NETHERLANDS REFERENCE LABORATORY FOR BACTERIAL MENINGITIS

BACTERIAL MENINGITIS IN THE NETHERLANDS

ANNUAL REPORT 2018

AMC
Academic Medical Center
University of Amsterdam

RIVM
National Institute of Public Health
and
Environmental Protection

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Academic Medical Center (AMC)
and
National Institute of Public Health and the Environment (RIVM),
Department of Medical Microbiology, AMC
PO Box 22660 , 1100 DD Amsterdam
The Netherlands
Telephone
+31 20 566 4874
+31 20 566 4864
+31 20 566 4861
E-mail: reflab@amc.uva.nl

Netherlands Reference Laboratory for Bacterial Meningitis (AMC/RIVM)
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CONTENTS

1 INTRODUCTION

This is the **47th** Annual Report of the Netherlands Reference Laboratory for Bacterial Meningitis of the Academic Medical Center (AMC) and the National Institute of Public Health and the Environment (RIVM). The Reference Laboratory is located within the Department of Medical Microbiology of the AMC in Amsterdam. Nearly all clinical microbiology laboratories of the Netherlands collaborate by submitting bacterial isolates and/or cerebrospinal fluid samples from patients with meningitis as well as other invasive diseases and we are most grateful to our colleagues for their cooperation.

The Reference Laboratory started collecting isolates of *Neisseria meningitidis* in 1959 and of other meningitis-causing bacteria in 1975.

In the archives of the Reference Laboratory approximately 75.600 isolates are now available for studies on the epidemiology of bacterial meningitis and on the pathogenicity and antibiotic susceptibility of isolates.

The objectives of the Reference Laboratory are:
- to perform national surveillance of bacterial meningitis;
- to describe the (molecular) epidemiology of bacterial meningitis in the Netherlands;
- to provide insights/leads for the development of potential vaccine components;
- to provide data about antibiotic susceptibility of isolates.

The information is presented in tables and figures and shortly discussed in the text.

We would appreciate receiving your opinion and suggestions on this report.

Amsterdam, July, 2020

dr. A. van der Ende PhD, biochemist
dr. W. Freudenburg, medical microbiologist

2 ISOLATES, CSF SPECIMENS AND SERA RECEIVED

The Netherlands Reference Laboratory for Bacterial Meningitis collects isolates from cerebrospinal fluid (CSF) and blood from patients with proven meningitis (CSF and possibly blood culture positive) or with bacteraemia and suspected meningitis (blood culture positive only). Unless otherwise indicated, every isolate from CSF represents a patient with meningitis, from CSF and blood represents a patient with meningitis and bacteraemia and from blood represents a patient with bacteraemia. When CSF is given as the source of isolation, this could either indicate an isolate from CSF or an isolate CSF and blood. Incidences have been calculated by dividing the number of isolates collected over one year (in a certain patient age group) by the number of inhabitants over one year (in that age group) multiplied by 100,000. Population statistics were obtained from Statistics Netherlands (Centraal Bureau voor de Statistiek, http://www.cbs.nl) using StatLine. By estimation, the Reference Laboratory receives about 90% of the isolates from meningitis patients in the Netherlands. Hence, incidences presented in this report are likely to be a slight underestimation of true incidences.

In 2018, the Reference Laboratory received isolates from CSF and/or blood from 2,654 patients, and 49 specimens of CSF and/or serum, which were positive in PCR. (table 2.1/table 11.1). Of these patients, 340 were confirmed cases of bacterial meningitis.

Table 2.1

	Number of specimens
Isolate (CSF and/or blood)	2654
Samples of CSF, Sera and other fluid, without isolate	174
Total	**2828**

In 2018, 50 clinical microbiology laboratories submitted isolates to the Reference Laboratory.

Table 2.2 shows the 2,654 isolates according to species and to laboratory where cases were diagnosed.

Table 2.2 Number of isolates from CSF and/or blood received in 2018, according to laboratory

Location	Laboratory	Nm	Hi	Sp	Ec	Sag	Lm	Spy	Sau	Cns	Cn	Ot	nv	Total
Alkmaar	MCA lab. Med. Microbiologie	3	5	52	1	3	1	-	-	-	-	1	-	**66**
Amersfoort	Meander Medisch Centrum	1	6	52	-	-	2	-	-	-	1	-	1	**63**
Amsterdam	Academisch Medisch Centrum	6	5	38	3	5	2	-	1	3	-	9	-	**72**
	Academisch ziekenhuis VU	1	1	7	1	3	2	-	-	-	-	1	-	**16**
	Onze Lieve Vrouwe Gasthuis	8	1	10	1	6	1	1	-	-	2	-	-	**30**
	Slotervaart / ATAL	3	4	41	-	2	1	2	-	-	-	1	-	**54**
Apeldoorn	Gelre Ziekenhuizen	8	7	64	3	-	2	1	-	-	-	-	-	**85**
Arnhem	Rijnstate	1	4	59	-	-	1	-	-	-	-	-	-	**65**
Breda	Amphia Ziekenhuis	1	7	58	2	6	3	-	2	1	-	1	-	**81**
Capelle ad IJssel	IJsselland Ziekenhuis	2	3	24	3	1	-	1	-	-	-	-	-	**34**
Delft	Reinier Haga MDC	6	3	3	3	2	2	-	-	-	-	-	-	**19**
Den Bosch	Regionaal laboratorium Den Bosch	6	9	64	-	1	2	-	-	-	-	2	-	**84**
Den Haag	Haga Ziekenhuis, loc. Leyenburg	8	4	34	1	7	-	1	-	-	-	-	-	**55**
	MA Haaglanden, loc Westeinde	4	1	3	1	-	-	-	-	-	-	-	1	**10**
Deventer	Deventer Ziekenhuis	2	6	31	-	2	1	-	-	-	-	-	-	**42**
Doetinchem	Slingeland Ziekenhuis	2	2	24	-	-	-	1	-	-	-	-	-	**29**
Dordrecht	RLM Dordrecht / Gorinchem	2	8	50	-	3	3	-	-	-	-	-	-	**66**
Ede	Gelderse Vallei	2	6	58	2	2	-	-	1	-	-	1	1	**73**
Goes	Lab. v. Med.Microb. & Imm., ADRZ	6	4	37	-	-	-	-	-	-	-	-	-	**47**
Gouda	Groene Hart Ziekenhuis	1	-	37	-	2	1	-	-	-	-	-	-	**41**
Groningen	Certe, Lab. v. Infectieziekten	4	10	87	1	2	4	-	-	-	-	2	-	**110**
	UMCG	2	6	8	-	-	-	-	-	-	-	-	-	**16**
Haarlem	Streeklab voor de Volksgezondheid	7	8	72	-	6	2	-	-	-	-	-	-	**95**
Harderwijk	St. Jansdal Ziekenhuis	2	1	1	-	-	-	-	-	-	-	-	-	**4**
Hengelo	LabMicTa	9	15	127	-	6	2	-	-	-	1	-	1	**161**
Hilversum	Centraal Bact. Ser. Lab.	2	3	4	-	1	1	-	-	-	-	-	-	**11**
Hoorn	Westfries gasthuis	6	4	32	1	3	2	-	-	-	-	-	-	**48**
Leeuwarden	Izore, centrum infectieziekten Friesland	6	4	100	-	3	-	-	1	-	-	-	-	**114**
Leiden	Alrijne ziekenhuis	1	9	75	1	6	-	-	-	-	-	-	-	**92**
	LUMC, KML, Lab.voor Bacteriologie	6	5	25	-	4	1	-	-	-	2	1	-	**44**
Maastricht	Acad. Ziekenhuis Maastricht	5	2	6	-	1	-	-	-	-	3	-	-	**17**
Nieuwegein	St. Antonius Ziekenhuis	7	6	61	-	-	2	1	-	-	-	-	-	**77**
Nijmegen	Canisius Wilhelmina Zknhs	3	1	44	-	-	2	-	-	-	-	1	-	**51**
	UMC St. Radboud	10	10	39	12	5	2	-	-	-	-	1	-	**79**
Roermond	St. Laurentius Ziekenhuis	2	-	-	-	-	-	-	-	-	-	-	-	**2**

Location	Laboratory	Nm	Hi	Sp	Ec	Sag	Lm	Spy	Sau	Cns	Cn	Ot	nv	Total
Roosendaal	St. Fransiscus Ziekenhuis	1	4	38	2	-	2	-	-	-	1	-	-	**48**
Rotterdam	Erasmus MC Med. Microbiologie	7	8	29	4	5	3	-	-	-	-	-	-	**56**
	Ikazia Ziekenhuis	2	3	21	1	2	2	-	-	-	-	-	1	**32**
	Maasstad Ziekenhuis	3	3	9	1	-	1	-	-	-	-	-	-	**17**
	St.Franciscus Gasthuis	3	6	65	2	3	-	1	1	-	-	1	2	**84**
Sittard	Zuyderland Medisch Centrum	5	6	82	1	2	3	2	-	-	-	-	-	**101**
Terneuzen	Zorgsaam Zeeuws-Vlaanderen	2	3	4	-	-	1	-	-	-	-	-	-	**10**
Tilburg	Streeklab. Tilburg	4	10	21	-	1	3	-	-	-	-	-	-	**39**
Utrecht	Diakonessenhuis	5	4	3	-	1	2	-	-	-	-	-	-	**15**
	UMC Med. Microbiologie	6	7	33	13	5	-	-	-	-	2	3	-	**69**
Veldhoven	PAMM, Lab. Med. Microbiologie	14	8	104	-	4	3	1	-	-	-	-	-	**134**
Vredenburg	Medical Microbology, Curacao/St.Maarten	-	-	10	-	-	-	-	-	-	-	-	-	**10**
Venlo	Vie Curie medisch centrum	3	2	4	-	-	-	-	-	-	-	-	-	**9**
Zwolle	Isala Klinieken LMMI	5	5	59	2	1	3	-	1	-	1	-	-	**77**
Total		**205**	**239**	**1909**	**62**	**106**	**65**	**12**	**7**	**4**	**13**	**25**	**7**	**2654**

Nm: *N. meningitidis*; **Hi:** *H. influenzae*; **Sp:** *S. pneumoniae*; **Ec:** *E. coli*; **Sag:** *S. agalactiae*; **Lm:** *L. monocytogenes*; **Spy:** *S.pyogenes*; **Sau:** *S. aureus*; **Cns:** Coagulase negative staphylococcus; **Cn:** *C. neoformans;* **ot:** other bacteria; **nv:** non-viable

The distribution of the isolates received in the 5 year period 2014 through 2018 is presented in table 2.3. The number of total isolates increased from 1,243 in 2014 to 2,654 in 2018. The number of cases of meningococcal disease increased from 73 in 2014 to 205 in 2018 (204% increase). Since June 2006, children born after the 1st April 2006 are vaccinated with a 10-valent conjugated polysaccharide vaccine against *Streptococcus pneumoniae*. The number of *S. pneumoniae* isolates from CSF decreased from more than 200 yearly before 2007 to 152 in 2018 (approximately 25% decrease). The number of *Listeria monocytogenes* isolates increased from 47 in 2015 to 65 in 2018 (64% increase). The number of *Haemophilus influenzae* isolates increased from 161 in 2014 to 216 in 2018, mainly due to a higher number of *H. influenzae* isolates from blood.

Table 2.3 Number of isolates from CSF and/or blood received in the years 2014 – 2018

Species	2014			2015			2016			2017			2018		
	CSF	Blood	Total	CSF	Blood	Total	CSF	Blood	Total	CSF	Blood	Total	CSF	Blood	Total
***N. meningitidis*[1]**	31	42	73	33	51	84	36	100	136	67	134	201	70	135	205
H. influenzae	21	140	161	22	173	195	26	162	188	30	194	224	23	216	239
S. pneumoniae	142	627	769	147	754	901	143	762	905	148	1255	1403	152	1757[2]	1909
E. coli	8	24	32	8	20	28	18	32	50	8	41	49	12	50	62
S. agalactiae	23	48	71	19	46	65	20	49	69	24	63	87	27	79	106
L. monocytogenes	19	51	70	8	39	47	11	59	70	20	71	91	9	56	65
S. pyogenes	2	6	8	3	13	16	5	5	10	7	11	18	3	9	12
S. aureus	13	10	23	8	8	16	10	1	11	5	0	5	7	0	7
Coag.neg.Staph.	2	0	2	2	0	2	2	0	2	6	0	6	4	0	4
C. neoformans	4	3	7	7	2	9	7	3	10	7	2	9	8	5	13
others	22	4	26	30	10	40	19	18	37	9	13	22	18	7	25
non viable	0	1	1	0	1	1	0	2	2	0	3	3	0	7	7
Total	**287**	**956**	**1243**	**287**	**1117**	**1404**	**297**	**1193**	**1490**	**331**	**1787**	**2118**	**333**	**2321**	**2654**

[1]Including PCR positive patients
[2] 655 blood isolates from 9 sentinel labs
CSF: CSF or CSF and blood
blood: blood only

The incidence of invasive bacterial infections of the different bacterial species from CSF and/or blood over the years 2014 to 2018 is shown in table 2.4. The incidence of *H. influenzae* infection was 34% lower than in the years before vaccination was introduced (2.1 in 1992; 1.4 in 2018). The incidence *of H. influenzae* infection increased from 2010 until now, mainly caused by an increase in the number of cases of bacteraemia caused by unencapsulated (non-typeable) *H. influenzae*.

Table 2.4 Number of isolates from CSF and/or blood per 100,000 inhabitants, 2014 - 2018

Species	2014	2015	2016	2017	2018
N. meningitidis	0.43	0.50	0.80	1.18	1.19
H. influenzae	0.96	1.15	1.11	1.31	1.39
S. pneumoniae	4.57	5.33	5.33	8.21	11.11
E. coli	0.19	0.17	0.29	0.29	0.36
S. agalactiae	0.42	0.38	0.41	0.51	0.62
L. monocytogenes	0.42	0.28	0.41	0.53	0.38
S. pyogenes	0.05	0.09	0.06	0.11	0.07
S. aureus	0.14	0.09	0.07	0.03	0.04
Coag. neg. Staph.	0.01	0.01	0.01	0.04	0.02
C. neoformans	0.04	0.05	0.06	0.05	0.08
others	0.15	0.24	0.22	0.13	0.15
non viable	0.01	0.01	0.01	0.02	0.04
Total	**7.39**	**8.31**	**8.78**	**12.40**	**15.45**

Table 2.5 Total number of isolates from CSF and/or blood received in 2018, according to bacterial species and source.

Species		CSF or CSF and blood	Blood only	Total	%
Neisseria meningitidis		70	135	205	**7.7**
Haemophilus influenzae [1]		23	216	239	**9.0**
Streptococcus pneumoniae [2]		152	1757[2]	1909	**71.9**
Escherichia coli [3]		12	50	62	**2.3**
Streptococcus agalactiae		27	79	106	**4.0**
Listeria monocytogenes		9	56	65	**2.4**
Streptococcus pyogenes		3	9	12	**0.5**
Staphylococcus aureus [4]		7	0	7	**0.3**
Coagulase-negative staphylococcus [5]		4	0	4	**0.2**
Cryptococcus neoformans		8	5	13	**0.5**
Others total		18	7	25	**0.9**
Others	*Klebsiella pneumoniae*	*1*	*0*	*1*	
	Psuedominas aeruginosa	*2*	*0*	*2*	
	Corynebacterium propinguum	*1*	*0*	*1*	
	Capnocytofaga canimorsus	*2*	*0*	*2*	
	Moraxella nonliquefaciens	*1*	*0*	*1*	
	Moraxella osloensis	*1*	*0*	*1*	
	Neisseria species	*0*	*1*	*1*	
	Streptococcus dysgalactiae ssp equisimilis	*0*	*1*	*1*	
	Streptococcus gallolyticus ssp pasteurianus	*1*	*1*	*2*	
	Streptococcus intermedius	*3*	*0*	*3*	
	Streptococcus lututiensis	*0*	*2*	*2*	
	Streptococcus mitis	*0*	*1*	*1*	
	Streptococcus oralis	*2*	*0*	*2*	
	Streptococcus salivarius	*0*	*1*	*1*	
	Enterococcus faecalis	*1*	*0*	*1*	
	Acinetobacter lwoffi	*1*	*0*	*1*	
	Enterobacter aerogenes	*1*	*0*	*1*	
	Propionibacterium acnes	*1*	*0*	*1*	
Non viable		0	7	7	**0.3**
Total %		**333**	**2321**	**2654**	**100.0**

1 In three patients *Haemophilus influenza* and *Streptococcus pneumoniae* were isolated from the blood.
2 In one patient *Streptococcus pneumoniae* and *Staphylococcus haemolyticus* were isolated from the CSF. (70 years of age)
3 In one patient *Streptococcus agalactiae* and *Eschericia coli* were isolated from blood (0 years of age)
4 In one patient *Staphylococcus aureus, Streptococcus oralis ssp. oralis* and *Abiotrophia defective* were isolated from the CSF.
5 Four Coagulase-negative staphylococcus were isolated from CSF. Two *Staphylococcus epidermidis* and two *Staphylococcus haemolyticus*

Table 2.5 shows the distribution of isolates according to the specimen from which they were cultured. The predominant species were *N. meningitidis, H. influenzae* and *S. pneumoniae*.

3 BACTERIAL MENINGITIS - general data

In 2018, the Reference Laboratory received CSF isolates or PCR-positive CSF samples from 340 patients (Table 11.1). The proportion of meningococcal and pneumococcal cases among meningitis patients was 20% and 45%, respectively (Figure 3.1).

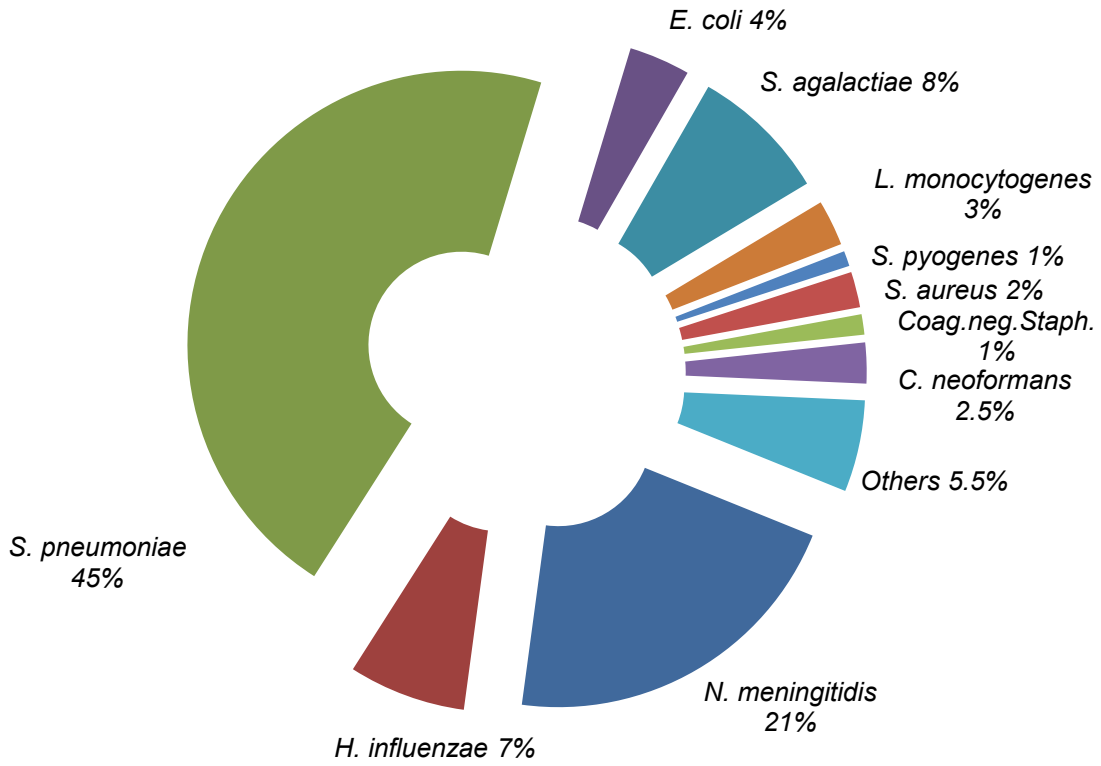

Figure 3.1 *Proportional distribution of CSF isolates and CSF positive samples, 2018*

Figure 3.2 shows the annual total number of bacterial isolates from CSF during the period 2009-2018. The 10-year trend line shows a slight decrease over the last decade. The incidence per 100,000 inhabitants also shows a slight decreasing trend and varied between 2.4 and 1.7 during the period 2009-2018 (Figure 3.2). Since 2013, the downward trend has stopped and a slight increase has been noted.

Data concerning meningitis caused by *N. meningitidis, H. influenzae* and *S. pneumoniae* during the same period are presented in figure 3.3. Since the introduction of vaccination against *H. influenzae* type b in 1993, the incidence of *Haemophilus influenzae* type b meningitis decreased from 1.6 per 100,000 to 0.18 per 100,000 and has remained at this low level. The number of cases of meningococcal meningitis (with an isolate or a positive PCR result from CSF) decreased from 480 cases (incidence of 3.1/100,000) in 1993 to 70 cases (incidence of 0.4/100,000) in 2018, mainly due to a decline in the number of cases of cause by serogroup B and C meningococci. Nationwide vaccination against serogroup C meningococci was started in 2002. The year 2003 was the first year, since two decades, in which *N. meningitidis* was not the main cause of bacterial meningitis in the Netherlands. In 2018, the number of meningococcal meningitis cases doubled to 70, which was mainly explained by an increased number of cases caused by serotype W. Pneumococcal meningitis showed a slight increase in annual incidence from 1.0 per 100,000 inhabitants in 1991 to 1.6 per 100,000 inhabitants in

2004. In 2018, incidence of pneumococcal meningitis has decreased to 0.88 per 100,000 inhabitants due to inclusion of 10-valent conjugated polysaccharide vaccine against pneumococci for children in the National Immunisation Programme in June 2006.

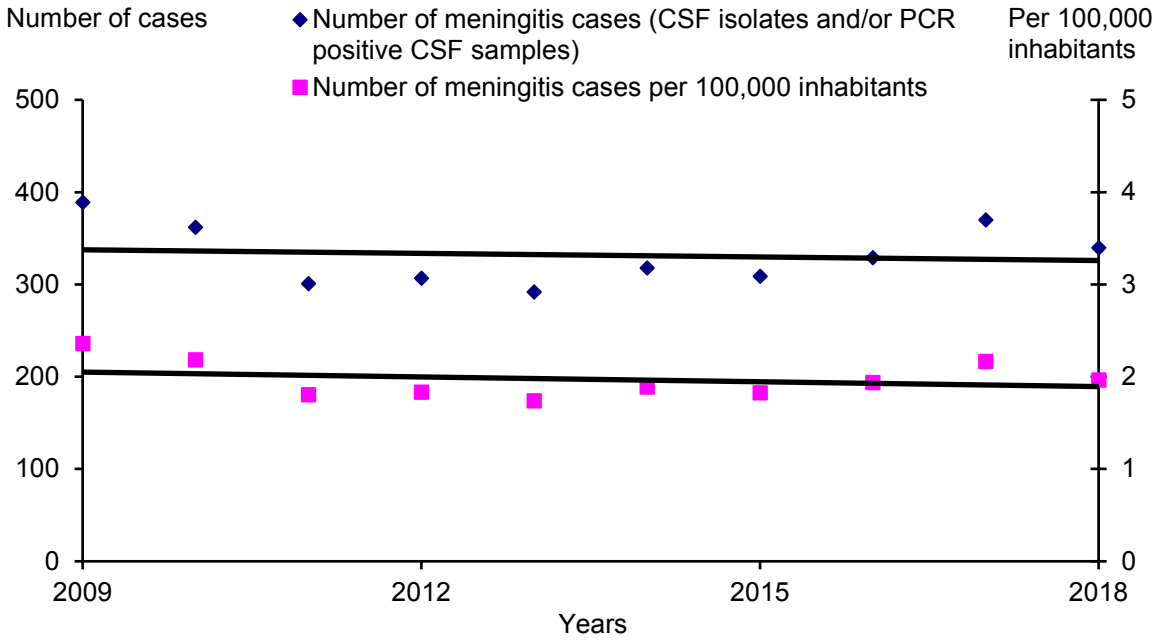

Figure 3.2 *Meningitis cases, 2009-2018*

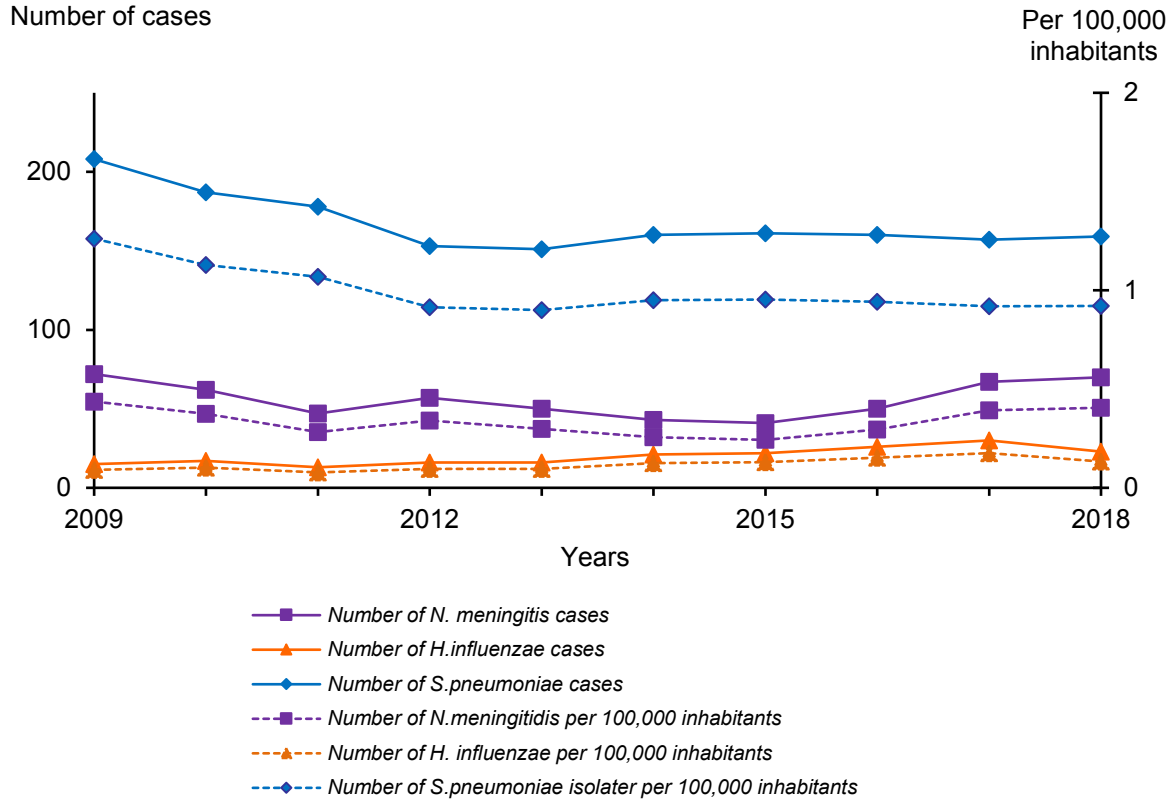

Figure 3.3 *Meningococcal, Haemophilus and pneumococcal meningitis (isolates and/or positive PCR from CSF), 2009-2018*

Table 3.1 shows the frequency of isolation of the different bacterial species from CSF by annual quarter. As in previous years, most isolates were received during the first quarter of the year.

Table 3.1 Isolates and PCR-positive samples from CSF by annual quarter, 2018

	ANNUAL QUARTER					
SPECIES	**First**	**Second**	**Third**	**Fourth**	**Total**	**%**
N. meningitidis	25	20	10	15	**70**	***20.6***
H. influenzae	7	4	6	6	**23**	***6.8***
S. pneumoniae	67	23	21	41	**159**	***46.8***
E. coli	3	3	3	3	**12**	***3.5***
S. agalactiae	3	9	8	7	**27**	***7.9***
L. monocytogenes	5	0	2	2	**9**	***2.7***
S. pyogenes	1	0	1	1	**3**	***0.9***
S. aureus	3	3	0	1	**7**	***2.1***
Coag.neg.Staph.	0	1	0	3	**4**	***1.1***
C. neoformans	3	2	2	1	**8**	***2.3***
Others	3	3	5	7	**18**	***5.3***
non viable	0	0	0	0	**0**	***0.0***
Total	**120**	**68**	**58**	**87**	**340**	***100.0***
%	***35.3***	***20.0***	***17.1***	***25.6***	***100.0***	

Tables 3.2 and 3.3 show the distribution of the bacterial species isolated from CSF according to the age of the patient and the age-specific incidence per 100,000, respectively. *Streptococcus agalactiae* is still the predominant species isolated from neonates (younger than 1 month), and represented 76% of the isolates in this age group, whereas in the age group 1-11 months the predominant species were *S. pneumoniae* and *N. meningitidis* (together 54%). Since the introduction of the vaccine against *H.influenzae* type b in 1993, the number of cases of *H. influenzae* b meningitis in the age group 0-4 year has strongly decreased (1992: 231; 2018: 8).

Table 3.2 Isolates and PCR-positive samples from CSF grouped according to patients' age, 2018

	AGE (MONTHS)			AGE (YEARS)									TOTAL	
Group	**0**	**1-11**	**12-59**	**0-4**	**5-9**	**10-14**	**15-19**	**20-29**	**30-39**	**40-49**	**50-64**	**65-79**	**≥80**	**Total**	**%**
N. meningitidis	0	10	15	25	1	3	12	3	0	2	16	7	1	**70**	***20.6***
H. influenzae	0	4	6	10	0	1	2	0	1	1	4	2	2	**23**	***6.8***
S. pneumoniae	1	15	4	20	7	2	1	5	13	17	35	53	6	**159**	***46.8***
E. coli	3	5	1	9	0	0	0	0	0	1	0	2	0	**12**	***3.5***
S. agalactiae	16	9	0	25	0	0	0	0	0	1	1	0	0	**27**	***7.9***
L. monocytogenes	0	0	0	0	0	0	0	0	1	1	4	3	0	**9**	***2.7***
S. pyogenes	0	1	0	1	1	0	0	0	0	0	1	0	0	**3**	***0.9***
S. aureus	0	1	2	3	0	0	0	0	0	1	0	3	0	**7**	***2.1***
Coag.neg.Staph.	0	0	0	0	1	0	0	0	0	0	2	1	0	**4**	***1.1***
C. neoformans	0	0	0	0	0	0	0	0	2	3	2	1	0	**8**	***2.3***
Others	1	1	1	3	1	1	0	2	0	1	9	1	0	**18**	***5.3***
non viable	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**	***0.0***
Total	*21*	*46*	*29*	*96*	*11*	*7*	*15*	*10*	*17*	*28*	*74*	*73*	*9*	**340**	***100***
%	**6.2**	**13.5**	**8.5**	**28.2**	**3.2**	**2.1**	**4.4**	**2.9**	**5.0**	**8.2**	**21.8**	**21.5**	**2.7**	***100***	

As anticipated from table 3.2, the incidence of bacterial meningitis was highest in the age group of 0 years (table 3.3).

Table 3.3 Age-specific incidence of bacterial meningitis per 100,000 inhabitants grouped according to species, 2018

SPECIES	AGE (YEARS)											
	0	1-4	5-9	10-14	15-19	20-29	30-39	40-49	50-64	65-79	≥80	Total
N. meningitidis	5.90	2.15	0.11	0.31	1.15	0.14	-	0.09	0.45	0.28	0.13	0.41
H. influenzae	2.36	0.86	-	0.10	0.19	-	0.05	0.04	0.11	0.08	0.26	0.13
S. pneumoniae	9.44	0.57	0.75	0.21	0.10	0.23	0.63	0.74	0.98	2.15	0.77	0.93
E. coli	4.72	0.14	-	-	-	-	-	0.04	-	0.08	-	0.07
S. agalactiae	14.74	-	-	-	-	-	-	0.04	0.03	-	-	0.16
L. monocytogenes	-	-	-	-	-	-	0.05	0.04	0.11	0.12	-	0.05
S. pyogenes	0.59	-	0.11	-	-	-	-	-	0.03	-	-	0.02
S. aureus	0.59	0.29	-	-	-	-	-	0.04	-	0.12	-	0.04
Coag.neg.Staph.	-	-	0.11	-	-	-	-	-	0.06	0.04	-	0.02
C. neoformans	-	-	-	-	-	-	0.10	0.13	0.06	0.04	-	0.05
Others	1.18	0.14	0.11	0.10	-	0.09	-	0.04	0.25	0.04	-	0.10
non viable	-	-	-	-	-	-	-	-	-	-	-	-
Total	**39.51**	**4.15**	**1.19**	**0.72**	**1.43**	**0.46**	**0.82**	**1.21**	**2.07**	**2.97**	**1.16**	**1.98**

Table 3.4 shows the frequency of the isolates per species from CSF according to patient gender. For most species the Male/Female ratio varied between 0.7 and 1.5. The overall M/F ratio was 1.2.

Table 3.4 Isolates and PCR positive samples from CSF according to patients' gender, 2018

SPECIES	M	F	M/F – ratio	Sex not known	Total	%
N. meningitidis	35	35	**1.0**	0	**70**	*20.6*
H. influenzae	12	11	**1.1**	0	**23**	*6.8*
S. pneumoniae	92	66	**1.4**	1	**159**	*46.8*
E. coli	7	5	**1.4**	0	**12**	*3.5*
S. agalactiae	11	15	**0.7**	1	**27**	*7.9*
L. monocytogenes	6	3	**2.0**	0	**9**	*2.7*
S. pyogenes	1	2	**0.5**	0	**3**	*0.9*
S. aureus	5	2	**2.5**	0	**7**	*2.1*
Coag.neg.Staph.	1	3	**0.3**	0	**4**	*1.1*
C. neoformans	5	3	**1.7**	0	**8**	*2.3*
Others	9	9	**1.0**	0	**18**	*5.3*
non viable	0	0	**0.0**	0	**0**	*0.0*
Total	**184**	**154**	**1.2**	**2**	**340**	*100*
%	***54.1***	***45.3***		***0.6***	***100***	

4 NEISSERIA MENINGITIDIS

4.1 General features

In 2018, the Reference Laboratory received 185 *Neisseria meningitidis* isolates of which 54 were isolated from CSF (or CSF and blood) (46 in 2017) and 131 from blood only (129 in 2017). In addition, 16 culture-negative CSF and 4 blood samples were tested positive for meningococcoi by PCR. In total, we received meningococcal isolates or PCR-positive CSF or blood from 205 patients. The distribution of isolates according to month of receipt shows the highest number of isolates in the first quarter (figure 4.1).

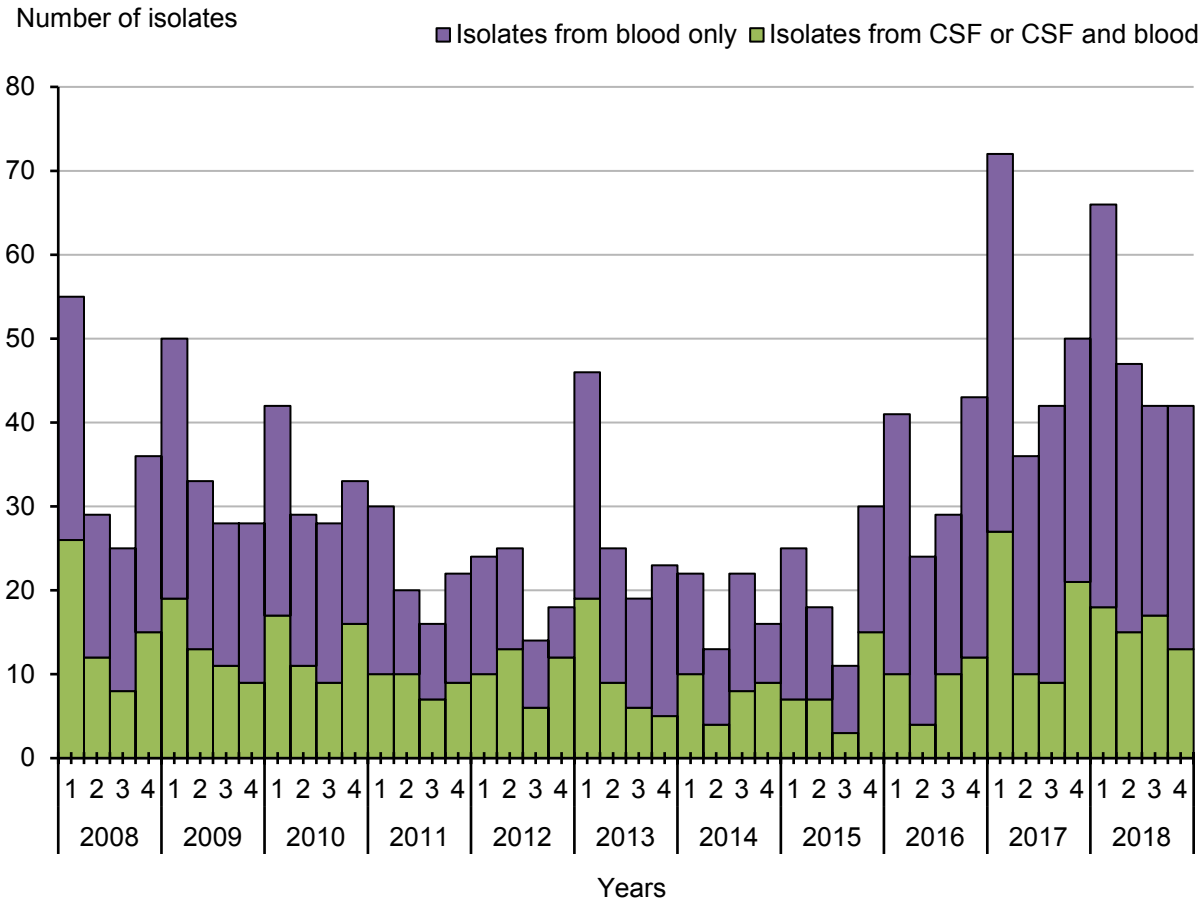

Figure 4.1 *Seasonal distribution of meningococcal disease, 2008-2018*

4.2 Antibiotic susceptibility

Seventy-five percent of all isolates (138/185) were susceptible to penicillin (MIC ≤ 0.064 µg/ml). This is a reduction compared to previous years. The proportion of susceptible isolates varied between 65% in 2012 to 95% in 2015. In general, mutations in *penA,* encoding a penicillin binding protein, confers reduced penicillin susceptibility to meningococcus. Nucleotide sequence analyses of *penA* confirmed the decrease in the number of reduced penicillin susceptible meningococcal isolates. All isolates were susceptible to Rifampicine.

Table 4.1 Susceptibility of *N. meningitidis* CSF and/or blood isolates to penicillin, 2018

	Penicillin*				
	MIC ≤ 0.064 (S)	0.064< MIC≤0.25 (I)	MIC>0.25 (R)	Total	%
CSF or CSF and blood	39	14	1	**54**	**29**
Blood only	99	30	2	**131**	**71**
Total	**138**	**44**	**3**	**185**	**100**
%	**75**	**24**	**1**	**100**	

* MIC values in µg/ml

Table 4.2 Susceptibility of *N. meningitidis* from CSF to penicillin, 2010-2018

	Penicillin*						Total
	MIC ≤ 0.064 (S)		0.064< MIC≤0.25 (I)		MIC>0.25 (R)		
	N	%	N	%	N	%	
2010	43	**81.1**	10	**18.9**	0	**0.0**	**53**
2011	29	**78.4**	8	**21.6**	0	**0.0**	**37**
2012	24	**58.5**	16	**39.0**	1	**2.4**	**41**
2013	35	**89.7**	3	**7.7**	1	**2.6**	**39**
2014	26	**83.9**	5	**16.1**	0	**0.0**	**31**
2015	32	**97.0**	1	**3.0**	0	**0.0**	**33**
2016	32	**88.0**	4	**12.0**	0	**0.0**	**36**
2017	37	**80.4**	9	**19.6**	0	**0.0**	**46**
2018	39	**72.2**	14	**25.9**	1	**1.9**	**54**

* MIC values in µg/ml

Table 4.3 Susceptibility of *N. meningitidis* isolated from blood only to penicillin, 2010-2018

	Penicillin*						Total
	MIC ≤ 0.064 (S)		0.064< MIC≤0.25 (I)		MIC>0.25 (R)		
	N	%	N	%	N	%	
2010	67	**84.8**	12	**15.2**	0	**0.0**	79
2011	34	**64.2**	19	**35.9**	0	**0.0**	53
2012	27	**67.5**	13	**32.5**	0	**0.0**	40
2013	53	**73.6**	18	**25.0**	1	**1.4**	72
2014	37	**88.1**	5	**11.9**	0	**0.0**	42
2015	48	**94.1**	3	**5.9**	0	**0.0**	51
2016	88	**88.0**	12	**12.0**	0	**0.0**	100
2017	104	**80.6**	24	**18.6**	1	**0.8**	129
2018	99	**75.6**	30	**22.9**	2	**1.5**	131

* MIC values in µg/ml

4.3 Serogroups

Serogroup B accounted for 36% of all isolates. This is a decrease compared to previous years: 2017: 41%; 2016: 49%; 2015: 74%. Group C and Y are responsible for 1.5% and 12% of all meningitis cases, respectively. The proportion of group W increased to 50%, compared to 41% in 2017, 34% in 2016 and 10% in 2015 (table 4.4). Observations across the entire collection period 1959 - 2018 (figure 4.2) show that in 2014 the number of group B isolates (53 cases) was the lowest since 1976. In 2018, the number of group B isolates (74) was slightly higher than the previous year. The proportion of group C isolates was 24% in 1991, decreased to about 10% in 1994 and has since then been increasing from 19% (105 cases) in 2000 to 40% (276 cases) in 2001 (figure 4.2). In June 2002, vaccination against serogroup C was included in the National Immunisation Programme, resulting in a rapid decline in the number of serogroup C isolates received by the Reference Laboratory. In 2017, there was a slight increase from 3 group C isolates in 2014 to 9 in 2017 (figure 4.3), but again a return to 3 isolates in 2018. Since November 2015, the proportion of group W isolates increased, similar to what was observed in England and Wales since 2009 (Ladhani SN et al. Increase in endemic *Neisseria meningitidis* capsular group W sequence type 11 complex associated with severe invasive disease in England and Wales. Clin Infect Dis. 2015;60:578-85).

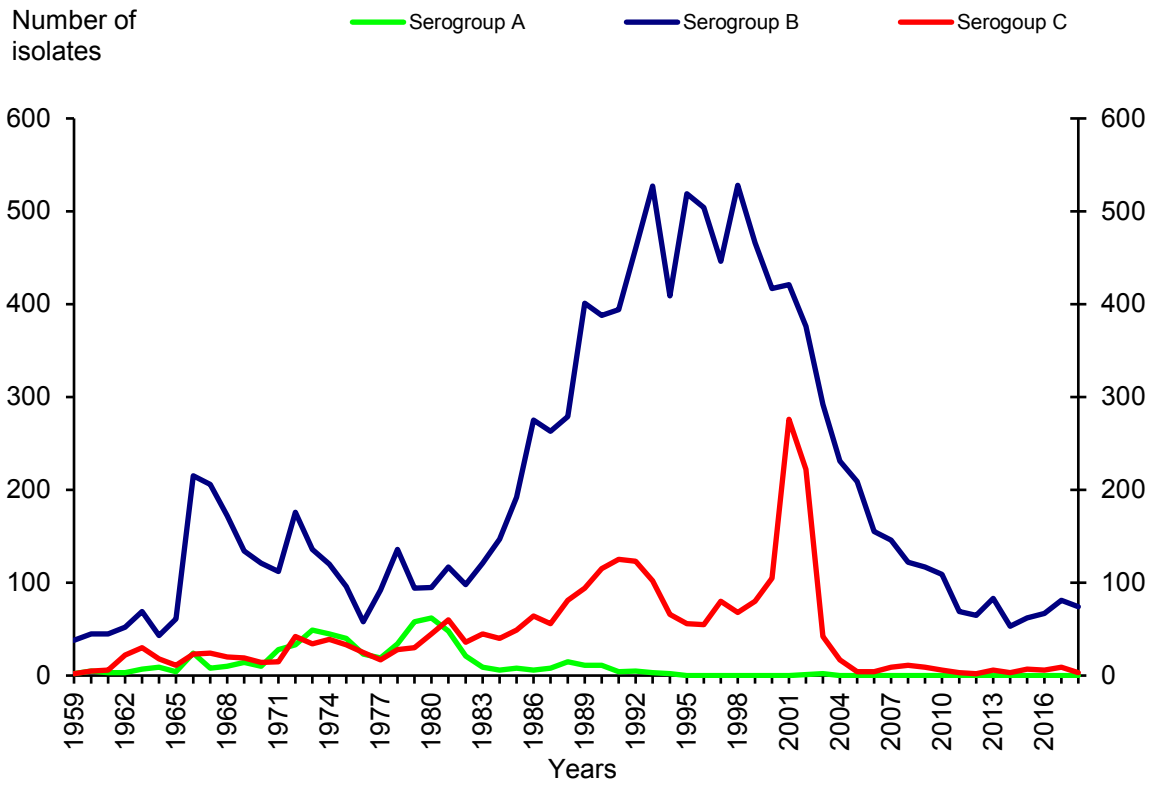

Figure 4.2. *Distribution of meningococcal serogroups A, B and C across the entire collection period from 1959-2018*

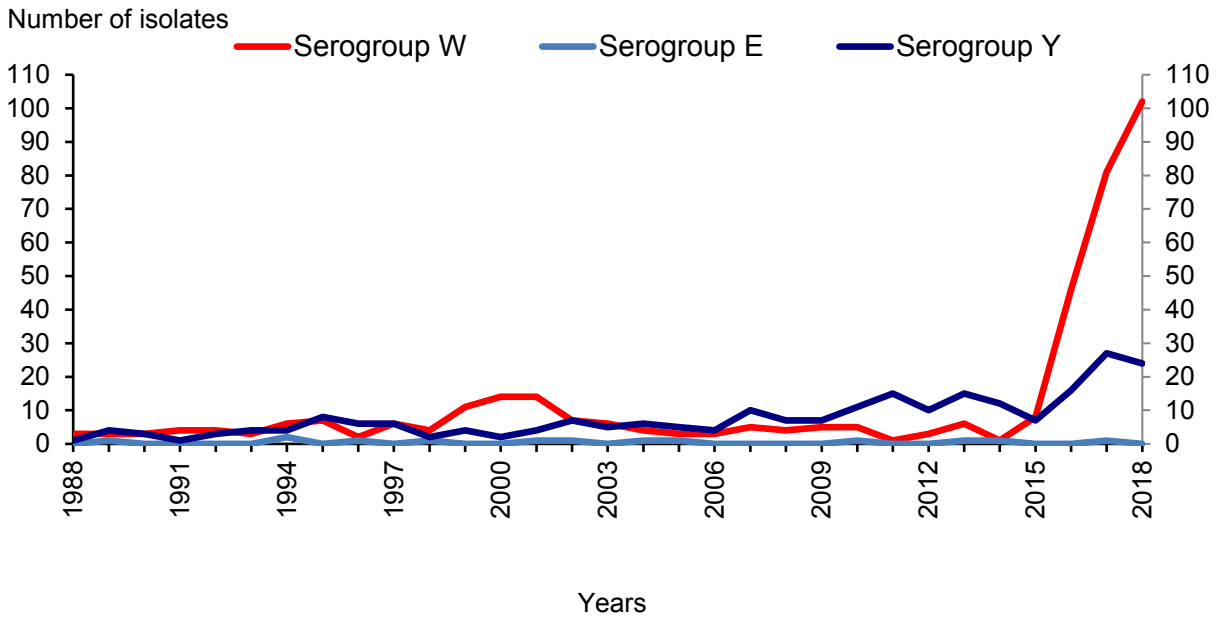

Figure 4.3. *Distribution of meningococcal serogroups Y, W and E, 1988-2018*

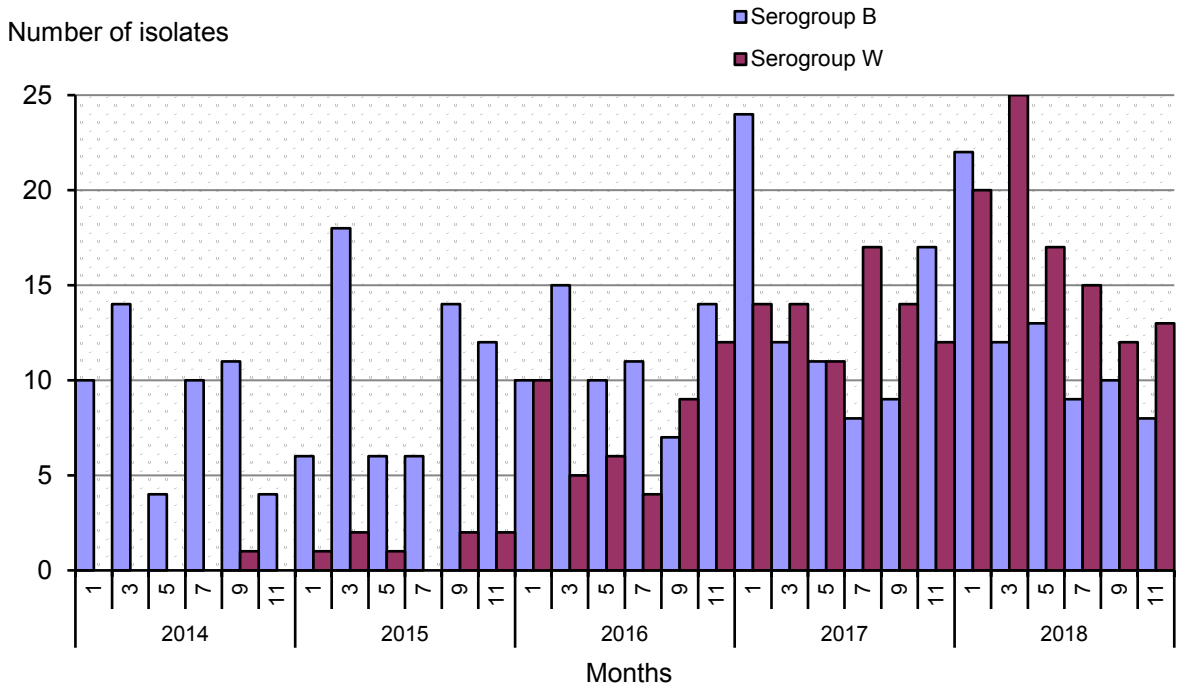

Figure 4.4 *Bimonthly distribution of meningococcal serogroups B and W, 2014-2018*

4.4 Serogroup and age

The age distribution of patients with meningitis and/or meningococcemia shows that 19.5% (40 of 205) of the patients was younger than 5 years (table 4.4). Among serogroup B cases, 65% (48/74) were younger than 25 years of age. In contrast, 61% (63/102) of the serogroup W cases were older than 50 years of age. In addition, of 74 serogroup B isolates, 42 (57%) were from CSF, while of 102 serogroup W isolates only 19 (19%) were from CSF (table 4.5). Of 135 patients from whom meningococci were isolated from blood only,15 (11%) were younger than 5 years of age, while 49 (36%) were older than 65 years of age (table 4.7). Table 4.6 and 4.8 shows the age distribution per 100,000 inhabitants.

Table 4.4 Serogroups of *N. meningitidis* (isolates or PCR-positive samples from CSF and /or blood; absolute numbers) by patient age, 2018

	AGE (MONTHS)			AGE (YEARS)								TOTAL	
Group	0	1-11	12-59	0-4	5-9	10-14	15-19	20-24	25-29	30-49	50-64	≥65	T	%
B	0	9	22	31	1	1	11	4	3	4	6	13	**74**	***36.1***
C	0	0	0	0	0	0	0	0	0	1	2	0	**3**	***1.5***
W	0	5	3	8	2	4	11	3	2	9	29	34	**102**	***49.8***
Y	0	1	0	1	0	0	6	0	0	2	6	9	**24**	***11.7***
NG*	0	0	0	0	0	0	0	0	0	0	1	1	**2**	***0.9***
Total	**0**	**15**	**25**	**40**	**3**	**5**	**28**	**7**	**5**	**16**	**44**	**57**	**205**	***100.0***
%	***0***	***7.3***	***12.2***	***19.5***	***1.5***	***2.4***	***13.7***	***3.4***	***2.4***	***7.8***	***21.5***	***27.8***	***100.0***	

*Non Groupable and not grouped

Table 4.5 Serogroups of *N. meningitidis* (isolates or PCR-positive samples from CSF) by patient age, 2018

	AGE (MONTHS)			AGE (YEARS)								TOTAL	
Group	0	1-11	12-59	0-4	5-9	10-14	15-19	20-24	25-29	30-49	50-64	≥65	T	%
B	0	6	14	20	1	1	7	2	1	1	4	5	**42**	***60.0***
C	0	0	0	0	0	0	0	0	0	0	1	0	**1**	***1.4***
W	0	3	1	4	0	2	4	0	0	0	7	2	**19**	***27.2***
Y	0	1	0	1	0	0	1	0	0	1	3	1	**7**	***10.0***
NG**	0	0	0	0	0	0	0	0	0	0	1	0	**1**	***1.4***
Total	**0**	**10**	**15**	**25**	**1**	**3**	**12**	**2**	**1**	**2**	**16**	**8**	**70**	***100.0***
%	***0.0***	***14.3***	***21.4***	***35.7***	***1.4***	***4.3***	***17.1***	***2.9***	***1.4***	***2.9***	***22.9***	***11.4***	***100***	

* From 7 patients with meningococci isolated from blood. CSF was culture-negative but CSF-PCR positive for meningococcal DNA.
**Not enough DNA for group PCR

Table 4.6 Age distribution of meningitis (incidence per 100,000 inhabitants) by different serogroups of *N. meningitidis* (isolates or PCR-positive samples from CSF, 2018)

	AGE (YEARS)										TOTAL
Group	0	1-4	5-9	10-14	15-19	20-24	25-29	30-49	50-64	≥65	T
B	3.54	2.00	0.11	0.10	0.67	0.19	0.09	0.02	0.11	0.15	**0.24**
C	-	-	-	-	0.10	-	-	-	0.03	-	**0.01**
W	1.77	0.14	-	0.21	0.38	-	-	-	0.20	0.06	**0.11**
Y	0.59	-	-	-	0.10	-	-	0.02	0.08	0.03	**0.04**
NG*	-	-	-	-	-	-	-	-	0.03	-	**0.01**
Total	**5.90**	**2.15**	**0.11**	**0.31**	**1.15**	**0.19**	**0.09**	**0.05**	**0.45**	**0.25**	**0.41**

*Non Groupable

Table 4.7 Serogroups of *N. meningitidis* (isolates or PCR positive samples from blood only; absolute numbers) by patient age, 2018

	AGE (MONTHS)			AGE (YEARS)								TOTAL	
Group	0	1-11	12-59	0-4	5-9	10-14	15-19	20-24	25-29	30-49	50-64	≥65	T	%
B	0	3	8	11	0	0	4	2	2	3	2	8	**32**	***23.7***
C	0	0	0	0	0	0	0	0	0	1	1	0	**2**	***1.5***
W	0	2	2	4	2	2	7	3	2	9	22	32	**83**	***61.5***
Y	0	0	0	0	0	0	5	0	0	1	3	8	**17**	***12.6***
NG*	0	0	0	0	0	0	0	0	0	0	0	1	**1**	***0.7***
Total	**0**	**5**	**10**	**15**	**2**	**2**	**16**	**5**	**4**	**14**	**28**	**49**	**135**	***100.0***
%	***0.0***	***3.7***	***7.4***	***11.1***	***1.5***	***1.5***	***11.9***	***3.7***	***2.9***	***10.4***	***20.7***	***36.3***	***100.0***	

*Non Groupable

Table 4.8 Age distribution of meningococcemia (incidence per 100,000 inhabitants) by different serogroups of *N. meningitidis* (isolates from blood only), 2018

	AGE (YEARS)										TOTAL
Group	0	1-4	5-9	10-14	15-19	20-24	25-29	30-49	50-64	≥65	T
B	1.77	1.15	-	-	0.38	0.19	0.18	0.07	0.06	0.25	**0.19**
C	-	-	-	-	-	-	-	0.02	0.03	-	**0.01**
W	1.18	0.29	0.22	0.21	0.67	0.28	0.18	0.21	0.62	0.99	**0.48**
Y	-	-	-	-	0.48	-	-	0.02	0.08	0.25	**0.10**
NG*	-	-	-	-	-	-	-	-	0.03	0.01	**0.01**
Total	**2.95**	**1.43**	**0.22**	**0.21**	**1.53**	**0.47**	**0.36**	**0.32**	**0.78**	**1.51**	**0.79**

*Non Groupable

4.5 Group B meningococci

Figure 4.5 shows the age distribution of meningococcal disease attributed to serogroups B and W. The age-specific incidence for serogroup B per 100,000 inhabitants in the age groups younger than 5 years and 15 - 19 years were 3.6 and 1.1, respectively (0.9 and 1.1 for serogroup W). The age-specific incidence per 100,000 inhabitants for all age groups >19 years was below 0.7. The age-specific incidence for serogroup W shows a different distribution, with highest incidences for the age groups younger than 5 years (0.9), 15-19 years (1.1), ages 50-60 years (1.0) and highest incidence between age 80-95 between 2.2 and 4.0.

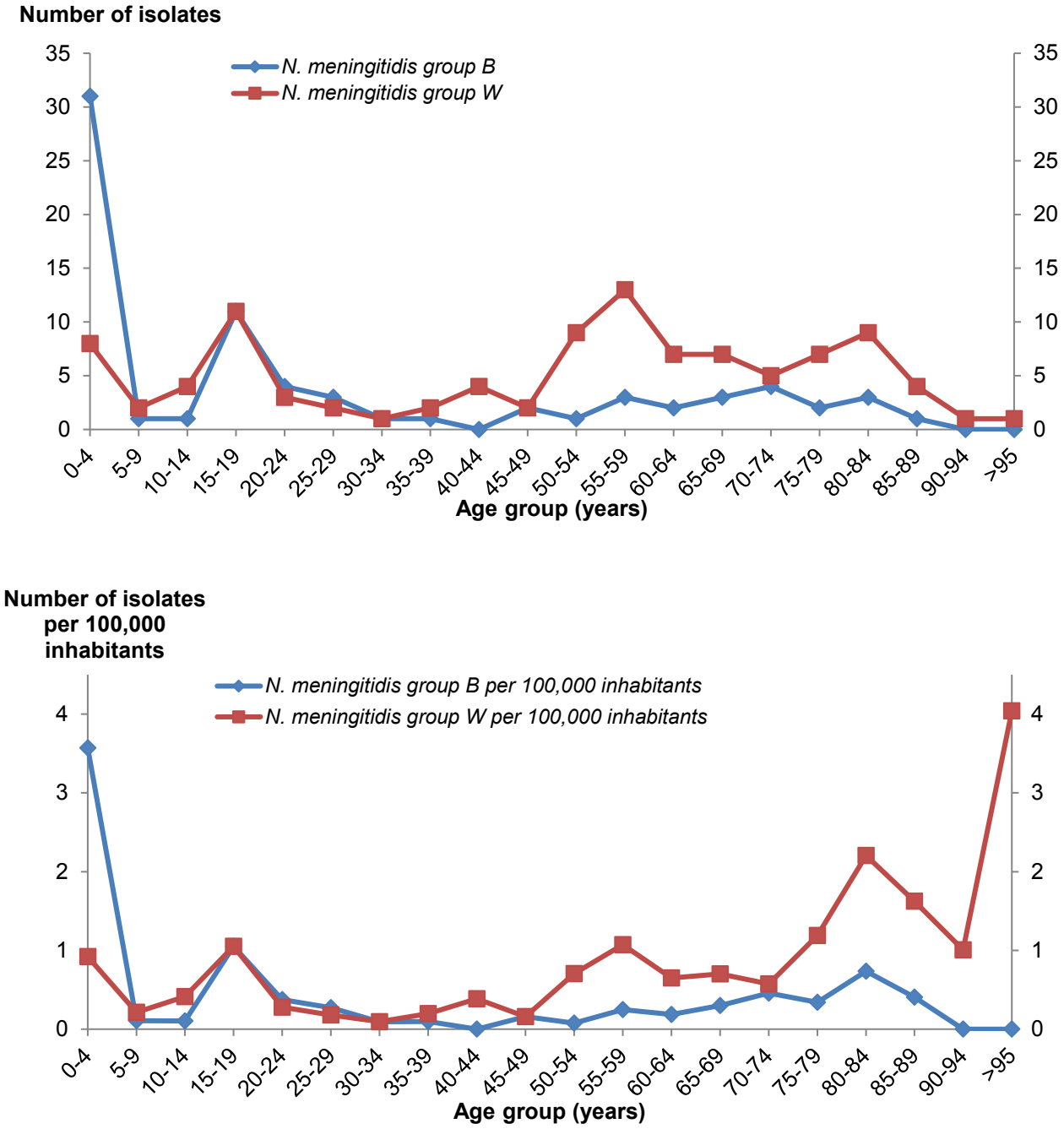

Figure 4.5 *Age distribution of serogroup B and W meningococcal disease according to number of isolates (above) and incidence (below) in 2018*

4.6 Distribution of PorA genosubtypes among serogroup B, C and W meningococci

In addition to serogrouping, meningococci can be further subtyped based on the variation in PorA and FetA proteins. Previously, subtyping was performed using specific monoclonal antibodies for these proteins. However, from January 1, 2005, the Reference Laboratory subtypes meningococcal isolates based on DNA-sequencing of PorA and FetA DNA coding regions due to discontinuation of the monoclonal antibodies.

The PorA epitopes that react with the monoclonal antibodies of the subtyping scheme are encoded by the *porA* variable regions VR1 and VR2. Since 2000, we routinely sequence the DNA regions which encode VR1 and VR2 of PorA of all meningococcal isolates. The DNA sequences are translated into putative amino acid sequences, which are then compared with the PorA epitopes present in the database available on the website: https://pubmlst.org/neisseria/PorA/

In 2018, 37 different VR1/VR2 combinations were encountered among 74 serogroup B meningococci (2014: 28; 2015: 32; 2016: 35; 2017: 36). The proportion of dominant PorA genosubtypes has shifted tremendously in the last two decades: in 2000 genosubtype P1.7-2.4 represented 40% of all serogroup B isolates and gradually decreased to only 4% in 2018 (figure 4.6, figure 4.8; table 4.9). Approximately 80% (59/74 isolates) of the serogroup B isolates had at least one of the PorA epitopes present in the NonaMen vaccine currently in development (Table 4.9). However, vaccine coverage based on PorA sequences is declining since 2014 (Table 4.9).

The three serogroup C isolates had 3 different VR1/VR2 combinations. P1.5.2; P1.5-1,10-8 and P1.18-1,3.

In 2018, we received 16 PCR-positive samples, of which nine complete typing was possible. Of 102 serogroup W cases, 92 (90%) had P1.5.2, three P1.18-1.3 and seven with a diffent PorA type.

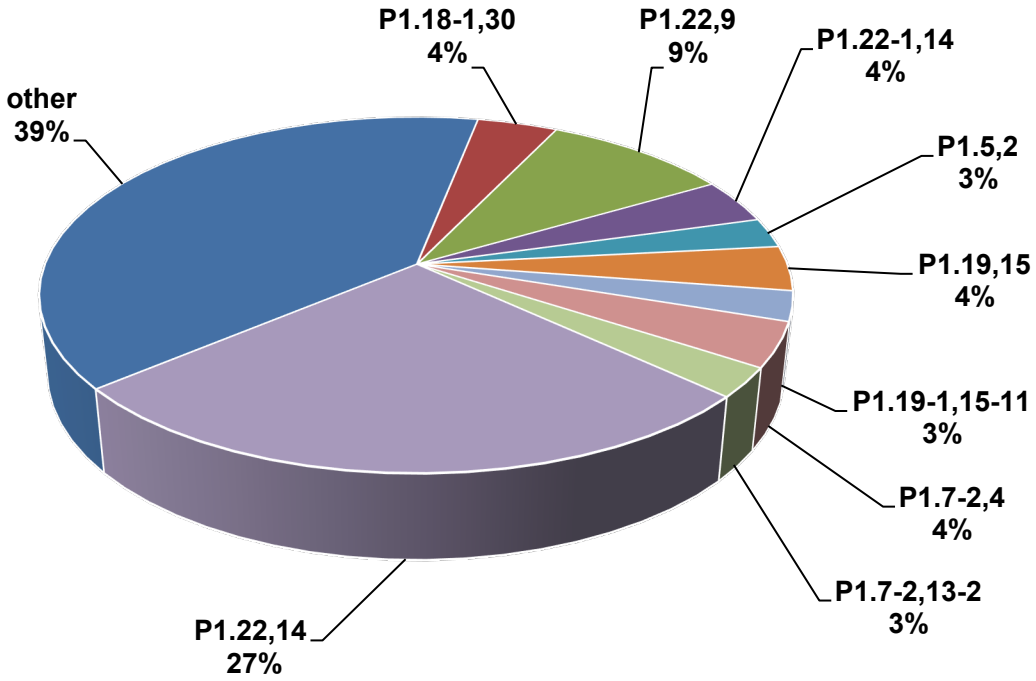

Figure 4.6 *Distribution of group B meningococcal PorA types, 2018*

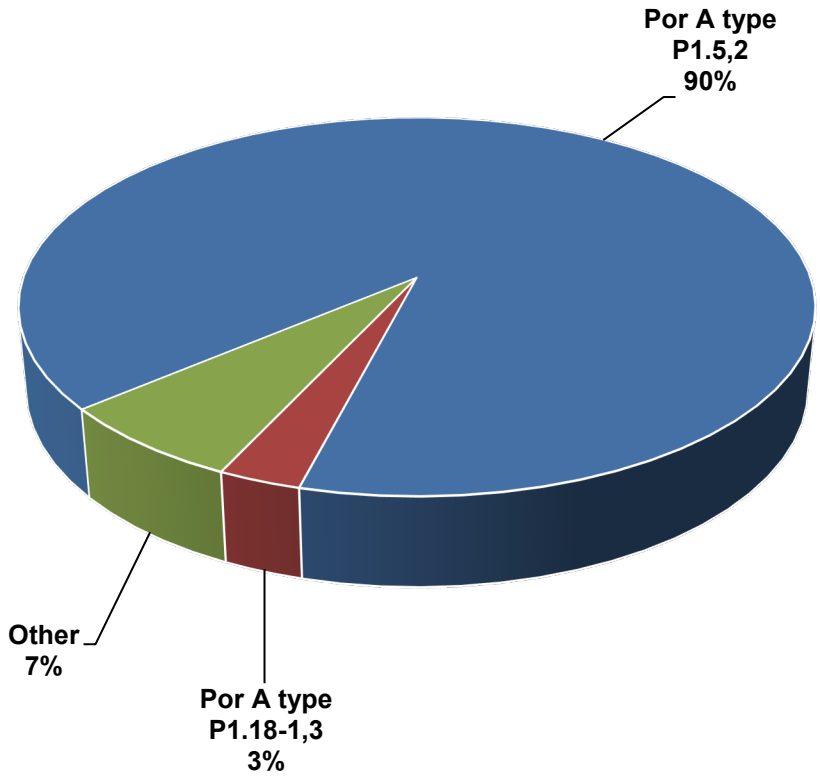

Figure 4.7 *Distribution of group W meningococcal PorA types, 2018*

Table 4.9 *N. meningitidis* serogroup B isolates according to PorA genosubtype, 2014-2018

	VR1.VR2 combination	YEAR									
		2014		2015		2016		2017		2018	
		No.	%	No.	%	No.	%	No.	%	No.	%
Vaccine types*	1.5-1, 2-2	0	**0**	0	**0**	1	**1.5**	1	**1.4**	0	**0.0**
	1.5-1, other	1	**1.9**	1	**1.6**	2	**3.0**	3	**4.2**	2	**2.7**
	1.5-2.10	4	**7.5**	3	**4.8**	3	**4.4**	2	**2.9**	0	**0.0**
	1.5-2, other	1	**1.9**	2	**3.2**	1	**1.5**	2	**2.9**	1	**1.3**
	1.7,16	0	**0**	1	**1.6**	2	**3.0**	1	**1.4**	1	**1.3**
	1.7, other	1	**1.9**	2	**3.2**	2	**3.0**	3	**4.2**	1	**1.3**
	1.7-1, 1	1	**1.9**	3	**4.8**	2	**3.0**	0	**0**	0	**0.0**
	1.7-1, other	1	**1.9**	0	**0**	1	**1.5**	1	**1.4**	0	**0.0**
	1.7-2,4	8	**15.0**	7	**11.3**	8	**11.9**	5	**7.0**	3	**4.1**
	1.7-2, other	3	**5.7**	5	**8.2**	4	**6.0**	2	**2.9**	6	**8.2**
	1.12-1,13	0	**0**	0	**0**	0	**0**	0	**0.0**	0	**0.0**
	1.12-1, other	1	**1.9**	2	**3.2**	2	**3.0**	1	**1.4**	0	**0.0**
	1.18-1,3	0	**0**	1	**1.6**	2	**3.0**	0	**0.0**	1	**1.3**
	1.18-1, other	9	**17.0**	5	**8.2**	4	**6.0**	4	**5.6**	5	**6.8**
	1.19,15-1	2	**3.7**	2	**3.2**	1	**1.5**	1	**1.4**	1	**1.3**
	1.19, other	3	**5.7**	3	**4.8**	3	**4.4**	4	**5.6**	5	**6.8**
	1.22,14	9	**17.0**	9	**14.6**	11	**16.4**	21	**29.6**	20	**27.0**
	1.22,other	3	**5.7**	3	**4.8**	4	**6.0**	4	**5.6**	8	**10.8**
	Other, 14	1	**1.9**	1	**1.6**	2	**3.0**	4	**5.6**	3	**4.1**
	Other, 16	1	**1.9**	2	**3.2**	1	**1.5**	2	**2.9**	2	**2.7**
	Subtotal vaccine types	49	**92.5**	52	**83.9**	56	**83.6**	61	**86.0**	59	**79.7**
NVT**	Other **Non Vaccine Type**	4	**7.5**	10	**16.1**	11	**16.4**	10	**14.0**	15	**20.3**
	Total	53	**100.0**	62	**100.0**	67	**100.0**	71	**100.0**	74	**100.0**

*based on a nonavalent PorA vaccine. NonaMen; serosubtypes P1.7,16; P1.5-1,2-2; P1.19,15-1; P1.5-2,10; P1.12-1,13; P1.7-2,4; P1.22,14; P1.7-1,1 and P1.18-1,3,6
**Non vaccine type

4.7 Distribution of FetA genosubtypes among serogroup B, C and W meningococci

In addition to sequencing of PorA epitopes, meningococcal isolates are also characterized by sequencing of an epitope of FetA. This outer membrane protein is involved in iron uptake by meningococci and is considered as a potential vaccine component. Therefore, the variability of this protein has been investigated intensively. The most variable part of the protein, called VR, has been used to establish a typing scheme. Analogous to PorA typing, the VR part of *fetA* is sequenced and translated to a putative amino acid sequence. So far, approximately 270 VR sequences comprising 6 classes have been identified, which are available at https://pubmlst.org/neisseria/FetA/
As an example of a type designation: F5-2, in which the first digit indicates the class and the second digit the variant of this class.

In 2018, 22 different FetA variants were observed among serogroup B meningococci. The dominant types were F5-1 and F5-5, accounting for 16% and 15% of group B meningococci, respectively (figure 4.6 and 4.7; table 4.10). In previous years, F1-5 consituted the dominant type within serogroup B meningococci, which was strongly linked to PorA VR1/VR2 P1.7-2.4 and together to the MLST clonal complex ST41/44. In 2018, 7 isolates were of the Fet A type F1-5 and all were linked to different PorA types (figure 4.8). For the dominant FetA type F5-1, 60% (7 out of 12 isolates) expressed PorA VR1/VR2 P1.22,14.

The three serogroup C meningococci had three different FetA types: F3-3, F3-6 and F3-9. In 2018, we received 102 serogroup W samples: 97 isolates and 5 PCR-positive samples. From only two PCR samples complete typing was not possible. The 102 meningococci W isolates displayed only 8 different FetA types (table 4.10) of which F1-1 was dominant (86%) and linked to PorA VR1/VR2 P1.5.2 and MLST clonal complex 11.

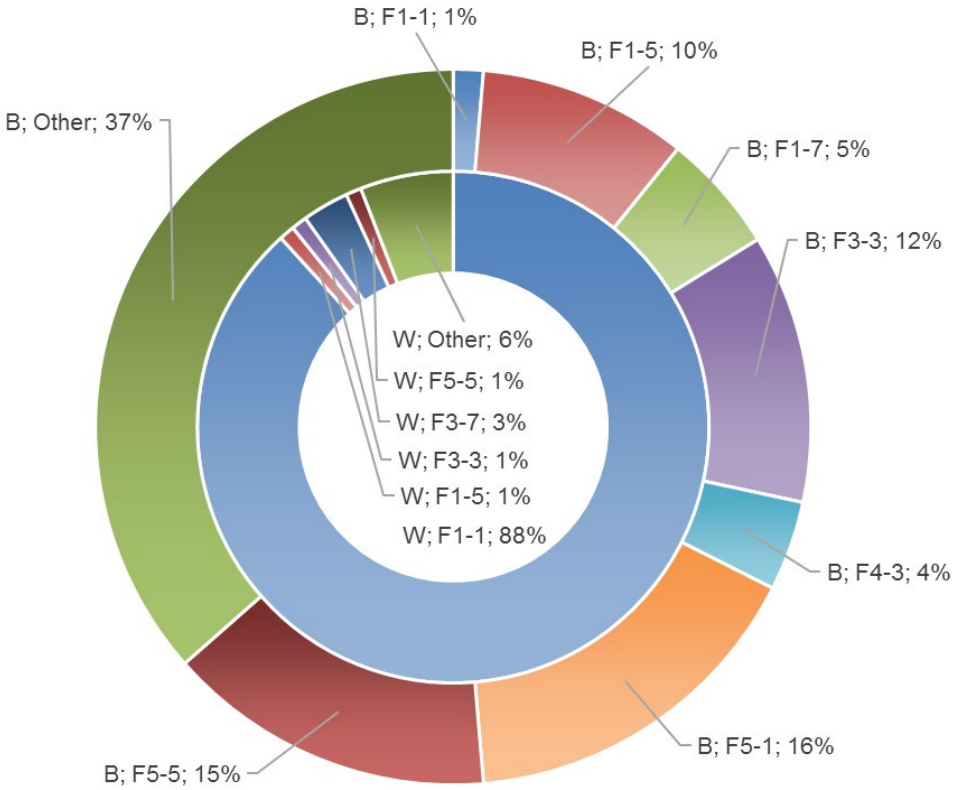

Figure 4.7 *Distribution of group B and W meningococcal FetA genosubtypes, 2018*

Table 4.10 *N. meningitidis* serogroup B, C sand W isolates according to Fet A genotype, 2014-2018

	YEARS														
	Men B					Men C					Men W				
FetA type	2014	2015	2016	2017	2018	2014	2015	2016	2017	2018	2014	2015	2016	2017	2018
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
F1-1	0	0	0	0	1	0	0	0	0	0	0	5	43	72	90
F1-5	8	10	16	12	7	0	0	0	1	0	0	0	0	0	1
F1-7	5	9	4	9	4	0	0	0	0	0	0	0	1	0	0
F1-15	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0
F3-3	10	9	7	7	9	1	7	2	3	1	0	0	0	0	1
F3-4	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1
F3-6	1	0	0	0	1	0	0	2	2	1	0	0	0	0	0
F3-7	0	0	1	0	0	0	0	0	0	0	0	0	0	2	3
F3-9	1	0	2	0	2	2	0	2	2	1	0	0	1	0	0
F4-1	1	2	0	3	2	0	0	0	0	0	1	2	0	1	0
F5-1	14	10	12	17	12	0	0	0	0	0	0	0	0	0	0
F5-2	0	2	1	1	2	0	0	0	0	0	0	0	0	0	0
F5-5	4	7	10	8	11	0	0	0	0	0	0	0	0	0	1
F5-8	1	1	1	0	1	0	0	0	0	0	0	0	0	0	1
F5-9	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0
F5-12	1	3	3	1	1	0	0	0	0	0	0	0	0	0	0
F5-36	0	0	0	2	1	0	0	0	0	0	0	0	0	0	2
Other	5	8	10	20	20	0	0	0	1	0	0	0	0	5	2
Total	**53**	**62**	**67**	**82**	**74**	**3**	**7**	**6**	**9**	**3**	**1**	**8**	**46**	**81**	**102**

In 2018, 36 different PorA VR1/VR2 combinations and 22 different FetA variants were encountered among serogroup B meningococci. Among the dominant FetA type F5-1, accounting for 16% of group B meningococci, 7 were of P1.22.14:F5-1, five had another combination. Frequently found combinations were P1.22.14:F5-5 (14%) , P1.22.14:F5-1 (8%) and P1.18-1,30:F3-3 (4%) (Figure 4.7).

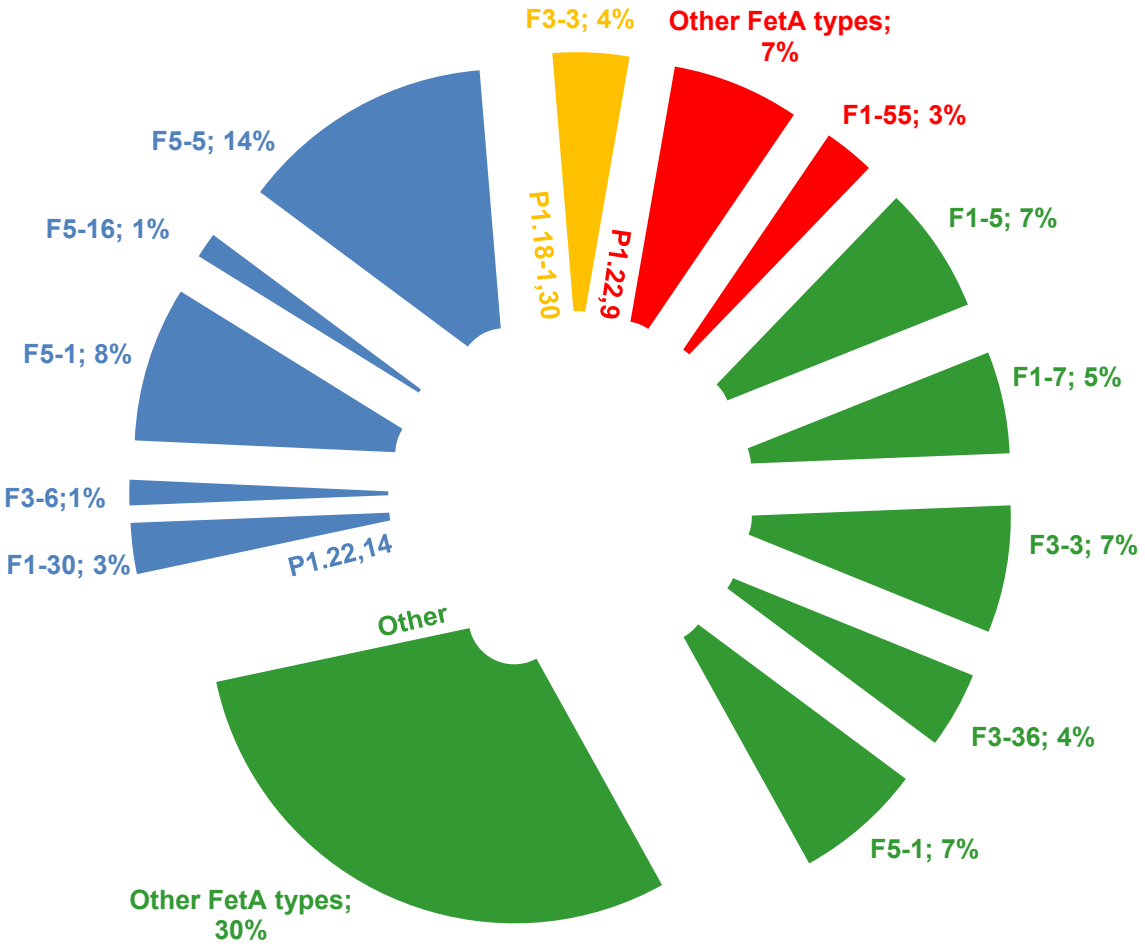

Figure 4.8 *Distribution and relation between PorA and FetA geno(sub)types within group B meningococcal isolates, 2018*

5 HAEMOPHILUS INFLUENZAE

5.1 General features

In total, 239 *Haemophilus influenzae* isolates were submitted to the Reference Laboratory, which is an increase compared to previous years (table 2.3, figure 5.1). Twenty-three isolates were from CSF (or CSF and blood) (2017: 30; 2016: 26; 2015: 22) and 216 from blood only. Fourty-five (18.8%) of the isolates were *H. influenzae* type b (table 5.1). From 1999 to 2004 the number of *H. influenzae* type b isolates received by the Reference Laboratory increased, but decreased after 2004. (table 5.4). The higher number of *H. influenzae* type b isolates was mainly due to an increase of *H. influenzae* type b cases among elderly people.

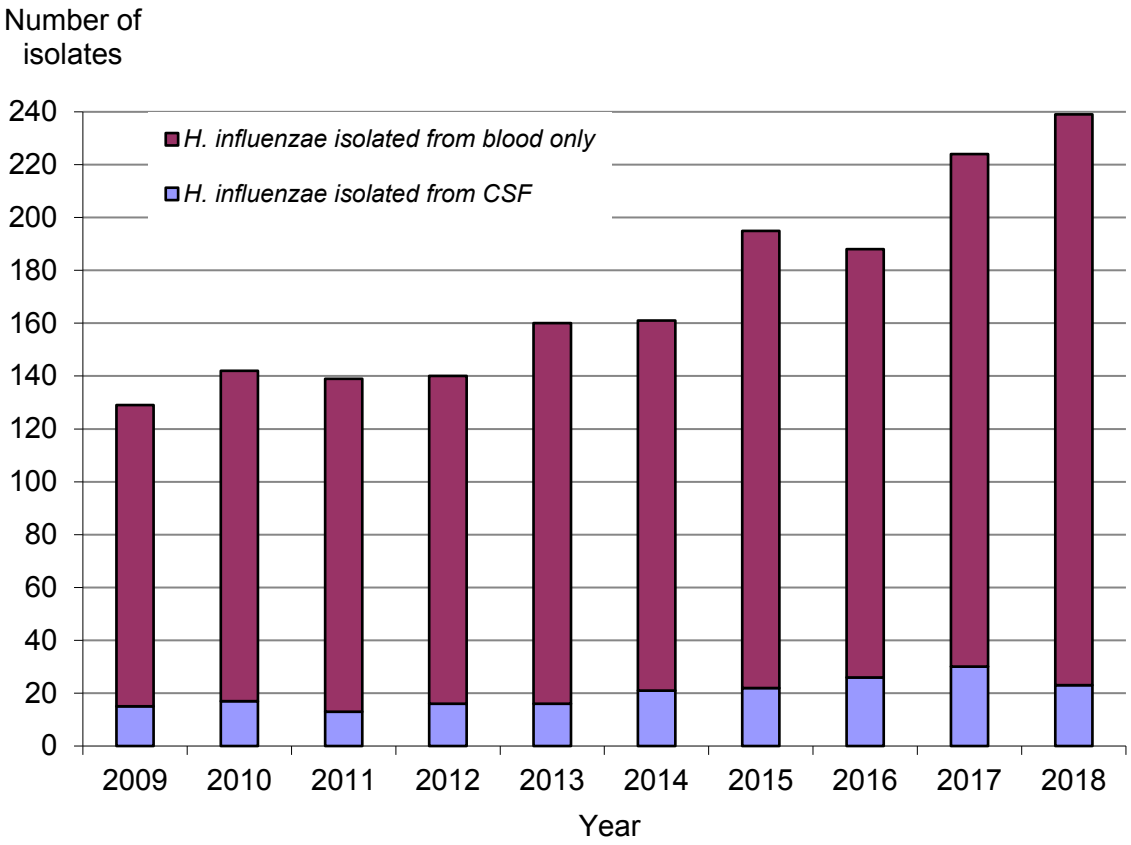

Figure 5.1 *Number and source of submitted H. influenzae isolates, 2009-2018*

5.2 Antibiotic susceptibility

The proportion of ß-lactamase-producing invasive *H. influenzae* isolates (CSF and/or blood) has been decreasing since 2004 and declined to less than 1% in 2008. In 2010, the proportion was 14.8%, which is the highest value in 25 years. During the history of the Reference Laboratory, the proportion of ß-lactamase-producing invasive *H. influenzae* isolates has always fluctuated for unknown reasons.

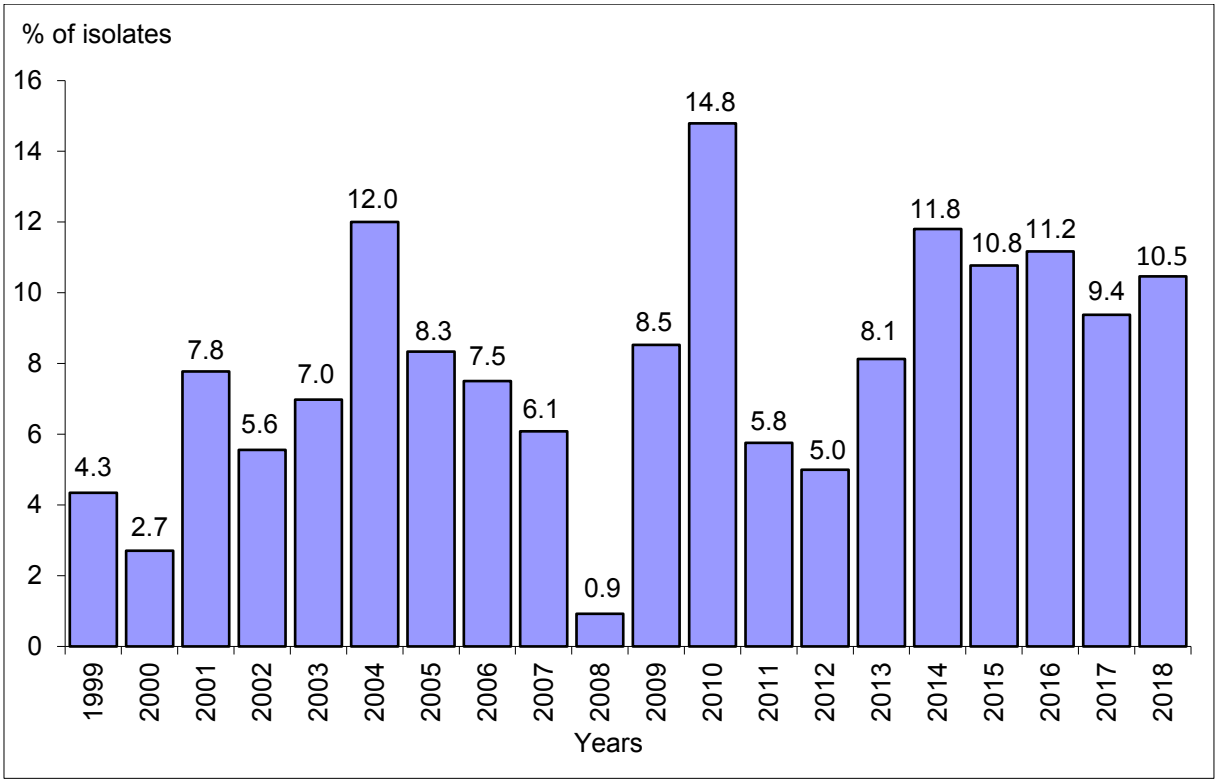

Figure 5.2 *Percentage β-lactamase producing H. influenzae among submitted isolates, 1999-2018*

5.3 Serotype and age

Fifteen cases of *H. influenzae* type b invasive disease were observed among children younger than 2 years of age (7 in 2017; 13 in 2016; 8 in 2015) (figure 5.3). Of 239 *H. influenzae* isolates, 168 were non-typeable (70%), 9 were isolated from CSF (or CSF and blood) and 159 were isolated from blood only (table 5.1. 5.2 and 5.3). Non-typeable strains were isolated more frequently than type b isolates (table 5.1).

Table 5.1 Total number of *H.influenzae isolates* from CSF and/or blood, according to serotype and age, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
a	0	0	1	1	0	0	0	0	**1**	***0.4***
b	0	8	11	19	2	1	6	17	**45**	***18.8***
e	0	0	0	0	0	0	1	4	**5**	***2.1***
f	0	0	1	1	0	0	3	16	**20**	***8.4***
n.t.*	4	9	3	16	2	7	22	121	**168**	***70.3***
Total	**4**	**17**	**16**	**37**	**4**	**8**	**32**	**158**	**239**	***100***
%	***1.7***	***7.1***	***6.7***	***15.5***	***1.7***	***3.3***	***13.4***	***66.1***	***100***	

* non-typeable

Table 5.2 *H.influenzae* isolates from CSF (or CSF and blood), according to serotype and age, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
a	0	0	1	1	0	0	0	0	**1**	***4.3***
b	0	3	5	8	0	1	0	0	**9**	***39.1***
e	0	0	0	0	0	0	0	0	**0**	***0.0***
f	0	0	0	0	0	0	1	3	**4**	***17.5***
n.t.*	0	1	0	1	0	2	1	5	**9**	***39.1***
Total	0	4	6	10	0	3	2	8	**23**	***100.0***
%	***0.0***	***17.4***	***26.1***	***43.5***	***0***	***13.0***	***8.7***	***34.8***	***100.0***	

* non-typeable

Table 5.3 *H. influenzae* isolates from blood only, according to serotype and age, 2018.

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
a	0	0	0	0	0	0	0	0	**0**	***0.0***
b	0	5	6	11	2	0	6	17	**36**	***16.7***
e	0	0	0	0	0	0	1	4	**5**	***2.3***
f	0	0	1	1	0	0	2	13	**16**	***7.4***
n.t.*	4	8	3	15	2	5	21	116	**159**	***73.6***
Total	**4**	**13**	**10**	**27**	**4**	**5**	**30**	**137**	**216**	***100.0***
%	***1.9***	***6.0***	***4.6***	***12.5***	***1.9***	***2.3***	***13.9***	***63.4***	***100.0***	

* non-typeable

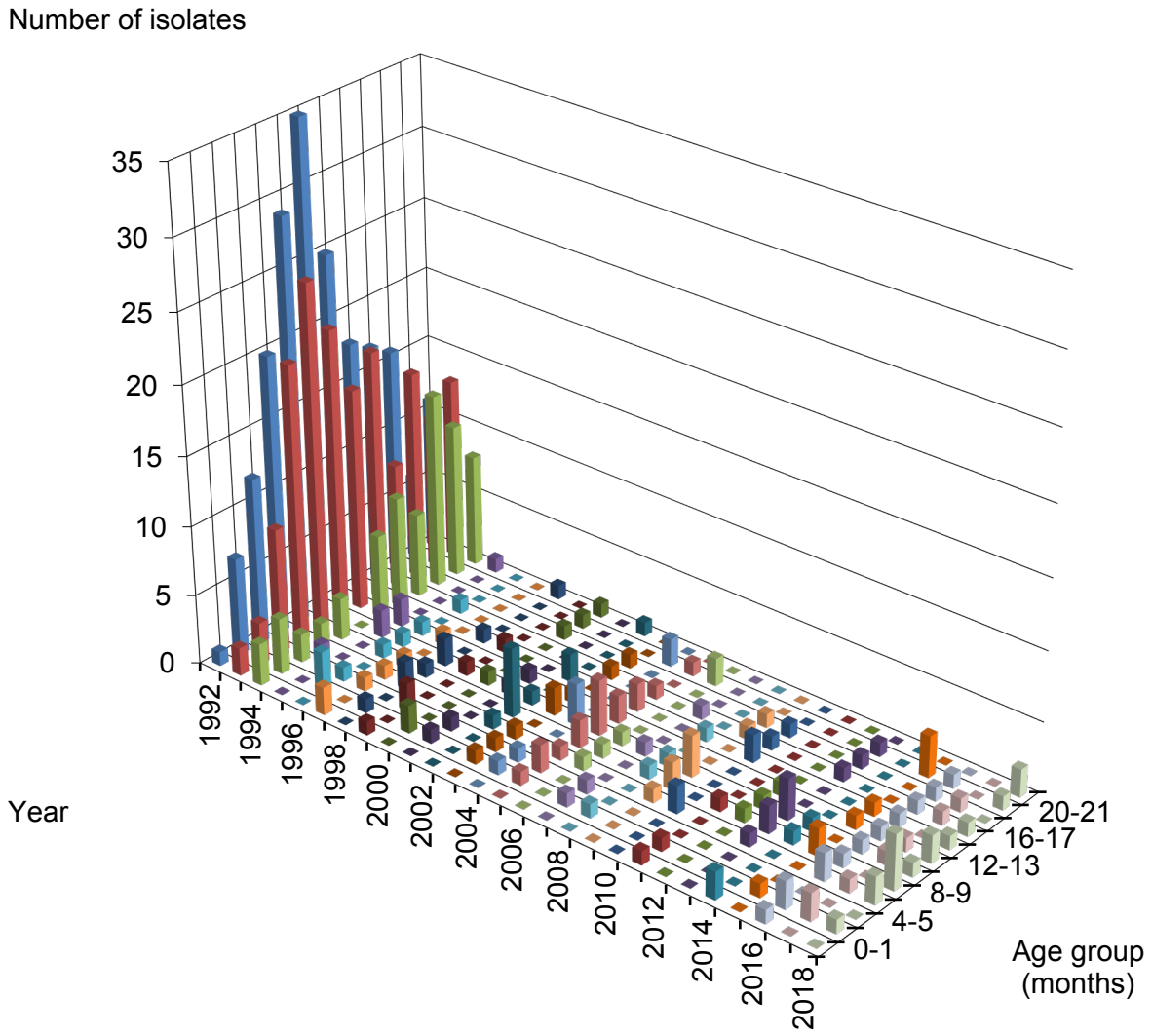

Figure 5.3 *Age distribution of H. influenzae type b invasive disease in the first two years of life, 1992-2018*

5.4 Distribution of non-typeable H. influenzae

The proportion of non-typeable isolates increased from 6% in 1992 to about 70% in 2018 (table 5.4). Also in absolute number the number of H. influenzae cases increased from 20 in 1992 to 168 in 2018 (Table 5.4).

Table 5.4 *H. influenzae* isolates from CSF and/or blood received from 1992 to 2018 according to year and serotype.

YEAR	SEROTYPE						TOTAL		CSF (or CSF and blood)	Blood Only
	a	b	d	e	f	n.t.*	Total	% n.t.*		
1992	-	294	-	-	1	20	315	**6.3**	241	74
1993	-	244	1	1	3	28	277	**10.1**	204	73
1994	-	148	-	-	2	26	176	**14.8**	112	64
1995	-	60	-	-	-	36	96	**37.5**	50	46
1996	-	30	-	-	6	52	88	**59.1**	28	60
1997	-	19	-	1	6	59	85	**69.4**	22	63
1998	-	19	1	-	5	63	88	**71.6**	31	57
1999	-	12	-	1	1	55	69	**79.7**	23	46
2000	4	15	1	2	4	48	74	**64.9**	24	50
2001	-	17	-	2	8	63	90	**70.0**	19	71
2002	-	31	-	1	13	63	108	**58.3**	28	79
2003	-	31	-	-	8	90	129	**69.8**	27	102
2004	-	48	-	2	4	71	125	**56.8**	32	93
2005	1	41	-	2	10	78	132	**59.1**	37	95
2006	-	24	-	4	7	85	120	**70.8**	25	95
2007	-	24	-	2	2	87	115	**75.7**	19	97
2008	-	25	-	-	11	72	108	**66.7**	19	89
2009	-	32	1	3	9	84	129	**65.1**	15	114
2010	1	37	-	3	5	96	142	**67.6**	17	125
2011	-	22	-	8	11	98	139	**70.5**	13	126
2012	1	28	-	2	8	101	140	**72.1**	16	124
2013	-	29	-	3	13	115	160	**71.9**	16	144
2014	1	30	1	3	8	118	161	**72.7**	21	140
2015	-	34	-	8	20	133	195	**67.7**	22	173
2016	1	44	1	5	12	125	188	**65.4**	26	162
2017	1	46	-	4	14	159	224	**71.0**	30	194
2018	1	45	-	5	20	168	239	**70.3**	23	216

* non-typeable

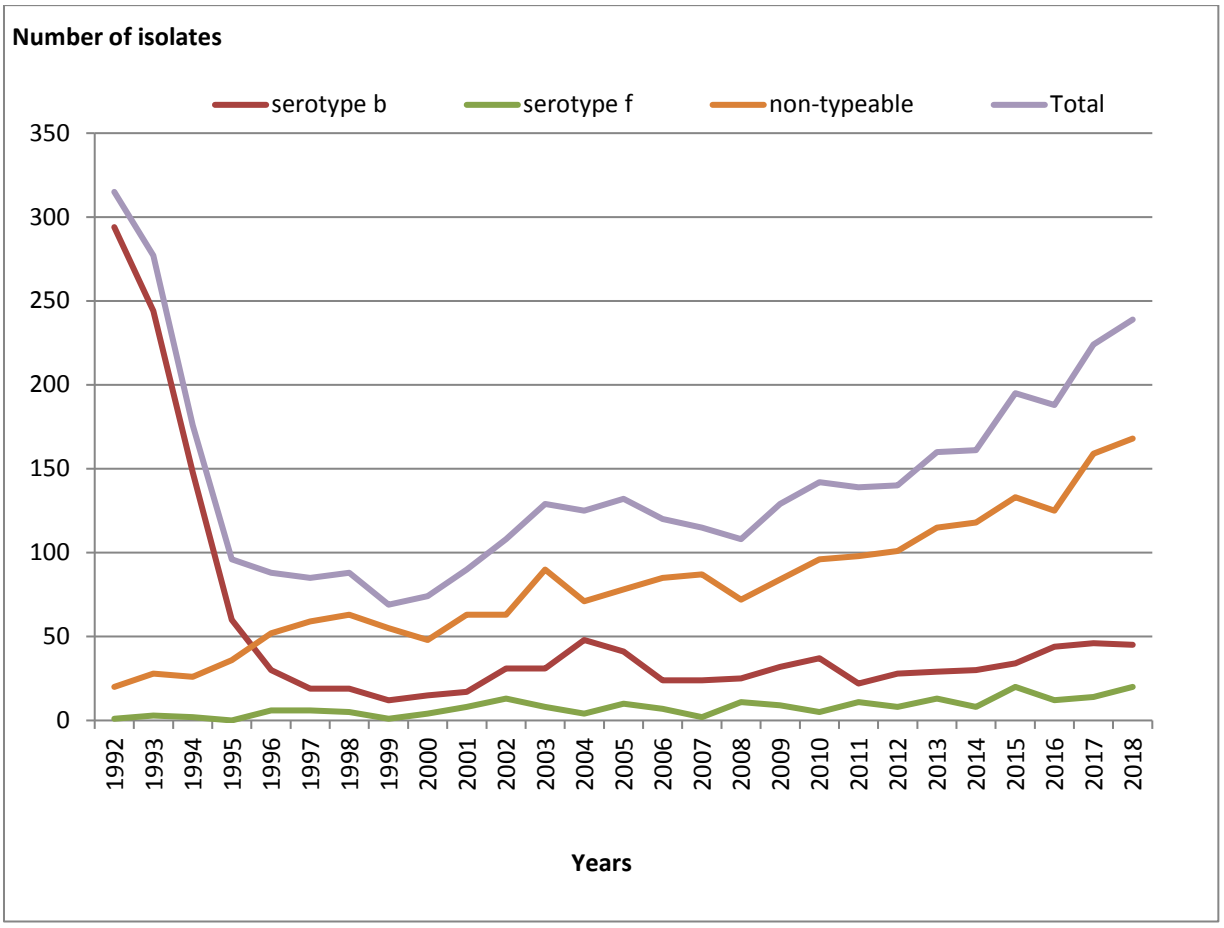

Figure 5.4 *Number of cases due to H. influenzae serotypes b and f and non-typeable H. influenzae, 1992-2018*

In 2018, the number of *H. influenzae* type b remained stable compared to the previous year which showed the highest number of cases since the last 13 years (Table 5.4). Since 2000, the number of cases of nontypeable and serotype b increased. In addition, since 2008, the number of cases due to serotype f is increasing, albeit slowly (Figure 5.4). The absolute number of non-typeable isolates from CSF has remained stable during the period 1992 to 2018 (figure 5.5). In 2018, 9 non-typeable isolates from CSF were received, which was a two-fold reduction compared to 2017. In contrast, the number of non-typeable *H. influenzae* isolates from blood has been steadily increasing during the period 1992 to 2018 from 15 to 159 (figure 5.4, 5,5).

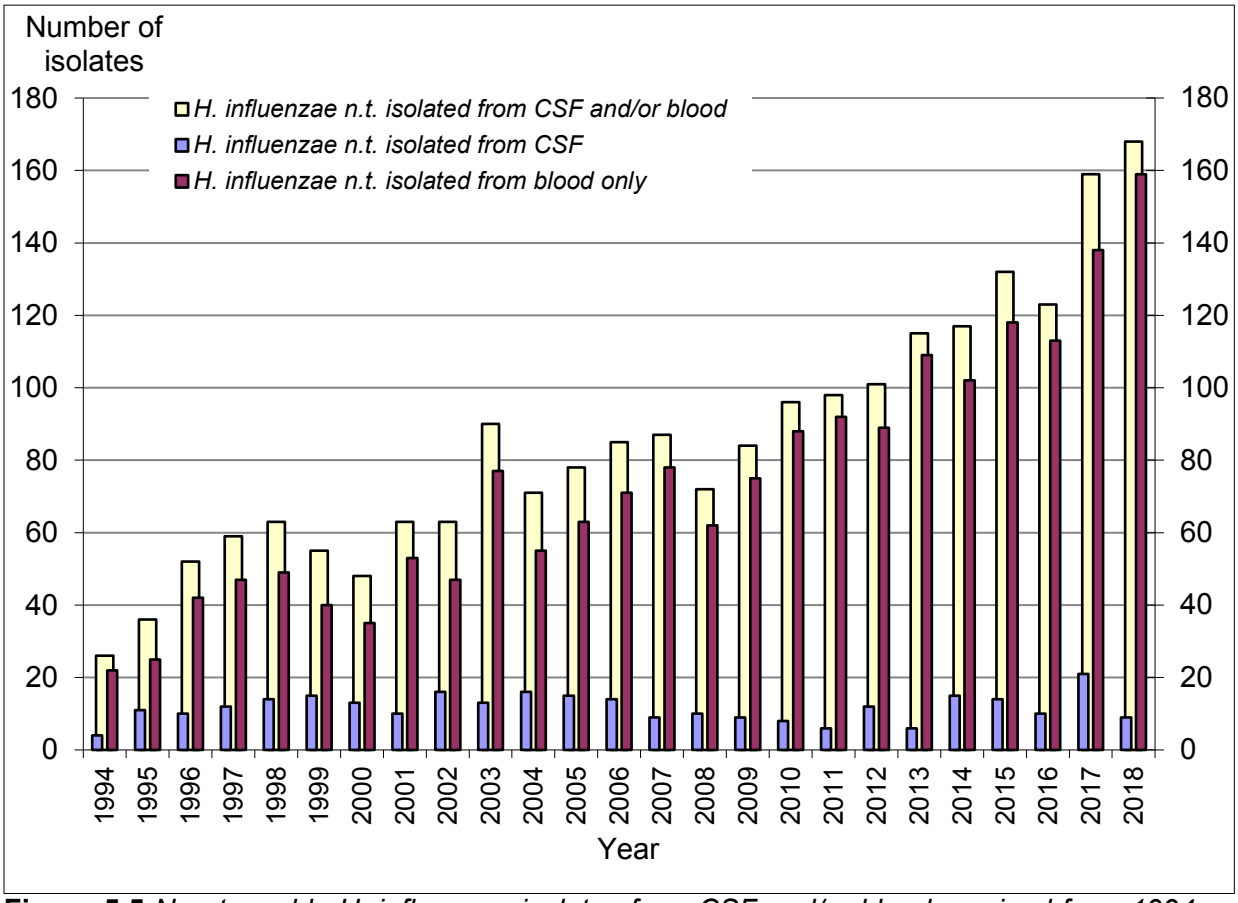

Figure 5.5 *Non-typeable H. influenzae isolates from CSF and/or blood received from 1994 - 2018*

Table 5.5 Non-typeable *H. influenzae* isolates from CSF and/or blood received from 2009 to 2018 according to year and biotype.

	Biotype							Total
	I	II	III	IV	V	VI	VII	
2009	28	30	12	10	3	1	-	**84**
2010	20	49	19	2	6	-	-	**96**
2011	27	41	24	3	2	1	-	**98**
2012	25	49	17	2	6	1	1	**101**
2013	25	44	30	7	7	2	-	**115**
2014	16	56	32	1	9	3	-	**117**
2015	22	55	45	1	8	-	1	**132**
2016	16	65	30	6	5	-	1	**123**
2017	15	80	51	1	9	3	-	**159**
2018	15	84	47	6	14	2	-	**168**

*non-typable

Among non-serotypeable *H. influenzae* isolates, biotype II was the predominant biotype during the last ten years (Table 5.5).

6 STREPTOCOCCUS PNEUMONIAE

6.1 General features

From 2003 onwards, the Reference Laboratory requested nine sentinel laboratories, evenly distributed across the country and covering 25% of the Dutch population to submit pneumococcal isolates from CSF and/or blood. All medical microbiology laboratories were asked to submit pneumococcal isolates from CSF (or CSF and blood). From 2006, all laboratories are requested to submit all invasive pneumococcal isolates from patients in the age group 0-4 years. In 2006, the 7-valent conjugate pneumococcal polysaccharide vaccine was introduced in the National Immunization Programme. This vaccine was replaced by the 10-valent conjugate pneumococcal polysaccharide vaccine from March 1, 2011 onwards. From 2017, all medical microbiology laboratories are requested to submit all invasive pneumococcal isolates without restriction to age of the patient. In 2018, the Reference Laboratory received 1,909 isolates nationwide of which 655 pneumococcal isolates were received from the 9 sentinel laboratories. Of the 1,909 nationwide submitted isolates, 152 isolates were from CSF (or CSF and blood). The Reference Laboratory also received 8 PCR positive, culture negative (CSF or blood) samples. The incidence of pneumococcal meningitis gradually increased from 1.0 per 100,000 individuals in 1990 to 1.6 per 100,000 individuals in 2004. The introduction of the polyscaccharide conjugate vaccines decreased pneumococcal meningitis incidence to 0.9 per 100,000 individuals in 2018 (Figure 6.1).

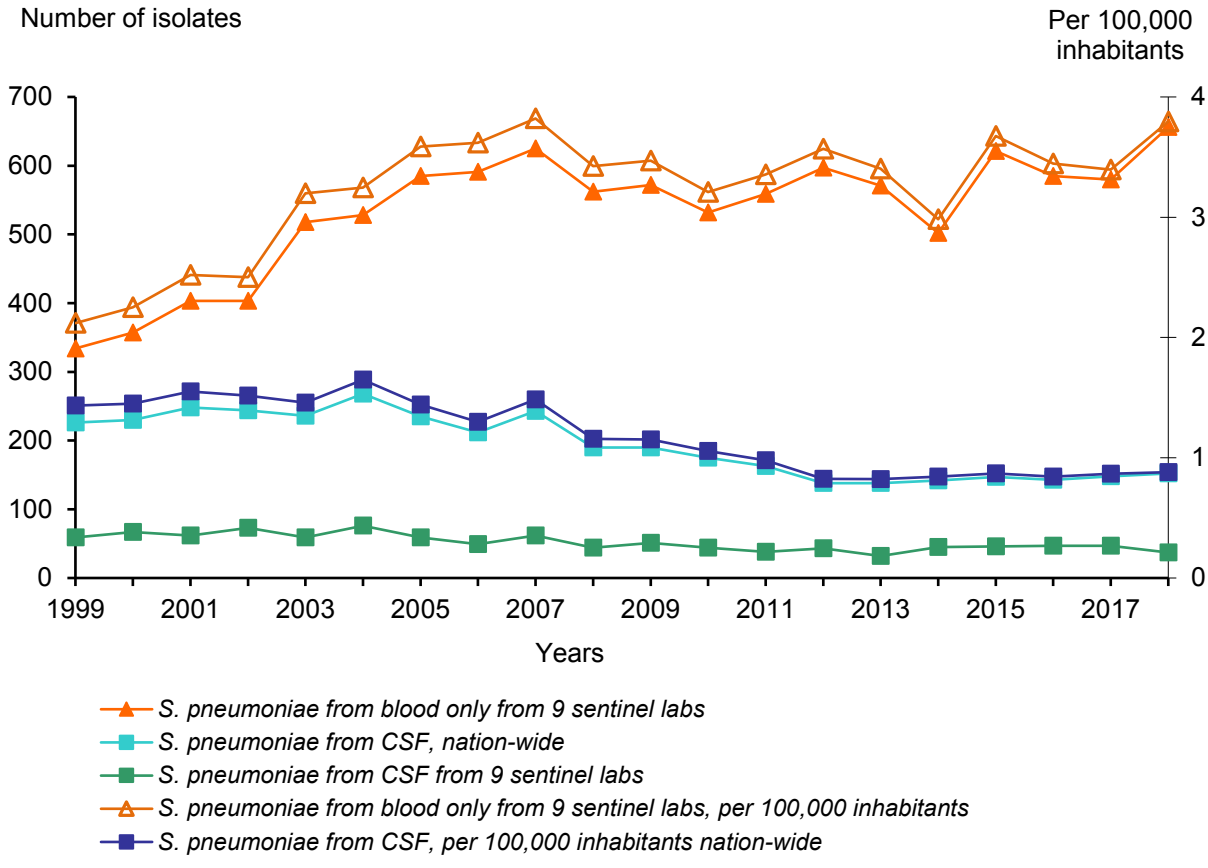

Figure 6.1 *Number of S. pneumoniae isolates and disease incidence, 1999-2018*

Figure 6.2 shows the distribution of *S. pneumoniae* isolates according to the patients' age. The incidence of pneumococcal meningitis is highest among patients in the age group 70 – 75 year.

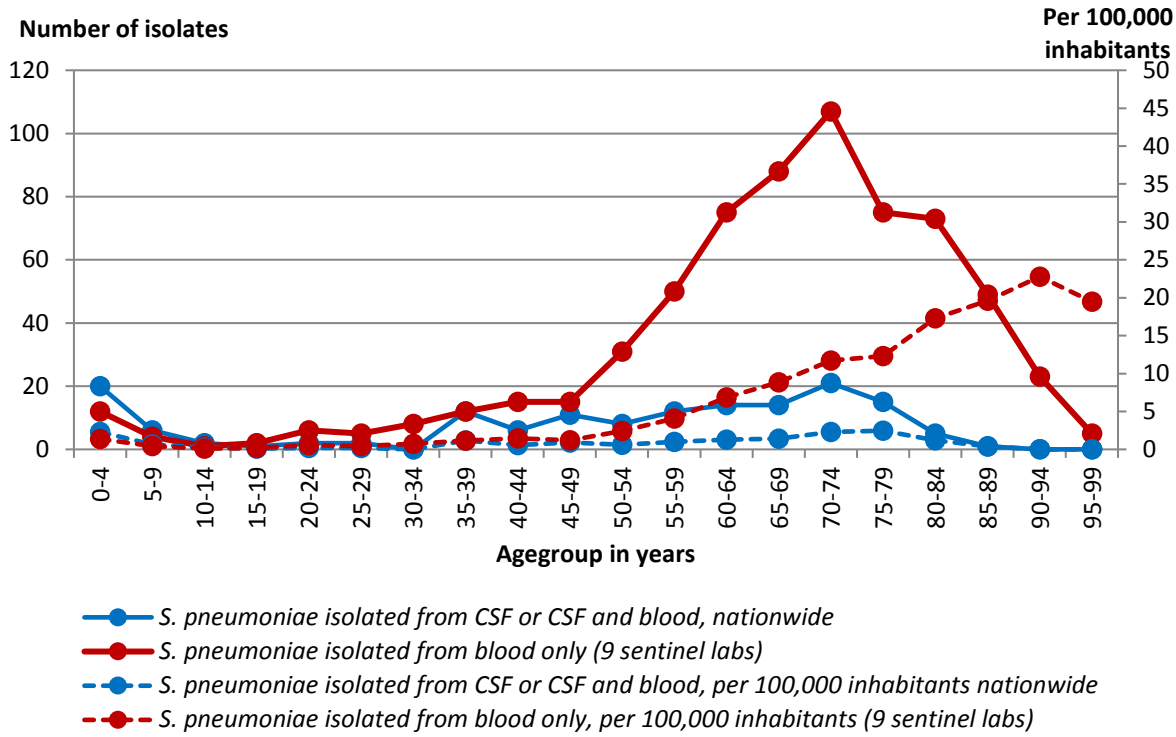

Figure 6.2 Age *distribution of S. pneumoniae isolates received in 2018 and grouped according to isolation source*

6.2 Antibiotic susceptibility

Among 655 isolates from blood only (9 sentinel labs), 31 (5%) isolates were intermediately susceptible to penicillin (0.06 < MIC ≤ 2.0 mg/L; table 6.1) and one isolate was resistant to penicillin (MIC > 2.0 mg/L). Among 152 nationwide *S. pneumoniae* isolates from CSF (or CSF and blood), 6 (3.7%) strains were resistant to penicillin (MIC > 0.06 mg/L).

Table 6.1 Susceptibility of *S. pneumoniae* isolates to penicillin, 2018

	Penicillin*				
	S	I	R	Total	%
MIC for CSF isolates (Nationwide)	MIC ≤ 0.06		MIC > 0.06		
CSF or CSF and blood	146	-	6	**152**	***18.8***
MIC for blood isolates (9 sentinel labs)	MIC ≤ 0.06	0.06< MIC ≤ 2.0	MIC >2.0		
Blood only	623	31	1	**655**	***81.2***
Total	**769**	**31**	**7**	**807**	***100.0***
%	***95.3***	***3.8***	***0.9***	***100.0***	

* MIC values in mg/L according to EUCAST guidelines

6.3 Distribution according to serotype

The relationship between age and major serotypes of isolates received from the 9 sentinel laboratories is shown in table 6.2. For nationwide isolates from CSF (or CSF and blood), the distribution of serotypes by age of the patient is presented in table 6.3. while the incidence of pneumococcal meningitis per serotype per 100,000 inhabitants is shown in table 6.4. The distribution of serotypes by age of the patient for pneumococcal isolates from blood only is shown in table 6.5. As aforementioned, incidences of *S. pneumoniae* from blood only are incomplete. Effect of the 10-valent vaccine can been seen in table 6.6 and table 6.7, which shows a reduction of the number of serotypes covered by the vaccine. However, the overall number of invasive pneumococcal disease isolates increased due to an increase of the number of isolates with non-vaccine serotypes.

Table 6.2 Serotype and age distribution of *S. pneumoniae* isolates from CSF and/or blood submitted by the 9 sentinel laboratories, 2018

	sero	AGE (MONTHS)			AGE (YEARS)											
	type	0	1-11	12-59	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-64	65-79	≥80	Total	%
23-valent vaccine / 10-valent vaccine / 7-valent vaccine	4	-	-	1	1	-	-	-	1	1	-	-	1	2	6	***0.9***
	6B	-	-	-	-	-	-	1	-	-	-	-	1	-	2	***0.3***
	9V	-	-	-	-	-	-	-	-	-	-	-	2	1	3	***0.4***
	14	-	-	-	-	-	-	-	-	-	1	1	1	-	3	***0.4***
	18C	-	-	-	-	-	-	-	-	-	-	-	1	-	1	***0.1***
	19F	-	-	-	-	-	-	-	-	-	-	2	3	2	7	***1.0***
	23F	-	-	-	-	-	-	-	-	-	-	-	-	-	-	***0.0***
	Subtotal	-	-	*1*	*1*	-	-	*1*	*1*	*1*	*1*	*3*	*9*	*5*	*22*	***3.1***
	1	-	-	1	1	-	1	-	1	1	1	1	2	-	8	***1.2***
	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	***0.0***
	7F	-	1	-	1	-	-	-	1	1	2	9	7	3	24	***3.5***
	Subtotal	-	1	2	3	-	1	1	3	3	4	13	18	8	54	***7.8***
	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**
	3	-	-	-	-	-	-	-	1	1	5	16	35	16	74	***10.7***
	8	-	1	-	1	2	-	-	4	10	8	46	66	26	163	***23.6***
	9N	-	-	-	-	-	-	-	-	1	2	5	17	9	34	***4.9***
	10A	-	-	-	-	-	1	-	-	-	-	2	7	-	10	***1.4***
	11A	-	-	-	-	-	-	-	-	-	2	1	3	3	9	***1.3***
	12F	-	1	-	1	-	-	-	2	3	-	6	13	3	28	***4.0***
	15B	-	-	1	1	-	-	-	-	-	-	1	4	3	9	***1.3***
	17F	-	-	-	-	-	-	-	-	-	1	-	3	1	5	***0.7***
	19A	1	2	-	3	1	-	1	1	2	4	33	32	26	103	***14.9***
	20	-	-	-	-	-	-	-	-	-	-	1	1	4	6	***0.9***
	22F	-	-	-	-	-	-	-	-	-	1	13	22	9	45	***6.5***
	33F	-	1	-	1	-	-	1	-	-	1	7	9	10	29	***4.2***
Subtotal 23-valent vaccine		*1*	*6*	*4*	*10*	*3*	*2*	*3*	*11*	*20*	*28*	*144*	*230*	*118*	*569*	***82.2***
	Other	-	1	6	7	2	-	-	1	2	5	22	51	33	123	***17.8***
	Total	**1**	**7**	**10**	**17**	**5**	**2**	**3**	**12**	**22**	**33**	**166**	**281**	**151**	**692**	***100.0***

Table 6.3 Nationwide serotype and age distribution of *S. pneumoniae* isolates from CSF (or CSF and blood), 2018.

			AGE (MONTHS)			AGE (YEARS)											
		TYPE	0	1-11	12-59	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-64	65-79	≥80	Total	%
23-valent vaccine	10-valent vaccine	7-valent vaccine 4	-	-	-	-	-	-	-	-	-	1	-	1	-	2	***1.3***
		6B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**
		9V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**
		14	-	-	-	-	-	-	-	-	-	1	-	1	-	2	***1.3***
		18C	-	1	-	1	-	-	-	-	-	-	-	-	-	1	***0.7***
		19F	-	-	-	-	-	-	-	-	-	-	1	-	-	1	***0.7***
		23F	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**
		Subtotal	-	1	-	*1*	-	-	-	-	-	*2*	*1*	*2*	-	*6*	***3.9***
		1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**
		5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**
		7F	-	-	-	-	-	-	-	-	-	-	1	1	-	2	***1.3***
		Subtotal	-	*1*	-	*1*	-	-	-	-	-	*2*	*2*	*3*	-	*8*	***5.2***
		2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**
		3	-	-	-	-	3	-	-	-	4	1	3	8	1	20	***13.2***
		8	-	1	-	1	1	-	-	-	-	4	9	8	-	23	***15.1***
		9N	-	-	-	-	-	-	-	-	-	1	2	1	-	4	***2.6***
		10A	-	1	1	2	-	1	-	-	-	2	-	2	-	7	***4.6***
		11A	-	-	-	-	-	-	-	-	2	3	1	2	-	8	***5.3***
		12F	-	2	-	2	-	-	-	-	2	-	3	4	-	11	***7.2***
		15B	-	-	-	-	-	-	-	-	-	-	2	-	-	2	***1.3***
		17F	-	-	-	-	-	-	-	-	-	-	-	2	-	2	***1.3***
		19A	-	2	-	2	-	-	1	-	1	1	3	4	1	13	***8.6***
		20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**
		22F	-	1	1	2	-	-	-	-	-	1	1	3	1	8	***5.3***
		33F	-	4	-	4	-	-	-	-	-	-	-	2	-	6	***4.0***
Subtotal 23-valent vaccine			-	*12*	*2*	*14*	*4*	*1*	*1*	-	*9*	*15*	*26*	*39*	*3*	*112*	***73.7***
		Other	1	3	2	6	2	1	-	4	3	2	8	11	3	40	***26.3***
		Total	**1**	**15**	**4**	**20**	**6**	**2**	**1**	**4**	**12**	**17**	**34**	**50**	**6**	**152**	***100.0***

* From 9 patients with a pneumococcus isolated from blood. CSF was culture-negative but PCR was positive for pneumococcal DNA. Cases were in age groups 40-49 years (2). 50-64 years (2), 65-79 years (4) and >80 years of age (1)

Table 6.4 Age-specific incidence of pneumococcal meningitis nationwide (isolates from CSF or CSF and blood) per 100,000 inhabitants according to serotype, 2018

	AGE (YEARS)										
TYPE	0	1-4	5-9	10-14	15-19	20-29	30-39	40-49	50-64	65-79	≥80	Total
7-valent	0.59	0.00	0.00	0.00	0.00	0.00	0.00	0.09	0.03	0.08	0.00	0.03
10-valent	0.59	0.00	0.00	0.00	0.00	0.00	0.00	0.09	0.06	0.12	0.00	0.05
23-valent	7.08	0.29	0.43	0.10	0.10	0.00	0.43	0.65	0.73	1.59	0.39	0.65
Other	2.36	0.29	0.22	0.10	0.00	0.18	0.14	0.09	0.22	0.45	0.39	0.25
Total	**9.44**	**0.57**	**0.65**	**0.21**	**0.10**	**0.18**	**0.58**	**0.74**	**0.95**	**2.03**	**0.77**	**0.88**

Table 6.5 Serotype and age-dependent distribution of *S. pneumoniae* isolates from blood submitted by the 9 sentinel laboratories, 2018.

			AGE (MONTHS)			AGE (YEARS)											
		TYPE	0	1-11	12-59	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-64	65-79	≥80	Total	%
23-valent vaccine	10-valent vaccine	7-valent vaccine 4	-	-	1	1	-	-	-	1	1	-	-	1	2	6	***0.9***
		6B	-	-	-	-	-	-	1	-	-	-	-	1	-	2	***0.3***
		9V	-	-	-	-	-	-	-	-	-	-	-	2	1	3	***0.5***
		14	-	-	-	-	-	-	-	-	-	-	1	1	-	2	***0.3***
		18C	-	-	-	-	-	-	-	-	-	-	-	1	-	1	***0.2***
		19F	-	-	-	-	-	-	-	-	-	-	2	3	2	7	***1.0***
		23F	-	-	-	-	-	-	-	-	-	-	-	-	-	-	***-***
		Subtotal	-	-	*1*	*1*	-	-	*1*	*1*	*1*	-	*3*	*9*	*5*	*21*	***3.2***
		1	-	-	1	1	-	1	-	1	1	1	1	2	-	8	***1.2***
		5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	***-***
		7F	-	1	-	1	-	-	-	1	1	2	9	6	3	23	***3.5***
		Subtotal	-	1	2	*3*	-	*1*	*1*	*3*	*3*	*3*	*13*	*17*	*8*	*52*	***7.9***
		2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	***-***
		3	-	-	-	-	-	-	-	1	-	5	16	33	16	71	***10.9***
		8	-	1	-	1	2	-	-	4	10	7	43	66	26	159	***24.3***
		9N	-	-	-	-	-	-	-	-	1	1	4	16	9	31	***4.7***
		10A	-	-	-	-	-	-	-	-	-	-	2	6	-	8	***1.2***
		11A	-	-	-	-	-	-	-	-	-	2	-	3	3	8	***1.2***
		12F	-	-	-	-	-	-	-	2	2	-	4	11	3	22	***3.4***
		15B	-	-	1	1	-	-	-	-	-	-	-	4	3	8	***1.2***
		17F	-	-	-	-	-	-	-	-	-	1	-	2	1	4	***0.6***
		19A	1	1	-	2	1	-	-	1	2	4	33	32	26	101	***15.4***
		20	-	-	-	-	-	-	-	-	-	-	1	1	4	6	***0.9***
		22F	-	-	-	-	-	-	-	-	-	1	13	22	9	45	***6.9***
		33F	-	-	-	-	-	-	1	-	-	1	7	9	10	28	***4.3***
Subtotal 23-valent vaccine			*1*	*3*	*3*	*7*	*3*	*1*	*2*	*11*	*18*	*25*	*136*	*222*	*118*	*543*	***82.9***
		Other	-	4	1	5	1	-	-	-	2	5	20	47	32	112	***17.1***
		Total	**1**	**7**	**4**	**12**	**4**	**1**	**2**	**11**	**20**	**30**	**156**	**269**	**150**	**655**	***100.0***

Table 6.6 Serotype distribution of nationwide pneumococcal CSF isolates, 2009-2018

		TYPE	Year 2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
23-valent vaccine	10-valent vaccine	7-valent vaccine	4	3	2	4	2	2	-	1	1	2
			6B	3	-	2	-	-	-	1	-	-	-
			9V	2	2	-	3	1	1	-	2	-	-
			14	3	5	2	1	-	-	1	-	-	2
			18C	6	5	5	2	2	-	1	-	1	1
			19F	10	2	6	4	2	4	2	5	6	1
			23F	5	4	2	1	-	-	1	-	1	-
			***Subtotal* 7-valent vaccine**	*33*	*21*	*19*	*15*	*7*	*7*	*6*	*8*	*9*	*6*
			1	8	3	1	1	3	4	1	2	1	-
			5	-	2	-	3	-	-	-	-	-	-
			7F	25	20	28	16	15	8	7	4	2	2
			***Subtotal* 10-valent vaccine**	*66*	*46*	*48*	*35*	*25*	*19*	*14*	*14*	*12*	*8*
			2	-	-	-	-	-	-	-	-	-	-
			3	24	20	7	13	16	13	16	25	20	20
			8	10	10	17	9	16	23	24	18	21	23
			9N	3	6	7	4	2	6	6	3	6	4
			10A	10	9	7	9	7	12	5	7	7	7
			11A	8	1	5	1	1	3	2	3	2	8
			12F	2	3	7	10	9	8	9	12	8	11
			15B	8	2	3	1	-	-	-	5	7	2
			17F	-	4	3	1	1	1	-	-	1	2
			19A	6	20	16	6	9	7	10	8	16	13
			20	-	1	-	-	1	1	1	-	-	-
			22F	13	14	16	11	8	8	11	11	8	8
			33F	6	7	5	6	3	2	4	4	6	6
			***Subtotal* 23-valent vaccine**	*156*	*143*	*141*	*106*	*98*	*103*	*102*	*110*	*114*	*112*
			6A	6	5	1	1	1	3	-	1	-	-
			6C	-	3	4	2	6	3	6	5	3	3
			7B	-	-	-	-	1	-	-	-	-	-
			10F	-	-	-	-	-	-	-	-	-	-
			10B	-	-	-	1	-	1	1	-	1	-
			12A	-	-	-	-	-	-	-	-	-	-
			13	1	-	-	-	-	-	-	-	-	-
			15A	-	1	1	1	4	6	7	2	4	3
			15C	1	2	-	3	-	-	1	-	3	1
			16F	-	5	4	-	5	2	1	3	1	5
			17A	1	-	-	-	-	-	-	-	-	-
			18F	-	-	-	-	-	-	-	-	-	-
			18A	-	-	-	-	-	-	-	-	-	-
			18B	-	-	-	1	-	-	-	-	-	-
			21	-	-	1	-	-	-	-	-	-	2
			22A	1	1	-	-	-	-	1	1	-	-
			23A	3	3	2	4	4	4	5	5	5	8
			23B	7	5	2	5	7	8	11	6	11	8
			24F	6	1	1	4	4	7	7	1	2	1
			24B	-	-	-	2	-	-	-	-	-	-
			25	-	-	-	-	-	-	-	-	-	-
			27	-	-	-	1	-	2	1	1	-	1
			28F	-	-	-	-	1	-	-	-	-	-
			28A	-	-	1	-	-	-	-	-	-	-
			29	-	-	-	1	-	-	-	-	-	-
			31	1	1	-	1	-	1	-	1	1	-
			33A	-	-	-	-	-	-	-	-	-	-
			34	1	-	1	-	-	-	1	1	1	2
			35F	2	4	1	-	2	1	2	5	1	3
			35B	-	1	-	1	3	1	1	1	-	2
			35D	-	-	-	-	-	-	-	-	-	1
			37	1	-	1	2	1	-	-	-	-	-
			38	3	1	-	2	1	-	-	-	-	-
			Rough (n.t.)	-	-	-	-	-	-	-	-	1	-
			Total	190	176	163	138	138	142	147	143	148	152

Table 6.7 Serotype distribution of *S. pneumoniae* from blood submitted by the 9 sentinel laboratories, 2009-2018

			TYPE	Year 2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
23-valent vaccine	10-valent vaccine	7-valent	4	26	17	27	11	13	6	6	6	6	6
			6B	12	8	3	3	3	3	4	1	-	2
			9V	26	21	5	2	4	1	5	-	2	3
			14	34	22	19	12	8	2	7	8	4	2
			18C	15	7	8	4	8	2	2	2	1	1
			19F	10	5	9	3	5	7	8	6	9	7
			23F	12	13	5	3	1	2	1	1	1	-
			Subtotal 7-valent vaccine	*135*	*93*	*85*	*38*	*42*	*23*	*33*	*24*	*23*	*21*
			1	65	53	40	50	40	41	41	22	8	8
			5	6	7	11	8	9	2	1	-	1	-
			7F	86	72	91	92	75	53	56	36	27	23
			Subtotal 10-valent vaccine	*292*	*225*	*227*	*188*	*166*	*119*	*131*	*82*	*59*	*52*
			2	-	-	-	-	-	-	-	-	-	-
			3	34	30	36	45	40	31	35	45	51	71
			8	52	60	59	88	108	93	136	151	143	159
			9N	18	19	17	20	19	21	26	32	29	31
			10A	9	9	14	8	6	16	15	11	11	8
			11A	12	12	9	14	16	8	6	6	9	8
			12F	5	13	19	25	22	28	30	18	28	22
			15B	6	7	4	1	7	7	2	8	6	8
			17F	7	4	8	7	4	8	6	6	5	4
			19A	30	57	63	78	61	44	78	75	82	101
			20	3	3	4	-	1	4	2	3	5	6
			22F	24	29	37	41	45	34	43	28	39	45
			33F	11	10	15	22	12	12	19	18	12	28
			Subtotal 23-valent vaccine	*503*	*478*	*503*	*537*	*507*	*425*	529	483	479	*543*
			6A	11	9	2	6	2	-	2	-	4	4
			6C	7	9	7	10	10	7	21	20	15	24
			7B	-	-	-	-	-	-	-	-	-	1
			7C	-	-	-	-	-	-	-	-	-	1
			9A	-	-	-	1	-	1	-	1	-	-
			10F	-	-	-	-	-	1	-	-	-	-
			10B	-	-	-	-	1	-	-	-	1	2
			12A	-	-	-	-	-	-	-	-	-	1
			13	-	-	1	-	-	-	-	1	-	-
			15F	-	-	-	-	1	-	-	1	-	-
			15A	1	-	2	7	13	14	18	21	16	14
			15C	2	1	2	1	4	4	3	2	1	1
			16F	8	10	7	6	7	5	2	9	9	5
			17A	-	-	2	-	-	-	-	-	-	-
			18F	-	-	-	-	-	-	2	-	-	-
			18A	1	1	1	-	-	-	-	-	-	-
			18B	-	-	-	1	1	-	-	-	-	-
			21	-	-	-	-	2	1	-	-	1	1
			22A	-	1	1	-	1	-	1	-	-	1
			23A	9	7	2	6	6	7	7	12	15	14
			23B	6	3	9	3	6	15	5	11	17	11
			24F	-	2	3	2	4	4	7	1	6	3
			25F	-	-	-	-	-	-	1	-	1	-
			27	1	-	1	-	1	-	1	1	-	-
			29	-	-	-	1	-	-	-	-	-	-
			31	1	4	2	6	2	2	4	4	3	6
			33A	-	-	-	1	-	-	-	1	-	1
			34	1	1	-	1	2	1	-	1	1	3
			35F	4	5	6	5	6	7	7	6	3	6
			35A	-	-	-	1	-	-	-	-	-	-
			35B	4	-	3	1	7	6	8	8	2	8
			37	-	1	-	-	-	1	1	-	-	-
			38	5	-	3	-	1	2	2	1	5	4
			40	-	-	-	-	1	-	-	-	-	-
			Rough (n.t.)	-	-	2	-	-	-	-	-	1	1
			Total	564	532	559	596	585	503	621	584	580	655

7 ESCHERICHIA COLI

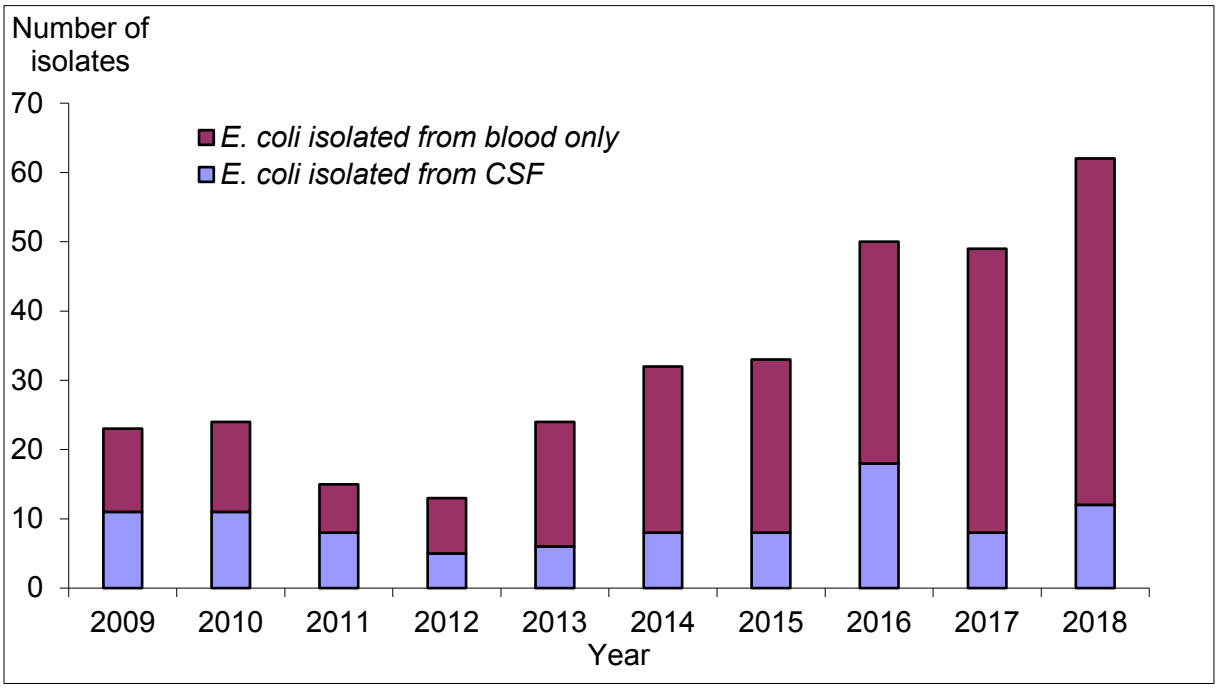

Figure 7.1 *Distribution of E. coli grouped according to isolation source, 2009-2018*

The Reference Laboratory received 62 *Escherichia coli* isolates, 12 isolated from CSF (or CSF and blood) and 50 from blood only (tables 7.1, 7.2 and 7.3). Sixty percent of the *E. coli* meningitis cases occurred in the first month of life.

Table 7.1 Serotype and age-dependent distribution of *E. coli* isolates from CSF and/or blood, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
Non K1	22	8	-	30	-	-	-	2	**32**	***52***
K1	15	14	-	29	-	-	-	1	**30**	***48***
Total	**37**	**22**	**-**	**59**	**-**	**-**	**-**	**3**	**62**	***100***
%	***60***	***35***	***0***	***95***	***0***	***0***	***0***	***5***	***100***	

Table 7.2 Serotypes of *E. coli* isolates from CSF (or CSF and blood), by age of patients, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
Non K1	2	-	-	2	-	-	-	2	**4**	***30***
K1	1	6	-	7	-	-	-	1	**8**	***70***
Total	**3**	**6**	**-**	**9**	**-**	**-**	**-**	**3**	**12**	***100***
%	***25***	***50***	***0***	***75***	***0***	***0***	***0***	***25***	***100***	

Table 7.3 Serotypes of *E. coli* isolates from blood only by age of patients, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
Non K1	20	8	-	28	-	-	-	-	28	***56***
K1	14	8	-	22	-	-	-	-	22	***44***
Total	**34**	**16**	**-**	**50**	**-**	**-**	**-**	**-**	**50**	***100***
%	***68***	***32***	***0***	***100***	***0***	***0***	***0***	***0***	***100***	

Since 2016, K1 is detected by phage typing. Additional O- and H-typing was performed using Whole Genome Sequencing since 2016. Sixty-five percent of all K1 isolates were of types H7, while 59% of the non-K1 isolates were H1, H4 and H18 (table 7.4)

Table 7.4 H-type distribution among K1 and non K1 *E. coli* isolates from CSF and/or blood, 2014 - 2018

TYPE	K1 / Non K1	K1 / Non K1	K1 / Non K1	K1 / Non K1	K1 / Non K1
	2014	**2015**	**2016**	**2017**	**2018**
H-	1 / 1	2 / 1	-	1 / 0	-
H1	1 / 1	1 / 0	0 / 2	0 / 7	1 / 6
H2	-	-	-	1 / 0	-
H4	5 / 0	6 / 0	6 / 7	4 / 1	3 / 7
H5	-	1 / 2	4 / 2	1 / 4	3 / 3
H6	0 / 3	2 / 0	4 / 1	3 / 1	2 / 2
H7	11 / 0	6 / 0	7 / 3	9 / 2	17 / 1
H8	-	-	-	0 / 1	-
H9	-	-	0 / 2	0 / 4	0 / 1
H10	0 / 3	-	1 / 1	-	-
H11	-	1 / 0	-	-	-
H14	-	-	-	-	0 / 2
H15	-	1 / 0	-	-	-
H16	-	-	0 / 1	-	0 / 1
H18	1 / 1	2 / 0	0 / 5	0 / 2	0 / 6
H18/H34	-	-	-	0 / 1	-
H19	0 / 2	-	-	-	-
H21	-	-	0 / 1	-	-
H25	-	-	0 / 1	-	0 / 1
H28	-	-	-	0 / 1	-
H31	1 / 0	2 / 0	-	0 / 2	-
H33	-	1 / 0	1 / 0	0 / 2	1 / 0
H38	0 / 1	-	-	-	-
H41	-	-	-	0 / 1	-
H42	-	-	1 / 0	-	0 / 2
H45	-	-	-	0 / 1	3 / 0
Total	**20 /12**	**25 / 3**	**24 / 26**	**19 / 30**	**30 / 32**
%	***63/37***	***89/11***	***48/52***	***39/61***	***48/52***

The types O6, O15 and O19 are most prevalent among non-K1 isolates, while the type O1 and O18ac were found among K1 isolates but numbers are small (Table 7.5).

Table 7.5 O-type versus K-type of *E. coli* isolates from CSF and/or blood, 2018

O type	K1	Non K1	Total
O-	1	0	**1**
O1	8	1	**9**
O2	3	1	**4**
O2/O50	1	1	**2**
O4	0	1	**1**
O6	0	5	**5**
O7	2	2	**4**
O8	0	1	**1**
O12	1	0	**1**
O13	1	0	**1**
O13/O135	0	1	**1**
O15	0	4	**4**
O16	0	2	**2**
O17	0	1	**1**

O type	K1	Non K1	Total
O17/O44/O77	0	1	1
O18	1	0	**1**
O18ac	7	0	**7**
O19	0	3	**3**
O21	0	1	**1**
O23	0	1	**1**
O25	1	1	**2**
O75	2	0	**2**
O80	0	2	**2**
O83	1	0	**1**
O84	0	1	**1**
O117	1	1	**2**
O161	0	1	**1**
Total	**30**	**32**	**62**

Among K1 isolates, the O/H combinations O18ac:H7 and O1:H7 were found 7 respectively 8 times.
Among non-K1 isolates, O6:H1 and O15:H18 were dominant (5 respectively 4 times)

8 *STREPTOCOCCUS AGALACTIAE* – (group B)

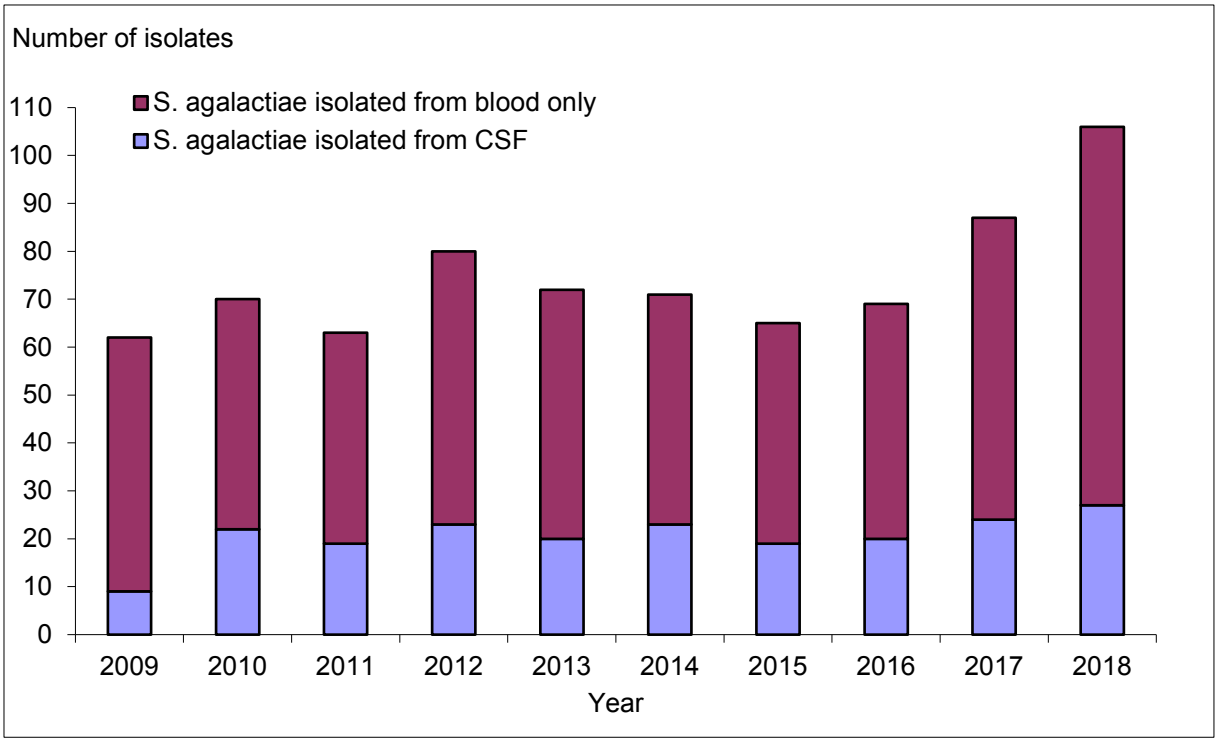

Figure 8.1 *Distribution of S. agalactiae, 2009-2018*

In 2018, the Reference Laboratory received 106 *Streptococcus agalactiae* isolates, which is an increase compared to the 87 isolates in 2017 and 69 isolates in 2016 (figure 8.1). Twenty-seven (25%) *S. agalactiae* isolates were from CSF (or CSF and blood) and 79 (75%) from blood only (table 8.1. 8.2 and 8.3). Sixty-five percent of the cases occurred in the first month of life. As is previuos years, Serotype III was most prevalent (table 8.1). In addition, compared to 2014, the absolute number as well as the proportion of serotype Ia isolates increased (figure 8.2). In 2014: 6 (8.5%); 2015: 16 (25%) and in 2018 Ia was increased to 21 (20%) cases.

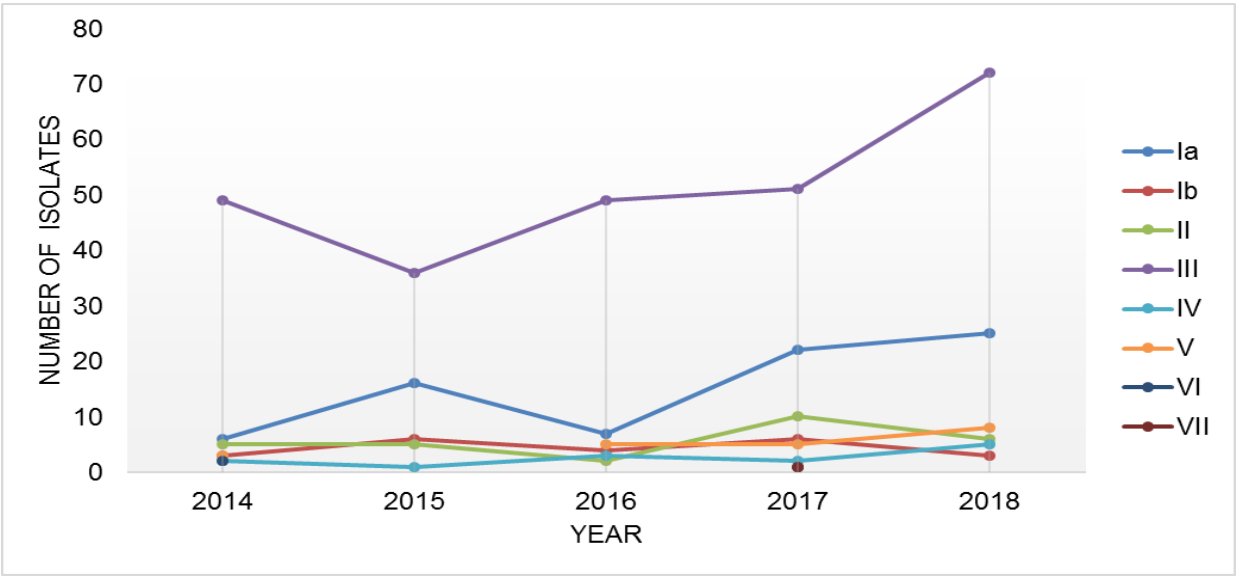

Figure 8.2 *Distribution of serotype, 2014-2018*

Table 8.1 Serotypes of *S. agalactiae* isolates from CSF and/or blood, by age of patients, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	Total	%
Ia	14	7	0	21	0	0	0	0	**21**	***20***
Ib	1	1	0	2	0	0	1	0	**3**	***3***
II	5	0	0	5	0	0	0	0	**5**	***5***
III	41	23	0	64	0	0	1	1	**66**	***62***
IV	3	1	0	4	0	0	0	0	**4**	***4***
V	5	2	0	7	0	0	0	0	**7**	***7***
Total	**69**	**34**	**0**	**103**	**0**	**0**	**2**	**1**	**106**	***100***
%	***65***	***32***	***0***	***97***	***0***	***0***	***2***	***1***	***100***	

Table 8.2 Serotype of *S. agalactiae* isolates from CSF (or CSF and blood), by age of patients, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	Total	%
Ia	2	0	0	2	0	0	0	0	**2**	***7***
Ib	0	1	0	1	0	0	1	0	**2**	***7***
II	0	0	0	0	0	0	0	0	**0**	***0***
III	14	8	0	22	0	0	0	1	**23**	***86***
IV	0	0	0	0	0	0	0	0	**0**	***0***
V	0	0	0	0	0	0	0	0	**0**	***0***
Total	**16**	**9**	**0**	**25**	**0**	**0**	**1**	**1**	**27**	***100***
%	***59***	***33***	***0***	***92***	***0***	***0***	***4***	***4***	***100***	

Table 8.3 Serotypes of *S. agalactiae* isolates from blood only, by age of patients, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	Total	%
Ia	12	7	0	19	0	0	0	0	19	***24***
Ib	1	0	0	1	0	0	0	0	1	***1***
II	5	0	0	5	0	0	0	0	5	***6***
III	27	15	0	42	0	0	1	0	43	***55***
IV	3	1	0	4	0	0	0	0	4	***5***
V	5	2	0	7	0	0	0	0	7	***9***
Total	**53**	**25**	**0**	**78**	**0**	**0**	**1**	**0**	**79**	***100***
%	***67***	***32***	***0***	***99***	***0***	***0***	***1***	***0***	***100***	

9 *LISTERIA MONOCYTOGENES*

Sixty-four *Listeria monocytogenes* isolates were submitted to the Reference Laboratory. Of these, 9 (14%) were from CSF (or CSF and blood) and 56 (86%) from blood only (figure 9.1). Most cases (81%) occurred among persons older than 50 years of age. Similar to previous years, serotypes 1/2a and 4b were most prevalent in 2018 (table 9.1).

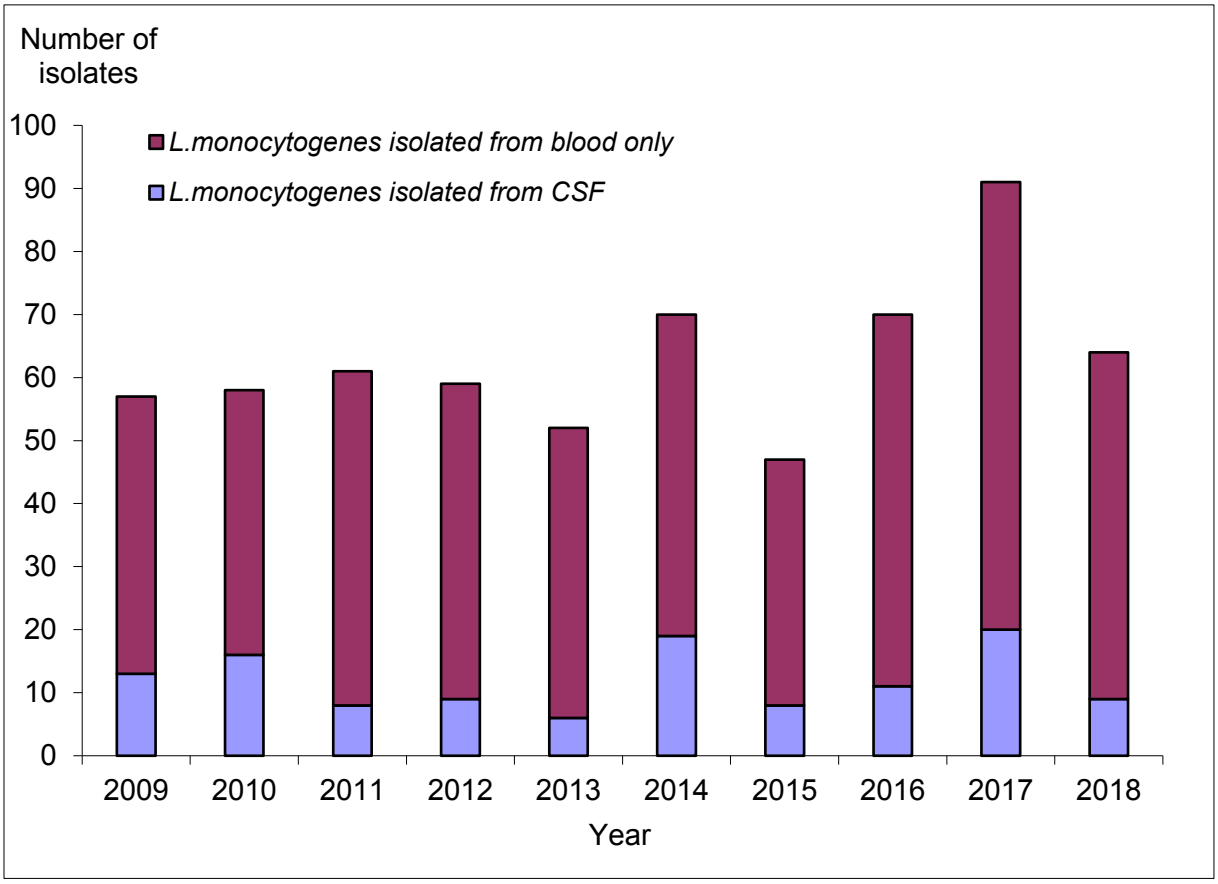

Figure 9.1 Number of *L. monocytogenes isolates grouped by isolation source, 2009-2018*

Table 9.1 *L. monocytogenes* isolates from CSF/blood, by type and age of patients, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
1/2a	0	0	0	0	0	0	0	20	**20**	***31***
1/2b	0	0	0	0	0	0	1	6	**7**	***11***
1/2c	0	0	0	0	0	0	0	1	**1**	***1***
4b	3	0	0	3	0	0	8	26	**37**	***57***
Total	**3**	**0**	**0**	**3**	**0**	**0**	**9**	**53**	**65**	**100**
%	***5***	***0***	***0***	***5***	***0***	***0***	***14***	***81***	***100***	

Table 9.2 *L. monocytogenes* isolates from CSF (or CSF and blood), by type and age, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
1/2a	0	0	0	0	0	0	0	5	5	***56***
1/2b	0	0	0	0	0	0	0	0	**0**	***0***
1/2c	0	0	0	0	0	0	0	0	**0**	***0***
4b	0	0	0	0	0	0	2	2	**4**	***44***
Total	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**7**	**9**	***100***
%	***0***	***0***	***0***	***0***	***0***	***0***	***22***	***78***	***100***	

Table 9.3 *L. monocytogenes* isolates from blood only, by serotype and age, 2018

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
1/2a	0	0	0	0	0	0	0	15	**15**	***27***
1/2b	0	0	0	0	0	0	1	6	**7**	***12***
1/2c	0	0	0	0	0	0	0	1	**1**	***2***
4b	3	0	0	3	0	0	6	24	**33**	***59***
Total	**3**	**0**	**0**	**3**	**0**	**0**	**7**	**46**	**56**	***100***
%	***5***	***0***	***0***	***5***	***0***	***0***	***13***	***82***	***100***	

10 *STREPTOCOCCUS PYOGENES – Group A*

Twelve *Streptococcus pyogenes* isolates were submitted to the Reference Laboratory, 3 isolated from CSF (or CSF and blood) and 9 from blood only.

Since 2015, the Reference Laboratory performs group A *emm*-typing based on sequencing of the hypervariable part of the *emm* gene, which encodes the surface expressed M protein. Currently, over 200 different *emm* genotype are recognized

Table 10.1 *S. pyogenes* isolates from CSF and/or blood received in 2018 according to source of isolation and age.

TYPE	AGE (MONTHS)			AGE (YEARS)					TOTAL	
	0	1-11	12-59	0-4	5-9	10-19	20-49	≥50	T	%
CSF	0	1	0	1	1	0	0	1	**3**	***25***
Blood	0	0	1	1	0	1	1	6	**9**	***75***
Total	**0**	**1**	**1**	2	**1**	**1**	**1**	**7**	**12**	***100***
%	***0***	***8***	***8***	***17***	***8***	***8***	***8***	***59***	***100***	

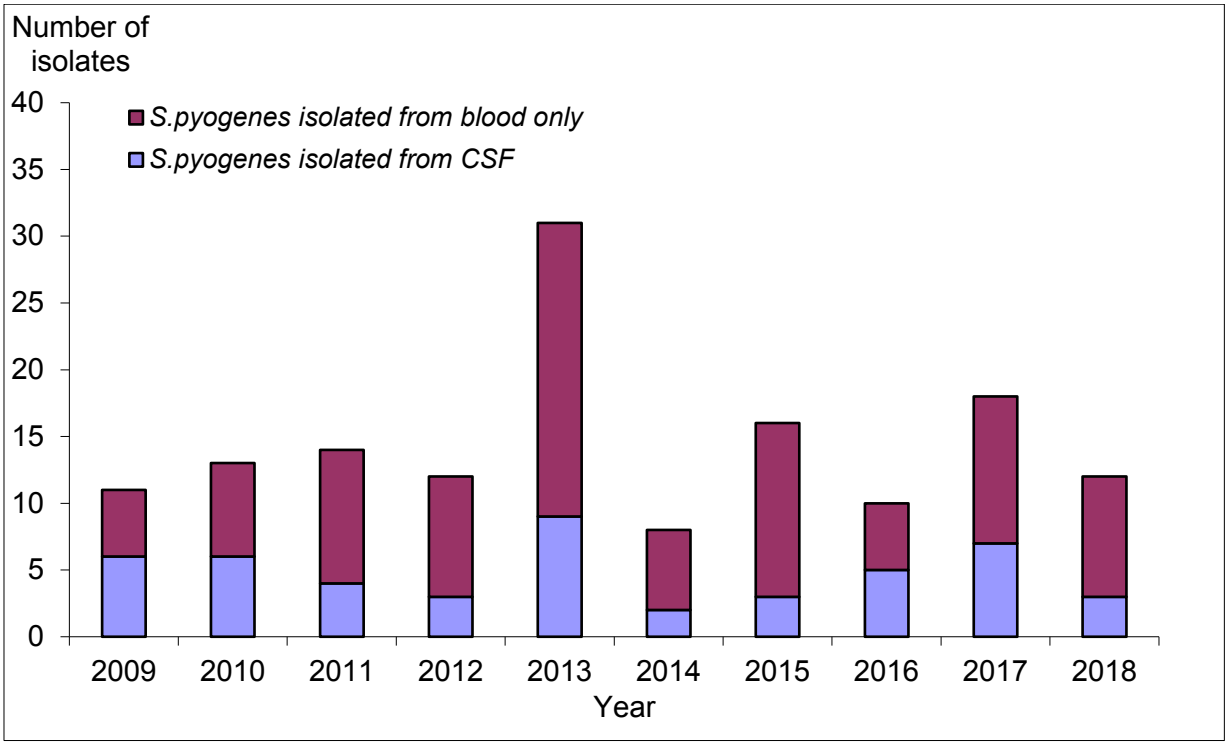

Figure 10.1 *Number of S. pyogenes isolates submitted to the Referene Laboratory grouped according to source of isolation, 2009-2018*

Table 10.2 Emm-type distribution of *S. pyogenes* isolates from CSF, 2015-2018

EMM-TYPE	2015	2016	2017	2018
1.0 Cluster A-C3	1	2	5	**0**
3.1 Cluster A-C5	1	0	0	**0**
3.5 Cluster A-C5	0	0	0	**1**
3.60 Cluster A-C5	0	1	0	**0**
3.93 Cluster A-C5	0	0	1	**1**
4.0 Cluster E1	1	0	0	**0**
6.0 Cluster M6	0	0	0	**1**
12.0 Cluster A-C4	0	0	1	**0**
22.3 Cluster E4	0	1	0	**0**
44.0	0	1	0	**0**
Total	3	5	7	3

11 *ANTIGEN AND DNA DETECTION*

The Reference Laboratory received 174 culture-negative specimens of CSF, serum or other bodily fluids for antigen or DNA detection. LFA assay was used to detect *C. neoformans*. PCR was performed with primers and probes specific for *N. meningitidis* (targeted on the *ctrA* gene) for *S. pneumoniae* (targeted on the *pia* gene) and for *H. influenzae* (*SiaT* gene). When CSF was positive in the meningococcal PCR, the same sample was subjected to serogroup-specific PCR.

Of 174 specimens, 49 (28%) were positive for one of the target species by PCR. Of these, 27 (16%) (23 CSF, 4 sera or DNA isolated from a skin biopsy) were positive for *N. meningitidis* and 17 (9%) were positive for *S. pneumoniae*.

Thus, in 2018, PCR-positive, culture-negative CSF samples accounted for 33% (23/70) of cases of meningococcal meningitis registered in the database of the Reference Laboratory. For *S. pneumoniae* this percentage was 10% (16/159).

Table 11.1 CSF and serum samples tested for antigens or DNA, 2018

Antigen of	CSF * (or DNA from CSF)	SERA	TOTAL
C. neoformans	1	2	**3**
DNA of			
N. meningitidis group	1	0	**1**
N. meningitidis group B	13	2	**15**
N. meningitidis group W	6	1	**7**
N. meningitidis group Y	3	1	**4**
S. pneumoniae	16	1	17
H. influenzae	1	1	2
Sub Total	**41**	**8**	**49**
Antigen and PCR negative	112	13	**125**
Total	**152**	**21**	**174**

* From 9 patients with a *S. pneumoniae* isolate from blood, the CSF was culture-negative but PCR-positive for pneumococcal DNA. Those were counted as CSF patients.
From 7 patients with a *N. meningitidis* isolated from blood, the CSF was culture-negative but PCR-positive for meningococcal DNA. Those were counted as CSF patients.

12 *VACCINATION PROSPECTS*

12.1 N. meningitidis

In the Netherlands, vaccination against serogroup C meningococcal disease was introduced in June 2002. All children born on or after June 1st, 2001 are vaccinated at the age of 14 months as part of the regular National Immunisation Programme. In addition, between June, 2002 and October, 2002 children and adolescents from 12 months to 19 years were vaccinated. In 2018, 3 cases of meningococcal disease (1.5% of all cases; table 4.4) were due to serogroup C, meningococci, which is a reduction compared to the 4.5% in 2017, 4.4% in 2016 and 8.3% in 2015). The three patients had not been vaccinated because of age. This indicates that the vaccination programme is successful (figure 12.1).

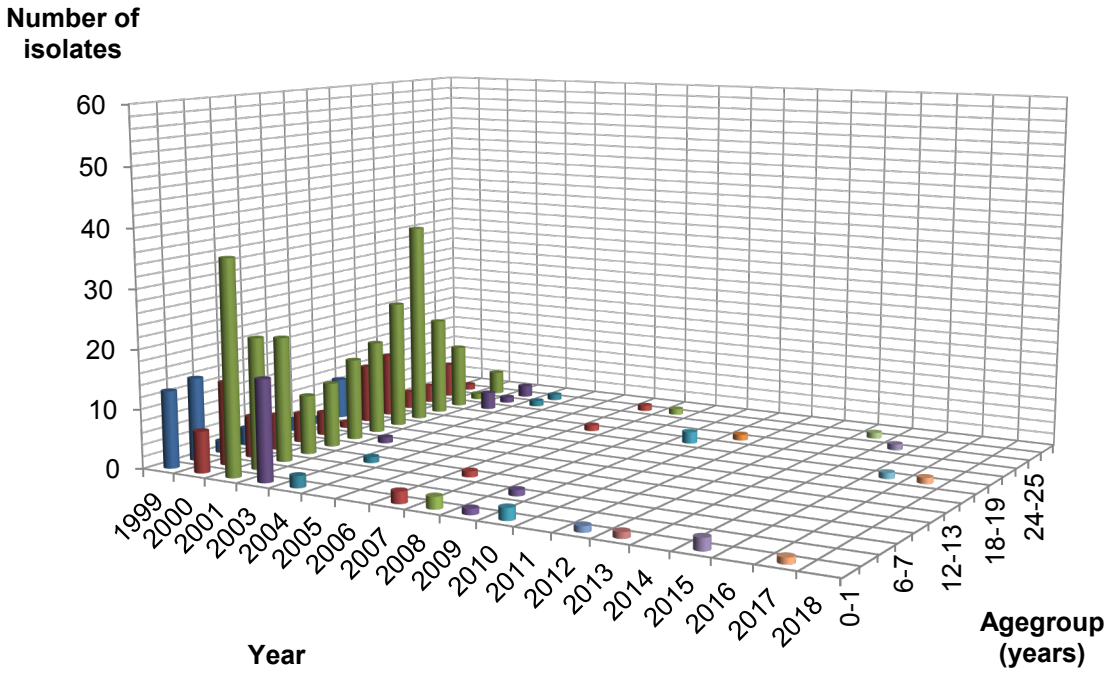

Figure 12.1 *Age distribution of N.meningitidis serogroup C invasive disease in the first 25 years of life, 1999-2018.*

A PorA-based protein vaccine composed of nine different genosubtypes (P1.7,16; P1.5-1,2-2; P1.19,15-1; P1.5-2,10; P1.12-1,13; P1.7-2,4; P1.22,14; P1.7-1,1 and P1.18-1,3,6), if available and introduced in the Netherlands, this vaccine would have prevented 60 cases (81%; table 4.9) of serogroup B meningococcal disease and 93 (46%; of all 205 cases of meningococcal disease. The latter proportion is lower than in the previous years due to the increase of serogroup W meningococcal disease. The vast majority of these cases is due to meningococci with PorA P1.5.2.

12.2 *H. influenzae*

The existing *H. influenzae* vaccine consists of the type b polysaccharide conjugated to the tetanus toxoid protein. Since July 1993, children born after the 1st of April 1993 are vaccinated with the PRP-T vaccine, at the ages of 3, 4, 5. and 11 months, and since 1999 at the age of 2, 3, 4 and 11 months. The effect of vaccination on the frequency of *H. influenzae* meningitis cases is shown in figure 12.2. The number of *H. influenzae* meningitis cases caused by *H. influenzae* type b gradually decreased since the introduction of the vaccine, while the number of meningitis cases caused by *H. influenzae* non-type b did not alter. In 2018, nine invasive meningitis isolates of *H. influenzae* type b were received from patients that should have been vaccinated (<25 years of age) (2017: 7; 2016: 11; 2015: 14) (figure 12.2 and 12.3). Of those 9 patients, three had received all doses and one received only three doses of the vaccine. Three patients were not vaccinated at all and from two patients, vaccination status was unknown.

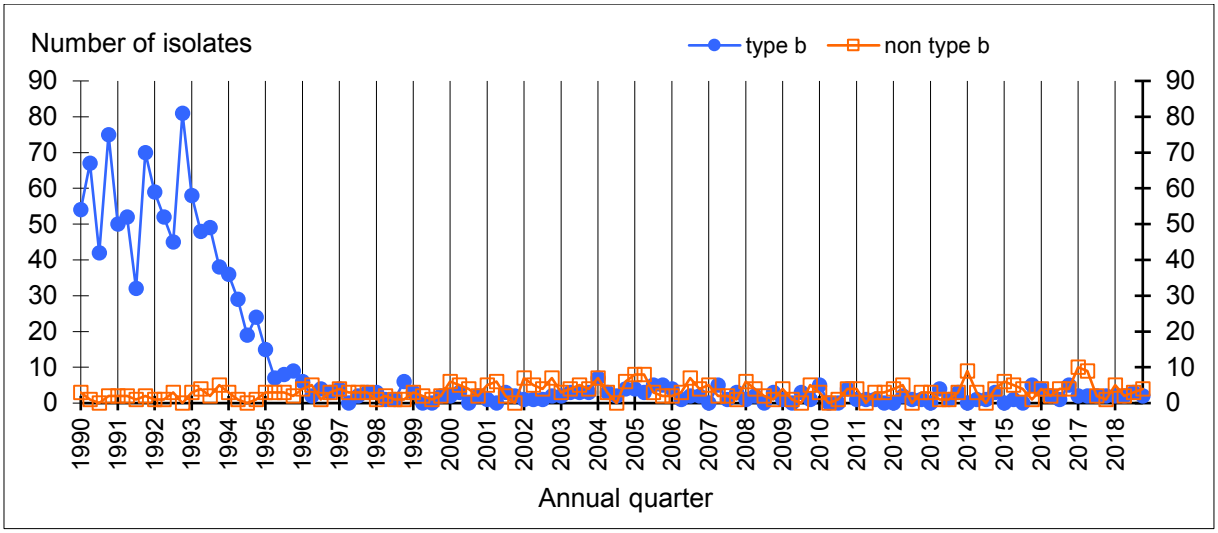

Figure 12.2 *The number of H. influenzae type b and non-type b meningitis cases according to annual quarter, 1990 –2018*

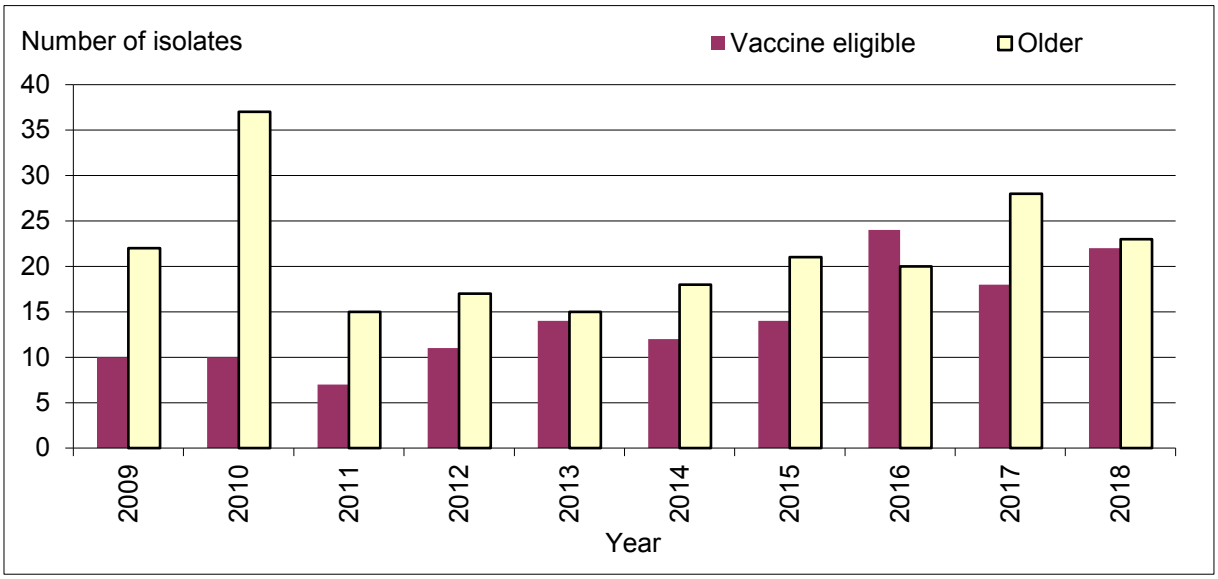

Figure 12.3 *The number of H. influenzae type b cases (CSF or blood) among patients eligible for vaccination and among older patients, 2009 –2018*

12.3 S. pneumoniae

The pneumococcal conjugated polysaccharide vaccine contains 7 serotype-specific polysaccharides linked to inactive diphtheria toxin (7-valent polysaccharide conjugate vaccine. PCV7). Since July 2006, children born after the first of April 2006 are vaccinated with this vaccine at the age of 2, 3, 4 and 11 months. In April 2011, the 10-valent vaccine (PCV10) was introduced for all newborns born since March 1st 2011. In 2018, 3.9% of the CSF isolates were of a serotype covered by this hepta-valent conjugate polysaccharide vaccine, while 5.2% of the isolates were covered by the 10-valent vaccine (table 6.6). In 2018, the proportion of CSF isolates with a PVC7 serotype had reduced more than ten compared to ten years ago (2006: 56%) as a result of the vaccination. There were 6 patients with invasive pneumococcal disease due to pneumonococci with a vaccine (PVC7) serotype (4, 14, 18C and 19F) and 2 patients with invasive pneumococcal disease due to pneumococci with a vaccine (PVC10 - 7) serotype (7F). Of these 8 patients, 7 were not yet vaccinated because of age. From one patient, vaccine status was onknown. The beneficial effect of vaccination is partly abrogated by an increase of the number of cases due to non-vaccine types (figure 12.4).

The pneumococcal non-conjugated polysaccharide vaccine covers 23 serotypes. Seventy-four percent of the CSF isolates were of a serotype, which is covered by this vaccine (table 6.6). (2018: 74%; 2007: 90%).

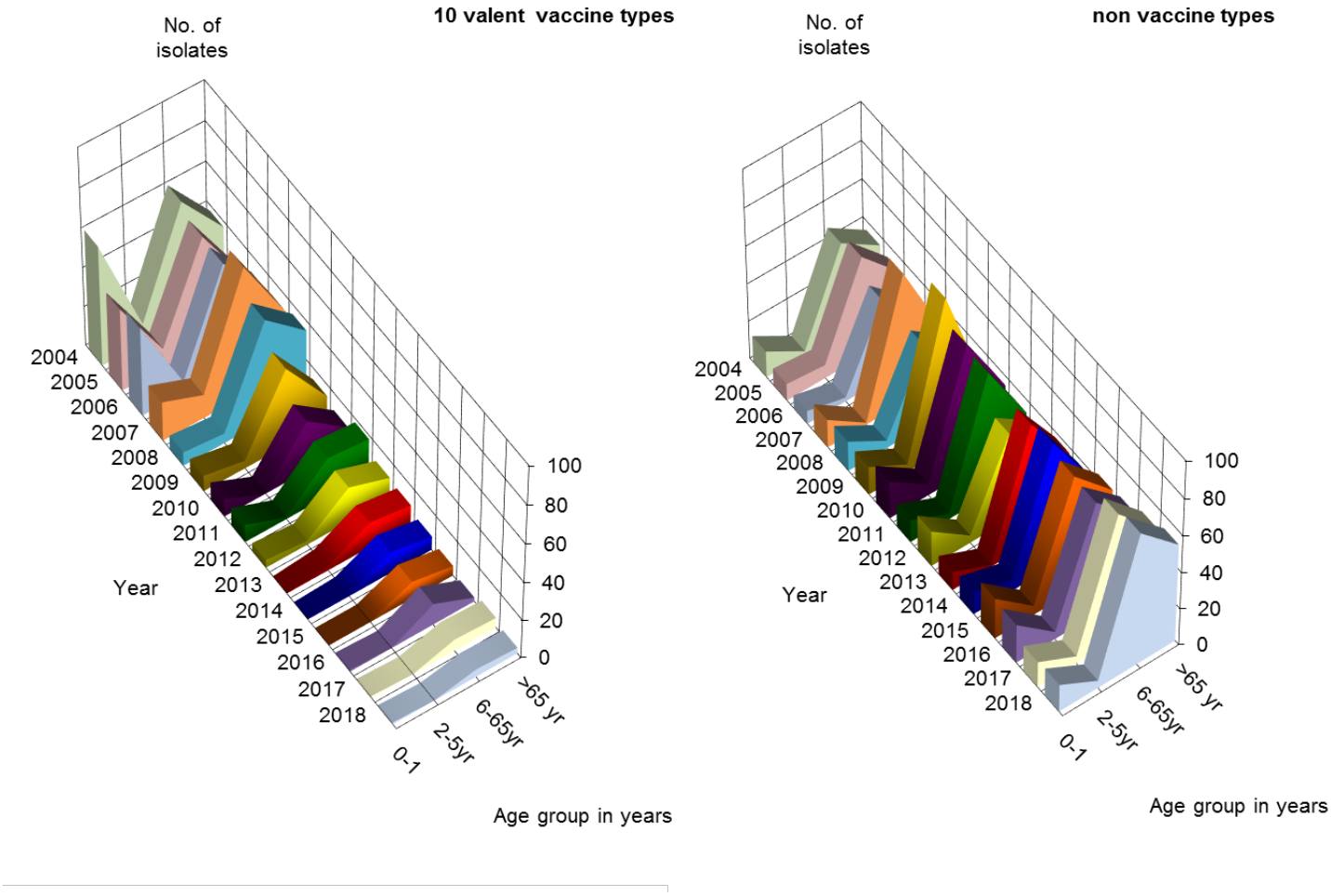

Figure 12.4 *The age distribution of S.pneumoniae invasive disease due to pneumococci of serotypes included in the hepta-valent conjugated polysaccharide vaccine. 2004-2018. Left: vaccine types. Right: types not included in this 10 valent vaccine*

13 PUBLICATIONS

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9 van Kassel MN, Bijlsma MW, Brouwer MC, van der Ende A, van de Beek D. Community-acquired group B streptococcal meningitis in adults: 33 cases from prospective cohort studies. J Infect. 2019;78:54-57

10 Vissers M, Wijmenga-Monsuur AJ, Knol MJ, Badoux P, van Houten MA, van der Ende A, Sanders EAM, Rots NY. Increased carriage of non-vaccine serotypes with low invasive disease potential four years after switching to the 10-valent pneumococcal conjugate vaccine in The Netherlands. PLoS One. 2018;13:e0194823.

14 ACKNOWLEDGEMENTS

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