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note finali coverage

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4 **NECROTIZING PNEUMONIA AMONG ITALIAN CHILDREN IN THE PNEUMOCOCCAL**
5 **CONJUGATE VACCINE ERA**
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9 Ines Carloni MD¹, Silvia Ricci MD², Chiara Rubino MD², Giovanni Cobellis MD³, Giampaolo
10 Rinaldelli MD⁴, Chiara Azzari MD², and Fernando Maria de Benedictis MD⁶

11
12
13 *¹Pediatric Infectious Disease Unit, Salesi Children's Hospital, Ancona, Italy*

14 *²Department of Health Sciences, Meyer Children's University Hospital, Florence, Italy*

15 *³Pediatric Surgery Unit, Salesi Children's Hospital, Ancona, Italy*

16 *⁴Pediatric Intensive Care Unit, Salesi Children's Hospital, Ancona, Italy*

17 *⁵Salesi Children's Hospital Foundation, Ancona, Italy*

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30 *Correspondence to:*

31 *Fernando Maria de Benedictis, MD*

32 *Salesi Children's Hospital Foundation*

33 *11, via Corridoni, I-60123 Ancona, Italy*

34 *Email: pediatria@fmdebenedictis.it*

35

36 **ABSTRACT**

37 **Background:** Necrotizing pneumonia (NP) is a severe complication of community-acquired
38 pneumonia. The impact of 13-valent pneumococcal conjugate vaccine (PCV13) on the
39 epidemiology of NP in children has not been formally assessed.

40 **Patients and methods:** Medical records of children <18 years admitted with NP to two
41 pediatric hospitals in Italy between 2005 through 2019 were retrospectively reviewed. The
42 following 4 periods were defined: 2005-2010 (pre-PCV13), 2011-2013 (early post-PCV13),
43 2014-2016 (intermediate post-PCV13), and 2017-2019 (late post-PCV13).

44 **Results:** Forty-three children (median age, 44 months) were included. Most of them (93%)
45 were previously healthy. No differences in age, sex, season of admission, comorbidity, clinical
46 presentation, or hospital course were identified between pre-PCV13 and post-PCV13 periods.
47 A significant decrease in the rate of NP-associated hospitalizations was found between the
48 early (1.5/1000 admissions/year) and the intermediate (0.35/1000 admissions/year) post-
49 PCV13 period ($p=0.001$). *Streptococcus pneumoniae* was the most common agent detected in
50 both periods (pre-PCV13: 11/18, 61%; post-PCV13: 13/25, 52%). Serotype 3 was the most
51 common strain in both periods (pre-PCV13: 3/11, 27%; post-PCV13; 4/13, 31%). There were no
52 changes in the bacterial etiology over time, but most patients with *Streptococcus pyogenes* or
53 *Staphylococcus aureus* infection were admitted during the post-PCV13 period.

54 **Conclusions:** The hospitalization rate for NP in children decreased a few years after the
55 implementation of PCV13 immunization in Italy. However, an increased trend in admissions
56 was found thereafter. *S. pneumoniae* was the most frequent causal agent in both pre- and
57 post-PCV13 periods. Pneumococcal serotypes were mainly represented by strain 3.

58

59 **INTRODUCTION**

60 Necrotizing pneumonia (NP) is a severe complication of community-acquired pneumonia.¹ It is
61 characterized by destruction and cavitation of the lung parenchyma (“Emmentaler lung”), and
62 is frequently associated with pleural involvement.² Since the first description of NP in
63 childhood,³ increasing cases have been reported in previously healthy children⁴ with special
64 emphasis to clinical,⁵ laboratory,⁶ pathology,⁷ radiology,⁸ and therapeutic² aspects.
65 *Streptococcus pneumoniae* is the most common agent identified in children with NP. A greater
66 physician’s awareness, improved diagnostics, temporal trends or vaccine-induced changes in *S.*
67 *pneumoniae* serotype prevalence, and the propensity of some strains to cause NP may account
68 for the high incidence of NP over the last twenty years.⁹

69 The introduction of the 7-valent pneumococcal conjugate vaccine (PCV7, containing serotypes
70 4, 6B, 9V, 14, 18C, 19F, and 23F) into immunization programs initially led to a declining
71 incidence of pneumonia in childhood,^{10,11} but was associated with an increased incidence of
72 empyema,^{12,13,14} primarily due to non-vaccine serotypes.¹⁵ Following global replacement of
73 PCV7 with 13-valent PCV (PCV13, containing additional serotypes 1, 3, 5, 6A, 7F, 19A),
74 incidence and hospitalization rates for empyema reduced substantially^{16,17,18,19,20} without
75 serotype shift.^{21,22,23,24}

76 The impact of the switch from PCV7 to PCV13 on NP incidence remains unclear. No study has
77 formally evaluated the epidemiology of NP in children before and after PCV13 implementation.
78 Therefore, the aim of our study was to assess the impact of PCV13 on hospitalization rate and
79 etiology of NP in children admitted to two tertiary care pediatric hospitals in Italy over a 15-
80 year period (2005-2019).

81

82 PATIENTS AND METHODS

83 Study design

84 A retrospective review of medical records of children <18 years hospitalized with NP in two
85 tertiary care pediatric hospitals in Italy (Salesi Children's Hospital, Ancona, and Meyer
86 Children's Hospital, Firenze) between January 2005 through December 2019 was conducted
87 using an electronic database. All the included data were obtained as part of routine clinical
88 activity and were evaluated anonymously. Therefore, a specific approval by the ethical
89 committee was not required.

90 Data collection and definitions

91 Clinical information extracted from medical records was registered on a standardized form,
92 which included demographics, time of admission, clinical presentation, comorbidities,
93 pneumococcal immunization status, laboratory results, imaging studies, treatment strategies,
94 hospitalization course and outcome. When the vaccination status was not available in the
95 medical record, the family was contacted by telephone in order to check the child's vaccination
96 card. In Italy, hospital discharges are coded in accordance with the International Classification
97 of Diseases, 9th revision (ICD-9). We included codes for NP (513.0), empyema (510.9) and
98 pleural effusion (511.9). Patients with known risk factors, such as congenital lung
99 abnormalities, cystic fibrosis, primary ciliary dyskinesia, neurological compromise,
100 immunodeficiency, cancer chemotherapy, and those with nosocomial pneumonia or
101 pneumonia due to *Mycobacterium tuberculosis* were excluded.

102 Diagnosis of NP and parapneumonic effusion/empyema was made as previously described.²¹
103 NP was defined by the combination of clinical symptoms and signs of pneumonia with specific
104 radiological findings (pulmonary consolidation, loss of normal lung architecture, and single or
105 multiple thin-walled parenchymal cavities filled with fluid and/or air) on chest radiograph
106 and/or computed tomography scan. Parapneumonic effusion/empyema was defined as the
107 presence of free pleural fluid on chest radiograph, or loculated pleural fluid on chest
108 ultrasound or computed tomography scan, in association with characteristic biochemical
109 criteria. A patient was considered as having prior antibiotic therapy if he had completed 48
110 hours of an appropriate antibiotic for the treatment of community-acquired pneumonia. A
111 comorbidity was defined as a chronic medical condition. Annual rates of NP per 1000
112 admissions were calculated by the number of NP cases per year by the total admissions under

113 the pediatric internal medicine team (as all patients with possible NP would be initially
114 admitted under this team).

115 We defined the following 4 periods according to PCV13 implementation: January 2005 to
116 December 2010, pre-PCV13 period, including a transitional period (switch from PCV7 to PCV13
117 in 2010); January 2011 to December 2013, early post-PCV13 period; January 2014 to
118 December 2016, intermediate post-PCV13 period; and January 2017 to December 2019, late
119 post-PCV13 period.

120 **Vaccine coverage**

121 In Italy, PCV13 was included in a national immunization plan with a 3-dose-schedule (3-5-12
122 months) in replacement of PCV7 in the last quarter of 2010. No catch-up campaign for children
123 >1 years of age has been carried out since the introduction of PCV13. Mean annual vaccination
124 coverage for PCV13 in Italian target populations in the post-PCV13 era was over 85% in the
125 years 2013-2018; data about national vaccination coverage were not available for the years
126 2011, 2012 and 2019 ([http://www.salute.gov.it/portale/documentazione/p62831.jsp?lingua =
127 italiano&id=20](http://www.salute.gov.it/portale/documentazione/p62831.jsp?lingua=italiano&id=20); accessed in June 2020). For our purposes, any dose of PCV13 given after six
128 weeks of age, at least four weeks after the previous dose, and at least 30 days before the
129 hospital admission date, was considered valid.

130 **Laboratory methods**

131 Microbiology included blood and pleural fluid cultures. Real-time polymerase chain reaction
132 (RT-PCR) was performed as previously described.²⁵ Briefly, a panel of primers and probes for
133 14 pathogens (*S. pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Escherichia coli*,
134 *Klebsiella pneumoniae*, *Streptococcus agalactiae*, *Listeria monocytogenes*, *Staphylococcus*
135 *aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Salmonella spp*, *Mycoplasma*
136 *pneumoniae*, *Fusobacterium spp*, and *Adenovirus*) was used for routine diagnosis. Etiological
137 diagnosis was made if RT-PCR and/or culture was positive in blood or pleural fluid samples.
138 When RT-PCR was negative for all primers/probes included in the panel, amplification and
139 sequencing of the 16S rRNA bacterial gene were performed. All samples positive for *S.*
140 *pneumoniae* were serotyped by RT-PCR using 33 primer couples and probes. Pneumococcal
141 serotypes were classified as PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), PCV13 serotypes
142 (PCV7 plus 1, 3, 5, 6A, 7F, 19A), and non-PCV13 serotypes (not included in the PCV13). If no
143 increase in fluorescent signal was observed after 40 cycles for any of the serotype-specific
144 primer/probe sets, in spite of a positive result with both RT-PCR (*lytA* gene) and end-point PCR

145 (cpsA gene), the sample was reported as non-typeable. Viral studies were performed in a
146 limited number of patients on a nasopharyngeal swab or on bronchoalveolar lavage fluid or on
147 both, as previously described.²⁶

148 **Statistical Analysis**

149 Results were summarized as medians and interquartile ranges (IQR) for continuous variables,
150 and percentages for nominal variables. Continuous variables were compared by means of
151 Mann–Whitney U test. Chi-square or Fisher’s test were performed to evaluate differences
152 between categorical variables. Chi-square for linear trend analysis was performed to
153 determine significance in incidence trends. $p < 0.05$ was considered statistically significant.
154 Statistical analysis was performed using SPSS (Version 26.0, SPSS, Inc., Chicago, IL, USA) and
155 the freely available “openepi” package (https://www.openepi.com/Menu/OE_Menu.htm).

156 RESULTS**157 Demographics and clinical data**

158 We identified 49 children with NP from our database. Six of them were excluded (congenital
159 lung abnormalities n. 1, cystic fibrosis n. 1, primary ciliary dyskinesia n. 1, neurological
160 compromise n. 1, haemophagocytic lymphohistiocytosis n. 1, pneumonia due to *M.*
161 *tuberculosis* n. 1). Therefore, 43 children (18 males, 25 females) were considered.

162 The median age was 44 months (IQR 32-62). Most children (40/43, 93%) were previously
163 healthy. Thirty-nine children had received antibiotic treatment before hospitalization. Thirty-
164 two children had associated empyema or parapneumonic effusion. Two patients developed
165 bronchopleural fistula. Two children suffered from haemolytic uremic syndrome, both in
166 association with pneumococcal pneumonia. Median hospitalization length was 20 days (IQR
167 17-28). Nineteen children (44%) were admitted to a pediatric intensive care unit (PICU) for a
168 median duration of 8 days (IQR 4-26), and eleven of them (58%) were intubated. Fifteen
169 patients received pleural drainage alone; intrapleural urokinase or video-assisted
170 thoracoscopic surgery were necessary in four and eight cases, respectively; one patient
171 underwent lobectomy. Demographic characteristics, season of hospitalization, clinical
172 features, etiologic agents and hospital course in the pre- or post-PCV13 period are shown in
173 the Table 1. No differences in age, sex, season of hospitalization, comorbidity, clinical
174 presentation, hospital course and etiologic agents were identified between pre- and post-
175 PCV13 periods. The median age of children admitted to PICU (32 months, IQR 32-62) was
176 lower than that of those who were not admitted to PICU (51 months, IQR 38-77) ($p=0.002$).

177 Necrotizing pneumonia-associated hospitalizations

178 When the rate of NP-associated hospitalizations of each study period was compared to the
179 previous one, a significant difference was found between the early (1.5/1000 admissions/year)
180 and the intermediate (0.35/1000 admissions/year) post-PCV13 period ($p=0.001$) (Figure 1). An
181 increase in hospitalization rate was found between the intermediate and the late post-PCV13
182 period (0.94/1000 admissions/year). Chi-square for linear trend in the late post-PCV13 period
183 was 2.14 ($p= 0.13$).

184 Bacterial species distribution

185 Overall, etiological diagnosis was achieved in 32/43 (74%) cases. *S. pneumoniae* was the most
186 frequent pathogen identified (24/43, 56%), followed by *S. pyogenes* (5/43, 12%) and *S. aureus*

187 (3/43, 7%). Bacterial etiologies of NP during all study period, pre-PCV13 period and post-PCV13
188 periods are shown in the Table 2. A significant difference in the hospitalization rate of NP
189 caused by *S. pneumoniae* was found between the early (0.86/1000 admissions/year) and the
190 intermediate (zero/1000 admissions/year) post-PCV13 period ($p=0.001$). An increasing trend in
191 the hospitalization rate was found between the intermediate and the late (0.58/1000
192 admissions/year) post-PCV13 period ($p=0.06$). There was no difference in the hospitalization
193 rate for NP caused by *S. pyogenes* or *S. aureus* between pre- and post-PCV13 periods. There
194 was no difference in the admission rate to PICU between different etiologic agents; however,
195 all three children with *S. aureus* infection had to be admitted to PICU.

196 **Vaccine coverage**

197 A documented vaccination status was available in 39/43 (91%) patients. Vaccination against
198 pneumococcus was ascertained in 37 children (86%); all of them had received at least two
199 doses of vaccine; 27 patients had received PCV7 vaccination, and 10 had received PCV13
200 vaccination. Pneumococcal vaccine coverage in children during the different study periods is
201 shown in the Table 3. All children with *S. pneumoniae* NP during the early post-PCV13 period
202 had received PCV7 vaccination. In children who had received PCV13 vaccination, *S.*
203 *pneumoniae* NP was present only in the late post-PCV13 period.

204 **Microbiological findings**

205 Cultures and RT-PCR analysis were obtained in 23 and 23 blood samples, and in 17 and 22
206 pleural fluid samples, respectively. Culture and RT-PCR analysis were positive in 5/23 (22%)
207 and 13/23 (57%) blood samples, and in 5/17 (29%) and 21/22 (95%) pleural fluid samples,
208 respectively. Overall, pleural fluid was more informative than blood in revealing etiology:
209 26/39 (67%) vs 18/46 (39%). RT-PCR analysis was 2.6 and 3.3 times more sensitive than culture
210 in achieving etiological diagnosis in blood and pleural fluid samples, respectively. Viral
211 coinfections were detected in 4 cases: influenza virus A H1N1 (n. 1), influenza B (n. 1),
212 respiratory syncytial virus (n. 1), rhinovirus (n. 1).

213 ***S. pneumoniae* serotyping**

214 The sample amount was not enough to perform serotyping in 5/24 patients with *S.*
215 *pneumoniae* infection. Pneumococcal serotype-specific detection was available in 17/19 (89%)
216 children. Serotype distribution in pre-PCV13 and post-PCV13 periods is shown in the Table 4.
217 Among 13 pneumococcal isolates recovered in the post-PCV13 periods, 9 serotypes were

218 available, and they were mainly vaccine serotypes (serotypes 1 [n=2], 3 [n=4], 7F [n=1]).
219 Serotype 3 was found in 4 of 5 (80%) children who had received PCV13 immunization.

220

221 **DISCUSSION**

222 To our knowledge, this is the first study reporting the epidemiology of NP in children before
223 and after PCV13 vaccination. Our study shows that the hospitalization rate for NP in Italy
224 significantly decreased a few years after PCV13 implementation. This finding is not surprising
225 since all children who developed NP during the early post-PCV13 period had received PCV7
226 vaccination, mainly because they were born in the pre-PCV13 era. However, an increased
227 trend in hospital admissions was found in the late post-PCV13 period, especially due to *S.*
228 *pneumoniae* cases. Noteworthy, all children with NP in such period had received PCV13
229 vaccination.

230 Albeit a reduced incidence of complicated pneumonia in childhood has been observed in many
231 studies following replacement of PCV7 with PCV13,¹⁶⁻²⁴ this finding has not been universal.
232 Indeed, recent studies reported increasing cases of complicated pneumonia over the last few
233 years. In a national surveillance study in Germany, the incidence of *S. pneumoniae* empyema
234 significantly decreased from 3.5 per million children in 2010/11 to 1.5 in 2013/14, followed by
235 a re-increase to 2.2 by 2016/17.²³ A retrospective study in Australia showed increasing rates of
236 admissions and higher severity of empyema cases in children between 2011 and 2018.²⁷ In a
237 population-based cohort study of invasive pneumococcal disease in Canada, rates of childhood
238 empyema increased from 2000 to 2004 (4.0%), 2005 to 2009 (7.2%) and 2010 to 2014
239 (15.7%).²⁸ Only one study has reported the epidemiology of NP in childhood over the years.
240 The annual average number of children hospitalized with NP in a tertiary medical center in
241 Jerusalem from 2015 to 2017 (n=5.3) doubled compared to that from 2001 to 2014 (n=2.6).²⁹
242 However, the lack of information on the immunization status of patients does not allow
243 inferring the effectiveness of pneumococcal vaccination.

244 The underlying causes of the increased trend in hospital admissions for complicated
245 pneumonia over the last years are not fully understood. We can reasonably exclude a reduced
246 primary care antibiotic prescription in our patients, since variations in this practice have not
247 been reported in Italy. ([https://www.ecdc.europa.eu/en/antimicrobial-
248 consumption/database/country-overview](https://www.ecdc.europa.eu/en/antimicrobial-consumption/database/country-overview)). A national study in Italian children with empyema
249 showed that the Red Queen hypothesis³⁰ - that is the increased incidence of non-PCV13
250 serotypes after PCV13 implementation - is hard to accept.²¹ Host genetic³¹ and microorganism
251 factors such as a high bacterial load in the blood³² may be responsible. Indeed, the higher

252 sensitivity of both RT-PCR (57%) and culture (22%) in blood samples of our patients compared
253 to that in children with empyema (17% and 7%, respectively)²¹ supports this hypothesis.

254 A recent review reported that *S. pneumoniae* was the most frequent etiologic agent (59%) of
255 NP, mostly in the pre-PCV13 period, followed by *S. aureus* (23%), *Mycoplasma pneumoniae*
256 (6%) and *S. pyogenes* (2.5%).⁴ We found that *S. pneumoniae* was still the most common cause
257 of NP (52%) in the post-PCV13 period. However, 10/19 (53%) children with NP caused by *S.*
258 *pneumoniae* in the post-PCV13 period had not been vaccinated with PCV13. The
259 hospitalization rate for NP associated with *S. pyogenes* and *S. aureus* did not differ between
260 pre- and post-PCV13 periods. This finding is in contrast with the reported change in the
261 bacterial etiology of childhood empyema after the implementation of PCV13.^{19,23,33,34,35}
262 Although we didn't find temporal changes in the bacterial etiology of NP, seven out of eight
263 patients with *S. pyogenes* or *S. aureus* infection were admitted during the post-PCV13 period.

264 The change induced by pneumococcal vaccination in the prevalence of *S. pneumoniae*
265 serotypes in invasive pneumococcal disease has been a matter of critical speculation.¹⁵ In
266 children with NP, non-vaccine serotypes have been most commonly implicated before and
267 after the introduction of the PCV7. In Northern England, serotypes 1 and 3 were found in 7/13
268 (53%) patients with cavitary lung disease associated with empyema.³⁶ In Texas, serotype 19A
269 was an emerging cause (4/11, 36%) of NP and was associated with a more complicated course
270 of illness.³⁷ In a series of 15 children with NP from Taiwan, serotypes 14 and 3 were found in
271 50% and 30% of cases, respectively.⁷ Furthermore, serotypes 3 and 19A accounted for 80% of
272 *S. pneumoniae* isolates in 41 children admitted with NP to a teaching hospital in France.³⁸

273 Our study shows that pneumococcal strains recovered in the post-PCV13 period were mainly
274 PCV13 vaccine serotypes (1, 3, 7F). Furthermore, all cases of PCV13 vaccine failure except one
275 were due to serotype 3. This finding confirms that the efficacy of PCV13 against serotype 3 in
276 invasive pneumococcal disease, especially complicated pneumonia,^{39,40} is modest.⁴¹ Serotype 3
277 has been reported to be associated with severe lung complications, such as pulmonary
278 necrosis⁴² and bronchopleural fistula.⁴³ Intrinsic properties may help serotype 3 evade and
279 minimize immune responses.⁴⁴ In addition, higher levels of anti-capsular polysaccharide
280 antibody concentration required to prevent infective complications may not be reached for
281 some serotypes by the standard vaccination protocol.⁴⁵ Worthy of note, a large cohort study in
282 UK demonstrated no impact of PCV13 vaccination on serotype 3 carriage or disease.⁴⁶

283 Two of our 24 patients with pneumococcal NP complicated with haemolytic-uremic syndrome.
284 Clinicians should be aware of this potential association, especially in young children.²⁰ Early
285 recognition is indeed important to reduce morbidity and mortality.⁴⁷

286 There are a number of limitations to our study. First, although a strict coding methodology was
287 used to review the medical records, the retrospective design may have resulted in registration
288 errors. Second, the relatively low number of patients may not allow unmasking ongoing
289 changes in the bacterial etiology of NP. Third, viral studies were not conducted systematically.
290 A high rate of viral coinfection has been reported in children with complicated pneumonia,²⁰
291 and virus-induced epithelial damage may be a predisposing factor for the bacteria-activated
292 necrotizing process.⁴⁸ Although we cannot exclude differences in the rate of viral infections
293 during the pre- and post-PCV13 periods, this is difficult to accept in the context of similar
294 distribution of cases over seasons during the whole study period.

295 The strengths of our study include the involvement of two tertiary care pediatric hospitals that
296 serve a stable population of about 500,000 children, the high pneumococcal vaccine coverage
297 of the population, a detailed assessment of clinical characteristics of the patients, standardized
298 microbiological analyses, and the 15-year period of the study.

299 In conclusion, our study showed a reduced incidence of hospitalizations for NP at two
300 children's hospitals in Italy a few years after PCV13 implementation. An increased trend in
301 hospital admissions was found in the late post-PCV13 period, especially due to *S. pneumoniae*
302 cases. *S. pneumoniae* serotype 3 was the most frequent causal agent in both pre- and post-
303 PCV13 periods. Although we didn't find ongoing changes in the bacterial etiology of NP, most
304 patients with *S. pyogenes* or *S. aureus* infection were admitted during the post-PCV13 period.
305 Future studies are needed to assess the epidemiology of NP in children who received PCV13
306 vaccination. Continued surveillance is also required to monitor pneumococcal serotype
307 replacements and shifts in the coming years. Future pneumococcal vaccines should not only
308 cover newly emerging serotypes, but also include a more effective component against
309 serotype 3.

310

311

312

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314 extracting data from electronic database.

315

316 **CONFLICTS OF INTEREST**

317 All the authors declare no competing interests.

318

319 **AUTHORS' CONTRIBUTION**

320 Conceived and designed the study: FMdB. Acquired and managed data: CR, GC, GR, SR.

321 Performed statistical analysis: CR, SR. Searched literature: IC. Grafted the manuscript: FMdB,

322 IC. Critical reviewing of the manuscript: CA, CR, SR. Revised and approved the final version of

323 the text: All authors.

324

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