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Epidemiology of vaccine-preventable invasive diseases in Catalonia in the era of conjugate vaccines

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Keywords: invasive pneumococcal disease, invasive meningococcal disease, invasive *Haemophilus influenzae* disease, serotypes, serogroups, *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae,* conjugate vaccines, enhanced surveillance

Abbreviations: Nm, *Neisseria meningitidis*; Sp, *Streptococcus pneumoniae*; Hi, *Hemophilus influenzae*; Hib, *H. influenzae* type b; NmC, *N. meningitidis* serogroup C; IPD, invasive pneumococcal disease; IMD, invasive meningococcal disease; IHiD, invasive *Haemophilus influenzae* disease; IR, incidence rate; CI, confidence interval; MRSC, Microbiological Reporting System of Catalonia; OR, odds ratio; PCR, polymerase chain reaction; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; RR, rate ratio; VPIBD, vaccine-preventable invasive bacterial disease; y, year; mo, month

We investigated the incidence and distribution of cases of invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD) and invasive *Hemophilus influenzae* disease (IHiD) notified by hospital laboratories to the Microbiological Reporting System of Catalonia between 2005 and 2009. Incidence rates were compared using the rate ratio (RR) and 95% CI were calculated. A value of $p < 0.05$ was considered statistically significant. Of the 6,661 cases, 6,012 were IPD, 436 IMD and 213 IHiD. The global annual incidence per 10^5 inhabitants was 16.62 (95% CI 16.20–17.04) for IPD, 1.21 (95% CI 1.09–1.32) for IMD and 0.59 (95% CI 0.51–0.67) for IHiD. IPD increased in 2009 compared with 2005 (RR: 1.55, 95% CI: 1.43–1.70) and IMD and IHiD remained stable. Pneumonia was the most-frequent clinical manifestation of IPD (75.6%) and IHiD (44.1%) and meningoencephalitis with or without sepsis for IMD (70.6%). The male:female ratio was 1.37 for IPD, 1.0 for IMD and 1.15 for IHiD. The age groups with the highest incidence were the ≤ 2 y and 2–4 y groups for IPD (66.40 and 50.66/100,000 persons-year) and IMD (14.88 and 7.26/100,000 persons-year) and the ≤ 2 y and ≥ 65 y groups for IHiD (1.88 and 1.89/100,000 persons-year). The most-frequent serotypes were serotype 1 (19.0%) in IPD and untypeable serotypes (60.8%) in IHiD. Serogroup B (78.3%) was the most frequent in IMD. *S. pneumoniae* is the most-frequent agent causing invasive disease in Catalonia. The main clinical manifestations were pneumonia in IPD and IHiD and meningitis in IMD. The main causative agent of meningitis was *N. meningitidis* in people aged < 20 y and *S. pneumoniae* in people aged ≥ 20 y. Vaccination with conjugate vaccines may reduce the risk of infectious disease in our setting.

Introduction

Invasive bacteria such as *Neisseria meningitidis* (Nm), *Streptococcus pneumoniae* (Sp) and *Hemophilus influenzae* (Hi) result in high morbidity and mortality in spite of the preventive antibiotic use and highly-effective vaccines.[1] Globally, these three bacteria are responsible for > 80% of cases of bacterial meningitis in children.[2] Sp and Hi are also a major cause of bacteremia, pneumonia and acute otitis media in children aged > 5 y.[3]

After the introduction of conjugate *H. influenzae* type b (Hib) and *N. meningitidis* serogroup C (NmC) vaccines, a reduction in the number of cases produced by these bacteria has been observed and this has changed the epidemiology of these diseases. Countries that have introduced vaccination with the 7-valent conjugate pneumococcal vaccine (PCV7) have detected a substantial reduction in the number of cases caused by vaccine serotypes followed by a rise in cases due to non-vaccine serotypes.[4-6]

In Catalonia, a region in the northeast of Spain, the conjugate Hib vaccine was the first of these vaccines to be included in the vaccination schedule, in 1999. Invasive *H. influenzae* disease occurred mainly in children and, in 95% of cases, was due to serotype b.[7] The estimated vaccination coverage was 91.5%.[8] In 2000, the meningococcal C conjugated vaccine (MCCV) was included in the vaccination schedule, due mainly to a substantial

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Table 1. Distribution of invasive pneumococcal disease by clinical manifestations and age group. Catalonia, 2005–2009.

Clinical presentation	Age groups											
	< 2 y		2 to 4 y		5 to 19 y		20 to 64 y		≥ 65 y		Total	
	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N [a]	IR (CI)
Pneumonia	314	39.26 (35.04–43.86)	484	42.35 (38.66–46.30)	333	6.65 (5.95–7.40)	1,718	7.37 (7.03–7.73)	1,647	27.81 (26.48–29.18)	4,546	12.56 (12.20–12.94)
Bacteremia without focus	128	16.01 (13.35–19.03)	73	6.39 (5.01–8.03)	57	1.14 (0.86–1.47)	353	1.51 (1.36–1.68)	303	5.12 (4.56–5.72)	928	2.56 (2.40–2.74)
Meningitis with or without sepsis	75	9.38 (7.38–11.76)	19	1.66 (1.00–2.60)	31	0.62 (0.42–0.88)	159	0.68 (0.58–0.80)	108	1.82 (1.50–2.20)	405	1.12 (1.01–1.23)
Sepsis	3	0.38 (0.08–1.10)	1	0.09 (0.00–0.49)	2	0.04 (0.00–0.14)	2	0.01 (0.00–0.03)	1	0.02 (0.00–0.09)	9	0.02 (0.01–0.01)
Others	11	1.38 (0.69–2.46)	2	0.18 (0.02–0.63)	2	0.04 (0.00–0.14)	61	0.26 (0.20–0.34)	46	0.78 (0.57–1.04)	124[b]	0.34 (0.29–0.41)
Total	531	66.40 (60.87–72.29)	579	50.66 (46.62–54.96)	425	8.48 (7.70–9.33)	2,293	9.84 (9.44–10.25)	2,105	35.54 (34.04–37.09)	6,012	16.62 (16.20–17.04)

Notes: N, number of cases; IR, incidence rate (cases / 100,000 persons-year); CI, confidence interval. [a]In some cases age was unknown. [b] include: 83 peritoneal fluid, 34 joint fluid, 2 mastoiditis, 2 bone tissue, 2 pericardial fluid, 1 cellulitis.

increase in the number of cases of meningococcal disease caused by this serotype in Catalonia and other Spanish regions and European countries during the 1990s, although the increases were not simultaneous.[9] It is estimated that serogroup C vaccine coverage in Catalonia is 88.5%.[8] Although meningococcal serogoup B disease now causes the majority of cases in Catalonia, no licensed vaccine is yet available.

PCV7 (only conjugated vaccine available during the study period) was licensed in Catalonia in 2001 but is not included in the routine vaccination schedule, and is only indicated in children aged < 5 y with risk factors.[10] The Spanish Society of Paediatrics recommends vaccination,[11] and the vaccine is administered in private pediatric clinics. The estimated vaccine coverage with PCV7 is around 50%.[12]

In addition to immunization and the use of antibiotics, other intrinsic and extrinsic host factors such as age, sex, risk disease and geographical region influence the epidemiology of invasive disease.

The aim of this study was to investigate the epidemiological characteristics of vaccine-preventable invasive bacterial disease (VPIBD) in Catalonia between 2005 and 2009. The diseases studied were invasive pneumococcal disease (IPD), invasive meningococcal disease (IMD) and invasive *Hemophilus influenzae* disease (IHiD).

Results

Of the 6,661 confirmed cases, 6,012 were IPD, 436 were IMD and 213 were IHiD. The global annual incidence per 100,000 inhabitants was 16.62 (95% CI 16.20–17.04) (**Table 1**) for IPD, 1.21 (95% CI 1.09–1.32) (**Table 3**) for IMD and 0.59 (95% CI 0.51–0.67) for IHiD (**Table 5**).

The incidence of IPD increased from 12.07 in 2005 to 18.75 /100,000 in 2009 (RR: 1.55, 95% CI: 1.43–1.70) (**Fig. 1**), but remained stable from 2007 onwards. The male:female ratio was 1.37. The highest incidence was in the < 2 y and 2–4 y age groups (66.40 and 50.66/100,000 persons-year, respectively) (**Table 1**). Pneumonia was the most-frequent clinical manifestation of IPD, with 4,546 cases (75.6%), of which pneumoniae with empyema represented 11.1% (506 cases). Information on the serotyped was obtained in 4,235 of the 6,012 cases (70.4%). More than 70 serotypes were identified. The most-frequent serotypes were 1 (19.0%), 19A (9.9%), 7F (7.8%), 3 (7.7%), 14 (6.8%) and 5 (4.4%) (**Fig. 2**).

Comparison of the evolution of serotypes during the study period showed a reduction in PCV7 serotypes [20.9% and 13.2% in 2005 and 2009, respectively; (RR: 0.63, 95% CI: 0.49–0.80)] and in serotypes not included in any of the available vaccines [23.6% and 18.0% in 2005 and 2009, respectively; (RR: 0.76, 95% CI: 0.61–0.95)]. No global changes were observed in PCV13 serotypes [69.4% and 67.5% in 2005 and 2009, respectively; (RR: 0.97, 95% CI: 0.86–1.10)], in PVC10 [(49.7% and 45.0% in 2005 and 2009, respectively; (RR: 0.91, 95% CI: 0.78–1.05)], although analysis of the most-frequent serotypes showed an increase in serotype 7F [0.8% and 9.8% in 2005 and 2009, respectively; (RR: 11.65, 95% CI: 4.86–36.52)] and a reduction

in serotype 5 [13.5% and 4.0% in 2005 and 2009, respectively; (RR: 0.29, 95% CI: 0.20–0.43)].

Table 2 shows the incidence rates of the most-frequent serotypes according to age groups. The highest incidence rates were for serotype 1 in children aged 2–4 y (14.96/100,000 persons-year) and serotype 19A in children aged < 2 y (12.38/100,000 persons-year).

Serotype 1 was the most-frequent serotype in children aged 2–4 y (171 cases; 41.3%) and 5–19 y (163 cases; 53.1%) and adults aged 20–64 y (315 cases; 19.4%). In adults aged ≥ 65 y, serotype 3 was the most frequent (165 cases; 11.5%). Serotype 1 was associated with the 2–4 y (OR: 3.56; 95% CI: 2.87–4.41) and 5–19 y (OR: 5.83; 95% CI: 4.59–7.41) age groups. Serotypes 19A and 14 were associated with the < 2 y age group (OR: 3.44; 95% CI: 2.67–4.43; OR: 1.94; 95% CI: 1.40–2.70, respectively). Serotype 7F was associated with the 20–64 y age group (OR: 1.62; 95% CI: 1.30–2.03) and serotype 3 and serotype 14 with the ≥ 65 y age group (OR: 2.14; 95% CI: 1.71–2.69; OR: 1.31; 95% CI: 1.03–1.68, respectively).

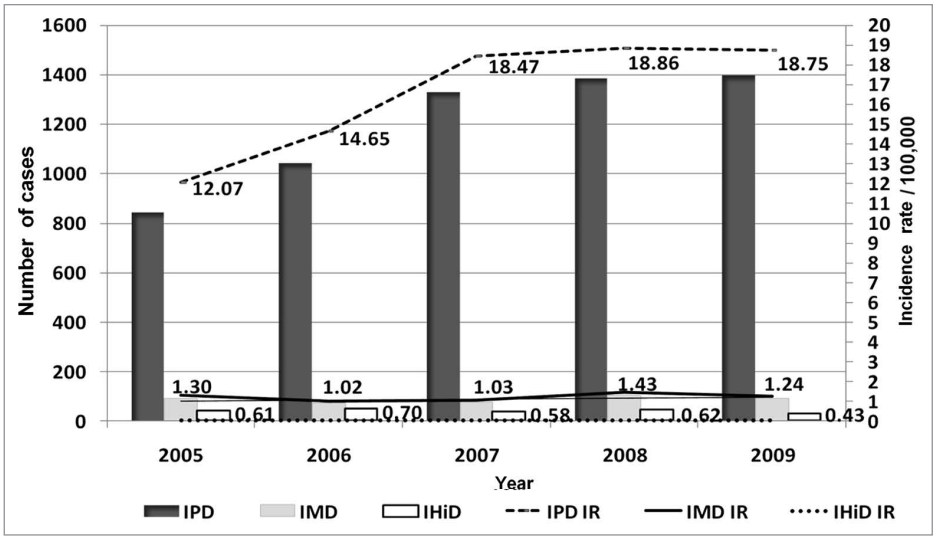

Figure 1. Annual incidence of vaccine-preventable invasive bacterial disease. Catalonia 2005–2009. Note: IPD: invasive pneumococcal disease; IMD: invasive meningococcal disease; IHiD: invasive *H. influenzae* disease; IR: incidence rate.

The distribution of the 4,235 cases serotyped according with the clinical presentation was: 3,402 pneumonia (366 pneumonia with empiema), 402 bacteriemia without focus, 306 meningoencefalitis and 105 other clinical forms.

Comparing the clinical presentation with the most frequent serotypes vs. the rest of serotypes, associations were found between serotype 1 and pneumonia (738 cases; OR: 3.27; 95% CI: 2.51–4.27), serotype 1 and empiema (136 cases; OR: 2.84; 95% CI: 2.26–3.56), serotype 19A and bacteriemia without focus (53 cases; OR: 1.40; 95% CI: 1.03–1.91), serotype 3 and empiema (51 presentations; OR: 2.11; 95% CI: 1.53–2.90), serotype 7F and pneumonia (285 cases; OR: 1.56; 95% CI: 1.15–2.15) and serotype 5 and pneumonia (159 cases; OR: 1.52; 95% CI: 1.01–2.31). There was no association between serotype 14 and any clinical presentations.

Pneumonia was the most-frequent clinical presentation in all age groups (**Table 1**), ranging between 59.1% in children aged < 2 y and 83.6% in children aged 2–4 y.

The incidence rates of IMD remained stable [1.30 and 1.24/100,000 in 2005 and 2009, respectively (RR: 0.96, 95% CI: 0.71–1.29)] (**Fig. 1**). The male:female ratio was 1.0. The highest incidence was in the < 2 y and 2–4 y age groups (14.88 and 7.26/100,000 persons-year, respectively) (**Table 3**). Meningoencephalitis, with or without sepsis, was the most-frequent clinical manifestation, with 308 cases (70.6%).

In 422 (96.8%) of 436 cases, information was obtained on the serogroup (**Table 4**). Five serogroups were detected, with serogroup B being the most-frequent (336 cases; 79.6%). The other serogroups were: C (45 cases; 10.7%), A (9 cases; 2.1%), W135 (6 cases; 1.4%), Y (5 cases; 1.2%) and W135/Y (4 cases; 9.5%). In 17 cases (4.0%) the strain was non-groupable/autoagluttinable.

Serogroups B and C remained stable during the study period compared with the other serogroups [(RR: 1.21, 95% CI: 0.85–1.73) and (RR: 0.48, 95% CI: 0.15–1.36), respectively].

Serogroup B was the most-frequent serogroup in all age groups. The highest incidence rates were in children aged < 2 y and 2–4 y (13.38 and 6.21/100,000 persons-year, respectively) (**Table 4**).

For all clinical presentations studied, serogroup B was the most-frequent serogroup, causing 239 (80.5%) of the 297 cases of meningitis with or without sepsis and 41 (64.1%) of the 64 cases of bacteremia without focus. Serogroup C caused 32 cases (10.8%) of meningitis with or without sepsis and 11 cases (17.2%) of bacteremia without focus. **Table 3** shows that, in all age groups, the most-frequent clinical presentation was meningitis with or without sepsis, ranging between 60.9% in people aged ≥ 65 y and 80.8% in people aged 20–64 y.

The incidence of IHiD remained stable during the study period [0.61 and 0.43 /100,000 in 2005 and 2009, respectively (RR: 0.70, 95% CI: 0.43–1.13)] (**Fig. 1**). The male:female ratio was 1.15. The highest incidence was in the < 2 y and ≥ 65 y age groups (1.88 and 1.89/100,000 persons-year, respectively) (**Table 5**). Pneumonia was the most-frequent clinical manifestation, with 96 cases (45.1%).

Serotyping was performed in 166 (77.9%) of 213 cases. Non-typeable Hi was the most-frequent result (101 cases; 60.8%), followed by serotype b (32 cases; 19.3%). Serotypes a, d, f and c represented 7.2% (12 cases), 1.2% (2 cases), 1.2% (2 cases) and 0.6% (1 case), respectively. In 9.6% (16 cases) were identified as serotype non-b (**Table 6**).

Cases of non-typeable Hi, Hib and Hi non-b remained stable compared with other serotypes [(RR: 1.0, 95% CI: 0.47–2.09), (RR: 0.90, 95% CI: 0.23–3.11) and (RR: 1.03, 95% CI: 0.53–1.97), respectively].

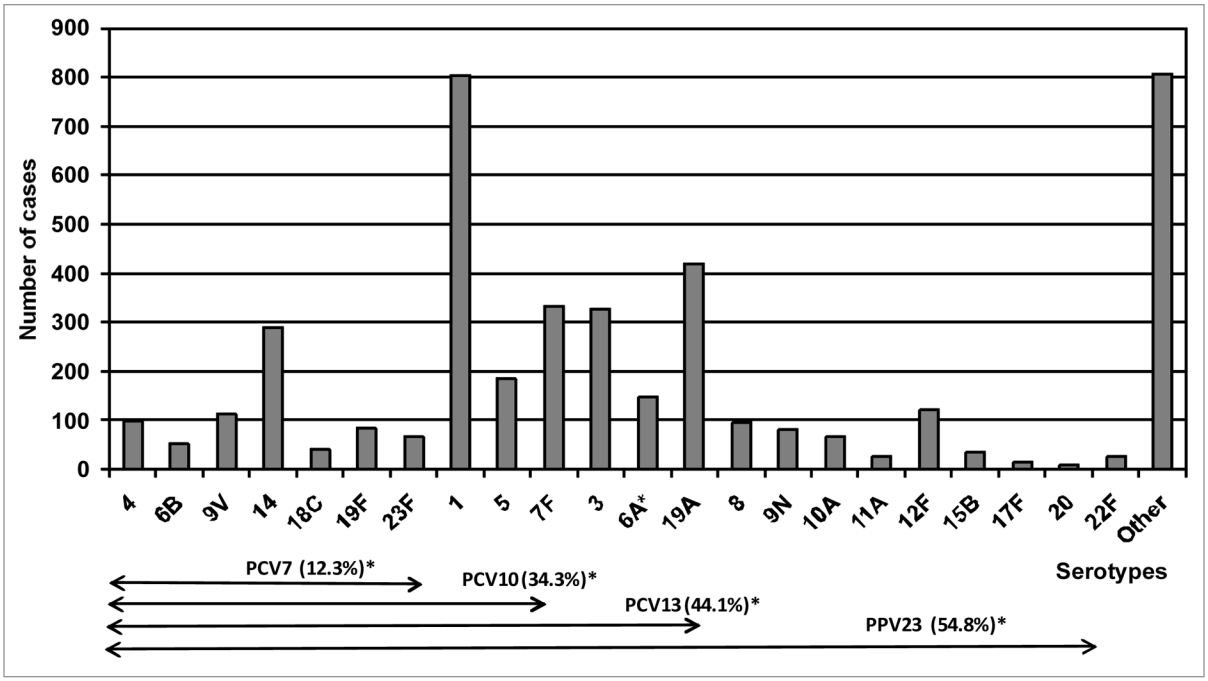

Figure 2. Distribution of invasive pneumococcal disease serotypes. Catalonia 2005–2009. *Percentage of cases caused by serotypes included in each vaccine. Note: Serotype 6A is not included in PPV23.

The highest incidence rates were for non-typeable Hi in the < 2 y and ≥ 65 y age groups (1.25 and 0.88/100,000 persons-year, respectively), followed by serotype b in children aged < 2 y (0.38/100,000 persons-year) and adults aged ≥ 65 y (0.27/100,000 persons-year) (**Table 6**). No Hi serotype were associated with groups of age.

Non-typeable *H. influenzae* was the most frequent serotyped in cases of pneumonia (68.1%), followed by serotype b (10.1%) and non-b (10.1%). In cases with sepsis, serotype b was the most-frequent serotype (83.3%; OR: 30.0, 95% CI: 6.16–146.21), followed by serotype non-b (16.7%).

Discussion

The incidence of invasive bacterial disease varies according to the epidemiological characteristics of the disease, the geographical area[13] and the use of preventive measures such as vaccination, and the sensitivity of the disease surveillance system.[14]

Our results show that the incidence of IPD was much higher than IMD and IHiD, as occurs in other countries,[15] due mainly to the systematic introduction of conjugated vaccines in the vaccination schedule (NmC and Hib vaccines). The current vaccination schedule is three doses at 2, 4 and 6 mo and a booster dose in the second year of life. In Catalonia, although the PCV7 has not been incorporated in the routine vaccination schedule, many pediatricians recommend vaccination, and it is paid for by parents. However, children aged < 5 y with risk factors receive the vaccine free of charge, following the same schedule as the NmC and Hib conjugated vaccines. The current estimated coverage of the PCV7 is around 50%,[12] compared with 88.5% for the NmC and 91.5% for the Hib vaccines.[8]

The global incidence of IPD observed was 16.62/100,000 persons-year, within the range observed in comparable developed countries of 8–34/100,000,[16] and in European countries (0.4–20/100,000).[17] The incidence in Catalonia was slightly higher than observed in the Community of Madrid (Spain) between 2007 and 2009 (10.74/100,000 persons-year), which has incorporated the PCV7 in the routine vaccination schedule since 2006.[18]

Children aged < 4 y, and especially aged < 2 y, had the highest rates of the disease (66.40/100,000 persons- year and 50.66/100,000 persons-year in < 2 y and in 2–4 y, respectively). In these age groups, the incidence observed was also somewhat higher than observed in other Spanish regions, such as the Community of Madrid, which had an incidence of 58.10/100,000 in infants aged < 1 y and 32.68/100,000 in children aged 1–4 y, one year after the incorporation of the PVC7 in the routine schedule.[18]

The main clinical presentation was pneumonia, which was much more frequent than cases of bacteremia without focus and meningitis with or without sepsis as is described in other regions.[19,20]

Globally, the most-frequent cause of meningitis was Sp, although the behavior was not the same in different age groups. Nm was the most-frequent cause of meningitis in people aged < 20 y and Sp in people aged ≥ 20 y.

In countries which have incorporated the PCV7 in the routine schedule,[5,6,21] considerable reductions in the number of cases of IPD caused by PCV7 serotypes, due to the effectiveness of the vaccine and the herd immunity it provides. PCV7 effectiveness against the seven vaccine serotypes is estimated as > 90%.[5,22]

However, a rise has been observed in cases due to non-vaccine serotypes, especially serotype 19A.[5,23,24]

Our results show an increase in the global number of cases, with a reduction in cases due to serotypes not included in any currently available pneumococcal vaccine and an increase in serotypes such as 7F.

More than 90 serotypes of Sp have been reported, but only 20 of these cause more than 80% of cases of invasive disease.[25,26] However, there are temporal changes in the distribution of pathogenic serotypes.[27,28] Our study detected more than 70 serotypes, and the most-frequent serotypes were those most-often detected in other Spanish and European regions.[19,20] The most-frequent serotypes were, in order, 1, 19A, 7F and 3. These PCV13 serotypes caused 44.4% of cases and have emerged after the introduction of the PCV7.[20,23]

As suggested by other authors,[18,19,29] different IPD serotypes were associated with specific clinical presentations and with different age groups. There was an association between pneumonia and serotype 1, between empyema and serotypes 1 and 3 and between non-focal bacteremia and serotype 19A, as reported in other regions.[18,20] Serotype 19A was associated with children aged < 2 y, serotype 1 with people aged 2–19 y, serotype 7 with the 20–64 y age group and serotype 3 with the ≥ 65 y age group.

The incidence rate of IMD remained stable during the study period, with a higher incidence in children aged < 4 y. The global incidence reported by other authors is 0.5–5/100,000 persons-year.[30] Our results were inside of this range. The most-frequent clinical presentation was meningitis with or without sepsis. Nm was the main cause of bacterial meningitis in children and adolescents aged < 20 y, as reported in other studies.[4]

Serogroup B was the most-frequent serotype, causing the majority of cases of invasive disease. Serogroup B causes the majority of meningococcal disease in Europe and is a major health problem.[31,32] Serogroup C, the second in frequency, caused 10.7% of the cases. In the 1990s, various European countries, including Spain, saw an increase in the incidence of cases due to serogroup C. In the United Kingdom, in 1996, 32% of notified cases of IMD were caused by serogroup C.[33] After the inclusion of the vaccine in the routine schedule,[34] the number of cases decreased by 80% to levels seen before the introduction of the vaccine.[35] In Catalonia, as in other Spanish regions, there was also an increase in the incidence, with cases produced by this serogroup representing 32% of all cases in 1996 and 46% in 1997, a substantial rise compared with the preceding years.[36] The polysaccharide vaccine campaign resulted in a substantial reduction in the incidence in 1998.[37,38] The introduction of the conjugated vaccine in 2000[39] resulted in a substantial decrease in the number of cases caused by this serogroup.

Hib was the leading cause of meningitis in children in the US and in most European countries before the introduction of the conjugate Hib vaccine.[4,40] Hib has been virtually erradicated as a cause of meningitis in children in countries that have incorporated the vaccine in the routine schedule.[4] The conjugated Hib vaccine was the first of the three conjugated vaccines, including the meningococcal C and PCV7, to become available. Vaccine

Table 2. Incidence rate of most-frequent serotypes of *S. pneumoniae* by age group. Catalonia, 2005–2009.

Serotypes	Age groups											
	< 2 y		2 to 4 y		5 to 19 y		20 to 64 y		≥ 65 y		Total	
	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N*	IR (CI)
1	28	3.50 (2.33–2.06)	171	14.96 (12.80–17.38)	163	3.25 (2.77–3.79)	315	1.35 (1.21–1.51)	119	2.01 (1.66–2.40)	803	2.22 (2.07–2.38)
3	23	2.88 (1.82–4.32)	26	2.28 (1.49–3.33)	5	0.10 (0.03–0.23)	103	0.44 (0.36–0.54)	165	2.79 (2.38–3.24)	327	0.90 (0.81–1.01)
19A	99	12.38 (10.06–15.07)	41	3.59 (2.57–4.87)	16	0.32 (0.18–0.52)	130	0.56 (0.47–0.66)	128	2.16 (1.80–2.57)	420	1.16 (1.05–1.28)
5	16	2.00 (1.14–3.25)	30	2.63 (1.77–3.75)	31	0.62 (0.42–0.88)	70	0.30 (0.23–0.38)	38	0.64 (0.45–0.88)	185	0.51 (0.44–0.59)
7F	30	3.75 (2.53–5.36)	19	1.66 (1.00–2.60)	14	0.28 (0.15–0.47)	163	0.70 (0.60–0.82)	103	1.74 (1.42–2.11)	331	0.91 (0.82–1.02)
14	48	6.00 (4.43–7.96)	22	1.93 (1.21–2.91)	8	0.16 (0.07–0.31)	93	0.40 (0.32–0.49)	115	1.94 (1.60–2.33)	290	0.80 (0.71–0.90)
Total serotyped	416		414		307		1,622		1,441		4,235	

Notes: IR, incidence rate (cases / 100,000 persons-year); CI, confidence interval; N, number of cases. *Of 4,235 serotypings, the age was not determined in 35 cases.

Table 3. Distribution of invasive meningococcal disease by clinical manifestations and age group. Catalonia, 2005–2009.

Clinical presentation	Age groups											
	< 2 y		2 to 4 y		5 to 19 y		20 to 64 y		≥ 65 y		Total	
	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N[a]	IR (CI)
Pneumonia	0	—	0	—	0	—	0	—	0	—	0	—
Bacteremia without focus	15	1.88 (1.05–3.09)	9	0.79 (0.36–1.49)	9	0.18 (0.08–0.34)	16	0.07 (0.04–0.11)	17	0.29 (0.17–0.46)	67	0.19 (0.14–0.24)
Meningitis with or without sepsis	87	10.88 (8.71–13.42)	55	4.81 (3.63–6.26)	54	1.08 (0.81–1.41)	80	0.34 (0.27–0.43)	28	0.47 (0.31–0.68)	308	0.85 (0.76–0.95)
Sepsis	17	2.13 (1.24–3.40)	19	1.66 (1.00–2.60)	20	0.40 (0.24–0.62)	1	0.00 (0.00–0.02)	1	0.02 (0.00–0.09)	58	0.16 (0.12–0.21)
Others	0	—	0	—	1	0.02 (0.00–0.11)	2	0.01 (0.00–0.03)	0	—	3[b]	0.01 (0.00–0.02)
Total	119	14.88 (12.33–17.81)	83	7.26 (5.78–9.00)	84	1.68 (1.34–2.08)	99	0.42 (0.35–0.52)	46	0.78 (0.57–1.04)	436	1.21 (1.09–1.32)

Notes: N, number of cases; IR, incidence rate (cases / 100,000 persons-year); CI, confidence interval. [a]In some cases age was unknown. [b]Include: 1 joint fluid, 1 peritoneal fluid, 1 petechial fluid.

effectiveness is estimated at around 98%[26,41,24] and its introduction was followed by a marked reduction in all clinical presentations of IHiD, including meningitis.[25] Surveillance data from European countries with routine Hib vaccination show an incidence rate of 0.28/100,000 persons-year of Hi in the post-vaccine era, with only 28% of Hib compared with 80% in the pre-vaccination era.[43] There has been a non-significant increase in invasive disease caused by non-b serotypes in these countries since the introduction of the vaccine.[43]

In Catalonia, before Hib vaccination was introduced, the incidence of invasive disease due to Hib was not as high as in other European countries, ranging between 4.9 and 9.6/100,000.[44,45] After the introduction of the vaccine, disease incidence has fallen to minimum levels, ranging between 0.61 and 0.43 /100,000 persons-year during the study period. The highest incidence was in the < 2 y and ≥ 65 y age groups. The mean incidence in Europe in the < 5 y age group in 2007 remained stable at 0.58/100,000 persons-years.[46] In contrast, the worldwide incidence rate in the < 5 y age group is 20–60 cases/100,000 persons-year.[47]

Hib mainly causes meningitis and pneumonia.[47] After the introduction of the vaccine, the most severe forms of the disease almost disappeared in children, although invasive disease due to other serotypes and non-typeable strains has increased.[48] Non-typeable strains of Hi are an important cause of cases of pneumonia worldwide.[48] Non-typeable strains of Hi were the most-frequent cause of disease in our study and the Hib does not protect against other serotypes or non-typeable strains.

Strain replacement is an important but unanswered question in the epidemiology of IHiD. It is not clear whether the elimination of Hib has increased the incidence of invasive disease caused by other serotypes.[49] Some data suggests this may be occurring in some countries such as Canada.[50]

Between 1996 and 2001, 60% of cases of invasive disease in children were caused by Hi non-b, mainly non-typeable strains.[51] Studies in some countries suggest a possible change in the epidemiology of Hi towards non-b serotypes,[52,53] while in other countries, no substantial increase in non-b serotypes has been observed.[53]

However, our knowledge of the immunology of the conjugated vaccines is far from complete. Increases in the incidence of invasive disease due to Hi, NmC and recently-detected emerging pneumococcal serotypes confirm the importante of continuous and enhanced surveillance.[25]

The potential for the replacement of strains after the introduction of effective conjugated vaccines is an important factor in both Hib and in other capsulated bacteria such as Sp and Nm.[54,55]

The main strength of this study is that the data come from the MRSC and were confirmed and completed by the use of other sources such as the Obligatory Disease Reporting System of Catalonia and the microbiological records of the national and regional reference centers of Spain and Catalonia, respectively. The sample size is another advantage, as it allows conclusions to be drawn on the epidemiology of all the invasive diseases studied.

One limitation of the study is that the serotype was not identified in a large number of strains of Hi, which could make it difficult to obtain conclusive results with respect to IHiD.

Materials and Methods

We analyzed all notifications by participating microbiologists to the Microbiological Reporting System of Catalonia (MRSC) between 2005 and 2009.

The MRSC consists of 50 centers (hospital and primary health care laboratories) representing 84% of hospital beds in public hospitals in Catalonia. This passive surveillance system covers bacterial, viral and parasitic infections including Sp, Nm and Hi.[56]

Notifications of vaccine-preventable invasive disease to the MRSC were compared with other sources of information, in order to capture non-reported cases and complete demographic and microbiological data to do enhanced surveillance. All cases were compared with sources from national (Spanish National Microbiology Center, Madrid) and regional (Hospital Sant Joan de Déu, Barcelona) reference centers. For IMD and IHiD, we also consulted notifications by physicians to the Obligatory Disease Reporting System.

Inclusion criteria. IPD was defined as the isolation of Sp, the detection of DNA by real-time PCR or the detection of antigen in any normally sterile site with compatible clinical manifestations. IMD and HiID were defined as the isolation of Nm or Hi, respectively, in any normal sterile site with compatible clinical manifestations. Strains isolated by culture were identified and serotyped by standard microbiological methods.[57] Serogrouping and serotyping were performed in the regional and national reference centers.

Variables. Sociodemographic, clinical and microbiological data collected included: age, sex, clinical presentation, serogroup and serotype. The clinical presentations evaluated were: pneumonia, meningitis (with or without sepsis), bacteremia without focus, sepsis and others (arthritis, peritonitis, etc.).

Data analysis. Descriptive statistics of cases of VPIBD and the distribution according to age, sex, clinical presentations, serogroup and serotype were analyzed. The incidence was calculated per 100,000 persons-year. The reference population was collected from the Statistical Institute of Catalonia.[58] Incidence rates were compared using the rate ratio (RR) and the 95% confidence intervals (CI) were calculated. The associations between serotypes and age groups, and between serogroups and clinical presentations were calculated using the odds ratios and their 95% CI. A value of $p < 0.05$ was considered statistically significant.

Conclusions

Sp is the most-frequent agent causing invasive disease in Catalonia. The incidence of IHiD and IMD has remained stable during the study period, while an increase in the incidence of IPD has been observed due to increase in non-PCV7 serotypes.

The < 4 y and ≥ 65 y age groups were those most affected by the three invasive diseases studied. Pneumonia was the main

Table 4. Incidence rate of serogroups of *N. meningitidis* by age group. Catalonia, 2005–2009.

Serogroups	Age groups											
	< 2 y		2 to 4 y		5 to 19 y		20 to 64 y		≥ 65 y		Total	
	N cases	IR (95% CI)	N cases	IR (95%CI)	N cases	IR (95%CI)	N cases	IR (95%CI)	N cases	IR (95%CI)	N* cases	IR (CI)
B	107 or Y	13.38 (10.96–16.17)	71	6.21 (4.85–7.84)	68	1.36 (1.05–1.72)	58	0.25 (0.19–0.32)	29	0.49 (0.33–0.70)	336	0.93 (0.83–1.03)
C	3	0.38 (0.08–1.10)	4	0.35 (0.10–0.90)	3	0.06 (0.01–0.18)	27	0.12 (0.08–0.17)	6	0.10 (0.04–0.22)	45	0.12 (0.09–0.17)
A	1	0.13 (0.00–0.70)	1	0.09 (0.00–0.49)	2	0.04 (0.00–0.14)	3	0.01 (0.00–0.04)	2	0.03 (0.00–0.12)	9	0.02 (0.01–0.05)
W-135	1	0.13 (0.00–0.70)	2	0.18 (0.02–0.63)	1	0.02 (0.00–0.11)	2	0.01 (0.00–0.03)	0	—	6	0.02 (0.01–0.04)
Y	0	—	0	—	1	0.02 (0.00–0.11)	2	0.01 (0.00–0.03)	2	0.03 (0.00–0.12)	5	0.01 (0.00–0.03)
W-135 Y or Y	0	—	0	—	1	0.02 (0.00–0.11)	2	0.01 (0.00–0.03)	1	0.02 (0.00–0.09)	4	0.01 (0.00–0.03)
Non- groupable / autoagluttinable	3	0.38 (0.08–1.10)	3	0.26 (0.05–0.77)	5	0.10 (0.03–0.23)	3	0.01 (0.00–0.04)	3	0.05 (0.01–0.15)	17	0.05 (0.03–0.08)
Total serogrouped	115		81		81		97		43		422	

Notes: N, number of cases; IR, incidence rate (cases / 100,000 persons-year); CI, confidence interval. *Of 422 strains serotyped, the age was not determined in 5 cases.

Table 5. Distribution of invasive *Hemophilus influenzae* disease by clinical manifestations and age group. Catalonia, 2005–2009.

Clinical presentation	Age groups											
	< 2 y		2 to 4 y		5 to 19 y		20 to 64 y		≥ 65 y		Total	
	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N	IR (95%CI)	N [a]	IR (CI)
Pneumonia	5	0.63 (0.20–1.46)	3	0.26 (0.05–0.77)	5	0.10 (0.03–0.23)	24	0.10 (0.07–0.15)	58	0.98 (0.74–1.27)	96	0.27 (0.21–0.32)
Bacteremia without focus	7	0.88 (0.35–1.80)	1	0.09 (0.00–0.49)	2	0.04 (0.00–0.14)	27	0.12 (0.08–0.17)	39	0.66 (0.47–0.90)	77	0.21 (0.17–0.27)
Meningitis with or without sepsis	1	0.13 (0.00–0.70)	2	0.18 (0.2–0.63)	1	0.02 (0.00–0.11)	11	0.05 (0.02–0.08)	7	0.12 (0.05–0.24)	24	0.07 (0.04–0.10)
Sepsis	2	0.25 (0.03–0.90)	0	0.00(0.00–0.32)	0	0.00 (0.00–0.07)	5	0.02 (0.01–0.05)	7	0.12 (0.05–0.24)	14	0.04 (0.02–0.06)
Others	0	—	0	—	0	—	1	0.00 (0–0.02)	1	0.02 (0–0.09)	2[b]	0.01 (0.00–0.02)
Total	15	1.88 (1.05–3.09)	6	0.53 (0.19–1.14)	8	0.16 (0.07–0.31)	68	0.29 (0.23–0.37)	112	1.89 (1.56–2.28)	213	0.59 (0.51–0.67)

Notes: N, number of cases; IR: incidence rate (cases / 100,000 presons-year); CI, confidence interval. [a]The age was not determined in 4 cases; [b]includes: 2 peritoneal fluid.

clinical presentations in cases due to IPD and IHiD and meningitis the principal clinical presentation in IMD. The main causal agent of meningitis was Nm in people aged < 20 y and Sp in adults aged ≥ 20 y.

The conjugate vaccines have been a determining factor in reducing the incidence of invasive disease. Correct surveillance of these diseases is necessary to determine the best public health activities at any given time and situation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Table 6. Incidence rate of serotypes of *Hemophilus influenzae* by age group. Catalonia, 2005–2009.

Serotypes	Age groups											
	< 2 y		2 to 4 y		5 to 19 y		20 to 64 y		≥ 65 y		Total	
	N cases	IR (95%CI)	N cases	IR (95%CI)	N cases	IR (95%CI)	N cases	IR (95%CI)	N cases	IR (95%CI)	N*	IR (CI)
b	3	0.38 (0.08–1.10)	2	0.18 (0.02–0.63)	1	0.02 (0.00–0.11)	9	0.03 (0.02–0.07)	16	0.27 (0.15–0.43)	32	0.09 (0.06–0.12)
a	0	—	0	—	2	0.04 (0.00–0.14)	4	0.02 (0.00–0.04)	5	0.08 (0.03–0.20)	12	0.03 (0.02–0.06)
c	0	—	0	—	0	—	1	0.00 (0.00–0.02)	0	—	1	0.00 (0.00–0.02)
d	0	—	0	—	1	0.02 (0.00–0.11)	0	—	1	0.02 (0.00–0.09)	2	0.01 (0.00–0.02)
f	0	—	0	—	0	—	0	—	2	0.03 (0.00–0.12)	2	0.01 (0.00–0.02)
Non-b	1	0.13 (0.00–0.70)	0	—	0	—	6	0.03 (0.01–0.06)	9	0.15 (0.07–0.29)	16	0.04 (0.03–0.07)
Non-typeable	10	1.25 (0.60–2.30)	1	0.09 (0.00–0.49)	3	0.06 (0.01–0.18)	33	0.14 (0.10–0.20)	52	0.88 (0.66–1.15)	101	0.28 (0.23–0.34)
Total serotyped	14		3		7		53		85		166*	

Notes: N, number of cases; IR, incidence rate (cases / 100,000 persons-year); CI, confidence interval. *Of 422 strains serotyped, the age was not determined in 5 cases.

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