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Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001–2012

A. Lepoutre[a,*], E. Varon[b], S. Georges[a], F. Dorléans[a], C. Janoir[b,c], L. Gutmann[b], D. Lévy-Bruhl[a], the Microbiologists of the Epibac[1] and the ORP Networks[2],

[a] Département des maladies infectieuses, Institut de Veille Sanitaire, Saint Maurice, France
[b] Centre National de Référence des Pneumocoques, AP-HP, Hôpital Européen Georges Pompidou, Paris, France
[c] Université Paris Sud, EA 4043 Châtenay-Malabry, France

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ABSTRACT

Context and aims: Vaccination with the 7-valent pneumococcal conjugate vaccine (PCV7) was recommended in France in 2003 for children <2 years. The 13-valent conjugate vaccine (PCV13) replaced PCV7 in 2010. We assessed the impact of PCVs vaccination on the incidence of invasive pneumococcal diseases (IPD) in French children (0–15 years) and adults (>15 years).
Methods: IPD rates were calculated using cases reported from 2001 to 2012 to Epibac, a laboratory network. The distribution of serotypes was assessed from invasive isolates serotyped at the National reference Centre for Pneumococci. IPD incidence rates were compared between the pre-PCV7 (2001–2002), late PCV7 (2008–2009) and post PCV13 (2012) periods.
Results: The PCVs coverage increased from 56% in the 2004 birth-cohort to 94% in the 2008 and following birth-cohorts. Following PCV7 introduction, IPD incidence decreased by 19% between 2001–2002 and 2008–2009 in children <2 years, but increased in children aged 2–15 years and adults, despite a sharp decline in PCV7-IPD in all age-groups. After PCV13 introduction, IPD incidence decreased by 34% in children <5 years, by 50% in those aged 5–15 years and 15% in adults from 2008–2009 to 2012. The incidence of PCV13-Non PCV7-IPD decreased by 74% in children <5 years and by 60% in those aged 5–15 years.
Conclusions: Vaccination with PCV13 was rapidly followed by a decrease in the incidence of all-type IPD in children, in relation with a sharp decrease in the incidence of PCV13-Non PCV7-IPD. Moreover, all-type IPD decreased after PCV13 introduction in older non-vaccinated age-groups, with a shift in the distribution of serotypes. Considering the whole 2001–2012 period, the vaccination with PCV7 and PCV13 resulted in a decline in the incidence of IPD in children up to the age of 5 but not in older children and adults.

1. Introduction

In the early 2000s, *Streptococcus pneumoniae* was the most frequent cause of bacterial invasive disease in France affecting mainly children under two years of age and elderly. This situation justified the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in the French immunization schedule in 2003. The vaccine was first recommended for children under two years of age at risk of pneumococcal invasive disease (IPD), in relation to medical or living conditions, i.e. children cared for more than 4 h/weeks with at least two other children, belonging to a family with more than 2 children, being breast-fed for less than 2 months, representing about 80% of each birth cohort [1]. Then the vaccine was recommended as a universal vaccination for all children under two years of age in June 2006 [2]. The 3+1 vaccination schedule (2, 3, 4 months, and a booster at 12–15 months) was changed in 2008 to a 2+1 schedule (2, 4 and 12 months). Analysis of surveillance data for the 2001–2006 period had shown a 71% decrease in vaccine-type (VT) IPD incidence in children under two years of age, but only a 21% decrease of overall IPD incidence in this age group. The impact of PCV7 on VT-IPD was partially offset by an increase in non-VT IPD incidence (+85%), related to serotype replacement. In older age

* Corresponding author at: Département des Maladies Infectieuses, Institut de Veille Sanitaire, 12 rue du Val d'Osne, 94415 Saint-Maurice Cedex, France. Tel.: +33 1 41 79 68 91; fax: +33 1 41 79 68 72.
E-mail address: a.lepoutre@invs.sante.fr (A. Lepoutre).

[1] List available at: http://www.invs.sante.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-prevention-vaccinale/Infections-invasives-d-origine-bacterienne-Reseau-EPIBAC/Methodes-de-la-surveillance.

[2] List available at http://www.sante-limousin.fr/public/observatoires/observatoire-des-pneumocoques/presentation/16e5496f74fa6e0319d340496390862b#bas.

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groups, no decline in IPD incidence was observed [2]. In 2010, as soon as the PCV13 vaccine was marketed in France, a recommendation was made to shift from PCV7 to PCV13 and the PCV7 was withdrawn from the market in July. We analyzed the French IPD surveillance data from the pre-PCV7 (2001–2002) period until two years after PCV13 introduction (2012), in order to assess the specific impact of PCV7 and PCV13 on the incidence of IPD and on the serotype distribution in French children (0–15 years) and adults (>15 years).

2. Methods

2.1. Vaccination coverage

PCV vaccination coverage is monitored through the Permanent Sample of Beneficiaries, extracted from the National Health Insurance Scheme (NHIS) database which covers the whole French population. This random sample of 1/97th of health insurance beneficiaries includes more than 500,000 individuals and contains their reimbursement claims for all drugs, including vaccines [3,4].

2.2. Surveillance of IPD

IPD surveillance relies upon data generated by two laboratory-based national surveillance networks, Epibac and the National Reference Centre for Pneumococci (NRCP) network. Since 1987, Epibac collects data on six severe invasive bacterial diseases including pneumococcal infections [2,5]. Pneumococcal invasive cases are defined as the isolation of pneumococcus or the detection of pneumococcal DNA, from cerebrospinal fluid (CSF) or blood (non-meningitis IPD). Information on IPD cases are collected prospectively and reported each year to the French Institute for Public Health Surveillance. Data collected include age, sex, and site of isolation. Epibac covers more than 74% of the French metropolitan population and the participating hospitals are distributed evenly across the national territory [2,5].

Since 2001, pneumococcal strains isolated from CSF (meningitis) and from blood in children (0–15 years of age) are collected from hospital-laboratories and sent to the NRCP by 22 regional laboratories organized into a pneumococcal surveillance regional scheme (*Observatoires Régionaux des Pneumocoques*). In addition a systematic 1/6 sample of pneumococcal isolates isolated from blood in adults (>15 years) are collected and sent to the NRCP by the 22 regional laboratories. Serotyping is performed using latex particles sensitized with antisera marketed by the Statens Serum Institute as described in previous publications [2,6]. Serotypes 6A and 6C were retrospectively identified for the 2001–2009 years using the two new respective factor sera marketed by the Statens Serum Institute in 2010.

2.3. Statistical methods

The annual incidence of IPD is calculated using the number of cases reported to the Epibac network as the numerator and the French population covered by the network's participating hospitals as the denominator. The latter is estimated from the proportion of national public and private acute-care hospital admissions covered by participating laboratories, as described in previous publications [2,5,7]. Annual population data are issued by the National Institute for Statistics and Economical Studies. Only hospitals that send data for the full 12-months period are considered participating laboratories [2,5,7]. More than three quarters of the participating hospitals (230/299, 77%) participated during the three time periods included in the analysis (i.e. 2001–2002, 2008–2009 and 2012).

Serotypes 4, 6B, 9V, 14, 18C, 19F and 23F were grouped as PCV7 serotypes (PCV7-ST), serotypes 1, 3, 5, 6A, 7F and 19A were grouped as PCV13-non PCV7 serotypes (PCV13-non PCV7-ST) and the other serotypes were grouped as non PCV13 serotypes (non PCV13-ST).

Serotype-specific incidence rates were calculated in children aged from 0–15 years by multiplying the overall incidence by the proportion of each serotype among all invasive isolates sent to the NRCP (stratified by age group and clinical presentation, meningitis and non-meningitis). As serotypes are determined in only a sample of pneumococcal isolates in adults we did not calculate serotype-specific incidence rates in adults.

Three periods were defined according to the dates of the introduction of PCV7 and PCV13 in the French immunization schedule: pre PCV7 period (2001–2002), late PCV7 period (2008–2009) corresponding to the last years of PCV7 exclusive use in France, and post PCV13 period (2012), two years after PCV13 introduction.

Incidence rate ratios (IRR) were computed for all types-, and specific serotypes-groups IPD between periods, confidence intervals for incidence rate ratios were computed using the "cohort study risk calculator" command of Stata 12.1. Incidence rates were compared between the periods by Fisher exact test. The significance level was set at 0.05. Percent change in the incidence of IPD between periods was computed as (IRR-1) $\times 100$. The analysis was done with STATA 12.1 (StataCorp®).

Cases diagnosed by a positive polymerase chain reaction (PCR) were excluded from the analysis as they were not included in IPD case definition before 2009.

3. Results

In the pre-vaccine years 2001–2002, 8241 IPD cases were reported, 771 (9%) were meningitis; in children aged of less than 2 years 675 IPD cases were reported and 181 (27%) were meningitis. The incidence of IPD was 9.3 cases/100,000 population 95% confidence interval, 95% CI, [9.1, 9.5], it was higher in children aged of less than 2 years (30.3/100,000) and in adults aged of 65 years and over (27.7/100,000).

The serotype was determined in 404 IPD cases in children aged of less than 2 years, 313 in children aged 2–15 years and 1916 in adults aged >15 years. Prior to its introduction, PCV7 covered 69%, 54% and 50% of IPD cases in children aged of less than 2 years, 2–15 years and in adults aged >15 years, respectively.

3.1. Vaccine coverage

PCV coverage for primary immunization at 24 months of age with PCV7 and PCV13 increased throughout the years from 56% (2894/5167) in children born in 2004, to 83% (4494/5428) in those born in 2006 and 94% (5328/5650) in those born in 2008 and after (Fig. 1).

3.2. Evolution of all-type IPD incidence

After PCV7 vaccination, from 2001–2002 to 2008–2009, the incidence of all-type IPD decreased by only 19%, in children aged of less than 2 years, targeted by PCV7 vaccination, and increased in older children and adults (Table 1, Fig. 1). These evolutions were observed for pneumococcal meningitis and other non-meningitis IPD (Table 1). All ages together, the incidence of IPD increased by 20%, from 9.3 to 11.2 cases/100,000 in the French population (Table 1).

Following the substitution of PCV7 by PCV13, the incidence of all-type IPD declined in all age-groups: from 2008–2009 to 2012 the incidence decreased by 30%, 38%, and 50% in children aged of less than 2 years, 2–4 years and 5–15 years, respectively, and by 20% and 15% in adults aged 16–64 years and 65 years or over, respectively (Table 1, Fig. 1).

Globally, from 2001–2002 to 2012, there was a decline in the incidence of all-type IPD in children up to the age of 5, but no

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Table 1
Number of invasive pneumococcal diseases cases and incidence rates by age, France 2001–2012.

Age-group (in years)	Clinical presentation	Mean number of cases/year			Incidence rates (number of cases/100,000 pop.)			IRR[a] (95% CI[b])	p[c]	IRR[a] (95% CI[b])	p[c]	IRR[a] (95% CI[b])	p[c]
		2001–2002	2008–2009	2012	2001–2002	2008–2009	2012	2008–2009 vs 2001–2002		2012 vs 2008–2009		2012 vs 2001–2002	
<2	Meningitis	91	68	53	8.1	5.6	4.5	0.69 (0.56–0.86)	0.00	0.81 (0.59–1.11)	0.21	0.56 (0.41–0.76)	$<10^{-3}$
	Non meningitis	247	231	148	22.1	19.0	12.7	0.86 (0.76–0.97)	0.02	0.67 (0.55–0.80)	$<10^{-3}$	0.57 (0.48–0.69)	$<10^{-3}$
	All <2	338	299	201	30.3	24.6	17.2	0.81 (0.73–0.91)	0.00	0.70 (0.60–0.82)	$<10^{-3}$	0.57 (0.49–0.67)	$<10^{-3}$
2–4	Meningitis	18	19	9	1.1	1.1	0.5	1.00 (0.63–1.58)	1.00	0.47 (0.23–0.98)	0.04	0.47 (0.23–0.98)	0.04
	Non meningitis	117	167	106	7.1	9.4	6.0	1.31 (1.12–1.56)	0.00	0.63 (0.51–0.79)	$<10^{-3}$	0.84 (0.66–1.05)	0.14
	All 2–4	135	186	115	8.2	10.5	6.5	1.28 (1.09–1.49)	0.00	0.62 (0.50–0.76)	$<10^{-3}$	0.79 (0.63–0.98)	0.03
5–15	Meningitis	19	32	18	0.3	0.5	0.3	1.56 (1.04–2.33)	0.04	0.57 (0.34–0.96)	0.03	0.88 (0.50–1.55)	0.78
	Non meningitis	91	151	74	1.5	2.3	1.1	1.56 (1.30–1.88)	$<10^{-3}$	0.49 (0.38–0.63)	$<10^{-3}$	0.77 (0.58–1.00)	0.06
	All 5–15	111	182	92	1.8	2.8	1.4	1.56 (1.32–1.84)	$<10^{-3}$	0.50 (0.40–0.63)	$<10^{-3}$	0.79 (0.62–1.00)	0.06
16–64	Meningitis	161	227	187	0.6	0.7	0.6	1.29 (1.11–1.48)	0.00	0.84 (0.71–1.00)	0.05	1.09 (0.91–1.30)	0.38
	Non meningitis	1377	2006	1553	4.9	6.5	5.2	1.33 (1.27–1.40)	$<10^{-3}$	0.79 (0.75–0.84)	$<10^{-3}$	1.06 (0.99–1.12)	0.09
	All 16–64	1538	2234	1740	5.4	7.2	5.8	1.32 (1.27–1.39)	$<10^{-3}$	0.80 (0.76–0.84)	$<10^{-3}$	1.06 (1.00–1.12)	0.06
>64	Meningitis	97	135	131	1.3	1.7	1.5	1.23 (1.03–1.48)	0.03	0.93 (0.75–1.15)	0.53	1.15 (0.92–1.43)	0.23
	Non meningitis	1904	2394	2127	26.3	29.4	24.9	1.12 (1.07–1.17)	$<10^{-3}$	0.85 (0.81–0.89)	$<10^{-3}$	0.95 (0.90–1.00)	0.04
	All ≥64	2000	2529	2258	27.7	31.1	26.5	1.12 (1.08–1.17)	$<10^{-3}$	0.85 (0.81–0.89)	$<10^{-3}$	0.96 (0.91–1.01)	0.09
All ages	Meningitis	386	481	398	0.9	1.0	0.8	1.14 (1.04–1.25)	0.01	0.83 (0.75–0.93)	0.00	0.95 (0.84–1.07)	0.43
	Non meningitis	3735	4949	4008	8.4	10.2	8.3	1.21 (1.17–1.25)	$<10^{-3}$	0.82 (0.79–0.85)	$<10^{-3}$	0.99 (0.95–1.03)	0.56
	All	4121	5429	4406	9.3	11.2	9.1	1.20 (1.17–1.24)	$<10^{-3}$	0.82 (0.79–0.84)	$<10^{-3}$	0.98 (0.95–1.02)	0.42

[a] Incidence rates ratio.
[b] Confidence interval.
[c] p value determined by Fischer exact test for the comparison of the number of cases and non-cases between the two periods.

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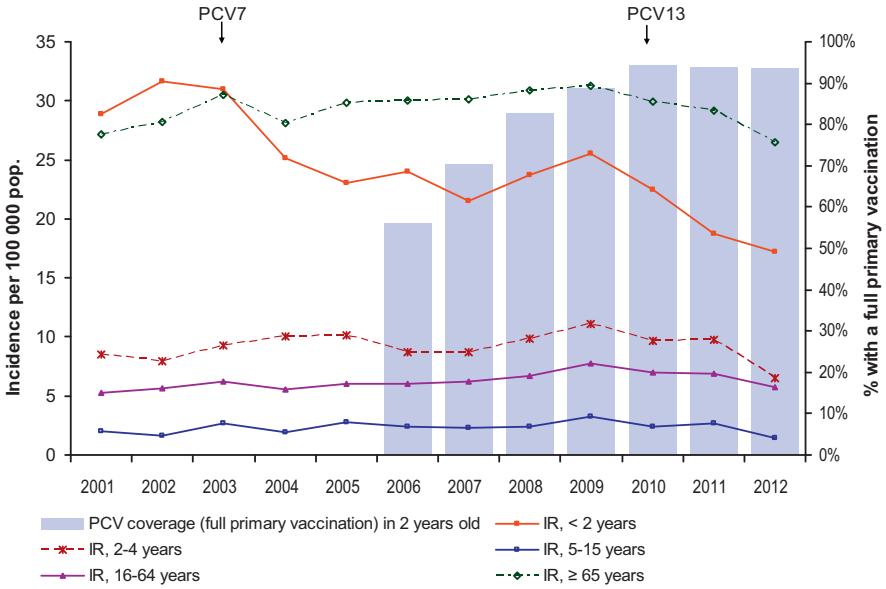


Fig. 1. Evolution of invasive pneumococcal diseases incidence rates (IR) by age-group and pneumococcal conjugated vaccines (PCV) coverage, France 2001–2012.

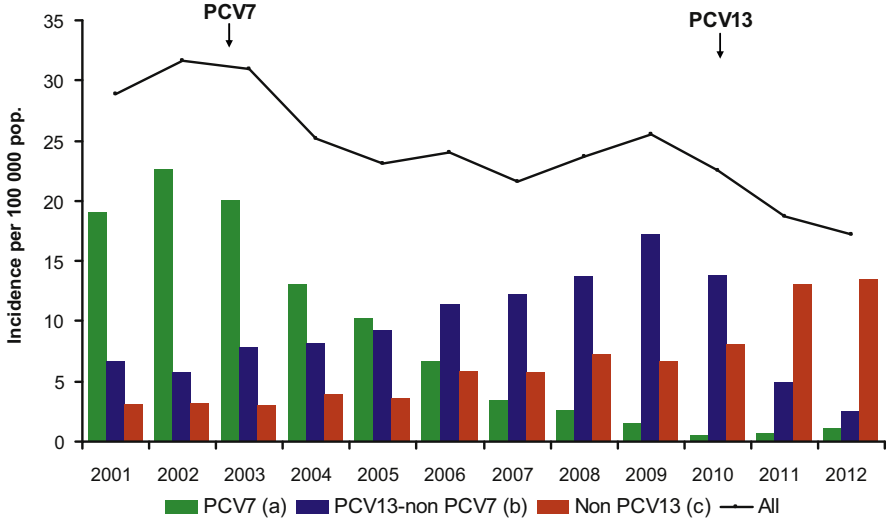
reduction was observed in older age-groups: the incidence decreased from 30.3 to 17.2 cases/100,000 (−43%) in children aged of less than 2 years and from 8.2 to 6.5 cases/100,000 (−21%) in children aged 2–4 years. A non-significant decrease (−21%) in the incidence of IPD was observed in older children aged 5–15 years (Table 1, Fig. 1). The incidence of IPD did not change significantly in adults aged 16–64 years (+6%), nor in those aged 65 years or over (−4%). All ages together, the incidence of all-type IPD did not change between the pre-PCV7 years (2001–2002) and 2012 (Table 1).

3.3. Evolution of the specific serotype incidence of IPD in children

After PCV7 introduction, from 2001–2002 to 2008–2009, the incidence of IPD due to PCV7-ST decreased by 90% in children up to 5 years of age and by 61% in children aged 5–15 years. During the same period, the incidence of IPD due to non PCV7 ST more than doubled in children up to 15 years of age inclusive (Table 2).

In 2008–2009, last years of PCV7 exclusive use, the serotype was determined for 483 IPD cases in children aged of less than 2 years, 500 in children aged 2–15 years and 1851 in adults aged >15 years. PCV13-non PCV7 ST accounted for 63%, 73% and 66% of IPD cases in children aged of less than 2 years, 2–4 years and 5–15 years, respectively. Serotype 19A ranked first in children up to 5 years of age (28%), and serotype 7F ranked second (18%). In 2008–2009, prior to its introduction, PCV13 covered 74% and 76% of IPD in children aged of less than 5 years and 5–15 years, respectively.

After PCV13 introduction, from 2008–2009 to 2012, the incidence of PCV7 IPD cases continued to decrease in children aged of less than 2 years (−46%) and in children aged 5–15 years (−67%) but the decrease (−13%) did not reach statistical significance in children aged 2–4 years (Table 2).



(a) PCV7 : PCV7 serotypes including serotypes , 6B, 9V, 14, 18C, 19F and 23F
(b) PCV13-non PCV7 : PCV13-non PCV7 serotypes, including serotypes 1, 3, 5, 6A, 7F and 19A
(c) Non-PCV13 : other serotypes than PCV7 and PCV13-non PCV7

Fig. 2. Evolution of invasive pneumococcal diseases incidence rates in children <2 years, by serotype-groups, France 2001–2012.

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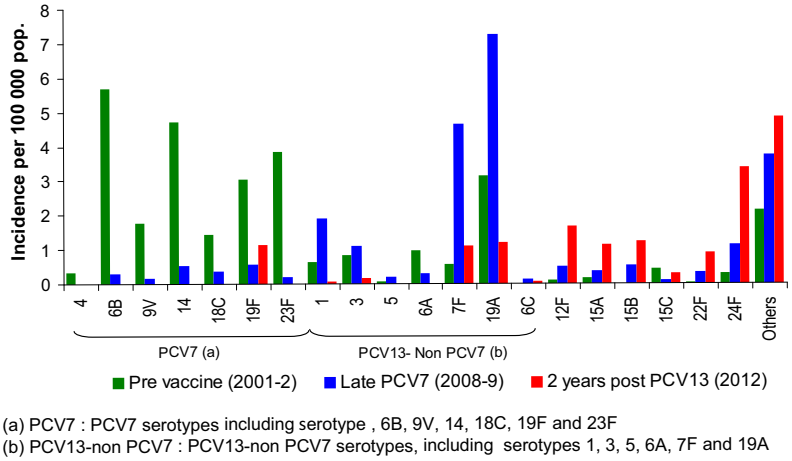


(a) PCV7 : PCV7 serotypes including serotype , 6B, 9V, 14, 18C, 19F and 23F
(b) PCV13-non PCV7 : PCV13-non PCV7 serotypes, including serotypes 1, 3, 5, 6A, 7F and 19A

Fig. 3. Incidence of invasive pneumococcal disease by serotype in children aged less than 2 years in pre-vaccine (2001–2002), late PCV7 (2008–2009) and 2 years post PCV13 (2012) periods, France.

More remarkably, the incidence of PCV13-non PCV7 IPD decreased sharply, by 84%, in children aged of less than 2 years (Table 2, Fig. 2). In this age-group the incidence of the four most prevalent PCV13-non PCV7 serotypes decreased significantly: by 83% (95% CI [72, 90]), 77% (95% CI [59, 87]); 96% (95% CI [73, 100]) and 85% (95% CI [36, 96]) for serotypes 19A, 7F, 1 and 3 respectively. The incidence of PCV13-non PCV7 IPD also decreased in older children (Table 2).

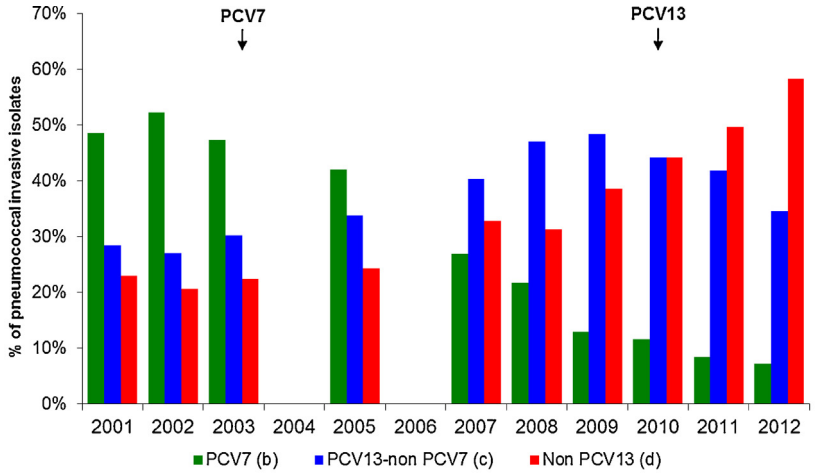
During the same period, the incidence of non PCV13 IPD almost doubled in children aged of less than 2 years (Table 2). In 2012, serotype 24F was the most frequent, accounting for a near 20% of IPD cases in this age-group, followed by serotype 12F (10%). No other individual serotypes reached 10% of IPD cases (Fig. 3). The incidence of non PCV13 IPD increased in children aged 2–4 years (+31%) but it did not increase in children aged 5–15 years (Table 2). The scarcity of IPD cases due to each individual serotype in these age-groups did not allow for the interpretation of their evolution since PCV13 introduction.

3.4. Evolution of serotype distribution in adults

In 2001–2002, prior to PCV7 introduction, PCV7 ST accounted for 45% (415/922) and 54% (539/994) of invasive pneumococcal isolates that were serotyped in adults aged 16–64 years and 65 years and over, respectively; these proportions declined to 14% (136/970, $p < 10^{-4}$) and 20% (173/881, $p < 10^{-4}$) in 2008–2009 and to 7% (24/352, $p < 10^{-4}$) and 9% (32/339, $p < 10^{-4}$) in 2012, in the 16–64 and ≥65 age-groups, respectively.

Conversely, from 2001–2002 to 2008–2009, the proportion of non PCV7 ST increased, from 55% (507/922) to 86% (834/970, $p < 10^{-4}$) and from 46% (455/994) to 80% (708/881, $p < 10^{-4}$) of invasive pneumococcal isolates in the 16–64 and ≥65 age-groups, respectively.

In 2008–2009, prior to PCV13 introduction, PCV13 ST accounted for 60% (586/970) and 61% (534/881) of invasive pneumococcal isolates in the 16–64 and ≥65 age-groups, respectively.



(a) The distribution of the three serotype-groups is standardized on the ratio of pneumococcal meningitis to other non meningitis pneumococcal invasive diseases cases in adults (>15 years), assessed from Epibac data for the respective time periods
(b) PCV7 : PCV7 serotypes including serotypes , 6B, 9V, 14, 18C, 19F and 23F
(c) PCV13-non PCV7 : PCV13-non PCV7 serotypes, including serotypes 1, 3, 5, 6A, 7F and 19A
(d) Non-PCV13 : other serotypes than PCV7 and PCV13-non PCV13

Fig. 4. Evolution of the distribution (a) of invasive pneumococcal isolates by serotype-groups in adults >15 years, France 2001–2012.

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Table 2
Incidence rates of invasive pneumococcal diseases by serotype- and age-groups in children aged of 0–15 years of age, France 2001–2012.

Age-group (in years)	Serotype-group	Incidence rates (number of cases/100,000 pop.)			IRR[a] (95% CI[b])	p^c	IRR[a] (95% CI[b])	p^c	IRR[a] (95% CI[b])	p^c
		2001–2002	2008–2009	2012	2008–2009 vs 2001–2002		2012 vs 2008–2009		2012 vs 2001–2002	
<2	PCV7[d]	20.8	2.1	1.1	0.10 (0.08–0.14)	$<10^{-3}$	0.54 (0.29–0.99)	0.04	0.05 (0.03–0.09)	$<10^{-3}$
	PCV13-non PCV7[e]	6.2.	15.5	2.5	2.49 (2.05–3.02)	$<10^{-3}$	0.16 (0.11–0.24)	$<10^{-3}$	0.41 (0.28–0.61)	$<10^{-3}$
	Non-PCV13[f]	3.2	7.0	13.6	2.18 (1.66–2.87)	$<10^{-3}$	1.93 (1.56 2.40)	$<10^{-3}$	4.22 (3.19–5.57)	$<10^{-3}$
2–4	PCV7[d]	5.3	0.5	0.5	0.10 (0.06–0.16)	$<10^{-3}$	0.87 (0.38–1.98)	0.84	0.09 (0.04–0.18)	$<10^{-3}$
	PCV13-non PCV7[e]	2.2	7.6	3.0	3.40 (2.63–4.40)	$<10^{-3}$	0.39 (0.29–0.53)	$<10^{-3}$	1.34 (0.94–1.90)	0.11
	Non-PCV13[f]	0.6	2.3	3.0	3.54 (2.19–5.72)	$<10^{-3}$	1.31 (0.92–1.84)	0.14	4.63 (2.79–7.67)	$<10^{-3}$
5–15	PCV7[d]	0.7	0.3	0.1	0.39 (0.27–0.57)	$<10^{-3}$	0.33 (0.14–0.79)	0.01	0.13 (0.06 0.30)	$<10^{-3}$
	PCV13-non PCV7[e]	0.7	1.8	0.7	2.52 (1.98–3.21)	$<10^{-3}$	0.40 (0.29–0.55)	$<10^{-3}$	1.01 (0.71–1.43)	1.00
	Non-PCV13[f]	0.3	0.7	0.6	2.04 (1.40–2.97)	$<10^{-3}$	0.86 (0.58–1.26)	0.50	1.75 (1.12–2.74)	0.02

[a] Incidence rates ratio.
[b] Confidence interval.
[c] *p* value determined by Fischer exact test for the comparison of the number of cases and non-cases between the two periods.
[d] PCV7: PCV7 serotypes including serotypes, 6B, 9V, 14, 18C, 19F and 23F.
[e] PCV13-non PCV7: PCV13-non PCV7 serotypes, including serotypes 1, 3, 5, 6A, 7F and 19A.
[f] Non-PCV13: other serotypes than PCV7 and PCV13-non PCV7 serotypes.

After PCV13 introduction, the proportions of PCV13-non PCV7 ST decreased from 46% (384/970) to 32% (112/352, $p < 10^{-4}$) and from 41% (361/881) to 32% (109/339, $p < 10^{-4}$) of invasive pneumococcal isolates in the 16–64 and ≥65 age-groups, respectively, while non PCV13 ST increased from 40% (384/970) to 61% (216/352, $p < 10^{-4}$) and from 39% (347/881) to 58% (198/339, $p < 10^{-4}$) of invasive pneumococcal isolates in the 16–64 and ≥65 age-groups, respectively.

From 2001–2002 to 2012, the proportion of PCV7 ST in IPD in adults >15 years decreased from 50% (954/1916) to 8% (56/691) of invasive isolates, the proportion of PCV13-non PCV7 ST increased from 27% (513/1916) to 32% (221/691) and the proportion of non-PCV13 serotypes increased from 22% (449/1916) to 60% (414/691), (Pearson $\chi^2(2)$ for changes in ST distribution = 437, $p < 10^{-3}$) (Fig. 4).

4. Discussion

The introduction of PCV7 was followed by a decline in the incidence of IPD due to PCV7 serotypes in all age-groups, but the increase of IPD due to non-vaccine serotypes partially compensated this decrease in children aged of less than 2 years and exceeded it in older, non-vaccinated age-groups. The situation in France and in some European countries such as Spain was characterized by an initial low uptake of PCV7 and an important and rapid increase of IPD due to non-vaccine serotypes, mainly serotypes 1, 19A and 7F [2,8–12]. This resulted in a far less favourable evolution than in the majority of other countries from North America or Europe [12,13]. The French and Spanish situation differs particularly from the situation observed in Nordic European countries such as Norway [14] and in the United States of America (USA) [15] where PCV7 introduction resulted in an important decline in all type IPD in children aged of less than 5 years of age (−77% from 1998–1999 to 2006–2007 in the USA [15], − 73% from 2004-[15], −73% from 2004–2006 to 2008 in Norway [14]) and a decline in IPD in older non vaccinated age-groups, resulting in overall reduction in IPD incidence in the population (−45% from 1998–1999 to 2006–2007 in the USA). The initial low vaccine coverage is likely to have played a role in France, but it is unlikely to be the only explanation as the decline in IPD incidence in children aged of less than 2 years halted in 2006 whereas the vaccine coverage improved (Fig. 1). Other factors may have played a role such as a lower coverage, by PCV7, of IPD serotypes in young children in France, prior to vaccine introduction, than in some of the other countries (69% in France *vs* 83% in the USA in children <5 years [15]), with a relatively high prevalence of non PCV7 19A serotype, which accounted for 10% of IPD cases in children aged of less than 2 years in 2001–2002.

Vaccination with PCV13 was rapidly followed by a decrease in the incidence of all-type IPD in young children targeted for vaccination, in relation with a sharp decrease in the incidence of IPD caused by the PCV13-non PCV7 serotypes (−84%). The decrease was significant for the four most prevalent serotypes in young children in the last period of PCV7 vaccination, i.e. serotypes 1, 3, 7F and 19A. However, our results on individual serotypes which are infrequent such as serotype 3 (and 1) rely on a very small number of cases observed on a short period of time and should be interpreted with caution. This is even truer for serotype 3, for which a recent effectiveness analysis indicated a lower efficiency of the PCV13 [16]. In addition to the decrease of all-type IPD in young children, IPD decreased in older non-vaccinated age-groups, in association with a shift in the distribution of serotypes. Our results are in line with the decrease in IPD observed in recent publications from Europe [17–21] or the [22,23]. Our results are also consistent with the important decrease in the nasopharyngeal carriage of PCV13-non PCV7 serotypes in young children presenting with an acute otitis media observed as early as a few months after PCV13 introduction in France [24]. The evolution of IPD in

non-targeted age-groups after PCV13 vaccination contrasts with the situation observed in the PCV7 years in France; the good uptake of pneumococcal conjugate vaccine (94% PCV13 coverage in the 2010 birth cohort vs 56% PCV7coverage in the 2004 birth cohort), and the inclusion of the predominant non PCV7 serotypes such as serotypes 19A and 7F in the PCV13 at the time of its introduction, are likely explanations for this early favourable evolution. All ages together, the incidence of all-type IPD decreased from 11.2 to 9.1 case/100,000 population, two years after PCV13 introduction. The extrapolation of this decrease to the French metropolitan population (63,700,000 inhabitants) yields an estimation of 1300 IPD cases prevented in 2012 compared to the last period of PCV7 vaccination, 950 (73%) of these cases being adults IPD cases.

Our study has some strengths and limitations inherent to the organization of invasive bacterial surveillance in France [5–7]. First, not all the French population is covered by this surveillance. However, our methodology for annual adjustment ensures that small variations over time in the proportions of hospital laboratories participating in the surveillance are accounted for [5,7]. In addition, one of the strengths of our study is that incidence of IPD is based on a continuous surveillance network that has used the same methodology since the mid 90s with little change in the participating hospitals (77% of the participating hospitals participated in the three time periods under study). The exhaustiveness of reporting has been ascertained through repeated two- or three-sources capture–recapture analysis, and has always been estimated around 80% or above [25–27]. Unlike in other countries, the practice of lumbar puncture for suspected cases of meningitis or blood culturing has not been questioned in France in recent decades, something which could have induced a diagnostic bias, which in turn could affect the estimation of trends in IPD incidence. This is further confirmed by the stable ratio of pneumococcal meningitis to all IPD incidence in young children (27% in 2001–2002 *vs* 26% in 2012) and in other age-groups (8% in 2001–2002 *vs* 8% in 2012). The exclusion of cases diagnosed by PCR only did not affect the results as only 0.5% of cases, (0–2% depending of the age and the year), were diagnosed by PCR since 2009. Also, cases diagnosed by the isolation of *S. pneumoniae* in other sterile sites than blood or CSF are not included in our surveillance, but these sites account for a small proportion of IPD cases and their exclusion is unlikely to impact significantly the changes observed. Incidence and serotype data are issued from two networks whose regional participation rates are not exactly identical. However, the coverage of both surveillance networks exceeds 70% of French hospitals and there is a high overlap between them; 69% of the CSF isolates collected by the NRCP in children aged 0–15 years were also reported by Epibac laboratories as shown by a three sources capture–recapture analysis [27]. Lastly, although all invasive isolates are not serotyped, this is unlikely to bias significantly our results as missing serotyping is the consequence of the non-participation of hospitals in the surveillance scheme and does not result from a selective serotyping of pneumococcal isolates in the participating hospitals. Another limitation comes from the short pre-vaccine period, which did not allow the adjustment for pre-vaccine trends.

Taking into account those factors, we remain confident that our data reflect the trends of IPD incidence and the shift in serotype distribution in the vaccination era. Whether these evolutions are fully attributable to the effects of PCV vaccination is less certain. The trends evidenced by our data might also be due to other unmeasured factors such as changes in serotype distribution due to natural pneumococcal serotype cyclic trends [10,28] or to change in antibiotic consumption, which decreased in France between 2002 and 2007 [29]. Increase in the prevalence of risk factors in the French population may also have contributed to the increase in IPD incidence in the adult population, as the number of French inhabitants who registered for the health coverage of chronic diseases increased by an average of 5.3% per year between 1997 and 2010 (data from the French institute for research and information in health economics, available at: http://www.irdes.fr/EspaceEnseignement/ChiffresGraphiques/Cadrage/ALD/IncidenceALD.htm#taux).

5. Conclusions

Considering the whole 2001–2012 period, the vaccination of young children with PCV7 and PCV13 resulted in a decline in the all-type incidence of IPD in children up to the age of 5 but not in older children and adults. Beyond the non-disputable impact of PCV vaccination, some other unmeasured factors may have contributed to this evolution, especially in adults. The early impact of PCV13 vaccination observed on IPD in children targeted for vaccination and, for the first time in France, in older age-groups should be confirmed in the years to come. A further decline in IPD in all age-groups in the short term, will depend on the balance between direct and indirect benefit of PCV13 vaccination and the importance of the increase of IPD due to non vaccine serotypes. The increase in non PCV13 IPD cases is already noticeable and may impair this benefit in the future. To date, emerging non vaccine serotypes are not as prevalent as was the serotype 19A in the post PCV7 period, but the increase in replacement disease, if sustained, may call for the introduction of new pneumococcal vaccines with broader serotype coverage in the future. There is therefore a need to continue to closely monitor IPD epidemiology, including the magnitude of serotype replacement, in the next years through ongoing epidemiological and bacteriological surveillance.

Conflict of interest

A. Lepoutre declares no potential conflicts of interest, E. Varon received fees from Pfizer and GlaxoSmithKline for participation in working groups on pneumococcal vaccines, S. Georges, F. Dorléans, C. Janoir, L. Gutmann and D. Lévy-Bruhl declare no potential conflicts of interest.

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