Vaccine xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Trends in serotypes and sequence types among cases of invasive pneumococcal disease in Scotland, 1999–2010☆

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ARTICLE INFO

Article history:
Received 1 March 2013
Received in revised form 22 April 2013
Accepted 20 May 2013
Available online xxx

Keywords:
Invasive pneumococcal disease
PCV7
Serotype
Sequence type

ABSTRACT

Introduction: The 7-valent pneumococcal conjugate vaccine (Prevenar®, Wyeth; PCV7) was introduced to the UK paediatric immunisation schedule in 2006. This study investigates trends in serotypes and multi locus sequence types (STs) among cases of invasive pneumococcal disease (IPD) in Scotland prior to, and following, the introduction of PCV7.
Methods: Scottish Invasive Pneumococcal Disease Enhanced Surveillance has records of all cases of IPD in Scotland since 1999. Cases diagnosed from blood or cerebrospinal fluid isolates until 2010 were analysed. Logistic and poisson regression modelling was used to assess trends prior to and following the introduction of PCV7.
Results: Prior to PCV7 use, on average 650 cases of IPD were reported each year; 12% occurred in those aged <5 years and 35% affected those aged over 65 years. Serotypes in PCV7 represented 47% of cases (68% in <5 year olds). The serotype and ST distribution was relatively stable with only serotype 1 and associated ST 306 showing an increasing trend. PCV7 introduction was associated with a 69% (95% CI: 50%, 80%) reduction in the incidence of IPD among those aged <5 years, a 57% (95% CI: 47%, 66%) reduction among those aged 5–64 years but no significant change among those aged 65 years and over where increases in non-PCV7 serotypes were observed. Serotypes which became more prevalent post-PCV7 are those which were associated with STs related to the PCV7 serotypes.
Conclusions: Routine serotyping and sequence typing in Scotland allowed the assessment of the relationship between the capsule and the clones in the post vaccination era. Changes in the distribution of serotypes post PCV7 introduction appear to be driven by associations between serotypes and STs prior to PCV7 introduction. This has implications for the possible effects of the introduction of higher valency vaccines and could aid in predicting replacement serotypes in IPD.

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http://dx.doi.org/10.1016/j.vaccine.2013.05.079

1. Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is responsible for a substantial burden of disease, accountable for approximately 1.6 million deaths annually worldwide [1]. In developed countries, the incidence of invasive pneumococcal disease (IPD) is between 8 and 75 cases per 100,000 individuals [2], with studies showing that most IPD is attributable to only 20–30 of the 94 pneumococcal serotypes [3].

Recent studies of serotypes involved in IPD compare pre- and post-vaccination periods to examine changes in serotype distribution potentially due to the use of the 7-valent pneumococcal conjugate vaccine (PCV7). The USA, and other countries subsequently, showed great reductions in IPD not limited to vaccine targeted groups [4]. However, increases in IPD caused by non-PCV7 serotypes, in particular 19A, following PCV7 use have been documented [4–10].

The pneumococcal capsule is thought to be the main determinant of carriage prevalence and invasiveness and hence the determinant of prevalence amongst disease isolates [11,12]. However, it has been speculated that increases in serotype 19A IPD in particular are perhaps attributable to a capsular switch event after being found associated with a sequence type (ST), ST695, previously only linked with vaccine serotype 4 [13,14]. Other studies have documented increases due to the expansion of multi-drug resistant STs such as ST276 and ST320 [15,16]. Thus, it is increasingly important to examine both STs and serotypes involved in IPD to determine the potential effectiveness of serotype-specific pneumococcal vaccinations.

In September 2006, PCV7 was introduced to the National Health Service childhood immunisation schedule in the UK in a three dose programme at age 2, 4, and 13 months, with a catch-up for those aged up to 2 years. In 2010, 94% of the targeted group had received three doses of PCV7 [17].

This study examines trends in serotype and ST distributions prior to PCV7 use in Scotland, adding to existing reports on the pre-vaccine period in Scotland [18,19]; the effect of PCV7 on IPD incidence; trends in serotype and ST distribution post-vaccination; and the association between serotype and ST pre- and post-vaccination.

2. Methods

2.1. Data

The Scottish Invasive Pneumococcal Disease Enhanced Surveillance (SPIDER) database contains all cases of IPD, identified by blood or cerebrospinal fluid, in Scotland from 1999–2010. The serogroup responsible for each case of disease was available for all years; serotype and ST information was available from 2002.

Clinical isolates (from blood or cerebrospinal fluid) of *S. pneumoniae* were sent to the Scottish Haemophilus, Legionella, Meningococcus and Pneumococcus Reference Laboratory (SHLMPRL) after identification at diagnostic microbiology laboratories. These were grown on Columbia blood agar (Oxoid, UK) at 37 °C under anaerobic conditions using an anaerobic pack (Oxoid, UK) and after a single subculture were stored at −80 °C on Protect beads (M-Tech Diagnostics, UK). Isolates were serotyped by a coagglutination method [20]. Multi-locus sequence typing was performed as described previously [21–23].

Epidemiological years from winter of one year to the end of autumn of the next were used ensuring winter seasons were grouped together since IPD predominantly occurs in winter.

Serotypes and STs were classified according to their joint occurrence prior to PCV7 use (1999–2005) and emergence post-PCV7 (2006–2010). STs were classified as associated with PCV7 serotypes if they occurred at least once in conjunction with a PCV7 serotype (labelled PCV7-ST); otherwise they were classified as not associated (NonPCV7-ST). STs which only occurred following PCV7 use were classified as PostPCV7-ST. The PCV7-ST group was subdivided into two groups: one with12 STs (9, 36, 113, 124, 138, 156, 162, 176, 205, 206, 246, 311) with a high frequency of co-occurrence with the PCV7 serotypes (labelled HF PCV7-ST), and a larger group with low frequency co-occurrence (LF PCV7-ST). Serotypes were categorised in four groups: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F); serotypes not in PCV7 but associated with STs linked through co-occurrence to PCV7 serotypes (PCV7-ST serotypes); serotypes not in PCV7 and not associated with STs linked to PCV7 serotypes (NonPCV7-ST serotypes); serotypes which only occurred post-PCV7 vaccination (PostPCV7 serotypes).

2.2. Statistical analysis

Logistic regression models were used to test whether or not there was evidence of a linear trend in the pre-PCV7 (1999/00–2005/06) serogroup, serotype and ST distributions. Serogroups, serotypes and STs responsible for ≥1% of IPD were considered. Analyses were conducted for the serogroups for age groups 0–4, 5–64, and ≥65 years separately. Bonferroni adjusted confidence intervals were calculated and the Benjamini and Hochberg adjustment for multiple testing used in determining the significance of the trend [24]. The Benjamini and Hochberg adjustment was used since no particular hypothesis about which serotypes or STs would have a trend was specified. As >20 serotypes and STs were examined, the standard 5% level would be more likely to report significant trends for one serotype or ST even if no trend was present.

Poisson regression models were used to assess changes in IPD incidence. The percentage change in the incidence of PCV7 serotypes and NonPCV7 serotypes from the pre-vaccine to the post-vaccine period was assessed by predicting post-vaccination incidence, allowing for a trend in the pre-vaccination years, and comparing the observed cases with the predicted as suggested elsewhere [25,26]; 95% confidence intervals were used. Cases with missing age (27, 0.4%) were omitted. For 637 cases (10.1%), no information on the serogroup was available. The number of vaccine type (VT) or non-vaccine type (NVT) serotypes was imputed, separately by year and age group, using observed proportions of VT serotypes. Imputation of serotype, from serogroup, was carried out when serotype information was not available based on observed proportions of serotypes within serogroups from 2002–2006, separately by age group. All analysis was conducted using R versions 2.8–2.12 [27].

3. Results

3.1. Trends in serotype and ST distributions prior to PCV7

From 1999/00–2005/06, on average 650 IPD cases per year were reported in Scotland, rising from 538 in 1999/00 to 743 in 2002/03. A subsequent drop occurred, primarily amongst those aged ≥65 years, following the introduction of the 23-valent pneumococcal polysaccharide vaccine (PPV23) for this age group in 2003, with a coverage of ∼74%. The number increased to 739 in 2005/06. IPD was most common amongst the elderly (44% of all cases). 12% of cases affected those aged <5 years.

3.2. Serogroup analysis

Thirty-six different serogroups were identified in IPD from 1999/00–2005/06. Serogroup 14 was most common, accounting

Please cite this article in press as: Lamb KE, et al. Trends in serotypes and sequence types among cases of invasive pneumococcal disease in Scotland, 1999–2010. Vaccine (2013), http://dx.doi.org/10.1016/j.vaccine.2013.05.079