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Impact of pneumococcal conjugate vaccine (PCV7 and PCV13) on pneumococcal invasive diseases in Italian children and insight into evolution of pneumococcal population structure

Romina Camilli [a,*], Fabio D'Ambrosio [a], Maria Del Grosso [a], Fernanda Pimentel de Araujo [a], Maria Grazia Caporali [a], Martina Del Manso [a], Giovanni Gherardi [b], Fortunato D'Ancona [a], Annalisa Pantosti [a], Pneumococcal Surveillance Group [1]

[a] Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy
[b] Department of Medicine, Campus Biomedico University, Rome, Italy

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ABSTRACT

Background: The use of PCV7 for children immunization was gradually implemented in the Italian regions starting from 2006 and was replaced by PCV13 in 2010–2011. In this study we aimed to assess the PCV impact on invasive pneumococcal diseases (IPD) incidence, serotype distribution and antibiotic resistance in Italian children under 5 years old.

Methods: All IPD cases in children from 5 Italian regions (Emilia-Romagna, Lombardia, A. P. Bolzano, A. P. Trento, and Piemonte) reported through the nationwide surveillance system during 2008–2014 were included in this study. Pneumococcal isolates were subjected to serotyping, antibiotic susceptibility testing, and clonal analysis according to standard methods.

Results: During the study period overall IPD incidence decreased from 7.8 cases/100,000 inhabitants in 2008 to 3.0 cases/100,000 in 2014 (61% decrease, $P < 0.001$). In particular, from 2008 to 2014, PCV7-type IPD decreased from 2.92 to 0.13 cases/100,000 inhabitants (95% decrease, $P < 0.001$) while PCV13-non-PCV7 type IPD decreased from 3.2 to 0.89 cases/100,000 inhabitants (72% decrease, $P = 0.008$).

Results: Conversely, non-vaccine serotype (NVS) IPD increased overtime, becoming more common than PCV13 serotype IPD in 2013–2014. Emergent NVS 24F and 12F were the most prevalent in 2014. Antibiotic resistance testing revealed an overall increasing trend in penicillin resistance, from 14% in 2008 to 23% in 2014. Erythromycin resistance showed a downward trend, from 38% in 2008 to 27% in 2014. While in 2008 PCV13 serotypes were the major responsible for antibiotic resistance, during the following years antimicrobial resistance due to NVS increased, mainly as a result of expansion of pre-existing clones.

Conclusions: Both PCVs led to a substantial decrease in vaccine-related IPD incidence in the children population. However NVS-related IPD increased, becoming the most prevalent in the last two-years period. Continuous surveillance is an essential tool to monitor evolution of pneumococcal population causing IPD in children.

1. Introduction

Streptococcus pneumoniae represents a major human pathogen causing life-threatening illnesses, such as meningitis and bacteraemia (namely Invasive Pneumococcal Diseases, IPD), as well as non invasive diseases such as community-acquired pneumonia and acute otitis media. Children, along with elderly people, represent the high-risk population for IPD. The World Health Organization estimated that pneumococcal infections are responsible for 11% of all deaths in children under 5 years of age [1]. Over the last decade three pneumococcal conjugate vaccines (PCVs) have been introduced for childhood vaccination leading to important changes in IPD epidemiology worldwide. PCV7 containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, introduced in the United States in

* Corresponding author at: Department of Infectious Diseases, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.
E-mail address: romina.camilli@iss.it (R. Camilli).
[1] Maria Paola Landini and Caterina Vocale, Bologna, Italy; Laura Daprai, Milano, Italy; Marinella Frenguelli, Trento, Italy; Elisabetta Pagani, Bolzano, Italy; Anna Maria Barbui, Torino, Italy.

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2000 and subsequently in Europe, was effective in reducing IPD caused by vaccine serotypes (VS) in children and also in adults due to herd immunity [2,3]. However, a gradual increase of IPD due to non-vaccine serotypes (NVS) was concurrently observed, a phenomenon called serotype replacement [2]. Replacement was primarily due to increase in NVS 19A [4,5], and to a lesser extent in serotypes 1 and 7F [2]. In subsequent years, PCV7 was replaced by higher-valent vaccines such as PCV10 and PCV13, containing 3 (1, 6A and 7F) or 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A), respectively. Following PCV10 or PCV13 introduction in pediatric vaccination programs, IPD incidence due to VS declined further but increases of NVS was soon reported although no specific serotype emerged [6–8].

Concurrently to PCVs use, a decline in antibiotic resistance rates, especially in resistance to penicillin and erythromycin was noted [9,10]. Prior to PCV7 introduction the majority of penicillin-resistant pneumococcal strains belonged to VS 14, 6B, 19F, and 23F; during the PCV7 era NVS 19A gained a prominent role as being associated with antibiotic resistance [11,12]. Further changes were observed after introduction of PCV13 since serotype 19A decreased but other NVS increasingly became antibiotic resistant [11].

In Italy, PCV7 was first licensed in 2001, but vaccine implementation depended on the different immunization policies of the Italian regions. By 2010, PCV13 replaced PCV7 in all regions and in 2012, PCV13 vaccination was recommended by the National Immunization Plan, according to the 2 + 1 schedule (vaccination uptake at 3, 5 and 11 months of age). The 21 Italian regions, that showed initially great differences in PCV immunization policies, gradually implemented PCV administration, so that the overall national PCV coverage at 24 months of age increased from 55.1% in 2008 to 87.5% in 2014 (www.salute.gov.it).

The Italian Surveillance of IPD is included in the National Surveillance System for Invasive Bacterial Diseases that was started in 2007 with the coordination of the Istituto Superiore di Sanità (ISS) and the financial support of the Italian Ministry of Health. IPD cases are reported in the surveillance database (http://www.iss.it/mabi) by hospitals or regional health authorities on voluntary bases. Since the starting of the surveillance, the Italian Regions have shown a different propensity to report cases and to submit the pneumococcal isolates to serotyping. Therefore, for the purpose of this study we selected data from 5 regions in Northern Italy that have been actively participating in the surveillance since 2007, representing >30% of the total Italian population. Using this dataset, we assessed the epidemiological changes, in terms of IPD incidence, serotype distribution, antimicrobial resistance profiles and evolution of the pneumococcal clonal population in children in the years 2008–2014.

2. Materials and methods

2.1. Study design

We analyzed all IPD cases in children aged 0–4 years reported to the MIB database (http://www.iss.it/mabi) by 5 regions in Northern Italy (Emilia-Romagna, Lombardia, Autonomouos Province (A.P.) of Bolzano, A.P. of Trento, and Piemonte) during the period 2008–2014.

The regional reference laboratories collected the pneumococcal isolates related to the reported cases and sent them to the National Reference Laboratory (NRL) at the ISS for further testing. Duplicated isolates from the same patient were excluded. For meningitis, if both Cerebrospinal fluid (CSF) and blood isolates were available, only the CSF isolate was included for characterization. No multiple isolates, due to relapse of disease from the same patient, were present among the reported cases.

2.2. Bacterial strains and serotyping

S. pneumoniae strains were cultured on 5% Columbia sheep blood agar plates and incubated overnight at 35 °C in 5% CO_2-enriched air. Serotyping was performed by latex agglutination and the Quellung reaction using commercially available antisera (Statens Serum Institut, Copenhagen, Denmark) by the regional laboratories and/or by the NRL.

2.3. Antimicrobial susceptibility testing

The pneumococcal isolates received at the NRL were tested for susceptibilities to penicillin, ceftriaxone, erythromycin, clindamycin, tetracycline, and chloramphenicol using the antimicrobial gradient strip diffusion method (Etest, bioMérieux, Durham, USA) following the EUCAST breakpoints (http://www.eucast.org/clinical_breakpoints/). Meningitis breakpoints were applied for penicillin and isolates with penicillin MIC > 0.06 mg/L were reported as resistant.

2.4. Pulsed Field Gel Electrophoresis (PFGE) and Multi locus sequence typing (MLST)

Isolates that were resistant to penicillin and/or erythromycin were analyzed by PFGE as previously described [13]. Representative isolates belonging to the most common PFGE types were submitted to MLST analysis (http://spneumoniae.mlst.net) and a sequence type (ST) and a clonal complex (CC) were assigned to each isolate. STs were compared with those of the international clones identified by the Pneumococcal Molecular Epidemiology Network (PMEN; http://www.sph.emory.edu/PMEN/). STs were considered related if they were identical, single locus variant (SLV) or double locus variant (DLV) of each other.

2.5. Statistical analysis

Incidence was calculated by using the estimated population of the age group <5 years at 1st January of each year, according to the National Institute for Statistics (http://demo.istat.it). Statistical analysis was corrected for missing serotypes by assuming that reports with no serotyping had the same serotype distribution of reports with a known serotype. The differences between proportions were evaluated by the χ^2 or Fisher exact test. A linear regression model was used to estimate the percentage of the average annual changes.

3. Results

3.1. Incidence rate of IPD

From January 2008 to December 2014, a total of 364 IPD cases in children 0–4 years were reported to the surveillance database by the 5 Italian regions. These cases represented 67.5% of the IPD cases reported to the database for this age group during 2008–2014 for the whole of Italy.

During the study period, a 61% decrease in IPD incidence was observed from 7.8 cases/100,000 inhabitants in 2008 to 3.0 cases/100,000 in 2014 ($P < 0.001$) (Fig. 1A-A1), with an average annual decrease of 0.71 cases/100,000 inhabitants. The largest decline (64%) was observed in the age group <1 year, where the IPD incidence dropped from 12.9 to 4.6 cases/100,000 inhabitants ($P < 0.001$) (Fig. 1A-A1).

Of the 364 IPD cases, 103 (28%) were pneumococcal meningitis (PM). PM occurred mainly in the age group < 1 year where a reduction of 54% of PM cases ($P > 0.05$) was observed during the whole