%), 8% (95% CI: -3%; -14%), 10% (95% CI: -8%; -13%) and 12% (95% CI: -8%; -13%) in age groups 2-4 years, 5-17 years, 18-49 years and 50-64 years, respectively. The overall CFP was 8.6% (14 deaths) and ranged from 3% among children 0-1 year old to 12% among 2-4 year olds.

During 2004-2014, information on *N. meningitidis* serogroups was available for 161 isolates (99% of cases). Serogroup B accounted for 85% (n=137) of isolates, C 11% (n=17), and Y 4% (n=7). In children <2 years, serogroup B caused 96% of cases. MCV-4 and MenB vaccine serogroups caused 15% and 85% of all cases, respectively.

Figure 2. Incidence rate (per 100 000) of bacterial meningitis by year and pathogen in Finland. 1995-2014



Haemophilus influenzae

From 1995 to 2014, 58 cases of *H. influenzae* were reported (0.06 cases/100000 population) (Table 1). Median age was 29 years and male-to-female IRR was 1.0 (Table 2). The incidence rate ranged from 0.0 cases per 100 000 population in 2010 to 0.25 cases in 2007 (Figure 2). Rates in all age groups were stable. From 2004 to 2014, there were no deaths due to *H. influenzae*.

In 2004-2014, non-encapsulated *H. influenzae* accounted for 69% (n=18) of isolates, serotype f 23% (n=6) and type b 8% (n=2).

Streptococcus agalactiae

Infection with *S. agalactiae* accounted for 141 cases of meningitis (0.13 cases/100000 population), including 24 early onset cases and 78 late onset cases (Table 1). The median age of cases was 30 days; male-to-female IRR was 1.03 (Table 2). During the study period annual rates ranged from 0.06 cases/100000 population in 1995, to 0.17 cases in 2014 (Figure 2) but overall rates of *S. agalactiae* did not change significantly (p=0.97) (Table 3). During 2004-2014, the CFP was 2% (2 deaths).

Listeria monocytogenes

During the study period, *L. monocytogenes* caused 101 cases of meningitis (0.13 cases/100000 population), mostly among elderly persons (median age, 68 years). Of cases, 70% were men (male-to-female IRR 2.5) (Table 2). Rates of listeria meningitis ranged from 0.04 cases/100000 population in 2002 to 0.21 in 1998 (Table 1). However, there was no significant trend during 20 years (Table 3). The overall CFP was 22% (11 deaths) and 28% in persons ≥65 years of age.

DISCUSSION

During 1995-2014, the most common causes of bacterial meningitis in Finland were *S. pneumoniae* and *N. meningitidis*. However, contribution of specific pathogens to the disease burden varied substantially by age. As in other developed countries, *S. agalactiae* was the most common cause of bacterial meningitis in children <1 years of age [6]. The mean age of cases increased significantly during the study period mainly because of the decrease in incidence in children associated with infant HiB and pneumococcal conjugate vaccine programs.

During the study period, significant declines were seen in overall incidence of bacterial meningitis - primarily due to decreases in rates of *N. meningitis* and *S. pneumoniae*. Of interest, the decrease in incidence of *N. meningitidis* was greater than for pneumococcal meningitis, although there is no routine vaccination program for meningococcal disease in Finland. Decreases in rates of meningococcal meningitis before introduction of adolescent vaccination with MCV4 were observed also in the US during 1998-2007 [18]. Several factors, such as secular trends, reduction in the prevalence of smoking and crowding have been hypothesized as contributors to decline in incidence [19]. Introduction of conjugate vaccination has changed the epidemiology of meningococcal disease in many countries. After the introduction of conjugate serogroup C meningococcal vaccine, vaccine serogroup disease nearly disappeared in the Netherlands [20] and England [21]. Declines were also observed in other European countries including Spain, Ireland and Belgium [22]. Reduced carriage and transmission of *N. meningitidis* serogroup C to unvaccinated population indicating herd immunity was also observed [23]. Consistent with reports from Europe and the US [24-25], serogroup B was the most common cause of meningococcal meningitis in Finland (85%). Immunization of high risk groups with recently licensed protein-based vaccines targeted against meningococcal serogroup B might also be considered in Finland. However, updated cost-effectiveness analysis is needed for decision-making about introduction of meningococcal vaccination programs.

The decline in pneumococcal meningitis incidence in children <2 years of age was associated with introduction of PCV10 in the National Vaccination Programme in 2010 [17]; PCV10 serotypes in this age

group were significantly reduced and, by 2014 no vaccine serotype meningitis cases were reported. In vaccine-eligible children, the overall rate of pneumococcal meningitis was reduced by 46% as a result of a 69% reduction in PCV10-type meningitis [17]. Many studies in the U.S. and Europe have also documented significant declines in the incidence of pneumococcal meningitis in both vaccinated and unvaccinated groups after introduction of PCV programmes [13-14, 26-28]. In Finland, it might be possible to achieve further reductions with higher valency conjugate vaccine formulations.

The incidence rate of *L. monocytogenes*, *N. meningitidis* and *S. pneumoniae* was higher in men than women. The rate difference was largest for *L. monocytogenes* meningitis; cases were 2.5 times as likely to be men. Higher rates in males have also been observed in other studies [7], possibly because of higher prevalence of underlying conditions such as smoking and alcoholism in pneumococcal disease [29]. As listeriosis is primarily transmitted through contaminated food, important prevention efforts include health education about dietary guidelines for high risk groups, such as pregnant women and the elderly [30].

The overall case-fatality proportion for meningitis did not change significantly during 1995-2014. However, the unchanged CFP may be related to the altered age distribution of cases. Older age is associated with higher risk of poor outcome [31]. In addition, pathogen distribution has changed and the case-fatality for meningococcal meningitis is lower compared with pneumococcal meningitis. The small number of fatal cases in our study did not allow to assess changes in CFP by age group and pathogen. However, the larger proportion of older cases and decrease in meningococcal meningitis rates may both have contributed to increase in overall CFP. The CFP was highest for *L. monocytogenes* (22%), which is comparable to results from the Netherlands and Spain [7, 32]. Most of the fatal cases of bacterial meningitis in persons ≥50 years were attributable to *S. pneumoniae*. Cases who had pneumococcal meningitis were older than those who were infected with other encapsulated bacteria and likely had high prevalence of comorbidities increasing the risk of pneumococcal infection and poor outcome [33]. The relatively high case fatality proportion emphasizes the importance of immediate initiation of treatment and supportive care after diagnosis to improve outcome of bacterial meningitis.

As expected, *H. influenzae* was the least common cause of bacterial meningitis. However, the stable number of cases over 20 years suggest existence of small group of individuals with risk factors for *H. influenzae* (such as chronic respiratory disease and impaired immunity) [34]. Conjugate vaccination has nearly eliminated *H. influenzae* type b meningitis in many high-income countries [35-36]. However, changes in the epidemiology of invasive *H. influenzae* have been observed and currently most cases occur in adults [37] and non-encapsulated, non-typable *H. influenzae* (ncHi) have dominated since 2004.

Our study has several limitations. As the data were from laboratory-based surveillance system, information on clinical presentation or treatment was not available. Therefore, culture-negative meningitis cases diagnosed on the basis of clinical symptoms and findings were not included in the analysis dataset. In addition, cases diagnosed by PCR or antigen detection were not included. As CSF cultures are negative in 11%–30% of patients with bacterial meningitis [38], the total number of meningitis cases is underestimated. Another limitation is that NIDR database does not include information on the cause of death. However, in an earlier study in Finland, most deaths associated with invasive bacterial infection occurred early, suggesting that they were related to the infection [39].

In conclusion, this study describes the epidemiologic characteristics of >1300 cases of bacterial meningitis reported to national surveillance over 20 years. It documents the population impact of infant conjugate vaccination against Hib and *S. pneumoniae*, as well as secular trends in meningococcal meningitis on reduced burden of bacterial meningitis. However, disease burden had shifted to older people and no changes in the overall proportion of fatal cases were seen. Data on changes in causative organisms and age distribution for meningitis cases are important for evaluating clinical guidelines for empiric antibiotic therapy in bacterial meningitis. Continued epidemiological surveillance is necessary to monitor changing trends and serotype distribution, assessing the impact of vaccination programs and developing future vaccination strategies.

Contributors: Study concept and design: AP, OL, PN Acquisition of data: MT, JO, OL, PN; Analysis and interpretation of data: AP, MT, JO, OL, PN; Drafting of the manuscript: AP, PN; Critical revision of the manuscript for important intellectual content: AP, MT, JO, OL, PN; Statistical analysis: AP, JO; Obtained funding: PN; Study supervision: PN; Final approval: AP, MT, JO, OL, PN

Competing interests: None declared.

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Ethics approval: Data used in the analysis were collected as a part of surveillance and infection control activities which falls under the existing mandate of the National Institute for Health and Welfare (THL).

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Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	4		
Objectives	3	State specific objectives, including any prespecified hypotheses	4		
Methods					
Study Design	4	Present key elements of study design early in the paper	5		

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	5 NA NA	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	5 NA NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	5,6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	5,6
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	5		

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Bias	9	Describe any efforts to address potential sources of bias	18		
Study size	10	Explain how the study size was arrived at	5		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5,6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	6		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	5,6

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Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	7-15 NA NA	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	7-15
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Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	NA

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BMJ Open

Bacterial meningitis in Finland, 1995-2014: a population-based observational study

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Date Submitted by the Author:	13-Mar-2017
Complete List of Authors:	Polkowska, Aleksandra; University of Tampere, School of Health Sciences Toropainen, Maija; National Institute for Health and Welfare, Department of Infectious Diseases Ollgren, Jukka; National Institute for Health and Welfare, Department of Infectious Diseases Lyytikainen, Outi; National Institute for Health and Welfare, Department of Infectious Diseases Nuorti, Pekka; University of Tampere, School of Health Sciences; National Institute for Health and Welfare, Department of Infectious Diseases
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Epidemiology
Keywords:	EPIDEMIOLOGY, Epidemiology < INFECTIOUS DISEASES, meningitis

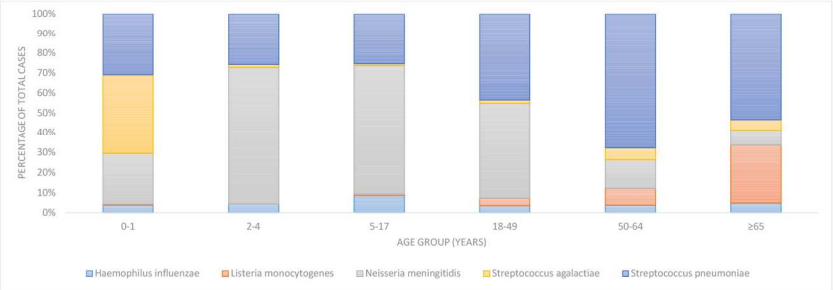

Figure 1. Proportions of bacterial meningitis cases caused by five pathogens according to age group, Finland, 1995-2014

173x122mm (300 x 300 DPI)

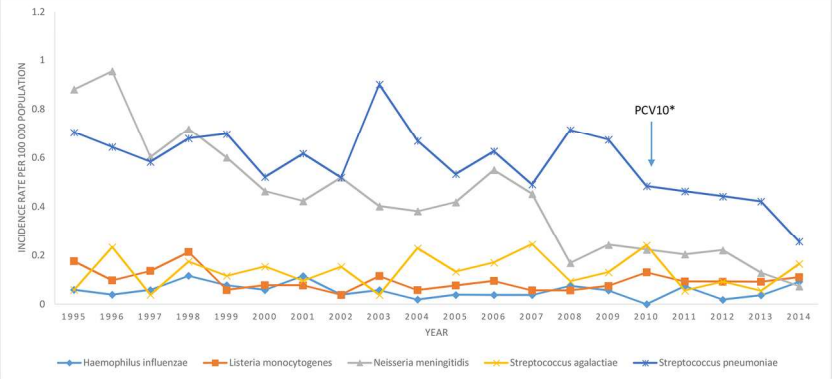

Figure 2. Incidence rate (per 100,000 person-years) of bacterial meningitis by year and pathogen, Finland, 1995-2014

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Bacterial meningitis in Finland, 1995-2014:

a population-based observational study

ALEKSANDRA POLKOWSKA[1], MAIJA TOROPAINEN[2], JUKKA OLLGREN[2], OUTI LYYTIKÄINEN[2], J. PEKKA NUORTI[1,2]

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Word count: 3126

ABSTRACT

Objectives: Bacterial meningitis remains an important cause of morbidity and mortality worldwide. Its epidemiologic characteristics, however, are changing due to new vaccines and secular trends. Conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (10-valent) were introduced in 1986 and 2010 in Finland. We assessed the disease burden and long-term trends of five common causes of bacterial meningitis in a population-based observational study.

Methods: A case was defined as isolation of *S. pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Listeria monocytogenes* or *H. influenzae* from cerebrospinal fluid and reported to national, population-based laboratory surveillance system during 1995-2014. We evaluated changes in incidence rates (Poisson or negative binomial regression), case-fatality proportions (chi-square) and age distribution of cases (Wilcoxon rank-sum).

Results: During 1995-2014, *S. pneumoniae* and *N. meningitidis* accounted for 78% of the total 1361 reported bacterial meningitis cases. *H. influenzae* accounted for 4% of cases (92% of isolates were non-type b). During the study period, the overall rate of bacterial meningitis per 100,000 person-years decreased from 1.88 cases in 1995 to 0.70 cases in 2014 (4% annual decline (95% Confidence Interval (CI) 3-5%). This was primarily due to a 9% annual reduction in rates of *N. meningitidis* (95% CI: 7-10%) and 2% decrease in *S. pneumoniae* (95% CI: 1-4%). The median age of cases increased from 31 years in 1995-2004 to 43 years in 2005-2014 (p=0.0004). Overall case-fatality proportion (10%) did not change from 2004-2009 to 2010-2014 (p=0.22).

Conclusions: Substantial decreases in bacterial meningitis were associated with infant conjugate vaccination against pneumococcal meningitis and secular trend in meningococcal meningitis in the absence of vaccination program. Ongoing epidemiological surveillance is needed to identify trends, evaluate serotype distribution, assess vaccine impact and to develop future vaccination strategies.

Strengths and limitations of this study:

- This study describes the epidemiologic characteristic of >1300 cases of bacterial meningitis reported to national surveillance during 20 years in Finland.
- The study provides clinically important information on the changing distribution of pathogens and age of cases.
- The study documents the sustained population impact of infant conjugate vaccination against *Haemophilus influenzae* type b; and introduction of 10- valent pneumococcal conjugate vaccination on reducing the burden of bacterial meningitis, as well as decline in meningococcal meningitis due to secular trend. As the data were from laboratory-based surveillance system, clinical information such as severity or treatment was not available.
- Incidence rate of bacterial meningitis may be underestimated since cases diagnosed by PCR or antigen detection and culture-negative meningitis cases diagnosed based on clinical symptoms and findings were not included in the analysis dataset.

INTRODUCTION

Despite the availability of vaccines, antibiotics and advances in intensive care, bacterial meningitis remains an important cause of morbidity and mortality worldwide. Persistent neurological sequelae including hearing loss, neuropsychological impairment or seizures are reported in 10-30% of survivors [1]. The case fatality proportion ranges from 5% to 30% for different bacteria [2-3].

Globally, *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* are the most important causes of bacterial meningitis, particularly in young children [4-5]. Among neonates the most common cause of bacterial meningitis is *Streptococcus agalactiae* [2, 6], while *Listeria monocytogenes* is important in newborns and elderly persons with comorbidities [7]. However, the leading organisms causing bacterial meningitis vary by age of the patient, time and geographical location [5]. As the choice of empiric antimicrobial treatment for bacterial meningitis should be based on local epidemiology, patient's age, presence of risk factors and regional resistance patterns [8-10], population-based surveillance data are important to help in formulating clinical guidelines.

The introduction of effective protein conjugate vaccines against *H. influenzae* type b (Hib), *S. pneumoniae* and *N. meningitidis* has changed the epidemiology of bacterial meningitis in many countries [11-12]. In Finland, universal vaccination against Hib since 1986 resulted in rapid elimination of the disease [13] and introduction of the ten-valent pneumococcal conjugate vaccine (PCV10) in September 2010 has resulted in substantial reduction in vaccine-type invasive disease [14-15]. Meningococcal conjugate vaccines have not been introduced into Finnish National Vaccination Programme (NVP). However, meningococcal polysaccharide vaccine has been offered to military conscripts since 1982.

To provide information for developing future prevention strategies and to help in formulating clinical guidelines, we conducted a population-based observational study to determine the contribution of specific pathogens to the total bacterial meningitis disease burden and to assess long-term trends in the incidence of common etiologies in Finland during 1995-2014.

MATERIALS AND METHODS

Data sources

Since 1995, all clinical microbiology laboratories in Finland have had legal obligation to report microbial isolations from blood and/or cerebrospinal fluid (CSF) to the National Infectious Diseases Register (NIDR) - a population-based, electronic laboratory surveillance system maintained by the National Institute for Health and Welfare (THL). Routinely collected information include: the microbe, specimen date, date of birth, sex, place of residence and unique Personal Identity Code (PIC). For blood or CSF findings concerning *S. pneumoniae*, *S. agalactiae*, *N. meningitidis*, *L. monocytogenes*, or *H. influenzae*, multiple notifications with the same PIC and microbe are merged into one case if they occurred within 3 months of the first notification. Since 2004, information on vital status after episode is routinely obtained from the Population Information System. All clinical microbiology laboratories also submit isolates from reported cases to THL reference laboratories for species verification and characterization of the isolates including serotyping or serogrouping. Since 2004, serotyping results are linked to NIDR notifications by using the PIC. Antimicrobial susceptibility data were not available.

Case definitions

We defined a case of bacterial meningitis as isolation of *S. pneumoniae*, *S. agalactiae*, *N. meningitidis*, *L. monocytogenes* or *H. influenzae* from CSF and notified to NIDR from 1995 through 2014.

For cases reported during 2004-2014, we calculated the pathogen-specific 30-day case fatality proportion (CFP) as number of cases resulting to death within 30 days from the first positive CSF culture, divided by all cases.

We calculated the proportions of *S. pneumoniae*, *N. meningitidis* and *H. influenzae* cases due to vaccine-preventable serotypes/serogroups during 2004-2014. Serotypes covered in PCV10 are: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F; the 13-valent pneumococcal conjugate vaccine (PCV13) adds serotypes 3, 6A, and 19A. Vaccine-preventable meningococcal serogroups include those in the quadrivalent meningococcal

conjugate vaccine (MCV-4, A, C, W, and Y) and serogroup B isolates targeted by novel protein-based vaccines (MenB). For *H. influenzae*, type b was considered vaccine preventable.

Statistical analysis

By using data from the Population Information System as denominators, we calculated pathogen- and age-specific annual incidence rates. Poisson regression was used to test for log-linear trend in rates of bacterial meningitis during 1995-2014. Incidence rate ratios (IRR), their 95% confidence intervals (CI) and p-values for yearly changes were calculated using time (year) as a continuous explanatory variable in the Poisson model. When appropriate, we used negative binomial regression to correct for overdispersion of data. To compare age distribution of cases across years we used Wilcoxon rank-sum test. To assess changes in case fatality proportion we used chi-square analyses; p-value <0.05 was considered statistically significant. All analyses were done with STATA version 13 (STATA Corp., Texas, USA) and Microsoft Excel 2013.

Ethical considerations

Data used in the analysis were collected as a part of national routine surveillance which falls under the existing mandate of THL. No formal Institutional Review Board (IRB) review was required for this study. Personal identifiers were removed after linkage with vital status data.

RESULTS

Overall incidence rates of bacterial meningitis

From 1995 to 2014, 1361 cases of bacterial meningitis caused by *S. pneumoniae*, *N. meningitidis*, *S. agalactiae*, *L. monocytogenes* or *H. influenzae* were reported (mean incidence rate, 1.29 cases/100,000 person-years) (Table 1). *S. pneumoniae* and *N. meningitidis* were the most common etiologies accounting for 78% (1061/1361) of cases. The median age of cases increased from 31 years in 1995-2004 to 43 years in 2005-2014 (p=0.0004). Rates were higher in men than women (1.52 vs 1.07 cases/100,000 person-years; IRR 1.42).

The mean annual rates of all bacterial meningitis ranged from 1.97 in 1996 to 0.70 cases/100,000 person-year in 2014, with an annual decrease of 4% (95% CI: -3%; -5%) (Table 1). During 2004-2014, 65 patients died within 30 days from culture (CFP, 10% (65/633)). There was no change in 30-day CFP from 2004-2009 (11% (43/402) to 2010-2014 (10% (22/231), p=0.22.

Characteristic of bacterial meningitis by age group

Children <2 years of age accounted for 20% of cases (268/1361) and had the highest incidence rate (11.38 cases/100,000 person-years) (Table 1). The most common pathogens in this age group were *S. agalactiae* (4.50 cases/100,000 person-years) and *S. pneumoniae* (3.52 cases/100,000 person-years) (Figure 1). From 1995 to 2014, the rate of bacterial meningitis in this age group decreased by 2% annually (95% CI: -4%; -1%) (Table 1). The average 30-day CFP in 2004-2014 was 2% (3/140). In children 2-4 years of age, 70 cases (5%) of bacterial meningitis were reported during 1995 to 2014; (1.94 cases/100,000 person-years). The most common pathogens in this age group were *N. meningitidis* (1.33 cases/100,000 person-years) and *S. pneumoniae* (0.50 cases/100,000 person-years) (Table 1). During the study period, the rate of all meningitis did not change significantly (Table 1). The 30-day CFP in 2004-2014 was 14% (4/128); all 4 deaths were due to *N. meningitidis.*

Table 1. Number of cases (N), incidence rates per 100,000 person-years (IR) and mean annual relative change in incidence of bacterial meningitis, according to age group (years), Finland, 1995-2014

	1995-1999		2000-2004		2005-2009		2010-2014		1995-2014		1995-2014	
Streptococcus pneumoniae	N	IR	N	IR	N	IR	N	IR	N	IR	% Change*	95% CI
<2	26	4.32	25	4.43	18	3.05	14	2.33	83	3.52	-4	-7; 0
2-4	6	0.63	3	0.35	6	0.69	3	0.33	18	0.50	-1	-8; 7
5-17	13	0.31	11	0.26	7	0.17	2	0.05	33	0.20	-7	-13; 1
18-49	59	0.50	54	0.48	35	0.32	30	0.27	178	0.40	-4	-6; 1
50-64	41	0.91	52	1.00	56	0.99	37	0.65	186	0.88	-2	-4; 1
≥65	25	0.67	23	0.57	39	0.89	26	0.51	113	0.66	-1	-4; 2
All age groups	170	0.55	168	0.65	161	0.61	112	0.41	611	0.58	-2	-4; 1
Neisseria meningitidis												
<2	23	3.83	23	4.07	8	1.36	14	2.33	68	2.89	-4	-8; 0
2-4	19	1.98	11	1.27	12	1.38	6	0.66	48	1.33	-6	-10; -1
5-17	37	0.88	16	0.38	24	0.60	7	0.18	84	0.52	-8	-14; -3
18-49	93	0.79	46	0.41	42	0.38	14	0.13	195	0.43	-10	-13; -8
50-64	15	0.33	15	0.29	7	0.12	2	0.04	39	0.18	-12	-17; -6
≥65	6	0.16	3	0.07	4	0.09	3	0.06	16	0.09	-7	-14; 2
All age groups	193	0.62	114	0.44	97	0.37	46	0.17	450	0.43	-9	-10; -7
Haemophilus influenzae												
<2	4	0.67	3	0.53	2	0.34	1	0.17	10	0.42	-7	-17; 4
2-4	0	0.00	3	0.35	0	0.00	0	0.00	3	0.08	NA	NA
5-17	5	0.12	4	0.10	0	0.00	2	0.05	11	0.07	-8	-17; 3
18-49	4	0.03	2	0.02	2	0.02	6	0.05	14	0.03	5	-5; 15
50-64	3	0.07	3	0.06	2	0.04	2	0.04	10	0.05	-3	-13; 8
≥65	2	0.05	0	0.00	7	0.16	1	0.02	10	0.06	1	-9; 12
All age groups	18	0.06	15	0.06	13	0.05	12	0.04	58	0.06	-2	-7; 2
Streptococcus agalactiae												
<2	25	4.16	24	4.25	32	5.43	25	4.16	106	4.50	0	-3; 5
2-4	1	0.10	0	0.00	0	0.00	0	0.00	1	0.03	NA	NA
5-17	0	0.00	1	0.02	0	0.00	0	0.00	1	0.01	NA	NA
18-49	2	0.02	1	0.01	1	0.01	2	0.02	6	0.01	1	-12; 16
50-64	4	0.09	2	0.04	7	0.12	3	0.05	16	0.08	1	-9; 8
≥65	0	0.00	7	0.17	1	0.02	3	0.06	11	0.06	-2	-11; 9
All age groups	32	0.10	35	0.13	41	0.15	33	0.12	141	0.13	0	-3; 3
Listeria monocytogenes												
<2	1	0.17	0	0.00	0	0.00	0	0.00	1	0.04	NA	NA
2-4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	NA	NA
5-17	1	0.02	0	0.00	0	0.00	0	0.00	1	0.01	NA	NA
18-49	9	0.08	3	0.03	0	0.00	3	0.03	15	0.03	-11	-19; -3
50-64	10	0.22	3	0.06	6	0.11	4	0.07	23	0.11	-6	-13; 1
≥65	14	0.37	13	0.32	13	0.30	21	0.42	61	0.35	0	-4; 4
All age groups	35	0.11	19	0.07	19	0.07	28	0.10	101	0.10	-2	-5; 1
Total bacteria meningitis												
<2	79	13.14	75	13.28	60	10.18	54	8.99	268	11.38	-2	-4,-1
2-4	26	2.71	17	1.97	18	2.07	9	0.98	70	1.94	-5	-10; 0
5-17	56	1.33	32	0.77	31	0.77	11	0.28	130	0.80	-8	-12; -4
18-49	167	1.43	106	0.94	80	0.73	55	0.50	408	0.91	-7	-8; -5
50-64	73	1.63	75	1.44	78	1.37	48	0.84	274	1.30	-4	-6; -2
≥65	47	1.25	46	1.15	64	1.46	54	1.07	211	1.23	-1	-4; 1
All age groups	448	1.45	351	1.35	331	1.25	231	0.85	1361	1.29	-4	-3; -5

NA- not applicable

*Mean annual relative change in incidence calculated by Poisson regression or negative binomial regression.

Children 5-17 years of age accounted for 130 cases (9%) of bacterial meningitis and had the lowest rate (0.80 cases/100,000 person-years) (Table 1). *N. meningitidis* and *S. pneumoniae* were the main causes (0.52 and 0.20 cases/100,000 person-years, respectively) (Figure 1). From 1995 to 2014 the rate of bacterial meningitis decreased by 8% annually (95% CI: -12%; -4%) (Table 1). The 30-day CFP was 7% (3/45); all 3 fatal cases were due to *N. meningitidis*.

Adults 18-49 years of age accounted for 408 cases (30%) of bacterial meningitis (0.91 cases/100,000 person-years) (Table 1). *N. meningitidis* and *S. pneumoniae* caused most of the cases (Figure 1); incidence rates, 0.43 and 0.40 cases/100,000 person-years, respectively. During 1995-2014, the overall rate decreased by 7% annually (95% CI: -8%; -5%) (Table 1). The 30-day CFP was 8% (13/152), with 9 deaths due to *S. pneumoniae* infection.

Among persons 50-64 years of age there were 274 cases (20%) of bacterial meningitis (1.30 cases/100,000 person-years) (Table 1), of which 186 cases (68%) were caused by *S. pneumoniae* (0.88 cases/100,000 person-years) (Figure 1). During the study period, the overall rate decreased by 4% annually (95% CI: -6%; -2%) (Table 1). The 30-day CFP was 13% (18/143), with most fatal cases attributable to *S. pneumoniae* (16 deaths).

In adults ≥65 years of age, there were 211 cases (15%) of bacterial meningitis (1.23 cases/100,000 person-years) (Table 1). *S. pneumoniae* caused 53% (113/211) of the cases (0.66 cases/100,000 person-years), followed by *L. monocytogenes*. There was no significant change in the overall rate during 1995-2014 (Table 1). This age group had the highest 30-day CFP (19%, 24/125). Half of the fatal cases were due to *S. pneumoniae* (12 deaths); *L. monocytogenes* caused 10 deaths.

Causes of bacterial meningitis

Streptococcus pneumoniae

From 1995 to 2014, 611 cases of pneumococcal meningitis were reported. Median age was 48 years; 57% of cases were male (male-to-female IRR, 1.4) (Table 2). The overall annual rate per 100,000 person-years

Table 2. Characteristics of bacterial meningitis cases, Finland, 1995-2014

Characteristic	***S. pneumoniae***	***N. meningitidis***	***S. agalactiae***	***L. monocytogenes***	***H. influenzae***	**Total**
Gender Number of cases (% of total)						
Male	347 (57)	268 (60)	70 (50)	71 (70)	28 (48)	784 (58)
Female	264 (43)	182 (40)	71 (50)	30 (30)	30 (52)	577 (42)
Age (years)						
Median	48	18	0	68	29	36
IQR	28-62	4-35	0	56-74	6-54	5-58
Case fatality*						
No of deaths (No of cases)	38 (308)	14 (163)	2 (86)	11 (50)	0 (26)	65 (633)
Case fatality proportion (%)	12.3	8.6	2.3	22	0	10.3

*Data are for cases reported during 2004-2014

decreased from 0.70 in 1995 to 0.26 in 2014 (Figure 2), a 2% annual decrease (95% CI: -4%; -1%) (Table 1). The incidence of pneumococcal meningitis decreased annually by 4% (95% CI: -7%; 0%), 7% (95% CI: -13%; -1%) and 4% (95% CI: -6%; -1%) in age groups <2 years, 5-17 years and 18-49 years, respectively. During 2004-2014, *S. pneumoniae* accounted for 58% (38/65) of fatal cases; (30-day CFP 12%, 38/308).

Of the 308 pneumococcal meningitis cases reported during 2004-2014, information on serotype was available for 296 (96%). The proportion of cases caused by PCV10 serotypes decreased from 61% (35/57) in 2004-2005 to 15% (9/36) in 2013-2014. PCV13 serotypes accounted for 70% (40/57) cases in 2004-2005 and 44% (16/36) in 2013-2014. In children less than 2 years, proportion of meningitis cases caused by PCV10 serotypes decreased from 75% (9/12) in 2004-2005 to 20% (1/5) in 2013-2014. In 2014, no meningitis cases were caused by PCV10 serotypes.

Neisseria meningitidis

During the study period, meningococcal meningitis accounted for 450 cases (0.43 cases/100,000 person-years) (Table 1). Median age was 18 years and 60% of cases were male (male-to-female IRR 1.5) (Table 2). The overall annual incidence per 100,000 person-years decreased from 0.88 in 1995 to 0.07 in 2014; the annual decrease was -9% (95% CI: -7%; -10%) (Table 1). The decline occurred in all age-groups except in <2 years and ≥65 years of age. The incidence decreased annually by 6% (95% CI: -1%; -10%), 8% (95% CI: -3%; -14%), 10% (95% CI: -8%; -13%) and 12% (95% CI: -8%; -13%) in age groups 2-4 years, 5-17 years, 18-49 years and 50-64 years, respectively. The overall 30-day CFP was 9% (14/163) and ranged from 3% (1/29) among children 0-1 year old to 21% (4/19) among 2-4 year olds.

During 2004-2014, information on *N. meningitidis* serogroups was available for 99% of cases (161/163). Serogroup B accounted for 85% (137/161) of isolates, C 11% (17/161), and Y 4% (7/161). In children <2 years, serogroup B caused 96% (26/27) of cases. MCV-4 and MenB vaccine serogroups caused 15% (24/161) and 85% (137/161) of all cases, respectively.

Haemophilus influenzae

From 1995 to 2014, 58 cases of *H. influenzae* were reported (0.06 cases/100,000 person-years) (Table 1). Median age was 29 years and male-to-female IRR was 1.0 (Table 2). The incidence rate ranged from 0.0 cases per 100,000 person-years in 2010 to 0.25 cases in 2007 (Figure 2). Rates in all age groups were stable. From 2004 to 2014, there were no deaths due to *H. influenzae*.

In 2004-2014, non-encapsulated *H. influenzae* accounted for 69% (18/26) of isolates, serotype f 23% (6/26) and type b 8% (2/26).

Streptococcus agalactiae

Infection with *S. agalactiae* accounted for 141 cases of meningitis (0.13 cases/100,000 person-years), including 24 early onset cases and 78 late onset cases (Table 1). The median age of cases was 30 days; male-to-female IRR was 1.03 (Table 2). During the study period annual rates ranged from 0.06 cases/100,000 person-years in 1995, to 0.17 cases in 2014 (Figure 2) but overall rates of *S. agalactiae* did not change significantly (p=0.97) (Table 1). During 2004-2014, the 30-day CFP was 2% (2/86).

Listeria monocytogenes

During the study period, *L. monocytogenes* caused 101 cases of meningitis (0.13 cases/100,000 person-years), mostly among elderly persons (median age, 68 years). Of cases, 70% were men (male-to-female IRR 2.5) (Table 2). Overall incidence rates of listeria meningitis did not vary significantly during the study period, ranging from 0.04 to 0.21/100,000 person-years (Table 1). The overall 30-day CFP was 22% (11/50) and 28% (10/36) in persons ≥65 years of age.

DISCUSSION

During 1995-2014, the most common causes of bacterial meningitis in Finland were *S. pneumoniae* and *N. meningitidis*. However, contribution of specific pathogens to the disease burden varied substantially by age. As in other developed countries, *S. agalactiae* was the most common cause of bacterial meningitis in children <1 years of age [6]. The mean age of cases increased significantly during the study period mainly because of the decrease in incidence in children associated with pneumococcal conjugate vaccine program and declining secular trend in meningococcal meningitis.

During the study period, significant declines were seen in overall incidence of bacterial meningitis - primarily due to decreases in rates of *N. meningitis* and *S. pneumoniae*. Of interest, the decrease in incidence of *N. meningitidis* was greater than for pneumococcal meningitis, although there is no routine vaccination program for meningococcal disease in Finland. Changes in rates of meningococcal disease have also been observed in other countries in Europe and worldwide [16-17]. The reasons for these declines in incidence are not clear but may be related to population immunity to circulating strains, changes in colonizing organisms in the nasopharynx or increasing use of influenza vaccine. Also changes in behavioral risk factors such as lower prevalence of smoking or crowding, might contribute [18-19]. In some countries, decreases were related to meningococcal vaccination. After the introduction of conjugate serogroup C meningococcal vaccine, vaccine serogroup disease nearly disappeared in England [20] and the Netherlands [21]. Direct and indirect (herd protection) vaccine effects were also reported from other European countries including Spain, Ireland and Belgium [22-23]. Immunization of high risk groups with recently licensed protein-based vaccines targeted against meningococcal serogroup B might also be considered in Finland. However, updated cost-effectiveness analysis is needed for decision-making about introduction of meningococcal vaccination programs.

Before the introduction of PCV10, considerable variation in pneumococcal meningitis incidence rates was seen. As there was no major changes in surveillance or diagnostic practices in Finland, these changes may be related to emergence of new serotypes, selective pressure from antibiotic use or natural fluctuation in

serotypes [24-26]. The decline in pneumococcal meningitis incidence in children <2 years of age was associated with introduction of PCV10 in the National Vaccination Programme in 2010 [15]; PCV10 serotypes in this age group were significantly reduced and, by 2014 no vaccine serotype meningitis cases were reported. In vaccine-eligible children, the overall rate of pneumococcal meningitis was reduced by 46% as a result of a 69% reduction in PCV10-type meningitis [15]. Many studies in the U.S. and Europe have also documented significant declines in the incidence of pneumococcal meningitis in both vaccinated and unvaccinated groups after introduction of PCV programmes [11-12, 27-29]. In Finland, it might be possible to achieve further reductions with higher valency conjugate vaccine formulations.

The incidence rate of *L. monocytogenes*, *N. meningitidis* and *S. pneumoniae* was higher in men than women. *L. monocytogenes* meningitis cases were 2.5 times more likely to be men. Higher rates of listeriosis in males have also been observed in other studies [7]. However, the reasons are unknown, but may be related to higher prevalence of underlying conditions, alcoholism among men and liver diseases (including alcoholic cirrhosis) [30]. In pneumococcal and meningococcal meningitis possible reasons may be higher prevalence of underlying conditions such as smoking and alcoholism [31]. As listeriosis is primarily transmitted through contaminated food, important prevention efforts include health education about dietary guidelines for high risk groups, such as pregnant women and the elderly [32].

The overall 30-day case-fatality proportion for meningitis did not change significantly during 1995-2014. However, the unchanged CFP may be related to the altered age distribution of cases. Older age is associated with higher risk of poor outcome [33]. In addition, pathogen distribution has changed and the case-fatality for meningococcal meningitis is lower compared with pneumococcal meningitis. The small number of fatal cases in our study did not allow to assess changes in CFP by age group and pathogen. However, the larger proportion of older cases and decrease in meningococcal meningitis rates may both have contributed to increase in overall CFP. The 30-day CFP was highest for *L. monocytogenes* (22%), which is comparable to results from the Netherlands and Spain [7, 34]. Most of the fatal cases of bacterial meningitis in persons ≥50 years were attributable to *S. pneumoniae*. Cases who had pneumococcal

meningitis were older than those who were infected with other encapsulated bacteria and likely had high prevalence of comorbidities increasing the risk of pneumococcal infection and poor outcome [35]. Because of lack of clinical data we could not assess the potential impact of treatment changes, such as dexamethasone use, on case fatality. The relatively high case fatality proportion emphasizes the importance of immediate initiation of treatment and supportive care after diagnosis to improve outcome of bacterial meningitis.

As expected, *H. influenzae* was the least common cause of bacterial meningitis. However, the stable number of cases over 20 years suggest existence of small group of individuals with risk factors for *H. influenzae* (such as chronic respiratory disease and impaired immunity) [36]. Conjugate vaccination has nearly eliminated *H. influenzae* type b meningitis in many high-income countries [37-38]. However, changes in the epidemiology of invasive *H. influenzae* have been observed and currently most cases occur in adults [39] and non-encapsulated, non-typable *H. influenzae* (ncHi) have dominated since 2004.

Because the data on laboratory confirmed cases are transmitted electronically directly from the clinical microbiology laboratories' database to the national surveillance database, a strength of our study is comprehensive case ascertainment. In addition, almost all isolates of *N. meningitidis*, *H. influenzae* and *S. pneumoniae* (98%) were available for serotyping/grouping at THL reference laboratory. However, our study has several limitations. As the data were from laboratory-based surveillance system, information on clinical presentation or treatment was not available. Therefore, culture-negative meningitis cases diagnosed on the basis of clinical symptoms and findings were not included in the analysis dataset. In addition, cases diagnosed by PCR or antigen detection were not included. As CSF cultures are negative in 11%–30% of patients with bacterial meningitis [40], the total number of meningitis cases is underestimated. Another limitation is that NIDR database does not include information on the cause of death. However, most of deaths associated with bacterial meningitis occur early (within 14 days of admission), suggesting that they were related to the infection [41].

In conclusion, this study describes the epidemiologic characteristics of >1300 cases of bacterial meningitis reported to national surveillance over 20 years. It documents the sustained population impact of infant conjugate vaccination against Hib, and introduction of pneumococcal conjugate vaccination on reducing burden of bacterial meningitis, as well as decline in meningococcal meningitis due to secular trend. However, disease burden had shifted to older people and no changes in the overall proportion of fatal cases were seen. Data on changes in causative organisms and age distribution for meningitis cases are important for evaluating clinical guidelines for empiric antibiotic therapy in bacterial meningitis. Continued epidemiological surveillance is necessary to monitor changing trends and serotype distribution, assessing the impact of vaccination programs and developing future vaccination strategies.

Contributors: Study concept and design: AP, OL, PN Acquisition of data: MT, JO, OL, PN; Analysis and interpretation of data: AP, MT, JO, OL, PN; Drafting of the manuscript: AP, PN; Critical revision of the manuscript for important intellectual content: AP, MT, JO, OL, PN; Statistical analysis: AP, JO; Obtained funding: PN; Study supervision: PN; Final approval: AP, MT, JO, OL, PN

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Ethics approval: Data used in the analysis were collected as a part of surveillance and infection control activities which falls under the existing mandate of the National Institute for Health and Welfare (THL).

Data sharing: No additional data

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Table 1. Number of cases (N), incidence rates per 100,000 person-years (IR) and mean annual relative change in incidence of bacterial meningitis, Finland, 1995-2014

Table 2. Characteristics of bacterial meningitis cases, Finland, 1995-2014

Figure 1. Proportions of bacterial meningitis cases caused by five pathogens according to age group, Finland, 1995-2014

Figure 2. Incidence rate (per 100,000 person-years) of bacterial meningitis by year and pathogen, Finland, 1995-2014

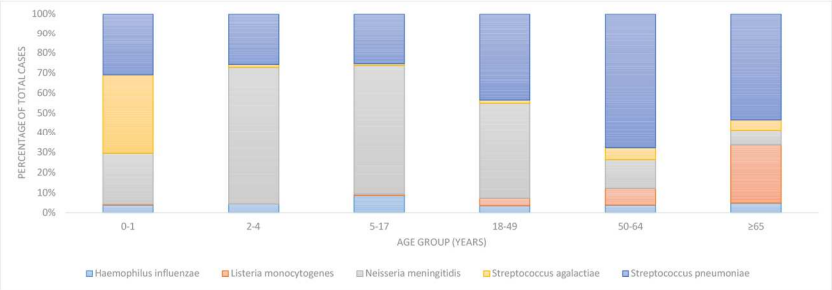

Figure 1. Proportions of bacterial meningitis cases caused by five pathogens according to age group, Finland, 1995-2014

173x122mm (300 x 300 DPI)

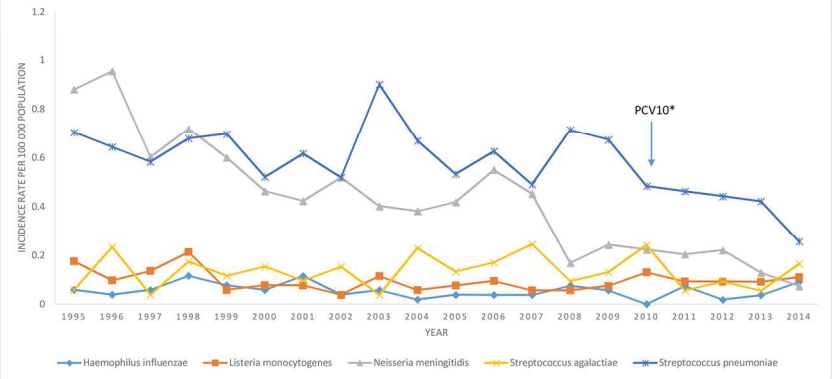

Figure 2. Incidence rate (per 100,000 person-years) of bacterial meningitis by year and pathogen, Finland, 1995-2014

173x122mm (300 x 300 DPI)

Bacterial meningitis in Finland, 1995-2014: a population-based observational study
Polkowska A et al.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported (page number)	RECORD items	Location in manuscript where items are reported (page number)
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	2 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	4		
Objectives	3	State specific objectives, including any prespecified hypotheses	4		
Methods					
Study Design	4	Present key elements of study design early in the paper	5		

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	5 NA NA	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	5 NA NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	5,6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	5,6
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	5		

		Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias	18		
Study size	10	Explain how the study size was arrived at	5		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5,6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	6		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	5,6

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	5,6
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	5,6
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	7-15 NA NA	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	7-15
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	7-15		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	7-15		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-15		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA		
Discussion					
Key results	18	Summarise key results with reference to study objectives	16-18		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	16-18		

		analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-18		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	NA

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.