# Respiratory viruses, such as 2009 H1N1 influenza virus, could trigger temporal trends in serotypes causing pneumococcal disease

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## Abstract

In order to determine if the novel influenza *A(H1N1)pdm09* was associated with temporal trends of main serotypes causing invasive pneumococcal disease (IPD), we studied 384 episodes of IPD in <18-year-old patients from 2007 to 2012. The number of IPD episodes diagnosed during the 2009 pandemic period meant almost one-third of all the episodes diagnosed in the five included influenza periods (51/156). The number of IPD episodes diagnosed during the 2009 pandemic period meant almost one-third of all the episodes diagnosed in the five included influenza periods. Most of them occurred in <5-year-old children. Serotype 1 was the main serotype detected over the period, except for the 2009 pandemic, when it practically disappeared. Seasonality and viral infections could trigger temporal trends of serotypes causing IPD.

**Keywords:** Influenza, pneumococcal disease, respiratory virus, serotypes, *Streptococcus pneumoniae*

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Concomitant detection of respiratory viruses occurs often among children <5 years old with invasive pneumococcal disease (IPD) [1]. Previous epidemiological studies have also reported a seasonal association of the epidemic peaks of both respiratory viral infection and pneumococcal pneumonia [2,3]. The effect of viral infection as facilitator of IPD could be different according to the attack rate of serotypes [1]. Some of these pneumococcal serotypes have low invasive capacity and are frequently detected in carriers. In contrast, there are serotypes with high invasive capacity that are seldom detected in carriers but often cause IPD [4,5].

The main serotypes causing IPD have changed over time. Serotypes 1 and 19A had been considered as emerging serotypes during the past years in our setting [6,7]. The 2009 pandemics offered the opportunity to analyse whether a high penetration of a respiratory virus traditionally associated with IPD [3,8] could have some effects on the distribution of serotypes causing IPD.

This study included all patients <18 years old with IPD who attended a tertiary care paediatric hospital, from week 40 of 2007 to week 39 of 2012. A detailed description of our institution and the geographical area has been reported elsewhere [6]. Demographic and clinical variables were prospectively collected. IPD was defined as the presence of clinical findings of infection together with isolation of *S. pneumoniae* and/or DNA detection of the pneumolysin gene and an additional capsular gene, the *wzg (CpsA)*, by real-time polymerase chain reaction (PCR) in any sterile fluid. All pneumococcal isolates were identified by standard microbiological methods. Serotyping of strains isolated by culture was carried out by the Quellung reaction at the National Center for Microbiology (Majadahonda, Madrid). Detection of pneumococcal serotypes in negative culture clinical samples was performed at our laboratory, according to a published Multiplex real-time PCR methodology [1]. Serotypes were classified as serotypes with high invasive capacity (1, 4, 5, 7F, 9V, 14, 18C and 19A) and with low invasive capacity (all others) according to the classification of Brueggemann and Sleeman [4,5].

Data from the Microbiological Catalan Notification System [9] was used in order to define the beginning of each influenza epidemic period, defined as a 3-month period (influenza quarter). The week of the beginning of the influenza quarter was considered to be the one when the rate of influenza-like illness was ≥100/100.000 inhabitants.

The study was approved by the institutional ethics committee and written informed consent was obtained from all included patients.

We report 384 episodes of IPD, among 381 patients. Two hundred and seven (53.9%) of the episodes occurred in male

patients. The median age was 36.2 months (IQR, 20.1–59.5); 122 (31.8%) were <2 years old, 169 (44.0%) were 2–5 years old and 93 (24.2%) were ≥5 years old. Pneumonia was the main clinical manifestation (308, 80.1%), followed by meningitis (37, 9.6%) and bacteraemia/sepsis (35, 9.1%). One hundred (66.7%) of the pneumonias were complicated pneumonia cases (mainly with empyema). Data on pneumococcal conjugated vaccination was available for 377 patients, of whom 122 (32.4%) were correctly vaccinated for age with PCV7, 32 (8.4%) with PCV10 and 31 (8.1%) with PCV13. Of 384 cases, 117 (30.4%) were diagnosed by culture and the remaining by real-time PCR.

Figure 1 shows the evolution of episodes of IPD during the study period. One hundred and fifty-six (40.6%) episodes of IPD occurred within influenza quarters; 51 of them (32.7%), were diagnosed during the 2009 pandemic influenza quarter. Table 1 shows the epidemiological, clinical and microbiological characteristics of IPD according to each influenza season. For the 2009 pandemic influenza quarter, the rate of IPD episodes caused by serotype 1 was significantly lower than in the pre-pandemic influenza outbreaks ($p < 0.01$) and it remained very low during the period that spanned the initiation of the 2009 pandemics to the following influenza season. For the first post-pandemic season (2010–2011), when the *A(H1N1)pdm09* was also the main transmitted influenza subtype, the rate of IPD episodes caused by serotype 1 was again similar to the two pre-pandemic influenza seasons (25.6% vs. 23.9%, p 0.87).

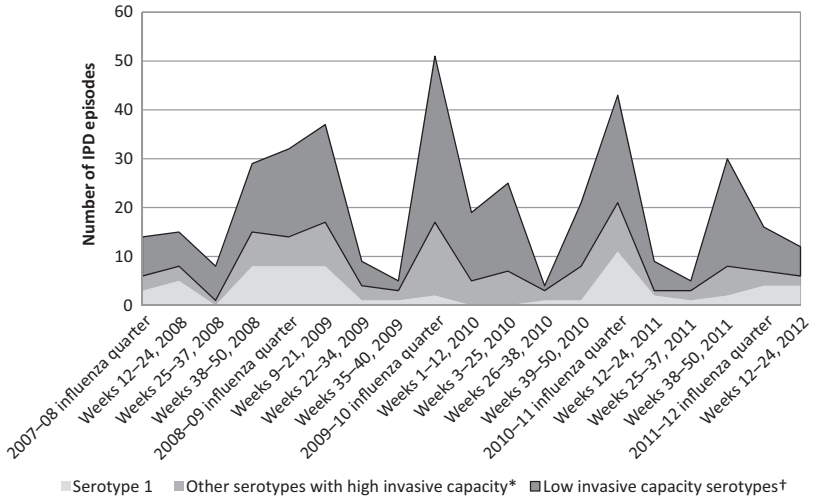


**FIG. 1.** Serotype distribution in children with invasive pneumococcal disease (IPD) admitted to Hospital Sant Joan de Déu (Barcelona) in the 2007–2008 to 2011–2012 influenza seasons. *Serotypes 4, 5, 7F, 9V, 14, 18C and 19A. †All other serotypes.

**TABLE 1. Epidemiological, clinical and microbiological characteristics of IPD in children diagnosed during the influenza epidemic periods[a]**

| | The pre-pandemic (2007–08 and 2008–09) seasons | The pandemic (2009–10) season | The post-pandemic (2010–11 and 2011–12) seasons | The 2009 pandemic vs. Pre-pandemic seasons, p | The 2009 pandemic vs. Post-pandemic seasons, p |
|---|---|---|---|---|---|
| Total IPD episodes | 46 | 51 | 59 | | |
| Age | | | | | |
| 0–2 years | 11 (23.9%) | 17 (33.3%) | 18 (30.5%) | | |
| 2–5 years | 20 (43.5%) | 19 (37.2%) | 27 (45.8%) | | |
| >5 years | 15 (32.6%) | 15 (29.5%) | 14 (23.7%) | | |
| Median age (months) | 41.8 (IQR, 24.7–64.5) | 41.6 (IQR, 16.5–61.8) | 34.4 (IQR: 16.9–59.3) | 0.52 | 0.66 |
| Sex | | | | | |
| Male | 23 (50.0%) | 29 (56.9%) | 32 (54.2%) | 0.50 | 0.78 |
| Female | 23 (50.0%) | 22 (43.1%) | 27 (43.8%) | | |
| Main clinical manifestations | | | | | |
| Non-complicated pneumonia | 10 (21.7%) | 19 (37.2%) | 18 (30.5%) | 0.09 | 0.46 |
| Complicated pneumonia | 28 (60.9%) | 25 (49%) | 30 (50.8%) | 0.24 | 0.85 |
| Meningitis | 7 (15.2%) | 3 (5.8%) | 6 (10.2%) | 0.18 | 0.50 |
| Bacteraemia/sepsis | 1 (2.2%) | 4 (7.8%) | 4 (6.8%) | 0.36 | 1.00 |
| Pneumococcal serotype | | | | | |
| Serotype 1 | 11 (23.9%) | 2 (3.9%) | 15 (25.4%) | **<0.01** | **<0.01** |
| Serotype 19A | 3 (6.5%) | 8 (15.7%) | 7 (11.9%) | 0.15 | 0.56 |
| High invasive capacity serotypes[b] | 6 (13.0%) | 7 (13.7%) | 6 (10.2%) | 0.93 | 0.59 |
| Low invasive capacity serotypes | 26 (56.6%) | 34 (66.6%) | 31 (52.5%) | 0.30 | 0.13 |
| Seasonality | Winter | Autumn | Winter | | |

Statistically significant values are marked in bold.
[a]Main circulating influenza viruses were: pre-pandemic A (H1N1) and B viruses for 2007–2008 and 2008–2009 seasons, the A (H1N1) pdm09 for 2009–2010 and 2010–2011 seasons, and A (H3N2) viruses for the 2011–2012 season.
[b]Other serotypes with high invasive capacity: 4, 5, 7F, 9V, 14 and 18C.