

Epidemiology of invasive pneumococcal disease in Catalonia. Report 2017-2018

Catalan Microbiological Reporting System (SNMC)

Subdirectorat-General for Epidemiological Surveillance and Public Health Emergency Response

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1 Introduction

Invasive pneumococcal disease (IPD) is an important public health problem on a world-wide scale with high morbidity that causes a wide range of more or less serious diseases from otitis media to sepsis or meningitis. IPD is defined as the isolation or detection of *Streptococcus pneumoniae* DNA or antigen in a normally sterile site (blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, joint fluid, among others).

Over 100 serotypes of *S. pneumoniae* have been identified depending on the composition of the polysaccharide capsule. The circulation of these serotypes and, therefore, the epidemiology of IPD have changed over the last few years in line with the introduction of 7-valent conjugate pneumococcal vaccine (PCV7) in 2000 in the United States and in 2001 in Europe. PCV7 includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. In Catalonia, the 10-valent conjugate pneumococcal vaccine (PCV10) was first marketed in 2009 and the 13-valent conjugate pneumococcal vaccine (PCV13) in 2010 thus replacing PCV7. PCV10 includes the same serotypes as PCV7 plus 1, 5 and 7F serotypes; and PCV13, the serotypes of PCV10 plus the 3, 6A and 19A serotypes.

In Catalonia, up to July 2016, none of these conjugate vaccines had been included on systematic vaccination schedule and vaccination was only recommended for children with risk factors. Nevertheless, the conjugate pneumococcal vaccines had been recommended by paediatricians and administered according to SPC indications. Since July 2016, the pneumococcal vaccine has been included on the systematic schedule and administered at 2, 4 and 11 months of age in accordance with the guidelines dictated by the Interregional Council of the National Health System.^{1,2} It is also administered to adult population risk groups.

Since 1999, the administration of 23-valent pneumococcal vaccine (PCV23) has been recommended for all people over 65 as well as risk groups.

Since 1995, surveillance of confirmed cases of IPD has been conducted through the Catalan Microbiological Reporting System (SNMC) which is coordinated by the Subdirectorat-General for Epidemiological Surveillance and Public Health Emergency Response (SGVRESP). The SNMC is a basic health information system, part of the Epidemiological Surveillance Network, and consists of a group of microbiology laboratories in public and private hospitals and medical centres in Catalonia ([list of centres](#)).

These centres (55 public hospitals, 1 private hospital and 3 primary care centres) represent 92.8% of acute patient hospital beds in the Public Hospital Network.

[Decree 203/2015](#),³ of 15 September, which created the Epidemiological Surveillance Network of Catalonia and which regulates reporting systems for

notifiable diseases and epidemic outbreaks, establishes SNMC as one of the systems for reporting notifiable diseases. The decree also creates a list of new notifiable diseases, which includes IPD as a notifiable disease exclusively by microbiological reporting.

On the other hand, since 2012, the Subdirectorate-General for Epidemiological Surveillance and Public Health Emergency Response (SGVRESP) of the Public Health Agency of Catalonia (ASPCAT) has participated in a European IPD active surveillance project "SpID-NET" (PROC/2012/031) "Assessing the impact of vaccination with conjugate vaccines where the epidemiology of invasive pneumococcal disease in Europe"⁴ together with nine other European regions. The aim of the project is to carry out active surveillance of IPD in Europe to increase knowledge of IPD epidemiology and explore the overall impact and effectiveness of vaccination for the disease using conjugate vaccines in infants under 5 years of age. The laboratory of the Sant Joan de Déu Hospital participates in this project as a laboratory providing support to the public health system for molecular surveillance of IPD.

Between 2015 and 2019 the IPD surveillance project (PROC/2015/020) was broadened to explore the overall impact, mortality and effectiveness of pneumococcal conjugate vaccines in infants aged under 5 and adults aged 65 and over. During this period, more European countries have joined the project, to create a network of 15 regions from 11 countries.⁴

The incidence of IPD in the 2-4 and 5-19 age groups showed a significant drop in 2016 compared to 2012.⁵ On the other hand, the incidence of the serotypes included in PCV13 dropped significantly in all age groups, except the 5-19 group. The case fatality rate of IPD in infants under 5 years of age was 0.7% during this period.

Among adults aged 65 and over, the incidence rate was between 29.0 and 33.0 cases per 100,000 persons/year during the period 2014-2016.⁶ The case fatality rate of IPD in adults was 17.5%, much higher among adults with diseases (36.8%) than in healthy adults (13.9%). The risk factors associated with mortality were age 85 or over, presence of meningitis or non-focal bacteraemia and one or more high risk conditions. On the other hand, the serotypes included in PCV23 and not included in PCV13 have been associated with low mortality rates.

2 Objectives

The aim of this report is to describe the epidemiology of IPD and changes in circulating serotypes among the different age groups during the years 2017-2018 and analyse the impact of PCV13 on the incidence of IPD during the period 2017-2018 compared to 2014-2015 in cases reported to the SNMC.

3 Method

The information in this report is based on confirmed cases of acute IPD reported by laboratories in the SNMC in the period 2014-2018. The criteria of the European Centre for Disease Prevention and Control (ECDC), whose case definition of IPD is: "Isolation of *S. pneumoniae* DNA or antigen from a normally sterile site".

During this period, in the context of the European IPD surveillance project, enhanced and proactive surveillance of the disease was carried out and microbiological variables were included through the following sources of information:

- 1) The Public Health Surveillance Support Laboratory for IPD at Sant Joan de Déu University Hospital, which is responsible for identifying the *S. pneumoniae* serotype using the PCR technique and multilocus sequence typing (MLST) with samples received from certain laboratories. In addition, the strains are sent to the Spanish Pneumococcal Reference Laboratory at the National Centre for Microbiology in Majadahonda.
- 2) The Spanish Pneumococcal Reference Laboratory of the National Centre for Microbiology in Majadahonda. This centre studies the *S. pneumoniae* serotype (by Quellung reaction) and the antibiotic sensitivity of the samples received.

The **serotype is identified** using the Quellung reaction or, when not possible, by PCR.

The **variables studied** are sex, age (age groups: <2 years, 2-4 years, 5-19 years, 20-64 years and 65 and over), diagnostic date, clinical presentation, clinical sample, microbiological technique and serotype. The serotype is also analysed in terms of its inclusion in the pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13).

With regard to **statistical analyses**, incidence rates were calculated based on demographic data from the Statistical Institute of Catalonia (IDESCAT) for the age groups studied.

The impact assessment was carried out by relative risk (RR) with 95% confidence intervals, assuming a Poisson distribution and comparing the period 2017-2018 with that of 2014-2015. Impact was analysed using the formula $(1-RR)*100$. The year 2016 was not taken into account as it was considered to be the first year when systematic administration of PCV13 was included for infants.

The analysis was performed using the Statistical Package for Social Sciences (SPSS 19.0) and R 3.2.0 (R Development Core Team 2015).

4 Results

4.1 Incidence by age group

During the period 2017-2018, a total of 2,067 cases of IPD were reported, representing an incidence rate of 13.6 cases per 100,000 persons/year. The highest incidence rate occurred in infants under 2 years of age (38.5 cases per 100,000 persons/year), adults of 65 and over: (36.5 cases per 100,000 persons/year) and in children age 2-4 (20.4 cases per 100,000 persons/year) (Figure 1). The number of men was higher than that of women in all age groups (1,241 cases; 60.0%).

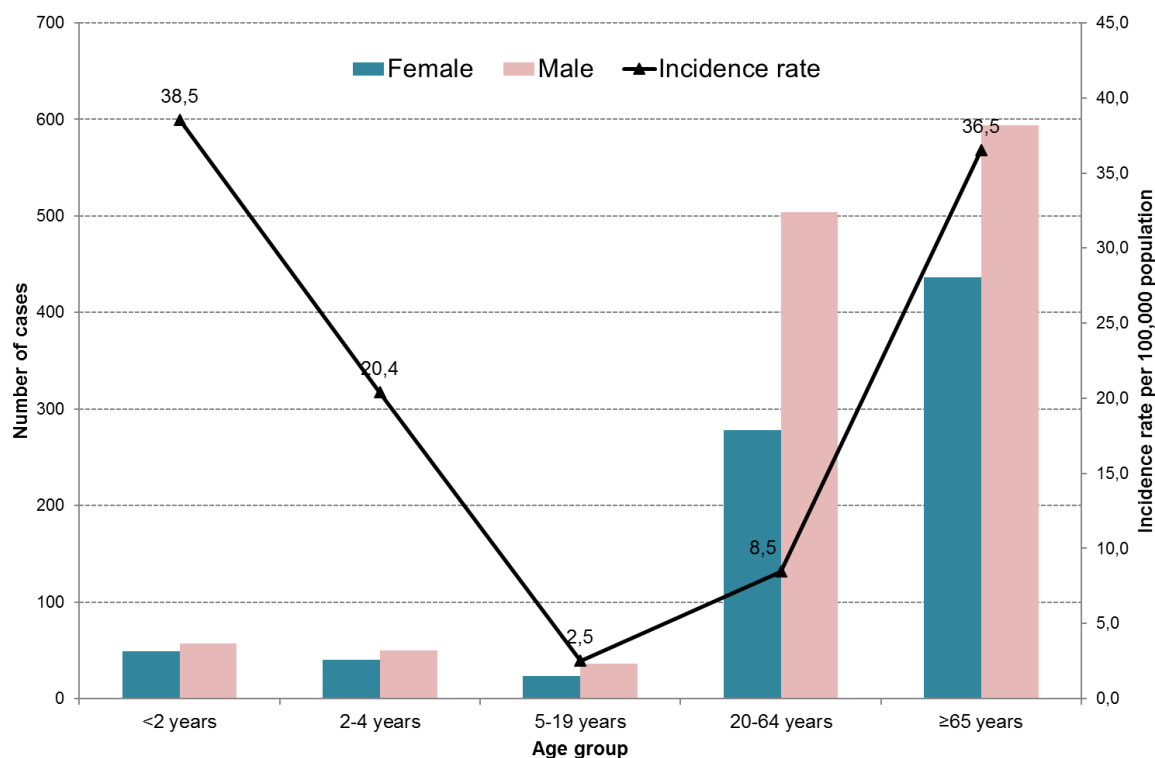
Diagnosis was by culture in 1,984 cases (96.3%); PCR in 62 cases (3.0%), and in antigen detection in 21 (1.0%) of cases.

4.2 Impact of the 13-valent conjugate pneumococcal vaccine on the incidence of invasive pneumococcal disease

During 2017 and 2018 there was an increase of the overall incidence rate of 15% compared to 2014 and 2015 (RR: 1.15; 95%CI: 1.08-1.23; $p<0.001$) (Table 1).

The increase in the incidence between 2017 and 2018 was significant in the 20 to 64 (18%) and 65 and over (18%) age groups, whereas in the other age groups the incidence remained stable.

Figure 1. Incidence of invasive pneumococcal disease by age group and sex. Catalonia, 2017-2018



Source: Catalan Microbiological Reporting System. Subdirectorat-General for Epidemiological Surveillance and Public Health Emergency Response. Public Health Agency of Catalonia.

Table 1. Incidence of invasive pneumococcal disease by age group and years. Catalonia, 2014-2018

Age group	2014 No.	2014 IR*	2015 No.	2015 IR*	2016 No.	2016 IR*	2017 No.	2017 IR*	2018 No.	2018 IR*
<5 years	97	24.5	117	30.6	103	27.8	93	25.6	103	29.1
<2 years	51	34.6	65	45.8	56	39.6	55	39.4	51	37.6
2-4 years	46	18.5	52	21.6	47	20.5	38	17.0	52	23.8
5-19 years	26	2.3	37	3.2	37	3.2	31	2.6	28	2.3
20-64 years	318	6.8	348	7.5	329	7.1	391	8.5	391	8.4
≥65 years	388	29.0	449	33.0	448	32.5	496	35.5	534	37.6
Total	829	11.0	951	12.7	917	12.2	1,011	13.4	1,056	13.9

Source: Catalan Microbiological Reporting System. Subdirectorat-General for Epidemiological Surveillance and Public Health Emergency Response. Public Health Agency of Catalonia.

No.: number of cases.

* Rate per 100,000 population/year.

Table 1. Continued

Age group	2014-2015 No.	2014-2015 IR*	2017-2018 No.	2017-2018 IR*	RR (CI95%) 2017-2018 vs. 2014-2015	p value
<5y	214	27.5	196	27.4	0.99 (0,82-1,21)	0.998
<2y	116	40.0	106	38.5	0.96 (0,73-1,26)	0.827
2-4y	98	20.1	90	20.4	1.02 (0,75-1,37)	0.969
5-19y	63	2.8	59	2.5	0.90 (0,62-1,30)	0.611
20-64y	666	7.2	782	8.5	1.18 (1,06-1,31)	0.002
≥65y	837	31.0	1,030	36.5	1.18 (1,07-1,29)	<0.001
Total	1,780	11.8	2,067	13.6	1.15 (1,08-1,23)	<0.001

Source: Catalan Microbiological Reporting System. Subdirectorat-General for Epidemiological Surveillance and Public Health Emergency Response. Public Health Agency of Catalonia.

No.: number of cases.

* Rate per 100,000 persons/year.

** RR: relative risk.

4.3 Clinical presentation

During the period analysed (2017-2018), the majority of cases presented pneumonia (79.8%; 1,649/2,067). Meningitis, non-focal bacteraemia and other clinical signs represented 8.8%, 7.7% and 3.8%, respectively (Table 2).

Pneumonia was the most frequent clinical presentation in all age groups. The incidence rate was higher in adults aged 65 and over (30.6 per 100,000 persons/year), followed by under-2s (20.7 per 100,000 persons/year). Meningitis had a higher incidence rate among under-2s (5.8 per 100,000 persons/year).

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Table 2. Incidence of the invasive pneumococcal disease by clinical presentation and age group. Catalonia, 2017-2018

Clinical presentation	<2y No.	<2y IR*	2-4y No.	2-4y IR*	<5y No.	<5y IR*	5-19y No.	5-19y IR*	20-64y No.	20-64y IR*	≥65y No.	≥65y IR*
Pneumonia	57	20.7	61	13.8	118	16.5	41	1.7	627	6.8	863	30.6
Meningitis	16	5.8	9	2.0	25	6.1	9	0.4	76	0.8	71	2.5
Bacteraemia with an unknown focus	28	10.2	16	3.6	44	3.5	6	0.3	48	0.5	61	2.2
Other**	5	1.8	4	0.9	9	1.3	3	0.1	31	0.3	35	1.2
Total	106	38.5	90	20.4	196	27.4	59	2.5	782	8.5	1,030	36.5

Table 2. Continued

Clinical presentation	Global IPD No.	Global IPD IR*
Pneumonia	1,649	10.9
Meningitis	181	1.2
Bacteraemia with an unknown focus	159	1.0
Other**	78	0.5
Total	2,067	13.6

Source: Catalan Microbiological Reporting System. Subdirectorat-General for Epidemiological Surveillance and Public Health Emergency Response. Public Health Agency of Catalonia.

No.: number of cases.

* Rate per 100,000 persons/year.

** Peritonitis: 24; arthritis: 23; cholecystitis: 7; endocarditis: 6; cellulitis: 4; endophthalmitis: 1; pancreatitis 4; lumbar spondylodiscitis 2; kidney 3; pyometra 1; myositis 1; abdominal 1, and cerebral 1.

4.4 Analysis of serotypes

In the period 2017-2018 the serotype was identified in 86.0% of diagnosed cases (1,751/2,067) and 50 different serotypes were detected. The most frequent serotypes were: 8, 3, 12F, 22F, 14, 24F and 19A, representing 51.9% of cases. The distribution of the serotypes identified during the period 2017-2018 is shown in Figure 2.

Analysis of the serotypes causing IPD by age groups over this period reveals that, in infants under 2 years of age, the serotypes included in PCV7, PCV10 and PCV13 represented 5.1%, 6.6% and 18.7%, respectively. The most frequent serotypes were: 24F (15.4%), 10A (9.9%), 3 (9.9%), 12F (7.7%) and 15A (5.5%).

In the 2-4 age group, the serotypes included in PCV7, PCV10 and PCV13 represented 15.0%, 16.3% and 41.3%, respectively. In this group, the most frequent serotypes were: 3 (17.5%), 24F (10%), 14 (6.2%), 19A (6.2%) and 23B (6.2%).

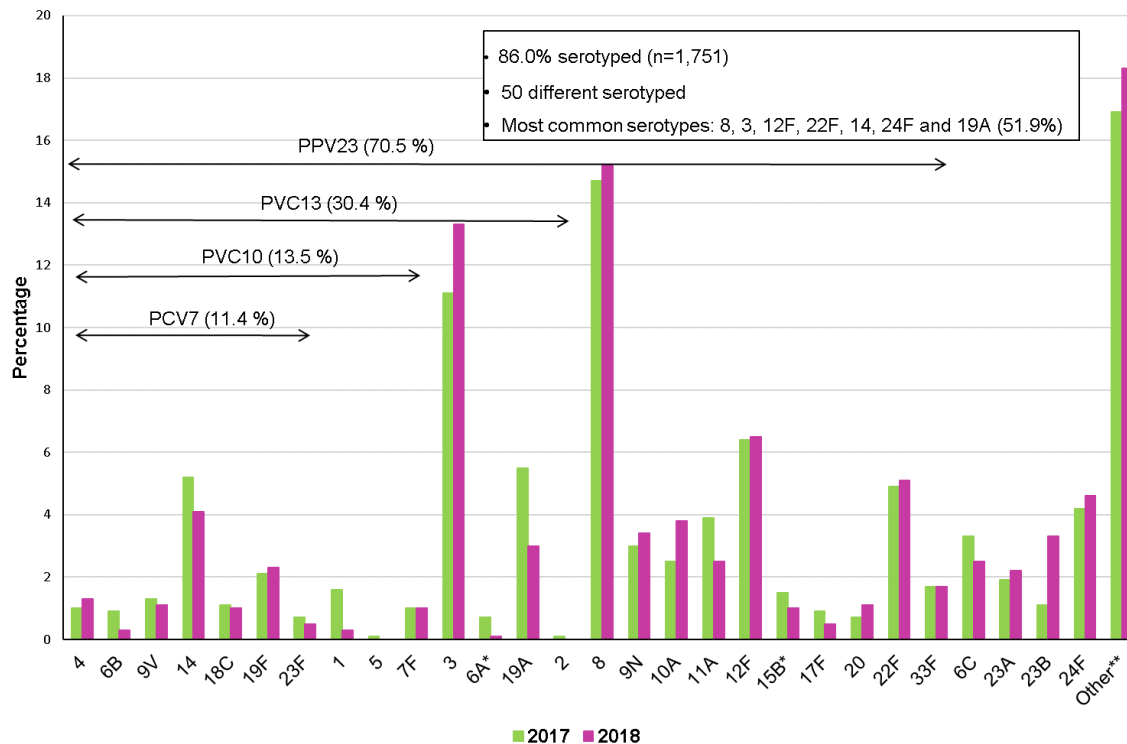
In the 5-19 age group, the serotypes included in PCV7, PCV10 and PCV13 represented 12.5%, 27.1% and 43.8%, respectively. Serotypes 8 (27.1%), 1 (14.6%) and 3 (12.5%) being the most frequent.

In cases in the 20-64 age group, the serotypes included in PCV7, PCV10 and PCV13 represented 11.7%, 14.4% and 30.8%, respectively. The most frequent serotypes were: 8 (22.2%), 3 (12.1%), 12F (8.5%), 22F (5.9%) and 14 (5.2%).

In the 65 and over age group, the serotypes included in PCV7, PCV10 and PCV13 represented 11.5%, 12.5% and 29.7%, respectively. The most frequent serotypes were: 3 (12%), 8 (10.9%), 12F (5.3%), 22F (5%) and 24F (4.7%).

The percentages of **serotypes included in PCV7, PCV10, PCV13 and PCV23**, during the period 2014-2015 were 14.8%, 23.7%, 40.4% and 73.6%, respectively. On the other hand, during the period 2017-2018 these percentages were 11.4%, 13.5%, 30.4% and 70.5%. Comparison of both periods showed a reduction of 23%, 40%, 25% and 4% respectively in the serotypes included in the PCV7, PCV10, PCV13 and PCV23.

Figure 2. Evolution of the serotypes causing invasive pneumococcal disease by years. Catalonia, 2017-2018



Source: Catalan Microbiological Reporting System. Subdirectorat-General for Epidemiological Surveillance and Public Health Emergency Response. Public Health Agency of Catalonia.

*In three cases the serotype was only identified on a group level: one 6A/B, one 6A/C/D and one 15B/C.

** 11B, 13, 15A, 15C, 16F, 18A, 21, 27, 28A, 29, 31, 34, 35A, 35B, 35C, 35F, 37, 38, 39, 7B, 7C and other non-vaccine serotypes.

PCV7: serotypes included in the 7-valent conjugate pneumococcal vaccine; PCV10: serotypes included in the 10-valent conjugate pneumococcal vaccine; PCV13: serotypes included in the 13-valent conjugate pneumococcal vaccine; PPV23: serotypes included in the 23-valent pneumococcal vaccine (serotype 6A is not included the PPV23 vaccine).

4.5 Impact of the 13-valent conjugate pneumococcal vaccine on serotype incidence and distribution.

The serotypes included in PCV7 reduced the incidence rate among under 2 year-olds by 74% (Table 3), mainly due to the drop in serotype 14 (Figure 3).

The incidence of the serotypes included in PCV10, specially serotypes 1 and 7F, dropped for all age groups between 23% and 71% during the period 2017-2018 when compared to 2014-2015. On the other hand, the serotypes included in PCV13 remained stable in all age groups because of the high incidence observed for serotypes 3 and 19A during both periods.

In regard to serotype 3, there were no changes in its incidence compared to 2014-2015 as it was the serotype with highest incidence in the under 5 and the 65 and over age groups during the period 2017-2018. Serotype 3 was in third and second position of frequency in the age groups of 5-19 and 20-64 age groups, respectively.

On the other hand, there was an increase of the incidence of serotypes not included in PCV13 (Non-PCV13) in the 2-4 (68%), 20-64 (35%) and 65 and over age groups: (27%). Of these serotypes, serotype 8 increased its incidence in all age groups and was especially significant among the over 5 year-olds.

Table 3. Distribution of serotypes causing invasive pneumococcal disease by age group and year. Catalonia, 2014-2018

Age group	2014 No.	2014 IR*	2015 No.	2015 IR*	2016 No.	2016 IR*	2017 No.	2017 IR*	2018 No.	2018 IR*
<2y	46	31.2	58	40.8	43	30.4	47	33.7	44	32.5
PCV13	18	12.2	14	9.9	12	8.5	12	8.6	5	3.7
PCV7	10	6.8	10	7.0	10	7.1	4	2.9	1	0.7
PCV10	11	7.5	11	7.7	10	7.1	5	3.6	1	0.7
Non-PCV13	28	19.0	44	31.0	31	21.9	35	25.1	39	28.8
2-4y	39	15.7	45	18.7	40	17.4	34	15.3	46	21.1
PCV13	26	10.5	27	11.2	18	7.8	15	6.7	18	8.2
PCV7	9	3.6	9	3.7	9	3.9	6	2.7	6	2.8
PCV10	17	6.9	14	5.8	10	4.4	7	3.1	6	2.8
Non-PCV13	13	5.2	18	7.5	22	9.6	19	8.5	28	12.8
5-19y	21	1.9	32	2.8	31	2.7	25	2.1	23	1.9
PCV13	16	1.4	19	1.7	21	1.8	13	1.1	8	0.7
PCV7	2	0.2	6	0.5	9	0.8	3	0.3	3	0.3
PCV10	15	1.3	15	1.3	18	1.6	9	0.8	4	0.3
Non-PCV13	5	0.4	13	1.1	10	0.9	12	1.0	15	1.3
20-64y	277	6.0	297	6.4	278	6.0	333	7.2	326	7.0
PCV13	120	2.6	116	2.5	79	1.7	111	2.4	92	2.0
PCV7	39	0.8	43	0.9	25	0.5	43	0.9	34	0.7
PCV10	75	1.6	72	1.6	38	0.8	56	1.2	39	0.8
Non-PCV13	157	3.4	181	3.9	199	4.3	222	4.8	234	5.1
≥65y	333	24.9	399	29.3	373	27.0	433	30.9	440	31.0
PCV13	136	10.2	133	9.8	116	8.4	133	9.5	126	8.9
PCV7	51	3.8	50	3.7	56	4.1	51	3.6	49	3.5
PCV10	72	5.4	64	4.7	60	4.4	54	3.9	55	3.9
Non-PCV13	197	14.7	266	19.5	257	18.6	300	21.4	314	22.1
Total	716	9.5	831	11.1	765	10.2	872	11.5	879	11.6
PCV13	316	4.2	309	4.1	246	3.3	284	3.8	249	3.3
PCV7	111	1.5	118	1.6	109	1.5	107	1.4	93	1.2
PCV10	190	2.5	176	2.3	136	1.8	131	1.7	105	1.4
Non-PCV13	400	5.3	522	7.0	519	6.9	588	7.8	630	8.3

Source: Catalan Microbiological Reporting System. Subdirectorat-General for Epidemiological Surveillance and Public Health Emergency Response. Public Health Agency of Catalonia.

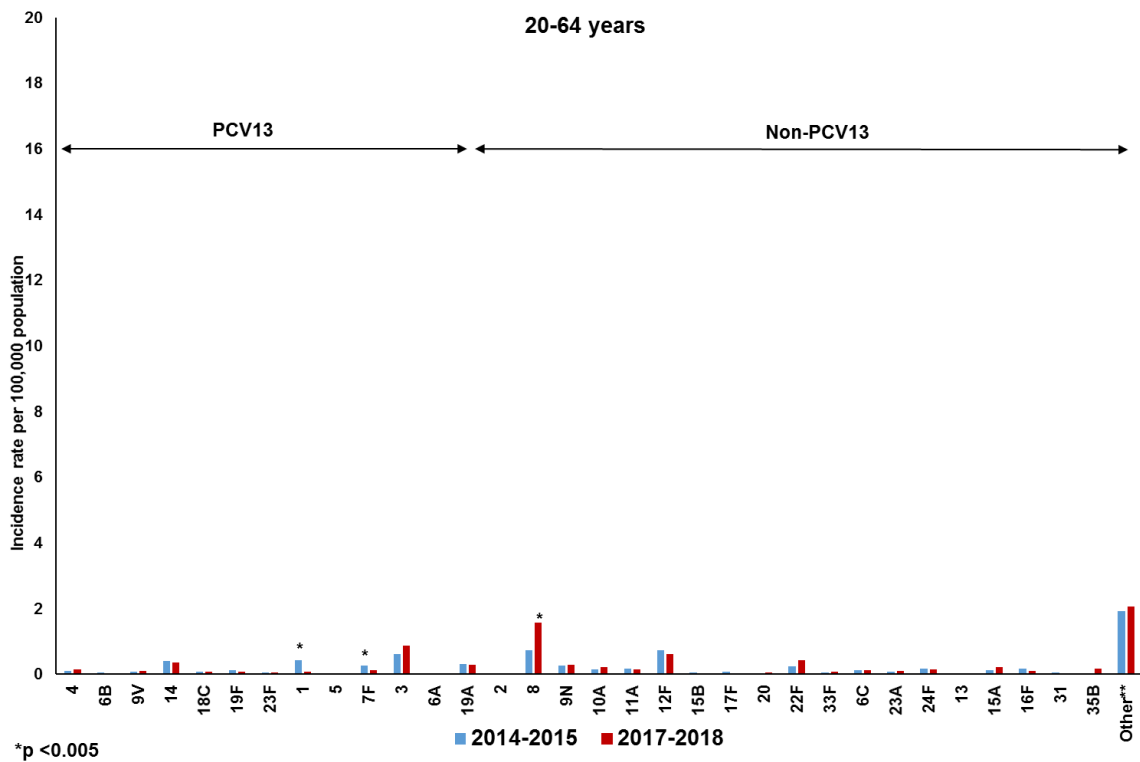
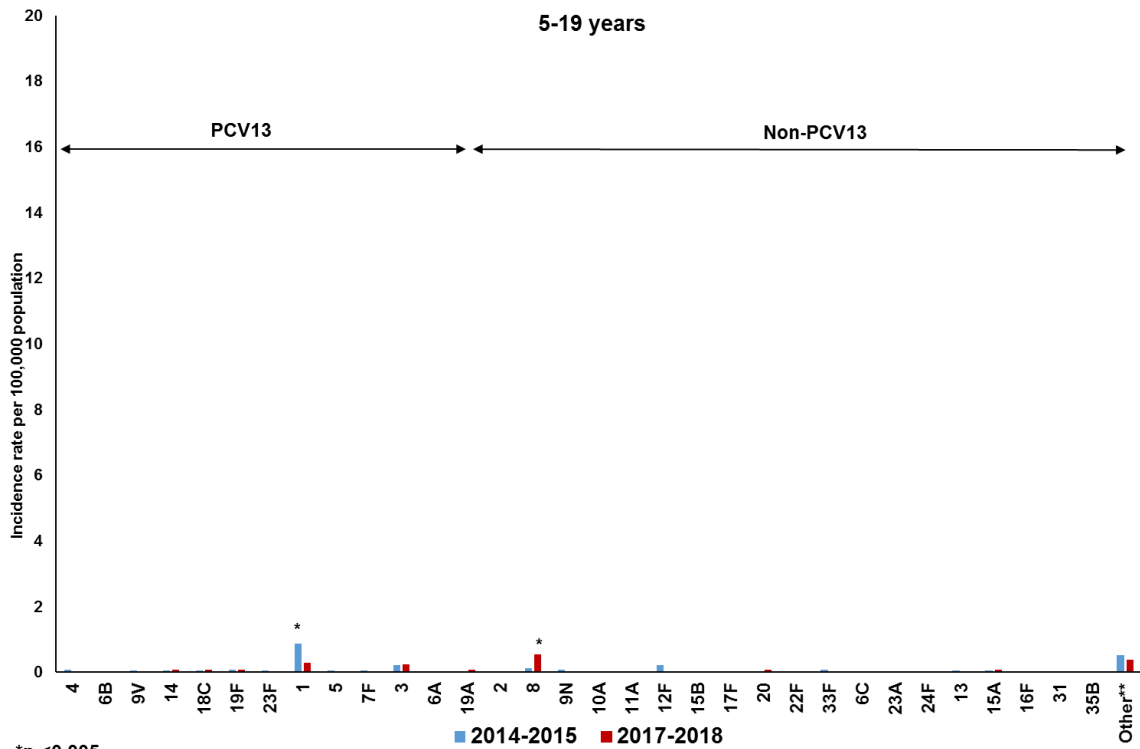
* Rate per 100,000 persons/year.

** RR: relative risk.

No.: number of cases; PCV7: serotypes included in the 7-valent conjugate pneumococcal vaccine; PCV10: serotypes included in the 10-valent conjugate pneumococcal vaccine; PCV13: serotypes included in the 13-valent conjugate pneumococcal vaccine.

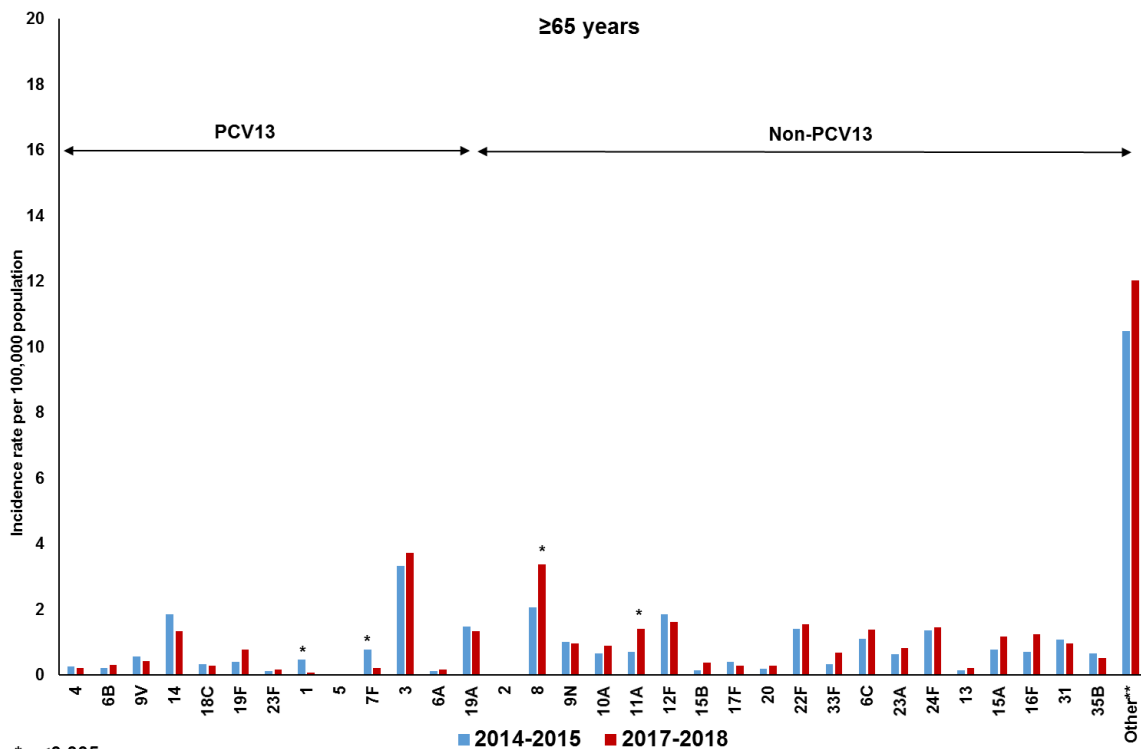
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Source: Catalan Microbiological Reporting System. Subdirectorate-General for Epidemiological Surveillance and Public Health Emergency Response. Public Health Agency of Catalonia.

** 11B, 11F, 15B/C, 15C, 17F, 18A, 21, 24B, 25F, 27, 28A, 29, 34, 35A, 35C, 35F, 37, 38, 39, 6A/B, 6A/C/D, 7B, 7C, 9V/A and other non-vaccine serotypes.

PCV13: serotypes included in the 13-valent conjugate pneumococcal vaccine; Non-PCV13: serotypes not included in 13-valent pneumococcal vaccine.

5 Conclusions

Period 2017-2018

- The overall IPD incidence rate was 13.6 cases per 100,000 population/year.
- The age group with the highest IPD incidence rate was infants under 2, followed by the 65 and over and the 2-4 age groups.
- The most frequent serotypes were 8, 3, 12F, 22F, 14, 24F and 19A; representing 51.9% of cases.
- The serotypes included in PCV7 represented 11.4%; those included in PCV10, 13.5%, and those included in PCV13, 30.4% of cases.
- In children under 2, the serotypes included in PCV7, PCV10 and PCV13 represented 5.1%, 6.6% and 18.7% of cases, respectively. The 24F, 10A and 3 serotypes were the most frequent.
- In the 2-4 age group, the serotypes included in PCV7, PCV10 and PCV13 represented 15%, 16.3% and 41.3%, respectively. The most frequent serotypes being 3 and 24F.
- In the 5-19 age group, the serotypes included in PCV7, PCV10 and PCV13 represented 12.5%, 27.1% and 43.8%, respectively. The most frequent serotypes being 8, 1 and 3.
- In adults aged from 20 to 64, the serotypes included in PCV7, PCV10 and PCV13 represented 11.7%, 14.4% and 30.8% of cases, respectively. The most frequent serotypes being 8, 3 and 12F.
- Finally, in the over 65 age group, the serotypes included in the PCV7, PCV10 and PCV13 represented 11.5%, 12.5% and 29.7% of cases, respectively. Serotypes 3 and 8 being the most frequent.

Comparative analysis of the periods 2017-2018 and 2014-2015

- The overall IPD incidence rate for the period 2017-2018 increased by 15% compared to the period 2014-2015.
- There was a significant increase in the incidence of IPD in the 20 to 64 (18%) and 65 and over (18%) age groups.
- The incidence of serotypes included in the PCV10 vaccine dropped significantly in all age groups due to the reduced incidence of serotypes 1 and 7F.
- The incidence of serotypes included in the PCV13 vaccine remained stable as serotype 3 maintains a high incidence in all age groups.
- There was an increase of non-PCV13 serotypes in almost all age groups, mainly due to the rise in the incidence of serotype 8.

Precise, continuous epidemiological surveillance of IPD is required to detect changes in the incidence of the disease and circulating serotypes as well as to assess the most suitable preventive measures.

6 References

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