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Nationwide trends of invasive pneumococcal disease in Spain (2009-2019) in children and adults during the pneumococcal conjugate vaccine era

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Summary. The manuscript demonstrates an increase of certain non-vaccine serotypes in children and adults comparing 2009-2019. The use of PCV13 in the vaccination calendar of immunocompetent adults aged 65 years and older reduces IPD cases by PCV13 serotypes including serotype 3.

Abstract

Background. Introduction of pneumococcal conjugate vaccines (PCVs) has shown a marked reduction in the disease caused by vaccine serotypes in children providing herd protection to the elderly group. However, the emergence of non-vaccine serotypes is of great concern worldwide.

Methods. This study includes national laboratory data from invasive pneumococcal disease (IPD) cases affecting pediatric and adult population during 2009–2019. The impact of implementing different vaccine strategies for immunocompetent adults comparing Spanish regions using PCV13 *vs* regions using PPV23 vaccine was also analyzed for 2017–2019.

Results. The overall reductions of IPD cases by PCV13 serotypes in children and adults were 88% and 59% respectively during 2009–2019 with a constant increase of serotype 8 in adults since 2015. IPD cases by additional serotypes covered by PPV23 increased from 20% in 2009 to 52% in 2019. In children, serotype 24F was the most frequent in 2019 whereas in adults, serotypes 3 and 8 accounted for 36% of IPD cases. Introduction of PCV13 or PPV23 in the adult calendar of certain Spanish regions reduced up to 25% and 11% respectively the IPD cases by PCV13 serotypes, showing a decrease of serotype 3 when PCV13 was used.

Conclusions. Use of PCV13 in children has shown a clear impact in pneumococcal epidemiology reducing the burden of IPD in children but also in adults by herd protection although the increase of serotype 8 in adults is worrisome. Vaccination with PCV13 in immunocompetent adults seems to control IPD cases by PCV13 serotypes including serotype 3.

Keywords. *Streptococcus pneumoniae*, IPD, Serotypes, PCV13, PPV23

Introduction

Prevention of invasive pneumococcal disease (IPD) is one of the leading challenges worldwide because despite the use of antibiotics or the availability of vaccines it is still being associated to high morbidity and mortality rates specially in young children and the elderly population [1, 2]. The most commonly used vaccines worldwide are the pneumococcal polysaccharide vaccine containing 23 serotypes (PPV23) and the pneumococcal conjugate vaccine (PCV) of 13 serotypes (PCV13) [3]. PPV23 is limited to adults and children of 2 years and older whereas PCV13 can be used in younger children and adults. The main disadvantages of these vaccines of polysaccharide nature are the limitation in the number of serotypes covered and the possibility of serotype replacement by non-vaccine serotypes [4, 5].

Spain is divided in 19 different regions and the vaccine policy is transferred to the public health system of each of these regions. The Spanish Ministry of Health can make general recommendations for vaccines policy although each Spanish region has the competence in health matters and applies its own vaccination policy based in their local epidemiology, regional cost-effectiveness and potential benefits for their local population. The use of PCVs in children has been heterogeneous among the entire territory. PCV7 was commercialized in 2001 although mainly in the private market. PCV10 was authorized in 2009 without generic use. PCV13 was available in 2010 for the private market. In 2015, the Ministry of Health approved the systematic use of PCV13 for pediatric population giving a deadline until the end of 2016 to include it at national level (2+1 schedule). In adults, the situation is also discrepant among the entire country. The general recommendation by the Ministry of Health for immunocompetent adults ≥ 65 years old is the use of PPV23 with a systematic use since 2004. However, up to seven different regions have introduced PCV13 in adults in the last 3 years [6]. This heterogeneous vaccine policy, allows the possibility of studying different

vaccine strategies (PPPV23 or PCV13 for adults) within the same country with similar heard protection.

In this manuscript, we show age-specific and serotype-specific trends in IPD in Spain for the last 11 years (2009-2019) in children and adults. We also have analyzed the impact of using different vaccines in immunocompetent adults ≥ 65 years for the period 2017-2019 comparing the burden of IPD among the regions that use PCV13 *vs* the rest of the country where PPV23 is used.

Methods

Study design and sites

We have performed a prospective national observational study including all the IPD isolates (29.786) reported by hospital laboratories to the Spanish Pneumococcal Reference Laboratory (SPRL) during the period 2009-2019. The SPRL notifies annually to the European Center for Disease Control (ECDC) all the IPD cases received following a passive surveillance system that cover 80% of the national level according to estimates by the National Center for Epidemiology reported to ECDC [7]. Serotyping was performed by Quellung reaction, dot blot assay and/or by capsular sequence typing [8, 9]. Data analyzing different vaccine strategies for adults was obtained by including all IPD cases in adults ≥ 65 years for the period 2017-2019 in six regions using PCV13 *vs* the 13 regions that use PPV23 (Supplementary Figure S1). Pneumococcal vaccine coverage rates are unavailable publically since 2006 in Spain.

Processing of data

The epidemiological year is from January to December. We grouped serotypes into five categories: all serotypes, PCV13 serotypes, non-PCV13 serotypes, additional PPV23 serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F), non-vaccine serotypes (serotypes not included in PCV13 nor PPV23). IPD was analyzed by different age groups for pediatric (< 2 years, 2-5 years and 0-17 years) and adult populations (>18 years, 18-64 years and ≥ 65 years). We determined the incidence of IPD in each year. For comparisons, we analyzed four different periods according to changes in the vaccination schedule; the pre-PCV13 (year 2009), the early pre-PCV13 period in which vaccine effect was mainly by private market (2010-2012), the middle-PCV13 period (2013-2016) and the late-PCV13 period (2018-2019) to see the impact of PCV13 after 3 years of global use in the national pediatric immunization program.

Statistical analysis

In this study, we calculated the annual incidence of IPD by dividing the number of cases per year by the population size for that year in Spain based in the public data from the Statistical National Institute. The impact of vaccination was calculated by comparing the rates of the different periods with the rates of the reference period by calculating the incidence rate ratio (IRR) through Poisson regression models. Vaccine coverage for adults aged 65 years and older was kindly provided by Public Health Directorate-Ministry of Health. It was calculated dividing the number of adults ≥ 65 years old who were vaccinated with PCV13 or PPV23 divided by the target population of the same age in each region. Statistical analyses were performed using STATA v.14.

Results

Evolution of IPD affecting children and adults

In children < 2 years, the incidence by PCV13 serotypes declined from 26.91 cases in the pre-PCV13 period (year 2009) to 3.89 cases in the last period 2018-2019 (IRR 0.14, 95% CI 0.11-0.19) demonstrating a reduction of 89% of IPD cases comparing 2009 (263 cases) *vs* 2019 (28 cases). Incidence by non-PCV13 serotypes increased from 9.41 cases in 2009 to 17.19 cases in 2018-2019 (IRR 1.83, 95% CI 1.44-2.31) (Figure 1, table 1 and supplemental Figure S2). In children aged 2-5 years old, the incidence by PCV13 serotypes declined from 14.55 in 2009 to 1.93 in 2018-2019 (IRR 0.13, 95% CI 0.1-0.17) resulting in a reduction of 88% of IPD cases comparing 2009 (279 cases) and 2019 (33 cases). The increase by non-PCV13 serotypes was less pronounced in this age group with an incidence of 2.03 in 2009 and 3.75 in the last period 2018-2019 (IRR 1.84 95% CI 1.29-2.63) (Figure 1, table 1 and supplemental Figure S2). Overall, these results confirm that vaccination with PCV13 in pediatric population progressively reduced the incidence of IPD in children including the early, middle and late vaccine periods. In addition, an increase of IPD cases by non-PCV13 serotypes occurred mainly for the middle and late periods.

In adults, the burden of disease by all serotypes remained constant for the age group of 18-64 and moderately higher for adults aged 65 and older when comparing the pre-vaccine period with the later periods (Figure 1, table 1). IPD cases by PCV13 serotypes declined up to 67% in adults aged 18-64 years (IRR 0.37, 95% CI 0.33-0.41) and 50% in adults aged ≥ 65 (IRR 0.47, 95% CI 0.43-0.52) comparing 2009 *vs* the 2018-19 period (Figure 1, table 1 and supplemental Figure S2). Hence, vaccination with PCV13 since 2010 followed by the systematic use in the pediatric calendar in 2016 was effective reducing the burden of disease by vaccine serotypes in adults of all ages, demonstrating an important herd protection effect.

Incidence rates by PPV23 serotypes, decreased until the middle vaccine period, although in the last years, we have recovered the incidence level of the pre-vaccine period despite the relative use of this vaccine in Spanish adults (Figure 1, table 1 and supplemental Figure S2). Incidence by additional PPV23 serotypes (those included in PPV23 but not in PCV13), remained similar until the middle period in adults aged 18-64 years, followed by a constant increase until the late period coinciding with the use of PCV13 in the pediatric calendar. In adults aged ≥ 65 years, incidence by additional PPV23 serotypes increased gradually since the introduction of PCV13 in the pediatric calendar in 2010 with the maximum peak in the late period (2.84 cases per 100000 in 2009 *vs* 7.61 cases per 100000 in 2018-19, IRR 2.68, 95% CI 2.32-3.09) (Figure 1, table 1 and supplemental Figure S2).

IPD by non-vaccine types in the age group of 18-64 years showed a stable trend since 2009 until the late period (2018-2019). For adults aged ≥ 65 years, we observed a constant rise comparing the pre-vaccine and late periods (IRR 1.54, 95% CI 1.35-1.76; Figure 1, table 1 and supplemental Figure S2).

Distribution of serotypes causing IPD in children and adults

To investigate the dynamics of serotype fluctuation we included the periods 2009 and 2015 coinciding with the years before PCV13 was available in private market and in the pediatric calendar respectively and the last epidemiological year 2019 (Figures 2-4). In pediatric population, 80% of IPD cases were caused by PCV13 serotypes in the pre-vaccine period decreasing from 542 cases in 2009 to 61 cases in 2019, demonstrating the contribution of PCV13 to decrease the burden of disease in children. Among non-PCV13, serotype 24F was the most frequent in all the periods investigated with an increase of serotype 8 in the last years (Figure 2, table 2).

In adults aged 18-64 years, IPD cases by PCV13 serotypes declined from 66% (924 cases) in 2009 to 24% (309 cases) in 2019 confirming the herd protection effect by the pediatric

population, with serotype 3 as the most frequent among PCV13 serotypes in 2019, (Figure 3, table 3). The increase of IPD cases by additional PPV23 serotypes was mainly due to the emergence of serotypes 8 (5.2% in 2009 *vs* 30% in 2019), followed by serotypes 12F, 9N and 22F. Non-vaccine serotypes remained relatively constant in this group.

In adults aged ≥ 65 years, IPD cases by PCV13 decreased from 65% (824 cases) in 2009 to 25% (415 cases) in 2019 demonstrating again the impact of indirect protection due to the pediatric vaccination (Figure 4). Serotypes 3 and 19A were the two most frequent PCV13 serotypes in all the periods investigated whereas an increase of additional serotypes covered by PPV23 (mainly by serotype 8) was also observed. The emergence of serotype 8 is worrisome rising from 5.8% (73 cases) in 2009 to 19% (232 cases) in 2019 (Figure 4, table 3). Other emerging serotypes in this age group are 22F (5.3%, 66 cases) and 12F (4.6%, 57 cases). Overall, IPD cases by serotypes 3 and 8 accounted for 32% of IPD cases in adults aged 65 and older (396 of 1239 total cases). Non-vaccine types also increased from 22% in 2009 (280 cases) to 30% in 2019 (367 cases) with serotypes 15A (4%), 6C (3.8%), and 16F (3.4%) among the most frequent in 2019.

Serotypes 3, 19A and 6A that are included in PCV13 and not covered by PCV10 also declined in children during the 11 years of the study, with reductions of 38% (32 cases to 20 cases), 85% (123 cases to 18) and 100% (23 cases to 0) respectively (Figure 5A). In adults ≥ 65, we found 66% (140 cases to 48 cases) and 93% (61 cases to 4 cases) reductions of IPD cases by serotypes 19A and 6A respectively, without reduction against serotype 3, confirming the lack of herd protection for serotype 3 in elderly people (Figure 5B).

Impact of different vaccine strategies for adults on serotype distribution

The use of PCV13 vaccine or PPV23 for immunocompetent adults showed a reduction of PCV13 serotypes, being greater in regions using PCV13 (IRR 0.73 *vs* 0.86). The trend for additional serotypes included in PPV23 or non-vaccine serotypes was similar (Figure 6 and

supplementary Figure S3). These results indicate that PCV13, despite containing less serotypes than PPV23, does not induce more serotype replacement than PPV23 in adults ≥ 65 years. The effect of both vaccine strategies was investigated against serotypes 3 and 19A (contained in both vaccines) or 8 and 22F (specific for PPV23). Interestingly, regions that use PCV13 showed a greater reduction of IPD cases by serotype 3 than regions using PPV23 serotypes (Figure 6 and supplementary Figure S3). Overall, the use of PCV13 for elderly population reduces PCV13 serotypes including serotype 3 without inducing serotype replacement.

Discussion

Surveillance of IPD is critical to understand national and local epidemiology including serotype distribution, which is essential to assess the impact of current and future vaccines. In Spain, the use of PCVs for children started in the private market in 2001 and its final introduction in the national immunization pediatric calendar was 2016. Use of PCV7 in Spanish vaccinated children reduced IPD cases by vaccine serotypes showing herd protection to the elderly population. However, the increased of serotype 19A was rapidly observed in children and adults after PCV7 use in Spain confirming the need for PCVs containing more serotypes such as PCV13 [8, 10]. Initially, PCV7 coverage based on vaccine sales was low, but its use increased from 2002 onwards with reported vaccine coverage below 50% before 2006 [10] and missing data on PCV coverage at national level in further years [8]. The missing data on pneumococcal vaccines coverage at national level is a limitation to this study. Despite its private use, a significant reduction of IPD cases by PCV13 serotypes has occurred in children. These results demonstrate that vaccination with PCV13 has been effective in the prevention of IPD in the pediatric population with a benefit of herd immunity to non-vaccinated children younger than 17 years. It is interesting that since 2016, an increase trend of non-PCV13 serotypes is observed in children < 2 years, suggesting that emerging

serotypes 24F and 8, might jeopardize the success of this vaccine in the next years. These data are in contrast to USA where non-PCV13 serotypes remain stable [11]. Among possible variations that may influence are different vaccine schedules for PCVs with a 3+1 in USA *vs* the 2+1 schedule in Spain or even geographical differences [12]. Other European countries using a 2+1 schedule have observed serotype replacement by non-PCV13 serotypes [5, 13-15]. The impact of different schedules in the pneumococcal epidemiology of IPD is not fully understood although in UK, based in the efficacy of their immunization pediatric program, the current recommendation is to change into a 1+1 schedule [16]. Further information is needed to address the best immunization practice and how can affect the local epidemiology.

Widely use of PCVs in children has shown to be effective reducing the cases by vaccine serotypes in the vaccinated group but also has promoted indirect protection against non-vaccinated individuals including the elderly people [17, 18]. Our national data support these important benefits in the Spanish population, with a substantial reduction in children and a moderate impact in adults ≥ 65 years confirming that a high proportion of IPD cases in adults are still being produced by PCV13 serotypes. In other countries such as USA with greater vaccine coverage in children and even in adults, the residual burden of disease by PCV13 serotypes in adults is much lower compared to Spain with a decreased of 68-71% of IPD cases by PCV13 serotypes [19]. Recent estimates predict that serotypes contained in PCV13 can be reduced up to 50% after vaccination for a period of about 3 years, and nearly eradicated within a decade of a sustained childhood vaccination programs [17]. In Spain, PCV13 was progressively introduced in the pediatric calendar at national level by the end of 2016. For that reason, herd protection will need several years to obtain the reduction rates predicted in children and adults. Serotypes 3, 6A and 19A that are included in PCV13 but not in PCV10 declined in Spanish children. This is interesting from the serotype 3 perspective because this serotype remains a significant cause of morbidity and mortality worldwide,

despite being included in PCV13 [20, 21]. Although, some countries have reported that PCV13 does not have an impact on serotype 3 in children [21, 22], our findings show reduction in pediatric and adult population directly vaccinated with PCV13 confirming recent studies demonstrating vaccine effectiveness of PCV13 against this serotype in children and adults [23, 24]. A major threat after massive use of current pneumococcal vaccines is the emergence of non-vaccine serotypes [8, 13]. Interestingly, geographic diversity of pneumococcal serotypes is a common event worldwide and continuous surveillance to evaluate vaccine coverage and detect serotype replacement is critical to guide vaccine recommendations [25]. In Europe, emerging of non-vaccine serotypes, has been reported by different countries [5, 12, 14, 15, 26] whereas in other parts of the world the situation is more stable [11, 12]. For example, the increase of the non-vaccine serotype 24F in children in France is similar to the increase in Spain [15]. It is noteworthy, the different pattern observed with serotype 8 between children and adults in Spain. In children, serotype 8 has shown a moderate increase since the pre-PCV13 period, whereas in adults, it has dramatically increased being the most frequent cause in adults. Similar results for serotype 8 have been reported in other European sites such as England, Austria and France [5, 13, 15], although in other countries and continents such as USA [27], Japan [28], Gambia [29] and Australia [30], the burden of IPD by serotype 8 remains low. This geographic variability is difficult to explain although it may be influenced by differences in the report systems for IPD cases among countries, variations in vaccine schedules, inclusion of risk factors and also the impact of carriage and invasiveness among the pneumococcal diversity [12].

An interesting aspect of our study is the possibility to assess the early effect of using PCV13 or PPV23 in the regional calendar of immunocompetent adults to evaluate the impact of both strategies in the elderly population. Herd protection will be similar in the investigated period (2017-2019) as PCV13 was introduced in the pediatric calendar by the end of 2016,

and therefore, differences would be mainly attributable to the direct vaccination of adults. In general, all the regions using PCV13 or PPV23 have a mixed urban/rural population and the age distribution is similar. Our results show that regions using PCV13 vaccine for adults had a greater reduction of IPD cases by PCV13 serotypes than regions using PPV23 (IRR 0.73 *vs* 0.86) including a decreasing trend of serotype 3 (IRR 0.82 *vs* 1.04), with similar impact against non-PCV13 serotypes (IRR 1.24 *vs* 1.23). This effect should be considered with caution in the context of low vaccine coverages in Spanish adults aged ≥ 65 (8% for PCV13-regions and 25% for PPV23-regions in 2017 *vs* 22% for PCV13-regions and 26% for PPV23-regions in 2018 without coverage information in 2019 (Figure S4). In USA, a recent study shows that pediatric vaccination with PCV13 had a higher impact reducing the burden of disease by vaccine serotypes than the direct use of PCV13 in adults [19]. Hence, the different epidemiological scenario in USA with no serotype replacement in children and adults [11], the long-term use of PCV7 and PCV13 since 2000 and 2010 respectively, followed by use of PCV13 in series with PPV23 in immunocompetent adults since 2014, may explain the lower effect of PCV13 in adults compared to Spain. Continuous epidemiological surveillance is needed as new vaccines with more serotypes such as PCV15 and PCV20 are coming in the next years that will increase the potential coverage in children and adults (Figure 7). Further evaluation of the impact of different vaccine strategies in adults will increase our understanding for establishing the best vaccine policies to the elderly population.

Notes

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Table 1: Number of cases and incidence of invasive pneumococcal disease in 2018-2019 compared to 2009 (pre-vaccine period), 2010-2012 (early effect after private use of PCV13 in children), and 2013-2016 (middle effect after PCV13 was available).

	2009 cases	2009 incidence (per 100000)	2010-12 cases	2010-12 incidence (per 100000)	2013-16 cases	2013-16 incidence (per 100000)	2018-19 cases	2018-19 incidence (per 100000)	IRR 2018-19 *vs* 2009	95% CI	IRR 2018-19 *vs* 2010-12	95% CI	IRR 2018-19 *vs* 2013-16	95% CI
< 2 years	355	36.33	612	21.35	566	16.57	325	21.08	0.58	0.5-0.67	0.99	0.86-1.13	1.19	1.11-1.46
PCV13	263	26.91	385	13.43	172	5.04	60	3.89	0.14	0.11-0.19	0.29	0.22-0.38	0.78	0.58-1.04
Non- PCV13	92	9.41	227	7.92	394	11.54	265	17.19	1.83	1.44-2.31	2.17	1.82-2.59	1.37	1.28-1.74
2-5 years	318	16.59	595	9.95	416	5.42	197	5.68	0.34	0.29-0.41	0.57	0.49-0.67	1.08	0.88-1.24
PCV13	279	14.55	464	7.76	199	2.59	67	1.93	0.13	0.1-0.17	0.25	0.19-0.32	0.71	0.56-0.98
Non-PCV13	39	2.03	131	2.19	217	2.82	130	3.75	1.84	1.29-2.63	1.71	1.34-2.18	1.42	1.07-1.65
18-64 years	1400	4.55	3058	3.32	3509	2.93	2570	4.35	0.96	0.9-1.02	1.31	1.25-1.38	1.49	1.41-1.56
PCV13	924	3.00	1756	1.90	1419	1.18	650	1.10	0.37	0.33-0.41	0.58	0.53-0.63	0.93	0.85-1.02
Non- PCV13	476	1.55	1302	1.41	2090	1.75	1920	3.25	2.10	1.9-2.33	2.30	2.15-2.47	1.86	1.75-1.98
PPV23	1195	3.88	2487	2.70	2794	2.33	2068	3.50	0.90	0.84-0.97	1.30	1.23-1.38	1.50	1.42-1.59
Add-PPV23	307	1.00	774	0.84	1393	1.16	1462	2.48	2.48	2.2-2.81	2.95	2.71-3.22	2.13	1.98-2.29
Non-vaccine	205	0.67	571	0.62	715	0.60	502	0.85	1.28	1.09-1.5	1.37	1.22-1.55	1.42	1.27-1.6
≥ 65 years	1262	16.22	3310	13.65	4520	13.29	3194	18.07	1.11	1.04-1.19	1.32	1.26-1.39	1.36	1,3-1,42
PCV13	824	10.59	1792	7.39	1693	4.98	878	4.97	0.47	0.43-0.52	0.67	0.62-0.73	1.00	0.92-1.08
Non- PCV13	438	5.63	1518	6.26	2827	8.31	2316	13.11	2.33	2.1-2.58	2.09	1.96-2.23	1.58	1.49-1.67
PPV23	982	12.62	2467	10.17	3145	9.25	2213	12.52	0.99	0.92-1.07	1.23	1.16-1.3	1.35	1.28-1.43
Add-PPV23	221	2.84	722	2.98	1483	4.36	1344	7.61	2.68	2.32-3.09	2.55	2.33-2.8	1.74	1.62-1.88
Non-vaccine	280	3.60	843	3.48	1375	4.04	981	5.55	1.54	1.35-1.76	1.60	1.46-1.75	1.37	1.27-1.49
OVERALL	3487	7.46	7803	5.52	9241	4.94	6395	6.85	0.92	0.88-0.96	1.24	1.2-1.28	1.39	1.34-1.43

IRR = incidence rate ratio. PCV13= serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV). Non-PCV13 = serotypes that are not included in PCV13. PPV23= serotypes that are included in the 23-valent pneumococcal polysaccharide vaccine (PPV). Add-PPV23 = Additional serotypes included in PPV23 but not in PCV13. CI= confidence interval.

Table 2: Most prevalent serotypes causing invasive pneumococcal disease in pediatric population by age group during the last epidemiological year 2019 in Spain.

	Children < 2 years		Children 2-5 years	
Serotype	n	(%)	n	(%)
24F	18	(14.52)	6	(9.23)
8	14	(11.29)	4	(6.15)
3	11	(8.87)	4	(6.15)
33F	11	(8.87)	0	(0)
15A	9	(7.26)	5	(7.69)
38	6	(4.84)	2	(3.08)
10A	6	(4.84)	1	(1.54)
19A	6	(4.84)	10	(15.38)
16F	5	(4.03)	0	(0)
15B	5	(4.03)	3	(4.62)
23B	5	(4.03)	4	(6.15)
12F	5	(4.03)	7	(10.77)
9N	5	(4.03)	0	(0)
22F	4	(3.23)	4	(6.159
35B	2	(1.61)	2	(3.08)
11A	2	(1.61)	1	(1.549
23A	2	(1.61)	2	(3.08)
9V	1	(0.81)	0	(0)
14	1	(0.81)	6	(9.23)
7B	1	(0.81)	0	(0)
Other	5	(4.03)	4	(6.15)
Total	124		65	

Table 3: Most prevalent serotypes causing invasive pneumococcal disease in adult population by age group during the last epidemiological year 2019 in Spain

	Adults ≥ 65 years		Adults 18-64 years	
Serotype	n	(%)	n	(%)
8	232	(18.72)	249	(30.29)
3	164	(13.24)	100	(12.17)
22F	66	(5.33)	38	(4.62)
12F	57	(4.60)	52	(6.33)
15A	51	(4.12)	18	(2.19)
9N	50	(4.04)	52	(6.33)
19A	48	(3.87)	26	(3.16)
6C	47	(3.79)	23	(2.80)
16F	42	(3.39)	9	(1.09)
11A	41	(3.31)	24	(2.92)
31	39	(3.15)	11	(1.34)
33F	39	(3.15)	18	(2.19)
23B	37	(2.99)	12	(1.46)
23A	34	(2.74)	17	(2.07)
14	32	(2.58)	14	(1.70)
15B	30	(2.42)	10	(1.22)
10A	23	(1.86)	19	(2.31)
24F	23	(1.86)	20	(2.43)
19F	22	(1.78)	9	(1.09)
35F	20	(1.61)	5	(0.61)
Other	142	(11.46)	78	(9.49)
Total	1239		822	

Figure legends

Figure 1: Trends of IPD in Spain in pediatric and adult population

Vertical lines represent the years when PCV13 was available for private market (2010) and into the national childhood immunization calendar (2016). Data show IPD cases and incidence rates for 0-2 years (A) 2 < 5 years (B) 18-64 (C) and aged 65 years and older (D). PCV13 represents the IPD cases due to serotypes included in the 13-valent conjugate vaccine (pink line with dots). NON-PCV13 represent the IPD cases due to serotypes that are not included in the 13-valent conjugate vaccine (blue dotted line with squares). Total represents all the IPD cases in the correspondent age group (purple line with triangles). Add-PPV23 represent the IPD cases due to additional serotypes included in PPV23 but not in PCV13 (orange dotted line with diamonds). NON-VAC represent all the IPD cases due to serotypes that are not included in PCV13 and PPV23 (green line with triangles).

Figure 2: Serotypes causing IPD in pediatric population 0-17 years

Pink bars represent IPD cases by serotypes included in PCV13 and green bars indicate the 10 most frequent non-vaccine serotypes causing IPD in years 2009 (A) 2015 (B) and 2019 (C). Tables include the number and % of IPD cases by the 5 most frequent serotypes in each group.

Figure 3: Serotypes causing IPD in adults 18-64 years

Pink bars represent IPD cases by serotypes included in PCV13. Orange bars indicate additional serotypes included in PPV23 and green bars represent the 5 most frequent serotypes not included in any pneumococcal vaccine IPD in years 2009 (A) 2015 (B)

and 2019 (C). Tables include the number and % of IPD cases by the 5 most frequent serotypes in each group.

Figure 4: Serotypes causing IPD in adults ≥ 65 years

Pink bars represent IPD cases by serotypes included in PCV13. Orange bars indicate additional serotypes included in PPV23 and green bars represent the 5 most frequent serotypes not included in any pneumococcal vaccine IPD in years 2009 (A) 2015 (B) and 2019 (C). Tables include the number and % of IPD cases by the 5 most frequent serotypes in each group.

Figure 5: Evolution of serotypes 3, 6A and 19A included in PCV13 and not in PCV10 during the period 2009-2019

Solid line with squares represents IPD cases due to serotype 3. Dotted line with triangles represents IPD cases due to serotype 6A and solid line with dots represents IPD cases due to serotype 19A. (A) Data from pediatric population 0-17 years. (B) Data from adults ≥ 65 years.

Figure 6: Comparison of IPD cases in adults ≥ 65 years between Spanish regions using PCV13 vaccine and regions using PPV23 vaccine in the adult immunization calendar for the period 2017 *vs* 2019

Incidence Rate Ratios (IRR) with 95% confidence intervals are indicated for regions using PCV13 vaccine (left side of the panel) *vs* regions using PPV23 (right side of the panel). Values are indicated for PCV13 serotypes, additional serotypes included in PPV23 and not in PCV13 (Add-PPV23), non-vaccine serotypes (those not included in PCV13 and PPV23) and individual serotypes 3, 19A, 8 and 22F.

Figure 7: Fraction of disease attributable to current and future polysaccharide vaccines based on epidemiological data from 2019

Proportion of serotypes included in pneumococcal conjugate vaccines (PCV13, PCV15 and PCV20) or the 23-valent polysaccharide vaccine (PPV23) is shown for children < 5 years and adults ≥ 65 years.

Figure 1

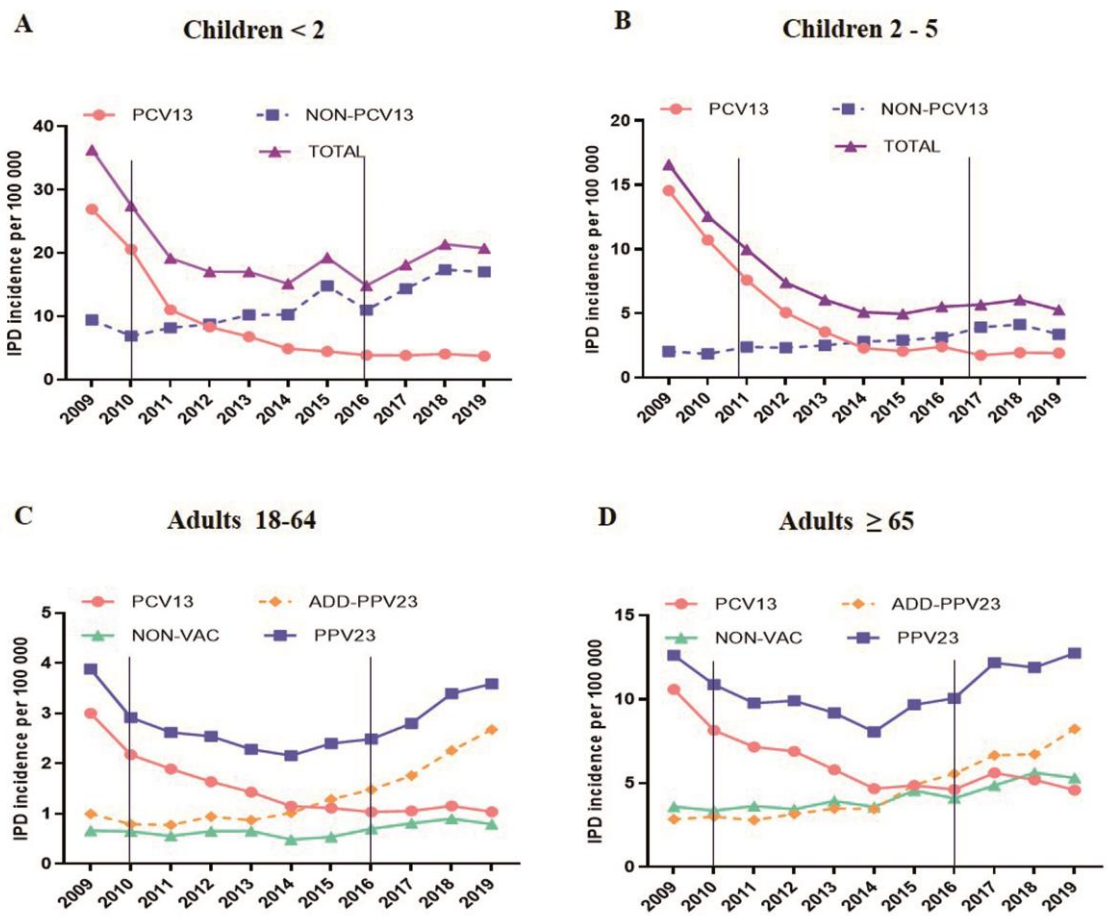

Figure 2

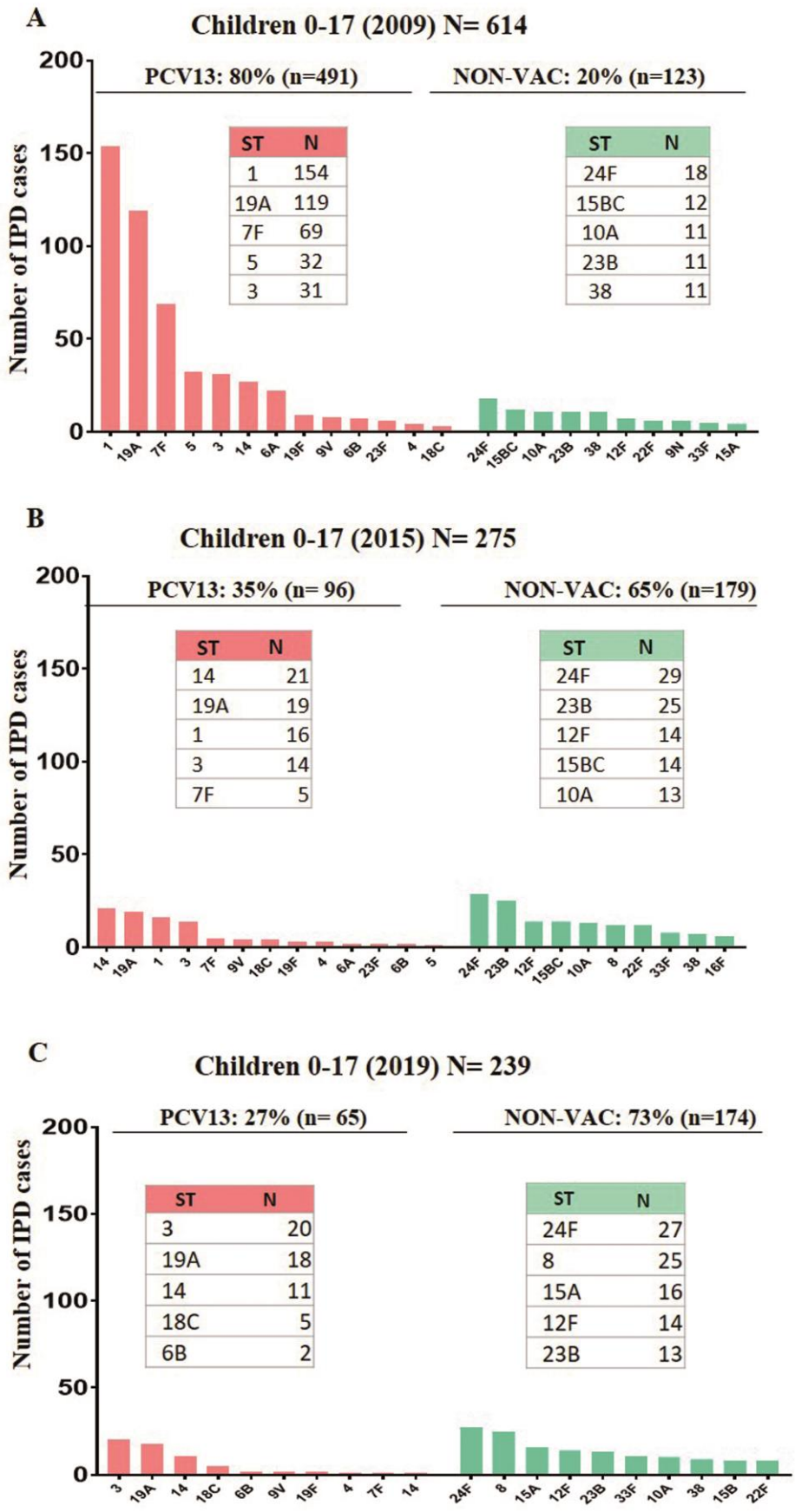

Figure 3

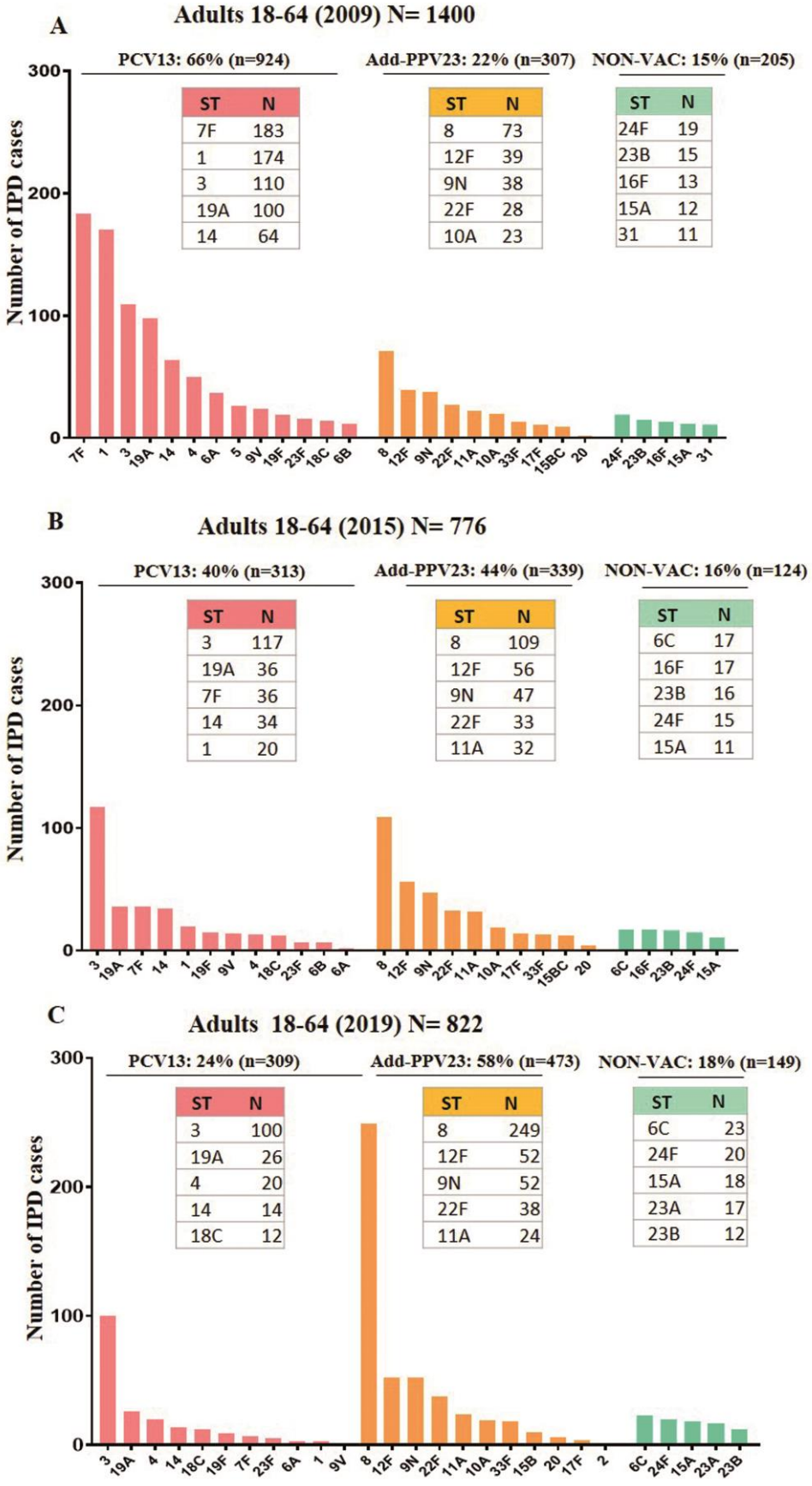

Figure 4

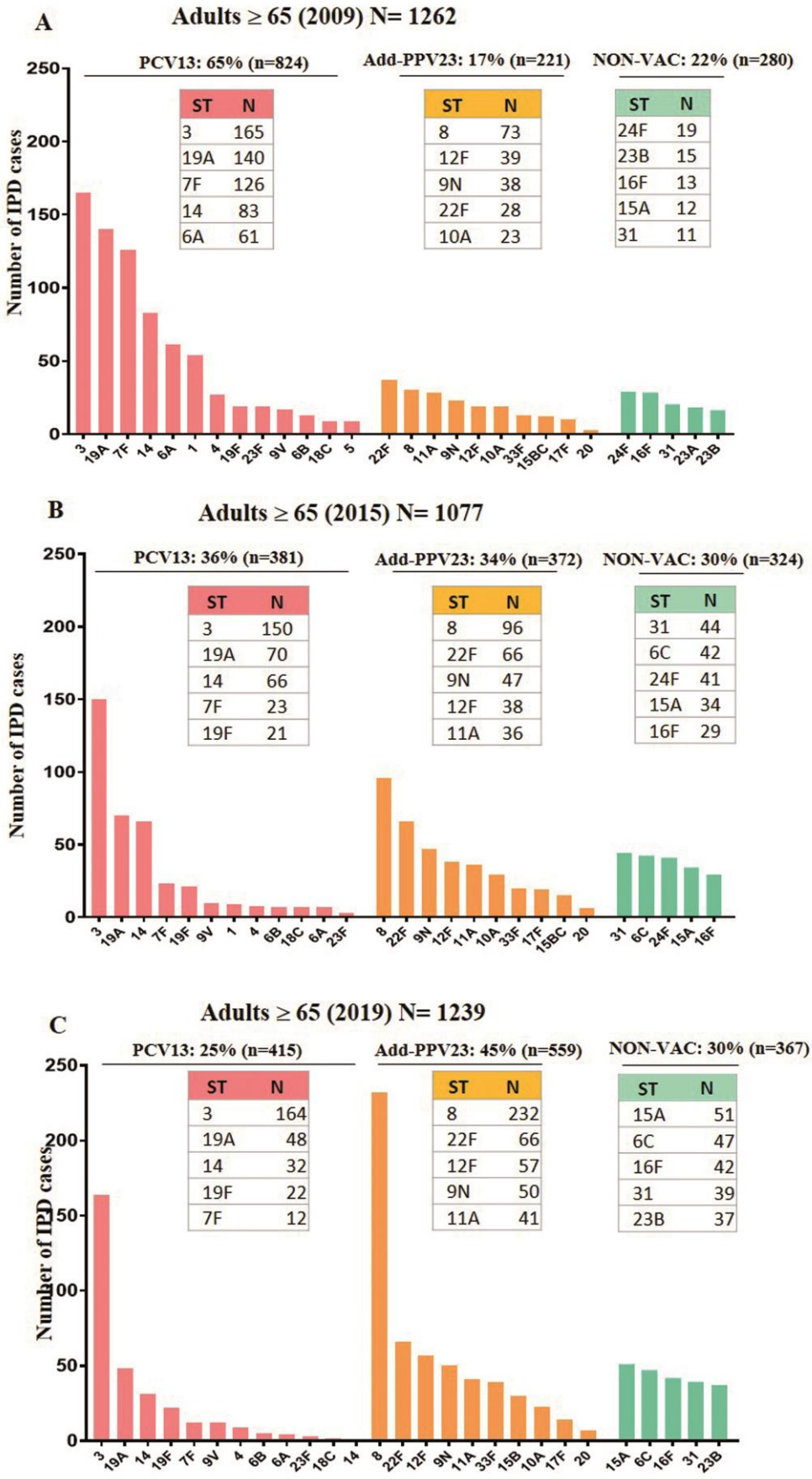

Figure 5

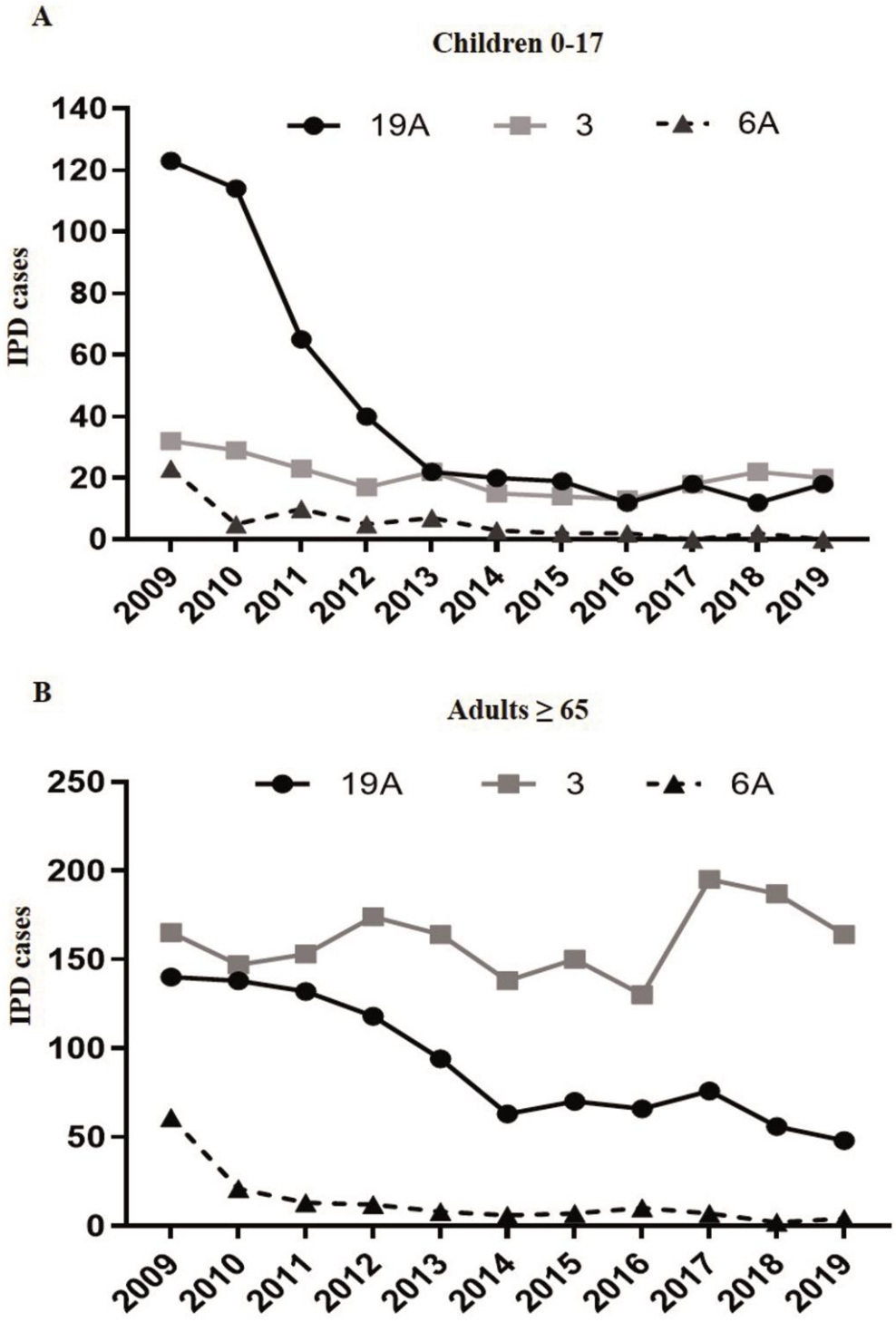

Figure 6

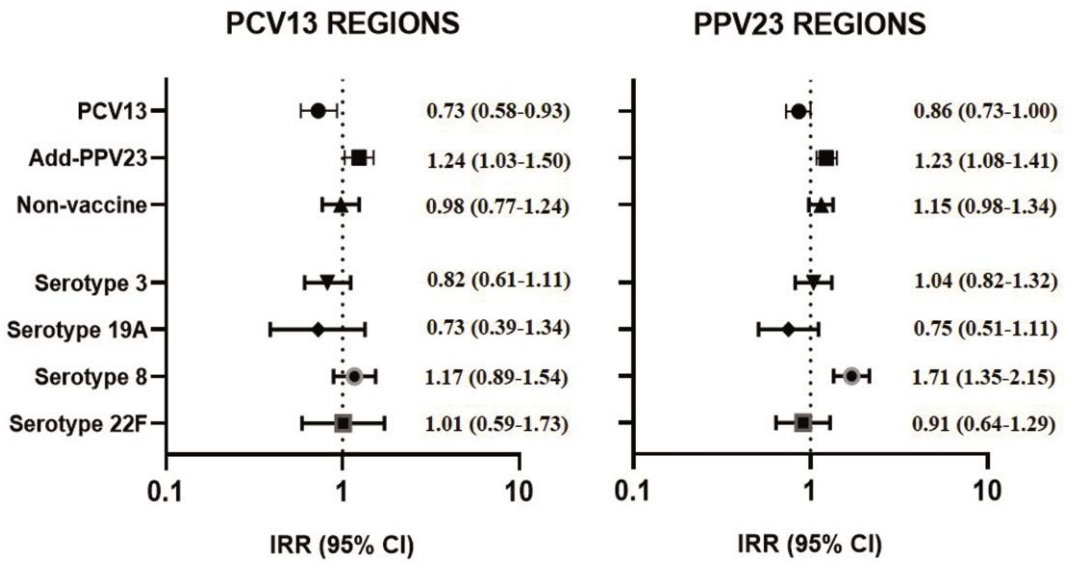

Figure 7