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A surveillance system of Invasive Pneumococcal Disease in North-Eastern Italy

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Key words: Streptococcus pneumonia, surveillance, serotypes, PCV13, immunization

Parole chiave: Streptococcus pneumoniae, sorveglianza, sierotipi, PCV13, immunizzazione

Abstract

Background. From 2007, in the Veneto Region (Italy), a surveillance system for invasive pneumococcal diseases (IPD) was implemented to estimate the regional epidemiology of IPD and to evaluate the impact of 13-valent pneumococcal conjugate vaccine (PCV13) vaccination.

Methods. Data were collected from 2007 to 2014 and the total, annual and age-specific IPD notification rates were calculated. A Poisson regression model was used to identify the possible risk factors for developing IPD.

Results. A total of 713 IPD cases were notified and the overall IPD notification rate was equal to 2.0 cases per 100,000 population (95% CI: 1.7-2.1), with an increasing trend between 2007 and 2014. The pneumococcal serotypes were identified in 608 (85.3%) isolates from biological specimens, and the most distributed serotypes were those contained in PCV13. Children < 5 year-old and the adults over 65 year-old showed the highest PCV13 vaccine-type IPD notification rate, equal to 2.7/100,000 and 2.8/100,000, respectively.

The risk to develop IPD was greater in children aged <5 years (RR = 8.9, 95% CI: 5.1-15.9; $p < 0.0001$) and in adults aged >65 years (RR = 4.3, 95% CI: 2.7-6.9; $p < 0.0001$), especially in males > 65 years of age (RR = 1.7, 95% CI: 1.0-2.8; $p = 0.042$). The invasive pneumococcal disease was mainly caused by the PCV13 serotypes (RR = 2.9, 95% CI: 2.3-3.9; $p < 0.0001$), principally after the PCV13 introduction (RR = 2.3, 95% CI: 1.4-3.8; $p < 0.001$). In spite of that, a significant reduction of the overall IPD incidence is evident in the period following the PCV13 vaccine introduction (RR = 0.4, 95% CI: 0.3-0.5; $p < 0.0001$), particularly in children aged <5 years (RR = 0.3, 95% CI: 0.2-0.7; $p = 0.002$), demonstrating the real efficacy of PCV13 immunization for children.

Conclusions. In the Veneto Region, the surveillance system has allowed to describe the detailed epidemiological profile of invasive pneumococcal disease, pointing out that the most circulating pneumococcal serotypes were those contained in the PCV13 vaccine.

Introduction

Streptococcus pneumoniae (pneumococcus) is a gram-positive bacterium with more than 90 known serotypes. It is a leading cause of serious illness, including

bacteraemia, meningitis, and pneumonia among children and adults worldwide. Although all serotypes may cause serious disease, a relatively limited number of serotypes cause the majority of invasive pneumococcal disease (IPD). In 2008,

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health status can be used in aggregate form in scientific studies (15)

Identification of isolates

The pneumococcal isolates sent to the Regional Reference Laboratory were identified using standardized laboratory procedures, and then serotyped using the Pneumotest Kit for Neufeld testing with type-specific antisera (Statens Serum Institute, Copenhagen, Denmark) (16).

The identified serotypes were recognized, respectively, as <vaccine serotypes> and <no-vaccine serotypes> as shown in Table 1.

Statistical analysis

The IPD notification rates (cases/100,000 population) were calculated considering the number of confirmed IPD cases divided by the estimated resident population in the Veneto Region. Estimates were based on data provided by the Veneto Regional Authority.

The Joinpoint regression analysis was designed to calculate the significance of annual notification rates trend. A Poisson regression model was used to estimate the contributions of major risk factors on the PCV13 vaccine-type IPD development and 95% confidence intervals were calculated.

A p-value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using Stata version 10 for Windows (Stata Corporation, College Station, TX, USA) and Joinpoint Regression Program, rel. 4.0.4. May 2013 (Statistical

Research and Applications Branch, National Cancer Institute, MD, USA).

Results

From 2007 to 2014, 713 cases of IPD were notified in the Veneto Region. The clinical characteristics of these IPD episodes were represented by 62.4% (445/713) bacteraemia, 30.2% (215/713) pneumonia, 20.8% (148/713) meningitis, while other clinical syndromes were identified in 6.0% (43/713) of cases. The frequency of IPD notification was highest in children under five years of age (78/713 cases, 11%), and adults over 65 (381/713 cases, 53.4%), and the number of IPD cases increased from 30 year-old onwards.

The overall IPD notification rate was 2.0/100,000 population, with an increasing trend from 2007 to 2014, showing the lowest rate in 2008 (1.6/100,000) and the highest in 2014 (2.3/100,000). In the observation period, children <5 years old and adults >65 years old showed the highest overall IPD notification rate, equal to 3.75/100,000 and 4.5/100,000, respectively. In particular, the PCV13 vaccine-type IPD resulted the most widespread with a specific notification rate of 2.7/100,000 and 2.8/100,000 among children and adults, respectively.

The pneumococcal serotypes were identified in 85.3% (608/713) of pneumococcal isolates from biological specimens. Among all serotypes, 63%

Table 1- Serotypes included in pneumococcal vaccines and no-vaccine serotypes

Vaccine type	Included serotypes	Additional serotypes*
PCV7 (7 serotypes)	4, 6B, 9V, 14, 18C, 19F, 23F	--
PCV13 (7 serotypes + 6 additional serotypes)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	1, 3, 5, 6A, 7F, 19A
No-vaccine serotypes	All serotypes not included in the pneumococcal conjugate vaccines	

*Additional serotypes compared with the previous vaccine formulation

(383/608) were vaccine-type serotypes (i.e. the same serotype as those included in the PCV13 vaccine), while 37% (225/608) were to be considered no vaccine-type (NVT) serotypes. Out of the 713 confirmed IPD cases, 105 (14.7%) bacterial isolates remained untypable because of some nonviable bacterial strains or because of some failure in sending the strains to the Regional Reference Laboratory.

The most circulating pneumococcal serotypes were those included in PCV13 and, in the two age groups most susceptible to IPD, these serotypes were found in 71.9% (46/64) of children < 5 years and in 62.1% (205/330) of subjects >65 years.

A high IPD notification rate was associated with the six additional serotypes contained in PCV13 with respect to serotypes of the hepta-valent vaccine in children <5 years. In particular, the rate of 3.8/100,000 population before the introduction of PCV13 was reduced to 0.8/100,000 after starting to use the PCV13 (RR=0.2, 95% CI: 0.1-0.5), demonstrating the beneficial effect of the PCV13 coverage since the beginning (Table 2).

Subjects aged >65 year-old also showed a high IPD notification rate attributable to PCV13 serotypes (2.5/100,000 population); this rate increased after the introduction of PCV13 vaccine (3.1/100,000 population), but without statistical significance.

About the clinical manifestations of notified IPD, the highest IPD notification rate has been found in children aged <5 years (4.3/100,000 population) in the period before the introduction of PCV13. In this age group, bacteraemia and pneumonia were the major pneumococcal clinical syndromes, equal to 2.2/100,000 and 1.8/100,000 respectively; after the introduction of PCV13 these clinical manifestations decreased to 0.7/100,000 and 0.5/100,000, respectively (RR=0.3; 95% CI: 0.1-0.8) (Table 3).

During the observation period, there were 59 IPD cases with fatal outcome (8.3%),

involving 43 subjects aged >65 years, 9 aged 50-64 years, and 2 children aged <5 years. Among these IPD related deaths, 29 (49.2%) were caused by PCV13 serotypes, 17 (28.8%) by NVT serotypes, and for 13 deaths (22%) the pneumococcal isolates were untypable.

The contribution of the main risk factors (age, gender, PCV13 serotypes and period before/after the PCV13 introduction) to develop invasive pneumococcal disease is shown in Table 4. The risk of developing IPD was greater in children aged <5 years (RR=8.9, 95% CI: 5.1-15.9; p<0.0001) and in adult > 65 years-old (RR=4.3, 95% CI: 2.7-6.9; p<0.0001), especially in males >65 years (RR=1.7, 95% CI: 1.0-2.8; p=0.042). The IPD was mainly caused by PCV13 serotypes (RR=2.9, 95% CI: 2.3-3.9; p<0.0001) and occurred mostly in the period after the PCV13 introduction (RR=2.3, 95% CI: 1.4-3.8; p<0.001). In spite of that, a significant reduction of overall incidence of PCV13 vaccine-type IPD is evident in the period after the introduction of this vaccine (RR=0.4, 95% CI: 0.3-0.5; p<0.0001). This IPD decline was most evident in children aged <5 years (RR=0.3, 95% CI: 0.2-0.7; p=0.002).

Discussion and conclusions

Estimating the burden of invasive pneumococcal disease is a relevant question for Public Health, however, the studies performed in different geographical areas are often not comparable due to the use of different surveillance methods that lead to variability in the IPD notification rate.

In Italy, few prospective regional surveillance studies have estimated the burden of invasive pneumococcal diseases and distribution of *Streptococcus pneumoniae* serotypes, but the real incidence of IPD, especially on the pediatric community, is unknown.

Table 2 - IPD notification rates (for 100,000 inhabitants) by age groups and serotypes before and after the introduction of the PCV13 vaccine

	2007-2010 (before PCV13)			2011-2014 (after PCV13)			RR [IPD(2)/ IPD(1)]	95%CI RR	
	IPD(1)	N	%	IPD(2)	N	%			
<5 year-old									
All	6.2			2.9	24		0.5	0.3	0.7
Serotyped	5.3	46	100	2.2	18	100	0.4	0.2	0.7
PCV13	4.3	37	80.4	1.1	9	50	0.3	0.1	0.5
7 serotypes	0.5	4	8.7	0.2	2	11.1	0.5	0.1	2.8
+ 6 serotypes	3.8	33	71.7	0.8	7	38.9	0.2	0.1	0.5
No PCV13 serotypes	1.0	9	19.6	1.1	9	50.0	1.0	0.4	2.6
05-14 year-old									
All	1.0	16		1.4	23		1.4	0.7	2.7
Serotyped	0.9	15	100	1.2	20	100	1.3	0.7	2.5
PCV13	0.8	13	86.7	0.6	11	55	0.8	0.4	1.8
7 serotypes	0.1	2	13.3	0.2	3	15.0	1.5	0.2	8.8
+ 6 serotypes	0.7	11	73.3	0.5	8	40.0	0.7	0.3	1.8
No PCV13 serotypes	0.1	2	13.3	0.5	9	45.0	4.4	0.9	20.3
15-29 year-old									
All	0.3	8		0.4	10		1.3	0.5	3.3
Serotyped	0.3	7	100	0.4	10	100	1.5	0.6	3.9
PCV13	0.2	5	71.4	0.2	5	50.0	1.0	0.3	3.6
7 serotypes	0.0	1	14.3	0.1	2	20.0	2.1	0.2	22.8
+ 6 serotypes	0.1	4	57.1	0.1	3	30.0	0.8	0.2	3.5
No PCV13 serotypes	0.1	2	28.6	0.2	5	50.0	2.6	0.5	13.3
30-49 year-old									
All	0.8	46		0.9	51		1.2	0.8	1.7
Serotyped	0.6	36	100	0.8	42	100	1.2	0.8	1.9
PCV13	0.5	29	80.6	0.4	20	47.6	0.7	0.4	1.3
7 serotypes	0.1	8	22.2	0.0	2	4.8	0.3	0.1	1.2
+ 6 serotypes	0.4	21	58.3	0.3	18	42.9	0.9	0.5	1.7
No PCV13 serotypes	0.1	7	19.4	0.4	22	52.4	3.3	1.4	7.8
50-64 year-old									
All	1.5	52		1.3	48		0.9	0.6	1.3
Serotyped	1.3	45	100	1.1	39	100	0.8	0.5	1.3
PCV13	0.9	31	68.9	0.5	18	46.2	0.6	0.3	1.0
7 serotypes	0.2	6	13.3	0.1	3	7.7	0.5	0.1	1.9
+ 6 serotypes	0.7	25	55.6	0.4	15	38.5	0.6	0.3	1.1
No PCV13 serotypes	0.4	14	31.1	0.6	21	53.8	1.4	0.7	2.8
>65 year-old									
All	4.2	151		6.1	230		1.4	1.2	1.8
Serotyped	3.5	124	100	5.4	206	100	1.6	1.3	2.0
PCV13	2.5	89	71.8	3.1	116	56.3	1.2	0.9	1.6
7 serotypes	0.7	26	21.0	1.2	45	21.8	1.6	1.0	2.6
+ 6 serotypes	1.8	63	50.8	1.9	71	34.5	1.1	0.8	1.5
No PCV13 serotypes	1.0	35	28.2	2.4	90	43.7	2.4	1.6	3.6

Table 3 - IPD notification rates (for 100,000 inhabitants) by age groups and clinical manifestation before and after the introduction of the PCV13 vaccine

	2007-2010 (before PCV13)		2011-2014 (after PCV13)		RR [IPD (2)/IPD (1)]	95%CI RR	
	IPD (1)	N	IPD (2)	N			
< 5 year-old							
All clinical syndromes	4.3	37	1.1	9	0.3	0.1	0.5
Bacteraemia	2.2	19	0.7	6	0.3	0.1	0.8
Pneumonia	1.8	16	0.5	4	0.3	0.1	0.8
Meningitis	0.6	5					
Other clinical syndrome	0.9	8	0.1	1	0.1	0.0	1.0
05-14 year-old							
All clinical syndromes	0.8	13	0.6	11	0.8	0.4	1.8
Bacteraemia	0.4	6	0.5	8	1.3	0.5	3.7
Pneumonia	0.6	10	0.3	5	0.5	0.2	1.4
Meningitis	0.1	1	0.1	2	2.0	0.2	21.5
Other clinical syndrome	0.2	3	0.1	1	0.3	0.0	3.1
15-29 year-old							
All clinical syndromes	0.2	5	0.2	5	1.0	0.3	3.6
Bacteraemia	0.1	3	0.1	3	1.0	0.2	5.1
Pneumonia	0.1	3	0.1	2	0.7	0.1	4.1
Meningitis	0.0	1					
Other clinical syndrome							
30-49 year-old							
All clinical syndromes	0.5	29	0.4	20	0.7	0.4	1.3
Bacteraemia	0.4	22	0.3	14	0.7	0.3	1.3
Pneumonia	0.2	10	0.2	9	1.0	0.4	2.3
Meningitis	0.1	7	0.0	2	0.3	0.1	1.5
Other clinical syndrome	0.0	1					
50-64 year-old							
All clinical syndromes	0.9	31	0.5	18	0.6	0.3	1.0
Bacteraemia	0.6	21	0.3	11	0.5	0.2	1.0
Pneumonia	0.2	7	0.2	6	0.8	0.3	2.4
Meningitis	0.2	6	0.1	5	0.8	0.2	2.6
Other clinical syndrome	0.0	1					
> 65 year-old							
All clinical syndromes	2.5	89	3.1	116	1.2	0.9	1.6
Bacteraemia	1.8	63	2.1	81	1.2	0.9	1.7
Pneumonia	0.8	29	0.9	34	1.1	0.7	1.8
Meningitis	0.3	12	0.4	14	1.1	0.5	2.4
Other clinical syndrome	0.1	2	0.2	7	3.3	0.7	15.8

Table 4 - Poisson Regression analysis of serotyped pneumococcal isolates (n. 608)

Variable	N	RR	95%CI	p-value
Age (years)				
< 5	64	8.9	(5.1-15.9)	<0.0001
05-14	35	1.2	(0.5-2.6)	0.722
15-29	17	0.3	(0.1-0.9)	0.048
30-49*	78	1		
50-64	84	1.8	(1.0-3.2)	0.044
> 65	330	4.3	(2.7-6.9)	<0.0001
Sex				
F*	244	1		
M	364	1.2	(0.8-1.9)	0.323
PCV13 serotypes				
No*	383			
Yes	225	2.9	(2.3-3.9)	<0.0001
Observation period				
2007-2010*	273	1		
2011-2014	335	2.3	(1.4-3.8)	0.001
Sex *Age				
M * age < 5 years		0.9	(0.5-1.8)	0.785
M * age 05-14 years		1.4	(0.6-3.3)	0.385
M * age 15-29 years		1.4	(0.5-4.1)	0.537
M * age 50-64 years		1.3	(0.7-2.5)	0.379
M * age > 65 years		1.7	(1.0-2.8)	0.042
Observation period*Age				
(2011-2014) * age < 5 years		0.3	(0.2-0.7)	0.002
(2011-2014) * age 05-14 years		1.1	(0.5-2.3)	0.897
(2011-2014) * age 15-29 years		1.2	(0.4-3.5)	0.741
(2011-2014) * age 50-64 years		0.7	(0.4-1.2)	0.203
(2011-2014) * age > 65 years		1.3	(0.8-2.1)	0.366
PCV13*Observation period				
Yes*(2011-2014)		0.4	(0.3-0.5)	<0.0001

An Italian study, based on 14-month IPD surveillance, indicated a pneumococcal bacteremia rate equal to 1.2% (95% CI: 0.9-1.6) in children aged less than 5 years. This rate is similar to the findings of a study in the USA, with 1.6% of children with pneumonia, treated as outpatients, and 1.9% febrile outpatients with no focal infections or immune suppression (9).

Another Italian study has matched two comparable Italian Regions (Piedmont and Apulia, representing 14% of the Italian

population) through 1-year population-based surveillance study. Overall, the IPD rate was 3.1/100,000 in Piedmont and 0.6/100,000 in Apulia. In children aged <2 years the IPD rate was 11.3/100,000 and 5.9/100,000 in Piedmont and Apulia, respectively; in the subjects aged >65 years, the incidence was 5.7/100,000 and 0.2/100,000 in the two regions, respectively (10).

Our results have reported an overall IPD notification rate equal to 2.0/100,000 inhabitants, with an increasing trend from

2007 to 2014. Children aged <5 years and adults aged >65 years showed the highest overall IPD notification rate, equal to 3.75/100,000 and 4.5/100,000 respectively. In particular, The IPD cases were mainly due to the serotypes included in the 13-valent pneumococcal conjugate vaccine and the children <5 years and adults >65 years showed the highest IPD incidence with a specific PCV13-IPD notification rate of 2.7/100,000 and 2.8/100,000 among children and adults, respectively.

Another surveillance study has demonstrated that in a cohort of Italian children (median age 4.1 years) the vaccine coverage for serotypes included in PCV7, PCV10 and PCV13 was 19.4%, 61.8% and 94.4% respectively, during the period 2008-2011 (11). These results, in association with our findings, suggest that the introduction of PCV13 in the infant vaccination program allowed to reduce significantly the burden of IPD in children.

Moreover, the investigation of contribution of the major risk factors to develop IPD confirmed the remarkable pressure of the serotypes included in the PCV13 on IPD incidence, especially in the most-affected age groups.

Therefore, the active surveillance system permitted to provide a detailed epidemiological profile of invasive pneumococcal diseases in the Veneto Region. This study also allowed to establish the serotype distribution of *S. pneumoniae* isolates, thanks to microbiology laboratories data, constantly monitoring the impact of pneumococcal conjugate vaccines, to achieve the objectives of improving vaccination policy and maintaining high vaccination coverage.

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The authors declare that they have no competing interest.

Riassunto

Il sistema di sorveglianza delle malattie pneumococciche invasive in un'area del Nord-Est Italia

Introduzione. Dal 2007, in Veneto (Italia), è stato implementato un sistema di sorveglianza per le malattie pneumococciche invasive (IPD) per valutare l'epidemiologia regionale delle IPD e l'impatto del vaccino pneumococcico coniugato 13-valente (PCV13).

Metodi. Sono stati raccolti i casi di IPD dal 2007 al 2014 e sono stati calcolati i tassi di notifica di malattia, totale, annuali e specifici per classe di età. I dati raccolti sono stati analizzati per stimare i possibili fattori di rischio implicati nello sviluppo delle IPD.

Risultati. Sono stati notificati 713 casi totali di IPD e il tasso complessivo di notifica di malattia è risultato pari a 2,0 casi per 100.000 abitanti (95% CI: 1,7-2,1), con un trend in aumento tra il 2007 e il 2014.

I sierotipi di pneumococco sono stati identificati in 608 (85,3%) isolati batterici derivati da campioni biologici e i sierotipi più diffusi sono risultati quelli contenuti nel vaccino PCV13. I bambini di età <5 anni e gli adulti over 65 anni, hanno mostrato il più alto tasso di notifica di IPD causata dai sierotipi contenuti nel vaccino 13-valente, pari a 2,7/100.000 e 2,8/100.000, rispettivamente.

Il rischio di sviluppare IPD è risultato maggiore nei bambini di età inferiore ai 5 anni (RR = 8,9, 95% CI: 5,1-15,9; $p < 0,0001$) e negli adulti over 65 anni (RR = 4,3, 95% CI: 2,7-6,9; $p < 0,0001$), soprattutto nei maschi di età > 65 anni (RR = 1,7, 95% CI: 1,0-2,8; $p = 0,042$). La malattia pneumococcica invasiva è stata principalmente causata dai sierotipi contenuti nel PCV13 (RR = 2,9, 95% CI: 2,3-3,9; $p < 0,0001$), in particolare dopo l'introduzione del PCV13 (RR = 2,3, 95% CI: 1,4-3,8; $p < 0,001$). Nonostante ciò, una significativa riduzione dell'incidenza complessiva di malattia è evidente nel periodo successivo all'introduzione del vaccino PCV13 (RR = 0,4, 95% CI: 0,3-0,5; $p < 0,0001$), principalmente nei bambini di età inferiore ai 5 anni (RR = 0,3, 95% CI: 0,2-0,7; $p = 0,002$), dimostrando la reale efficacia del vaccino PCV13 nei bambini.

Conclusioni. Nella Regione Veneto, il sistema di sorveglianza ha permesso di descrivere il profilo epidemiologico dettagliato di malattia pneumococcica invasiva, evidenziando che i sierotipi di pneumococco maggiormente circolanti sono quelli contenuti nel vaccino PCV13.

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