Serotype replacement following the introduction of the PCV7 in the UK - Impact on the characteristics of pneumococci causing meningitis

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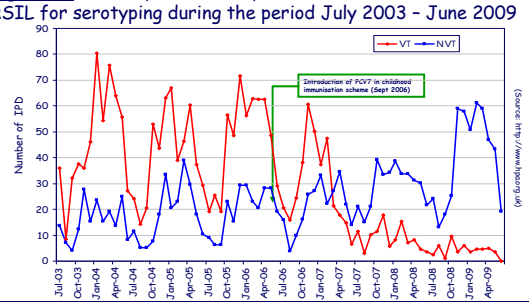
Introduction

In September 2006, the 7-valent Pneumococcal Conjugate Vaccine (PCV7) was introduced in the UK childhood immunisation scheme. The Health Protection Agency (HPA) has developed a surveillance programme to assess the impact of PCV7 on invasive pneumococcal diseases (IPD) and on the characteristics of pneumococci causing paediatric IPD (children <5Y) in England and Wales. The HPA has reported **(Figure 1)** that the number of IPD cases due to any of the 7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) included in PCV7 has decreased, from 70% of the total paediatric invasive isolates in epidemiological year (EY: July to June) 2005/06 to only 10% in EY 2008/09. The number of cases of IPD attributed to serotypes not included in the PCV7 (NVT) has significantly increased: in EY 08/09, the top 10 serotypes were (by decreasing order) 7F, 19A, 1, 3, 22F, 33F, 6A, 15C, 19F and 8.

Figure 1 monthly number of paediatric IPD isolates referred to RSIL for serotyping during the period July 2003 – June 2009



Methods

Multi Locus Sequence Typing method was performed on all paediatric (children age less than 5 years) IPD isolates referred to the Respiratory and Systemic Infection Laboratory (RSIL) from July 2004 to June 2009. From 2175 invasive isolates – RSIL receives annually almost 80% of all pneumococcal isolates from reported paediatric IPD in England and Wales – complete MLST allelic profile was obtained for 2169 isolates. A total of 362 Sequence Types (ST) have been identified. Genetic analyses using eBURST algorithm predicted the presence of 105 distinct lineages within this pneumococcal population.

Results

Longitudinal study of the population genetic structure revealed that, so far, serotype replacement is mainly due to the expansion of STs that were present in the pre-PCV7 period (**Figure 2**). In EY 2008/09, amongst 306 NVT paediatric IPD isolates, 78 STs have been identified. Eight of them were emerging ST (STs never detected in the past). ST191 (7F), ST306 (1), ST199 (19A) and ST180 (3) were the most prevalent clones accounting for more than 40% of the total number of IPD cases. Interestingly, the first two prevalent clones associated with paediatric IPD were, so far, rarely found in pneumococcal carriage. It has been reported that PCV7 may reduce the prevalence of VT in pneumococcal carriage (Millar *et al.* Clin Infect Dis. 2006. **43**: 8-15) freeing the nasopharyngeal niche and therefore enhancing colonization and invasion by NVT pneumococci.

Figure 2 Distribution of sequence types from invasive isolates referred to RSIL for serotyping, in children < 5 years, by epidemiological year (July to June) since July 2004 to June 2009

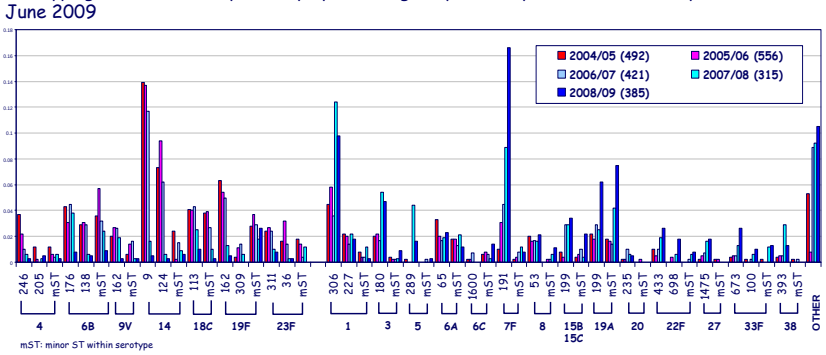


Figure 3 Number of paediatric (<5 years) pneumococcal meningitis by epidemiological year

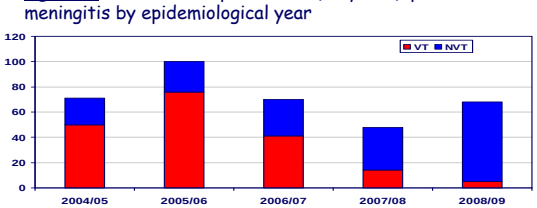


Figure 4 Distribution of the most prevalent sequence types from paediatric pneumococcal meningitis isolates, by epidemiological year (July to June) since July 2004 – June 2009

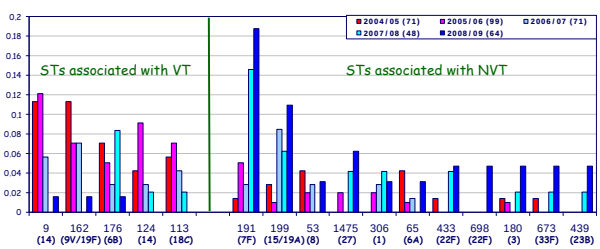
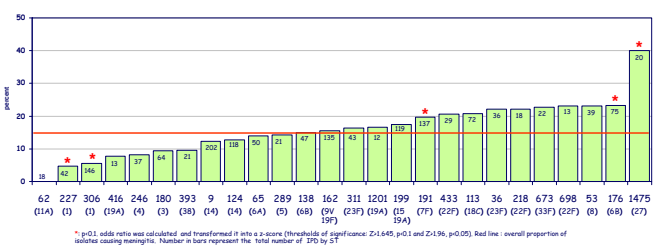


Figure 5 proportion of pneumococci causing paediatric meningitis by ST



*: p<0.1, odds ratio was calculated and transformed it into a z-score (thresholds of significance: Z>1.645, p<0.1 and Z>1.96, p<0.05). Red line : overall proportion of isolates causing meningitis. Number in bars represent the total number of IPD by ST

PCV7 and Meningitis:

The proportion of isolates causing paediatric meningitis referred to the HPA for serotyping (including isolates from declared meningitis or culture positive CSF) has not changed significantly (around 15% of total IPD per annum during the 5-years period 2004/05 – 2008/09). However since the introduction of the vaccine, rapid serotype replacement has occurred. NVTs represented in 2004/05 and 2005/06 respectively 28% and 24% (**Figure 3**) versus 93% in 2008/09.

A total of 210 STs were associated with paediatric meningitis. In 2008/09, ST191 and ST199 were the major STs associated with pneumococcal meningitis (**Figure 4**). The Ability of STs to cause meningitis was estimated by calculating odds ratio (**Figure 5**). Three clones presented an increased probability of causing meningitis, one is associated with VT (ST176 - 6B), and two with NVT (ST191 - 7F and ST1475 - 27). Other clones, associated with NVT, such as ST53 (8), ST433 (22F), ST673 (33F) and ST698 (22F) tend to have higher proportion of isolates causing meningitis. With regard to the recent serotype replacement, these results suggest that the number of paediatric meningitis cases may increase during the next few years.

Interestingly, ST306 and ST 227 (serotype 1) were rarely identified as a cause of meningitis. Serotype 1 pneumococci are commonly associated with severe pneumonia (Obando *et al.* Pediatr. Infect. Dis. J. 2006 **25**:962-963)

Conclusion

The success of PCV7 has been compromised to some extent by rapid serotype replacement. The introduction of the 10-valent PCV (PCV7 +1, 5, 7F) or the 13-valent PCV (PCV10+3, 6A, 19A) - which would have prevented in EY 08/09 respectively 31% and 54% of IPD and respectively 23% and 43% of meningitis cases -, may be similarly compromised by expansion of other serotypes (e.g. 22F, 33F) which are already featuring in the top 10 of paediatric IPD serotypes.

Acknowledgments:
- Funding: Meningitis Research Foundation and Health Protection Agency
- Statistical analyses: Dr Anne Segonds-Pichon, Bioinformatics Department, Babraham Institute, Cambridge