

COMMUNICATIONS C17
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h. 11.30
Amber Room 1

Invasive pneumococcal disease in children and adults in seven Italian regions after the introduction of the conjugate vaccine, 2008-2014

Infezioni invasive da *Streptococcus pneumoniae* nel bambino e nell'adulto in 7 Regioni italiane dopo l'introduzione del vaccino glicoconiugato, 2008-2014

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Abstract

Objective. To describe the trend of invasive pneumococcal disease in the years 2008-2014; to verify the impact of the conjugate vaccine and monitor the occurrence of serotype replacement.

Design. Prospective observational study based on data from the national surveillance for invasive bacterial diseases coordinated by the Istituto superiore di sanità.

Setting and participants. Seven Italian regions (A.P. Bolzano, A.P. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), accounting for 43% of the national population.

Main outcome measures. Number of cases and incidence of invasive pneumococcal diseases: global, stratified by age groups and by serotypes included or not in the PCV13.

Results. In 2008-2014, in the 0-4 age group IPD incidence for all serotypes decreased from 7.1 to 2.9/100,000; incidence for vaccine serotypes (VT) decreased from 5.5 to 1.1/100,000, while incidence for non-vaccine serotypes (NVT) increased from 1.6 to 2.0/100,000 (2.5 in 2013). In the >64 age group, IPD incidence increased from 5.3 to 7.5/100,000; VT incidence decreased from 3.9 to 3.2 (4.9 in 2010 and 4.3 in 2013), whereas NVT incidence increased from 1.4 to 4.4/100,000.

Conclusion. Use of the conjugate vaccine has reduced the number of cases of IPD by VT in children; the increase in IPD by NVT, above all in older age groups, suggests a serotype replacement.

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Key words: invasive bacterial diseases, surveillance, *Streptococcus pneumoniae*, vaccination, serotype replacement, invasive pneumococcal diseases

Riassunto

Obiettivi. Descrivere l'andamento dei casi di malattia invasiva pneumococcica (IPD) negli anni 2008-2014 per verificare l'impatto del vaccino coniugato e monitorare l'insorgenza del rimpiazzo dei sierotipi.

Disegno. Studio prospettico osservazionale, basato sui dati della sorveglianza nazionale delle malattie batteriche invasive, coordinata dall'Istituto superiore di sanità.

Setting e partecipanti. Dati da 7 Regioni italiane (Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, P.A. di Bolzano, P.A. di Trento, Veneto), corrispondenti al 43% della popolazione nazionale.

Principali misure di outcome. Numero di casi e incidenza di malattia invasiva da pneumococco: globale, stratificata per fascia di età e per sierotipi inclusi e non inclusi nel vaccino PCV13.

Risultati. Nel periodo 2008-2014, in 0-4 anni l'incidenza delle IPD per tutti i sierotipi è diminuita da 7,1 a 2,9 casi/100.000, quella da sierotipi vaccinali (TV) è diminuita da 5,5 a 1,1/100.000, mentre quella da sierotipi non vaccinali (TNV) è aumentata da 1,6 a 2,0/100.000 (2,5/100.000 nel 2013). Nella fascia >64 l'incidenza delle IPD è passata da 5,3 a 7,5/100.000, quella da TV è passata da 3,9 a 3,2 (4,9 nel 2010 e 4,3 nel 2013), mentre quella da TNV è aumentata da 1,4 a 4,4 casi/100.000.

Conclusioni. L'uso del vaccino coniugato ha portato a un decremento dei casi di IPD da TV tra i bambini; l'aumento dell'incidenza delle IPD da TNV, soprattutto negli anziani, suggerisce un rimpiazzo dei sierotipi.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 134-138)

Parole chiave: malattie batteriche invasive, sorveglianza, *Streptococcus pneumoniae*, vaccinazione, rimpiazzo dei sierotipi

BACKGROUND

Streptococcus pneumoniae (*S. pneumoniae* or pneumococcus) is an important human pathogen causing upper and lower respiratory tract infections (otitis, sinusitis, and pneumonia) and invasive pneumococcal diseases (IPDs), such as meningitis and sepsis. Children under 5 years of age and elderly people are the population groups most affected by these diseases. The World Health Organization estimated that 476,000 deaths due to pneumococcal infections in HIV-negative children under five years of age occurred globally in 2008, representing 5% of all cause-child mortality under five in HIV-negative children.¹

In Italy, universal paediatric vaccination against *S. pneumoniae* was introduced at the national level with the 2012-2014 National Immunization Plan.² However, since the 21 Italian regions can decide autonomously about immunization programs and vaccination schedules, many regions recommended and offered this vaccination free of charge before the introduction of the national recommendation.³ In Italy, vaccination coverage for the pneumococcal conjugate vaccine (PCV) (7-valent PCV until mid-2010 and then 13-valent PCV) has progressively increased; in 2013, national coverage, assessed at 24 months (2011 birth cohort), was 88%.

The aim of this paper, mainly based on data from the national surveillance system for invasive bacterial diseases, is to report the incidence of IPD and time trends in the years 2008-2014, the frequency of isolated serotypes, and vaccination coverage, in order to describe the impact of vaccination programs against *Streptococcus pneumoniae* in Italy.

METHODS

Surveillance and laboratory data

In Italy, cases of IPD are reported through a national voluntary passive enhanced surveillance system of invasive bacterial diseases,⁴ the MIB, which is coordinated by the national Public Health Institute (Istituto superiore di sanità, ISS) with the financial support of the Ministry of Health (MoH). The system was implemented in 1994 as a surveillance system for all bacterial meningitis and in 2007 it was extended to all invasive diseases by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.⁵

A case of invasive pneumococcal disease is defined as a patient of any age with symptoms of invasive disease (e.g., sepsis, meningitis, bacteremic pneumonia, cellulitis, arthritis) diagnosed with one or more of the following positive tests: culture from blood or cerebrospinal fluid (CSF) or other sterile site; PCR from blood or CSF; antigen test from CSF. The only difference compared to the EU case definition is the presence of symptoms compatible with IPD. Hospitals report any confirmed case to local health units, generally using a paper form. The local health units start the investigation and upload the information about the case on the database of the invasive bacterial disease surveillance system (the MIB database) through a web form. Even the National Reference Laboratory (NRL), located at the ISS, can access the MIB database; the NRL adds the results of the laboratory tests and characterizations for the isolates that are sent from local or regional laboratories. All autho-

rized users (local/regional/national staff in charge of managing notifications or investigation of invasive bacterial diseases) can view and edit all notifications concerning the geographical area of their competence archived in the MIB database, including NRL results. The database includes demographic information, clinical picture (i.e., meningitis, sepsis, or other IPD), vaccination status, antimicrobial resistance, serotype, laboratory results, thus making it possible to share information among different levels.

For this analysis we included all reports with reporting date or date of positive test between 1st January 2008 and 31st December 2014. Serotyping data were provided by the local laboratories or the NRL; if results were provided both from the local laboratories and the NRL, priority was given to the latter.

At the NRL, isolates are serotyped by Quellung reaction using sera from the Staten Serum Institut of Copenhagen (Denmark) and tested for antimicrobial resistance using E-test with EUCAST breakpoint and ATCC 49619 as reference isolate.

Incidence was calculated using the estimated population at 1st January of each year, according to the National Institute for Statistics (Istat).⁶ Beside national incidence, we focused on incidence data of a sample of the seven Italian regions (Autonomous Province of Bolzano, Autonomous Province of Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto) that have a more solid regional surveillance system and are less prone to under-reporting or under-diagnosis. The population of these 7 regions accounts for 43% of the overall Italian population.

In order to estimate the quota of preventable cases with the use of the vaccine, we estimated a stratified incidence by serotype (i.e., serotype included in PCV13, VT; serotype not included in PCV13, NVT). As more than 50% of the confirmed cases were not serotyped, for each year of reporting the proportion of VT and NVT found in all serotyped confirmed cases was applied to those confirmed cases for which serotype was unknown.

Differences among the incidences were calculated as $(1-IRR)*100$, where IRR is Incidence Risk Ratio. Statistical analysis for the trends was performed using Student's t-test with $p < 0.05$ as the level of significance.

Vaccination coverage data

Vaccination coverage at 24 months for the 2005-2009 birth cohorts was collected through a dedicated survey conducted in 2013; representatives from the 21 Italian regions involved in vaccine-preventable diseases were invited to fill in a web form, powered by SurveyMonkey®.⁷

Provisional coverage of the 2010 and 2011 birth cohorts was provided by the MoH, which has routinely collected pneumococcal vaccination coverage since 2013. In Italy, vaccine coverage at 24 months is estimated by an administrative method, using the number of children of a specific birth cohort immunised with a complete series of a pneumococcal conjugate vaccine by 24 months as numerator and the total birth cohort population as denominator. Vaccination coverage stratified by 7-valent PCV and 13-valent PCV is not available at the national level.

RESULTS

Number of cases and incidence

A total of 5,694 cases of IPD (7 without information about age) were reported at the national level in the study period, with an incidence of 1.2/100,000 in 2008 (6.6/100,000 for children less than 1 year of age, 3.5/100,000 for children 0-4 years of age, 2.7/100,000 for the >64 age group) and 1.4/100,000 in 2014 (3.3/100,000 for children less than 1 year of age, 1.6/100,000 for children 0-4 years of age, 3.6/100,000 for the >64 age group).

In the seven regions selected, the number of cases during the study period was 4,975, 87% of the overall cases reported at the national level. The incidence calculated including only the seven regions was approximately double than the national incidence: in 2008 it was 2.3/100,000 (12.0/100,000 for children less than 1 year of age, 7.1/100,000 for children 0-4 years of age, 5.3/100,000 for the >64 age group), and in 2014 it was 2.9/100,000 (5.9/100,000 for children less than 1 year of age, 3.1/100,000 for children 0-4 years of age, 7.5/100,000 for the >64 age group).

As expected, children aged 0-4 years and adults >64 years had the highest incidence rate.

In the selected regions, incidence declined significantly (table 1) in the age group that is the target of vaccination (0-4 years; $p < 0.001$) and increased significantly in the >64 age group ($p < 0.01$). The decline for the 0-4 age group from 2008 to 2014 was 56%. This decline was mainly attributable to the decrease in cases in the first year of life (from 12.0/100,000 to 5.9/100,000).

In the >64 age group, incidence showed an increase of 30% from 2008 (5.3/100,000) to 2014 (7.5/100,000). Regarding clinical presentation, in 43% of cases of all ages presentation was meningitis or meningitis + sepsis in 2008, whereas in 2014 this percentage was 36%.

Diagnostic methods and serotypes

Information on the tests used to confirm IPD cases was available in 4,739 cases (95%). Culture was still reported as the main diagnostic method (81% alone; 93% together with one or more other tests). PCR was reported to be used only in 3% of cases, but there was an increasing trend (2% in 2008-2011;

4% in 2012-2014). PCR alone was reported to be used in 2% of cases.

The percentage of overall reported cases with a result of serotyping was 31% and 58% in 2008 and 2014, respectively. However, this percentage presented differences by age group: for the 0-4 age group it was 62% in 2008 and 70% in 2014; for the >64 age group it was 27% and 56% in 2008 and 2014, respectively. The estimated incidence by serotype group (VT or NVT) is reported in figure 1. A significant decline in incidence of VT ($p < 0.001$) was observed in the 0-4 age group from 2008 to 2014. In this class of age, the percentage of serotypes included in PCV13 was 77% in 2008, 64% in 2011, and 35% in 2014. A significant increase ($p < 0.001$) in the incidence of NVT cases was observed in the >64 age group. The VT incidence decrease, a sign of a possible herd immunity effect of the vaccinated children on the older population, was not significant ($p = 0.40$). The percentage of serotypes included in PCV13 for the >64 age group was 78% in 2008, 53% in 2011, and 42% in 2014.

Vaccine coverage

National VC for PCV7/PCV13 progressively increased from 46% in 2007 (2005 birth cohort) to 88% in 2013 (2011 birth cohort). Overall, VC is good, but it varies widely between regions and years; some regions, like Abruzzo, Calabria, and Sardinia, still reported a coverage lower than 65% in 2013 (table 1). As reported at the bottom of table 1, VC in the seven selected regions is similar or slightly lower compared to the national VC (table 2).

DISCUSSION AND CONCLUSION

In Italy IPDs still represent a public health problem as frequent, and often severe, vaccine-preventable diseases. Monitoring the number of cases, incidence, and serotypes causing the infections makes it possible to evaluate the impact of the vaccination programs and the serotyping replacement that is a concern for pneumococcal infections.⁸⁻¹⁰

The MIB surveillance system collects notifications from all 21 Italian regions, but many of them report a very low number of cases; since a large number of cases is expected even in regions with very high VC because around 50% of IPDs are curren-

	0 yy		1-4 yy		5-9 yy		10-14 yy		15-24 yy		25-64 yy		>64 yy		All ages	
	N	Inc	N	Inc	N	Inc	N	Inc	N	Inc	N	Inc	N	Inc	N	Inc
2008	29	12.0	56	5.9	16	1.4	6	0.6	8	0.4	177	1.2	280	5.3	572	2.2
2009	26	10.5	46	4.7	14	1.2	6	0.5	10	0.4	252	1.7	327	6.1	683	2.7
2010	23	9.3	50	5.1	17	1.4	6	0.5	7	0.3	263	1.8	380	7.0	748	2.9
2011	21	8.6	51	5.1	18	1.5	1	0.1	5	0.2	185	1.3	354	6.5	636	2.4
2012	18	7.7	33	3.4	19	1.6	5	0.4	5	0.2	217	1.5	433	7.9	730	2.9
2013	12	5.2	32	3.3	30	2.5	7	0.6	9	0.4	294	2.1	479	8.5	863	3.4
2014	13	5.9	24	2.5	15	1.2	8	0.7	6	0.3	241	1.7	435	7.5	743	2.8

Inc: incidence

Table 1. Estimated number of cases and incidence of IPD per 100,000 inhabitants by age group in 7 Italian regions (P.A. Bolzano, P.A. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), 2008-2014.

Tabella 1. Numero stimato dei casi e dell'incidenza di IPD per 100.000 abitanti per classe d'età in sette regioni italiane (P.A. Bolzano, P.A. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), 2008-2014.

Year of reference	2007	2008	2009	2010	2011	2012	2013
Birth cohort	2005	2006	2007	2008	2009	2010	2011
Abruzzo	30.30	34.43	39.66	40.07	40.19	49.63	56.09
Basilicata	92.68	95.23	96.34	97.27	98.46	98.60	98.73
Campania	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Calabria	57.13	68.12	75.28	81.36	86.91	94.00	44.54
Emilia-Romagna*	43.30	n/a	94.30	94.60	94.10	94.40	94.10
Friuli-Venezia Giulia*	n/a	n/a	n/a	n/a	74.90	84.00	86.53
Lazio	n/a	n/a	n/a	n/a	n/a	n/a	90.80
Liguria	85.12	89.09	90.17	91.26	91.29	n/a	93.66
Lombardia*	35.91	46.90	58.46	66.10	71.73	77.88	83.70
Marche	24.20	35.50	45.50	59.70	91.90	88.20	93.39
Molise	n/a	n/a	n/a	n/a	n/a	88.86	95.95
Piemonte*	10.85	19.31	27.80	29.11	44.68	89.61	92.68
P. A. Bolzano*	14.30	23.60	40.20	72.60	75.50	81.40	78.78
P. A. Trento*	37.72	69.55	85.13	84.03	84.58	86.10	87.64
Puglia	56.40	71.40	75.70	80.40	92.60	95.10	92.93
Sardegna	n/a	n/a	n/a	n.a.	90.73	91.24	64.76
Sicilia	83.90	88.70	90.70	93.60	95.00	94.95	92.90
Toscana	n/a	n/a	n/a	88.21	93.50	92.06	94.01
Umbria	n/a	n/a	n/a	76.90	93.30	93.88	94.86
Valle d'Aosta	n/a	n/a	85.40	89.70	92.10	89.60	89.68
Veneto*	83.70	86.10	87.50	88.30	90.30	87.90	88.4
average coverage	46.19	55.81	70.13	75.46	81.81	87.55	87.10
average coverage for the regions included in the study	42.44	51.04	65.73	70.01	75.31	85.90	87.71

*regions included in the study; n/a: not available

Table 2. Vaccination coverage (completed series) by birth cohort and region for conjugate vaccine against *S. pneumoniae*. Italy, 2007-2013.

Tabella 2. Vaccino coniugato contro *S. pneumoniae*: copertura vaccinale (ciclo completo) per coorte di nascita e Regione. Italia, 2007-2013.

tly not vaccine-preventable, we hypothesize an under-notification/under-diagnosis in some geographical areas; a recent comparison with data from hospital discharge records supports this hypothesis (data not shown).

To obtain a more realistic incidence, we selected data from seven regions (representing 43% of the Italian population) which provided 87.4% of all Italian IPD notifications in the period 2008-2014. The incidence in this group of regions is approximately double than the national one.

At first glance, several years of use of 7-valent and 13-valent PCV did not reduce the overall incidence of IPD in Italy. However, when we stratify data by age and serotype groups, we can observe the positive impact of the vaccine (a 56% incidence reduction) in children aged 0-4 years, who are the main target of PCV and, together with adults >64 years of age, the age group with the higher incidence of IPD.

Our data show a slight decrease in IPD due to VT in the older population, a possible sign of a herd immunity effect already observed in other countries.^{10,11} This trend, however, lacks statistical significance.

The incidence of IPD in the >64 age group increased by 30% as a consequence of a higher number of cases due to NVT. The interpretation of this increase is not easy and several hypotheses can be formulated: is it a true increase, as reported by other studies,¹⁰ or the result of a recent growing attention to the etio-

logical diagnosis of invasive disease in adults, or just a greater inclination to disease reporting? This study was not designed to answer this question, but theoretically the use of more sensitive diagnostic tests (i.e., PCR)¹² could lead to an increase in NVT IPD cases and hide a decrease in VT in older people. However, in our study we found that PCR was used as a diagnostic test in only 4% of IPDs in the seven selected regions. This study suggests the need of a comparison with other sources of data, like hospital discharge records, and focus on regional diagnostic attitudes and reporting practices to verify the temporal trend of pneumococcal infections.

This study has many limitations. We analyzed the data from the seven selected regions as a single entity, however PCV was introduced in the regional immunization plans at different times and VC varied among the regions; consequently, the aggregated data are not fully homogeneous.

Incidence by VT and NVT cases was estimated by applying, to the isolates with unknown serotype, the same distribution of serotypes observed in the same year for all confirmed cases; however, the distribution of serotype is slightly different among children and elderly patients, and this could affect the estimation.

The study shows the incidence trend for VT and NVT categorizing the serotypes as included or not included in PCV13; however the cohorts before 2011 were vaccinated with PCV7

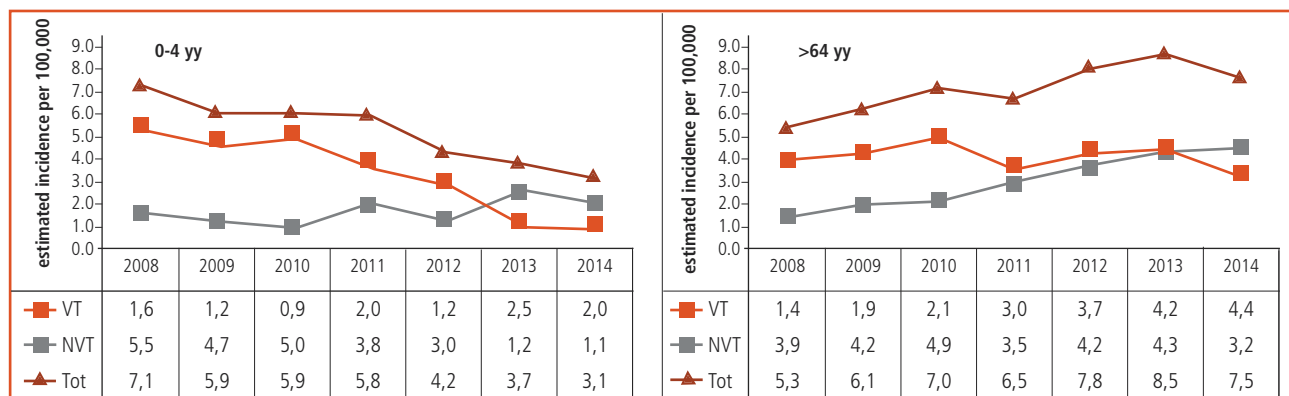


Figure 1. Estimated incidence of IPD in the 0-4 and >64 year age groups, by year of notification and serotype group in 7 Italian regions (P.A. Bolzano, P.A. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), 2008-2012.

Figura 1. Incidenza stimata dei casi di IPD nei gruppi d'età 0-4 e >64, per anno di notifica e serotipo in 7 Regioni italiane (P.A. Bolzano, P.A. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), 2008-2012.

and an unknown quota of children received one dose of PCV13; this could make it more difficult to interpret the trend of incidence by groups of serotypes.

The possibility of under-diagnosis was not investigated in the selected regions, so there is no information about whether the sensitivity of the system is homogenous among the seven regions. In conclusion, despite the limitations mentioned above, our data show a positive impact of pneumococcal conjugate vaccination in children. More studies should be performed to verify the representativeness of the surveillance system. These future efforts might also prove useful to improve the representativeness of the Italian data provided at European level; the national surveillance of invasive bacterial diseases is in charge of sending to the ECDC the IPD data, which are published in the ECDC surveillance report of invasive bacterial diseases on a yearly basis.¹³

A better knowledge of data could help to decide whether to continue to send only national data (which at the moment is providing a “diluted” incidence) or switch to a subnational sample that it is proven to produce more realistic data. Another important issue is the use of PCR in diagnosis: use of this method is slowly increasing because it allows to identify within a few hours the pathogen responsible for meningitis or sepsis, thus providing useful clinical support.

However there is no national protocol/guideline that recommends the use of this method and provides indications on how to use it (i.e., in which clinical picture to use it). At the moment, although the indication to use PCR for meningitis cases is present in many regional laboratories, our data does not indicate a widespread use of this method.

Conflicts of interest: none declared

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