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The safety of pneumococcal vaccines at the time of sequential schedule: data from surveillance of adverse events following 13-valent conjugated pneumococcal and 23-valent polysaccharidic pneumococcal vaccines in newborns and the elderly, in Puglia (Italy), 2013-2020

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Parole chiave: AEFI, valutazione di causalità, PCV13, PPSV23, vaccinazione

Abstract

Background. *Nowadays, two types of anti-pneumococcal vaccine are available: pneumococcal 13-valent conjugate vaccine (PCV13), first licensed in the United States (US) in 2013, and pneumococcal 23-valent polysaccaridic vaccine (PPSV23), first licensed in the US in 1999. These vaccines are recommended in Italy for the immunization of newborns and of the elderly, using a combined sequential schedule for the latter. This report aims to describe the PCV13- and PPSV23-related AEFIs notified in Puglia in 2013-2020, in order to design these products' safety profile in a real-life scenario, three years after the official recommendation about the sequential schedule for people over 60 years of age.*

Methods. *This is a retrospective observational study. Data were gathered from the list of AEFIs notified following PCV13 and PPSV23 administration in Puglia in 2013-2020. The number of administered vaccine doses was obtained from the regional immunization database. AEFIs were classified according to WHO's algorithm, and causality assessment was carried out in case of serious AEFIs.*

Results. *From January 2013 to December 2020, 764,183 doses of PCV13 and 40,382 doses of PPSV23 were administered in Puglia. In the same period, 71 PCV13 AEFIs (Reporting Rate: 9.29 x100,000 doses) and 5 PPSV23 AEFIs (Reporting Rate: 12.4 x100,000 doses) were reported.*

The overall male/female ratio in AEFIs was 0.85. The majority of AEFIs occurred in subjects aged less than 2 (64/76, 84.2%), while 10 out of 76 (13.2%) occurred in patients aged 60 or older. 22 AEFIs were classified as serious and for 12 (54.5%) causality assessment showed a consistent relationship with immunization. The most commonly reported symptoms were fever (Reporting Rate: 4.72 x100,000 doses) and neurological

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symptoms (Reporting Rate: 3.23 x100,000 doses). Only one death was notified, classified as non-vaccine-related.

Conclusions. *The benefit of pneumococcal vaccination appears to be greater than the risk of AEFIs for both PCV13 and PPSV23. In fact, AEFIs occur in less than 0.1‰ of patients and the majority of AEFIs are mild and self-limiting.*

Introduction

Streptococcus pneumoniae is a gram-positive, facultative anaerobic organism whose encapsulated form represented, in the pre-vaccine era, the most common cause of pneumonia (~95% of cases worldwide). Currently, the bacterium is estimated to account for up to 15% of pneumonia cases in the United States (US) and 27% of cases worldwide. Besides pneumococcal pneumonia, *S. pneumoniae* is also responsible for otitis media and invasive diseases, and complications of pneumococcal pneumonia may include necrotizing pneumonia, lung abscess, parapneumonic effusion, empyema, septicemia and septic shock. As of 2021, a total of 92 separate serotypes have been isolated (1).

Due to its vast worldwide presence, *S. pneumoniae* is frequently observed colonizing the nasopharynx of both children (~40-50%) and healthy adults (~20-30%). These figures have decreased in the last decades though, following the introduction of childhood conjugate pneumococcal vaccination (1).

Pneumococcal vaccines are powerful means of prevention of invasive pneumococcal disease (IPD) caused by *S. pneumoniae* in children, the elderly and adults with frailty conditions such as anatomic or functional asplenia, immunodeficiency and chronic respiratory diseases (1, 2).

Nowadays, two types of pneumococcal vaccine are available. Pneumococcal 13-valent conjugate vaccine (PCV13), first licensed in the US in 2013, is recommended for active immunization in patients six weeks old through 6 years of age for the prevention of both IPD and otitis media caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. This vaccine is also recommended in older subjects since 2014, for the prevention of pneumococcal pneumonia (2).

Pneumococcal 23-valent polysaccharidic vaccine (PPSV23) was first licensed in the US in 1999. It is indicated for all adults 65 years of age and older, as well as younger patients (>2 years old) at high risk for developing pneumococcal pneumonia or IPD caused by *S. pneumoniae* serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. All patients who received PPSV23 before 65 years are recommended to be revaccinated at age 65, unless they were vaccinated less than ten years earlier; in that case, patients should be vaccinated again ten years following the first dose. Moreover, patients with asplenia or immunodepression should repeat doses of PPSV23 every ten years after the first one (2).

Since 2017, for both the elderly and adult people at increased risk of IPD for the presence of certain diseases (asplenia, diabetes, lung diseases, etc), a sequential schedule was recommended, with the use of a dose of PCV13 followed by a dose of PPSV23 with an inter-administration interval of at least 2 months and a recommended interval of 12 months. (3).

Both PCV13 and PPSV23 were authorized for marketing after the revision of pre-licensure data about the safety profile (4) but no data are actually available about the safety profile of sequential schedule. In fact, only two studies are available about this topic and in both papers the vaccines examined are the

7-valent pneumococcal vaccine and PPSV23 used among young people (5, 6).

Surveillance of Adverse Events Following Immunization (AEFIs) in the post-marketing life of new vaccines is recommended by the World Health Organization (WHO) in order to better understand new drugs' safety profile and effectiveness (7). Indeed, post-marketing surveillance can lead to the detection of rare sanitary events which were not identified during pre-licensure studies through the revision of reporting rates and the analysis of the vaccine's safety profile in subgroups that were not represented in its pre-marketing life (8, 9). In order to grant a more ordinate approach to AEFIs surveillance, WHO has recommended the application of a standardized Causality Assessment methodology, instead of the "emotional" approach, which would threaten to increase vaccine hesitancy (10).

Immunization strategies in Italy are designed by the Ministry of Health and described in the National Immunization Plan (NIP). Each of the 20 Italian Regions must follow the guidelines stated by the NIP, but may also offer other vaccines to target populations not covered by the National Plan itself. Furthermore, since 2012 the Ministry of Health has promoted the "Vaccination calendar for life", an immunization schedule that follows every phase of an individual's life with the objective of protecting them for the whole duration of their life. According to the Ministry of Health official recommendations, PCV13 is offered actively and free of charge to all newborns since 2013 and since 2014 to the elderly and population at high risk of pneumococcal complications. The NIP 2017 edition highlights the importance of sequential PCV13-PPSV23 pneumococcal vaccination in 65-year-old subjects, in order to reduce the incidence of *S. pneumoniae*-related pneumonia and IPD in the elderly (11).

Puglia is a region in the South-East of Italy with about 4 million inhabitants. In 2018 Regional Immunization Plan, PCV13 was offered free-of-charge for all children with an administration schedule counting three doses at 3, 5 and 12 months of age, respectively. An additional 2 doses are indicated for high-risk subjects between 1 and 2 years of age. Subjects at high risk of pneumococcal complications, between 5 and 65 years of age, may receive a dose of PCV13 followed by a dose of PPSV23 administered at least 56 days after the first one. Finally, 65-year-olds and older people are offered a dose of PCV13 followed by a dose of PPSV23 at least one year after the first one (12).

This report aims to describe the PCV13- and PPSV23-related AEFIs notified in Puglia in 2013-2020, in order to determine these products' safety profile in a real-life scenario, at the time of "sequential schedule".

Methods

This is a retrospective observational study.

Data were gathered from the list of AEFIs notified following PCV13 and PPSV23 administration in Puglia in 2013-2020, and the number of doses of these vaccines administered during the same period.

The list of PCV13- and PPSV23-related AEFIs was collected from the Italian Drug Authority (AIFA) database. In Italy, reporting AEFIs is in fact mandatory for all healthcare workers. Reports must be submitted to the National Pharmacovigilance Network (RNF), an online platform managed by AIFA itself. AEFIs may also be reported by the person who suffered from them or their legal representatives.

The number of PCV13 and PPSV23 administered per year in Puglia was extrapolated from the regional online immunization database (GIAVA).

For every subject who experienced one or more AEFIs, a form was filled in including

information on date of birth, gender, date of vaccine administration, other vaccines administered at the same time and information about the AEFIs (date of onset and date of computing in RNF, clinical characteristics, case description, duration and treatment, hospitalization or emergency room access, final outcome).

An Excel spreadsheet was used to build the database and perform the required analyses.

The total reporting rate was calculated as the total number of reported AEFIs/the number of PCV13 or PPSV23 doses administered, while the annual reporting rate was calculated as the number of AEFIs occurred in a year/the number of doses of each vaccine administered in the same year.

WHO guidelines were used to classify AEFIs as "serious" or "non-serious". An AEFI is considered serious if it results in death, is life-threatening, requires in-patient hospitalization or prologation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or requires intervention to prevent permanent impairment or damage. Additionally, in 2016 AIFA published a list of particular health conditions that must be considered as serious AEFIs when occurring after vaccination. This list is the Italian edition of the EMA important medical events list (13, 14).

For serious AEFIs, we retrospectively applied the WHO causality assessment algorithm to classify AEFIs as "consistent causal association", "inconsistent causal association", "indeterminate" or "non-classifiable". In particular, for AEFIs that required hospitalization, we examined data from the medical record (15). Causality assessment is carried out by two different physicians expert in vaccinology and results are compared; in case of different results, a review of the literature is carried out and a third physician is consulted.

Results

From January 2013 to December 2020, 764,183 doses of PCV13 and 40,382 doses of PPSV23 were administered in Puglia. In particular, 89,221 doses of PCV13 were administered in 2013, 90,858 in 2014, 87,245 in 2015, 86,269 in 2016, 88,028 in 2017, 85,119 in 2018, 105,753 in 2019 and 131,690 in 2020; as for PPSV23, 38 doses were administered in 2013, 29 in 2014, 22 in 2015, 54 in 2016, 85 in 2017, 182 in 2018, 15,391 in 2019 and 24,581 in 2020. The number of PPSV23 doses administered per year increased one years after the introduction of the recommendation about the sequential schedule.

During the study period, a total of 76 AEFIs were reported in Puglia (reporting rate: 9.45 / 100,000 doses administered), 71 of which following vaccination with PCV13 (reporting rate: 9.29 / 100,000) and 5 following vaccination with PPSV23 (reporting rate: 12.4 / 100,000).

Among these, 22 (28.9%) were classified as serious and 52 (68.4%) as non-serious, according to the latest WHO guidelines. 2 (0.02%) AEFIs had not been classified. 17 out of 22 serious AEFIs (77.3%) lead to the patient's hospitalization.

In particular, for PCV13 AEFIs, 49/71 (69.0%) were classified as non-serious and 20/71 (28.2%) as serious. 2 of these AEFIs (2.82%), were not classified by the reporting subject. The reporting rate was 2.62 x100,000 doses for serious PCV13 AEFIs and 6.67 x100,000 doses for non-serious PCV13 AEFIs.

For PPSV23 AEFIs, 3/5 (60.0%) were classified as non-serious and 2/5 (40.0%) as serious. The reporting rate was 4.95 x100,000 doses for serious PPSV23 AEFIs, while it was and 7.43 x100,000 doses for non-serious PPSV23 AEFIs.

Figure 1 shows the distribution of PCV13 AEFIs per years and the reporting rate for 100,000 doses.

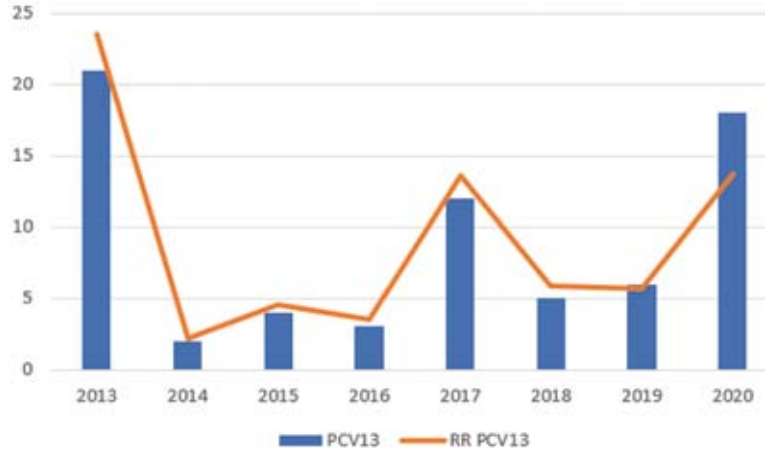

Figure 1 - PCV13 AEFIs distribution per year and reporting rate per 100,000 doses

The 5 PPSV23 AEFIS were notified 2 in 2018 (reporting rate: 1098.9 / 100,000 doses) and 3 in 2020 (reporting rate: 12.2 / 100,000 doses).

The overall male/female ratio in PCV13 AEFIs was 0.816, with 31 males and 38 females reporting one or more adverse events (two of these patients' genders were not reported). 64 out of 71 (90.1%) patients were aged under 2 at the time of the AEFI's reporting, 3 patients (4.3%) were between 61 and 70 years old, one (1.4%) was between 71 and 80 and one (1.4%) was over 80. For two patients (2.8%), age had not been provided.

Out of the 5 PPSV23 AEFIs, 3 occurred in male subjects and 2 in female ones (male/female ratio 1.5). One of them (20.0%) occurred in patients aged 61-70, while the other 4 (80.0%) were reported in patients between 71 and 80 years of age.

Table 1 - Distribution of signs and symptoms described in PCV13 and PPSV23 AEFIs reports and reporting rate /100,000 doses.

Signs/symptoms	N°	% (out of 76 AEFIs)	Reporting rate (/100,000 doses)	N° PCV13	% (out of 71 AEFIs)	Reporting rate (/100,000 doses)	N° PPSV23	% (out of 5 AEFIs)	Reporting rate (/100000 doses)
Fever/hyperpyrexia/ chills	38	50.0	4.72	37	52.1	4.84	1	20.0	2.48
Neurological symptoms	26	34.2	3.23	25	35.2	3.27	1	20.0	2.48
Allergic reactions	18	23.7	2.24	14	19.7	1.83	4	80.0	9.90
Gastro-intestinal symptoms	17	22.4	2.11	17	23.9	2.22	0	0.00	0.00
Local pain/tenderness/ aedema/swelling	13	17.1	1.62	11	15.5	1.44	2	40.0	4.95
Respiratory symptoms	3	3.90	0.373	2	2.82	0.262	1	20.0	2.48
Lymphoadenopathy	1	1.30	0.124	1	1.41	0.131	0	0.00	0.00
Other symptoms	20	26.3	2.49	19	26.8	2.49	1	20.0	2.48

Table 1 shows the distribution of signs and symptoms described in PCV13 and PPSV23 AEFIs reports and the reporting rate / 100,000 administered doses.

For 12 out of 22 serious AEFIs (54.5%), the classification was "consistent causal association", and for 6 (27.2%) "inconsistent causal association". One of them (4.54%) was deemed "non-classifiable", and 3 out of 22 (13.6%) lacked classification.

As for the 12 serious AEFIs classified as vaccine-related, 2 of them (16.7%) followed a PPSV23 administration, and none of them occurred after a sequential schedule of vaccine administration. The other 10 serious AEFIs (83.3%) happened after a PCV13 administration. 9 of these AEFIs (75.0%) lead to the patient's hospitalization.

The most commonly occurring symptoms in serious PCV13-related AEFIs were fever and hyperpyrexia (4 cases out of 10, 40.0%) and neurological symptoms (4 cases, 40.0%). Respiratory and gastrointestinal symptoms were reported in 1 (10.0%) and 2 (20.0%) patients, respectively. Other AEFIs were pallor, asthenia, cyanosis and loss of consciousness.

As for the two serious PPSV23-related AEFIs, they were both characterized by allergic reactions. One of these patients reported swelling near the injection site as well, while the other suffered from dyspnea and intense sweating.

The outcome of 52 out of 71 PCV13 AEFIs (73.2%) was complete recovery, while in one case (1.41%) the patient recovered partially. 1 AEFI (1.41%) had not resolved by the time data were collected; 9 (12.7%) patients reported an improvement of their symptoms, and one (1.41%) died as a consequence of the AEFI. The patient was a 67-year-old male who suffered from cardiac arrest following vaccination with PCV13, but subsequent evaluations ruled out any causal relationships with the vaccine itself.

As for the AEFIs following PPSV23 administration, 2 out of 5 (40.0%) patients recovered completely, while 2 of them (40.0%) were still suffering from the adverse events by the time of data collection.

Data about the AEFIs' outcome were not available for 7 PCV13 adverse events and 1 PPSV23 reaction.

Discussion

Our study describes data referring to the safety profile of both pneumococcal vaccines currently offered in Puglia as part of the Region's routine vaccination schedule. The vaccines were offered actively and free-of-charge, and 764,183 doses of PCV13 and 40,382 doses of PPSV23 were administered in Puglia between 2013 and 2020. Data from passive surveillance of AEFIs showed that more than 9 subjects out of 100,000 receiving PCV13 and more than 12 subjects out of 100,000 receiving PPSV23 experienced one or more adverse events. Almost 3 subjects in 100,000 reported a serious adverse event following vaccination with PCV13, and little less than 5 in 100,000 reported a serious adverse event following PPSV23 administration. The most commonly occurring symptoms were fever and chills, reported in 38 patients. Neurological symptoms such as headache and irritability were reported in 26 cases. Only one of the reported AEFIs followed a sequential schedule of pneumococcal vaccine administration, and it was a non-serious one.

These data are similar to pre-licensure evidence. EMA summary product characteristics for PCV13 described that decreased appetite, fever, and reactions at the site of injection were very common both in infants and in the elderly, having been reported in more than 1 patient in 10 (16), while for PPSV23 the US Food and Drug Administration (FDA) identified local reactions and neurological symptoms as the most frequent AEFIs, occurring in >10% of patients (17). In our study fever, neurological symptoms and injection site

reactions were confirmed to be the most frequently occurring adverse events, although the percentage of patients experiencing one or more AEFIs was much lower than in pre-licensure studies, in which it is around 10%. This divergence in results may be caused by the different data collection methods: while in pre-licensure studies data are collected via active surveillance, data in our study came from passive surveillance. As already observed in other studies, this determines a lower reporting rate due to the high risk of under-reporting (15).

In an experimental study carried out in the US, the prevalence of adverse events was significantly higher than the one observed in ours: local reactions were reported in 82.2% of patients older than 60 treated with PCV13 and 75.9% of patients treated with PPSV23. Fever was much less frequent, with a 4.0% prevalence in subjects administered with PCV13 and 1.1% in patients treated with PPSV23 (18). The difference between this study's and ours' results can be explained by the different surveillance method too, since the former employed an active call system, thus identifying even milder adverse events which could have escaped a passive surveillance.

A French post-licensure safety study for PCV13 estimated the prevalence of serious AEFIs at 2.1 (IC 95%: [1.88-2.41]) / 100,000 doses); in the same study, local reactions and neurological symptoms were the most frequent adverse events (19). The lower reporting rate of serious AEFIs in this study may be due to the tendency of Apulian healthcare workers not to notify non-serious AEFIs, which was already discussed in other surveys by our study group (8, 19, 20), but also to differences in the application of WHO's Causality Assessment Algorithm.

The main strength of our study consists in the high numerosity of the reference population, with 764,183 doses of PCV13 and 40,382 doses of PPSV23 administered over the course of 8 years, significantly higher than the population observed in pre-licensure studies. Moreover, for PCV13, safety profile was evaluated in the timespan following its market authorization, when the attention of both healthcare workers and patients towards safety issues is at a high level. For PPSV23, the evaluation is referred to the first three years of sequential schedule offer. As a matter of fact, the reporting rate of AEFIs decreased over the course of the study period, except for year 2020, during which the SARS-CoV-2 pandemic may have had a role in increasing the healthcare workers' alert towards fever and other influenza-like symptoms.

On the other hand, the main weakness of the study is represented by the passive surveillance method, which may have affected reporting rates and the serious/non-serious adverse events ratio. Another liability lies in the missing information for some of the reported AEFIs, which lowered the study's power.

Summarizing, the risk of AEFIs following pneumococcal vaccinations is very low (<0.1‰ of administered doses), and the risks/benefits ratio of these vaccines tends in favor of the latter. Moreover, the only case of death following pneumococcal vaccination reported in the study period was classified as non-related to the vaccine administration, and no AEFIs leading to permanent or severe impairment were registered.

The safety profile of vaccines has become a focal point of correct medical information, and is often central in the debate against anti-vaccination groups as the main reason for vaccination skepticism among the general population (21). As shown by the "AstraZeneca case", in which a hasty withdrawal of the vaccine from the market led to a significant decrease in the public's trust towards vaccination (22), communication between healthcare workers and the public itself is nowadays the cornerstone on which to build a solid relationship of trust between the patients and their physicians.

Conflict of interest: The authors have no conflicts of interest to declare.

Riassunto

Sicurezza dei vaccini antipneumococcici al tempo della schedula sequenziale: dati dalla sorveglianza degli eventi avversi dopo vaccinazione con vaccino antipneumococcico 13-valente coniugato e 23-valente polisaccaridico negli infanti e negli anziani, in Puglia (Italia), 2013-2020

Introduzione. Attualmente, due tipi di vaccino antipneumococcico sono disponibili: un vaccino pneumococcico coniugato 13-valente (PCV13), approvato per l'uso negli Stati Uniti (USA) nel 2013, e un vaccino pneumococcico polisaccaridico 23-valente (PPSV23), approvato negli USA nel 1999. In Italia, essi sono raccomandati per la vaccinazione dei neonati e degli anziani; per questi ultimi è impiegata una schedula sequenziale combinata. Questo report descrive gli eventi avversi (AEFIs) correlate a PCV13 e PPSV23 notificati in Puglia dal 2013 al 2020, allo scopo di tracciare il profilo di sicurezza di questi prodotto in uno scenario di vita reale.

Metodi. Lo studio è di tipo retrospettivo osservazionale. I dati sono stati raccolti dalla lista di AEFIs notificati in Puglia dal 2013 al 2020 in seguito alla somministrazione di PCV13 e PPSV23. Il numero di dosi di vaccino somministrate è stato estrapolato dal database regionale di vaccinazione. Gli AEFIs sono stati classificati seguendo l'algoritmo WHO, e per gli eventi gravi sono stati sottoposti a causality assessment.

Risultati. Da gennaio 2013 a dicembre 2020, in Puglia sono state somministrate 764,183 dosi di PCV13 e 40,382 dosi di PPSV23. Nello stesso periodo, sono stati riportati 71 AEFIs dopo somministrazione di PCV13 (Reporting Rate: 9.29 / 100,000 dosi) e 5 dopo somministrazione di PPSV23 (Reporting Rate: 12.4 / 100,000 dosi).

Il rapporto uomini/donne per la notifica di AEFIs è stato pari a 0.85. La maggioranza degli AEFIs si è verificata in soggetti con meno di due anni (64/76, 84.2%), mentre 10 eventi su 76 (13.2%) sono stati riportati in soggetti over-60. 22 AEFIs sono stati classificati come gravi, e 12 (54.5%) sono stati identificati come correlabili alla vaccinazione dopo causality assessment. I sintomi più frequenti sono stati febbre (Reporting Rate: 4.72 / 100,000 dosi) e sintomi neurologici (Reporting Rate: 3.23 / 100,000 dosi). Solo un decesso è stato segnalato, ma è stato classificato come non correlabile alla vaccinazione.

Conclusioni. I benefici della vaccinazione antipneumococcica risultano superare il rischio di AEFIs per entrambi i vaccini considerati. Gli eventi avversi occorrono in meno dello 0.1‰ dei pazienti e sono in gran parte lievi e auto-limitanti.

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