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Non-invasive pneumococcal serotypes and antimicrobial susceptibilities in a paediatric hospital in the era of conjugate vaccines

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ABSTRACT

To evaluate the effects of 7-valent pneumococcal conjugate vaccine (PCV7) introduction to the routine childhood immunisation schedule in 2008 and its replacement by PCV13 in 2010 in Ireland, we surveyed the serotypes and antimicrobial susceptibilities of 339 pneumococci associated with carriage and non-invasive infection (NII) in a Dublin paediatric hospital from 2009 to 2012. Furthermore, we compared the distribution of pneumococcal serotypes collected from 2009 to 2012 to 105 NII pneumococci isolated in 2007, the year before conjugate vaccine introduction. PCV7 serotypes declined from 2007 to 2012 as follows: carriage, 67–23% ($p = 0.0004$); conjunctivitis, 58–0% ($p < 0.0001$); non-bacteraemic lower respiratory tract infection, 50–19% ($p = 0.0363$) and otitis media 54–27%. Notably, antimicrobial resistant (AMR) PCV7 serotypes showed a significant decrease by the end of the study period (i.e. 2012) ($p < 0.0001$). Compared with 2007 the overall occurrence of serotype 19A increased from 1.9 to 10% in 2010 ($p = 0.0132$) and to 15% in 2011 ($p = 0.0005$). Importantly, serotype 19A declined significantly from 2011 levels to an overall prevalence of 4.8% in 2012 ($p = 0.0243$). Most striking was the significant reduction of AMR 19A ($p = 0.0195$). Conversely, increases were observed in non-vaccine type (NVT) pneumococci in 2009–2012, of which serotypes 11A ($n = 30$), 15B/C ($n = 17$), 22F ($n = 14$), 35B$n = 13$), non-typeable pneumococci ($n = 13$) and 23A ($n = 12$) were the most prevalent. Moreover, an increase in NVT non-susceptible to at least one antimicrobial in 2009–2012 was noted, attributable to serotypes 35B ($n = 10$) and 15A ($n = 7$). In summary, this study has shown that PCV7 and PCV13 introduction has had a positive impact on their target serotypes and antimicrobial resistance amongst pneumococci within a paediatric hospital within a short time period. However, the increase in NVT prevalence highlights the need for continued surveillance.

1. Introduction

Streptococcus pneumoniae (pneumococcus) is an encapsulated organism with 94 capsular types (serotypes) [1]. Non-capsulated pneumococci are considered non-typeable (NT). The organism is a significant cause of invasive infections such as meningitis and bloodstream infection (BSI). Annually, over 1.6 million people are estimated to die of pneumococcal infections [2]. Additionally, pneumococci cause less serious infections including otitis media (OM), acute conjunctivitis and non-BSI lower respiratory tract infection (nbLRTI). Such non-invasive infections (NII) represent increased costs for health systems and result in significant patient morbidity.

Pneumococci may be carried asymptomatically in the upper respiratory tract of the paediatric population and carriage is

Abbreviations: NT, non-typeable; BSI, bloodstream infection; OM, otitis media; nbLRTI, non-BSI lower respiratory tract infection; NII, non-invasive infection; PCV7, 7-valent pneumococcal conjugate vaccine; AMR, antimicrobial resistant; NVT, non-vaccine type pneumococci; PCV13, 13 valent pneumococcal conjugate vaccine; CLSI, Clinical Laboratory Standards Institute; MDR, multi-drug resistant; CC, clonal complex.

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considered a pre-requisite for infection [3]. Moreover, common colonising pneumococcal serotypes frequently cause invasive infections and NII [4].

The 7-valent pneumococcal conjugate vaccine targets pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F which has reduced carriage of and infection caused by these serotypes through a direct effect at individual level or through 'herd immunity' [3,5–7]. A further benefit of PCV7 has been the reduction of antimicrobial resistant (AMR) PCV7 serotypes [8]. However, an increase in non-PCV7 serotypes has been reported after PCV7 introduction [5–7]. PCV13 targets the serotypes contained in PCV7 plus serotypes 1, 3, 5, 6A, 7F and 19A, and has replaced PCV7 in routine childhood immunisation schedules in many countries [9].

PCV7 was introduced in Ireland in 2008 with a catch-up campaign targeting children born from 2006. This vaccine was recommended for high-risk groups since 2002. Data on the uptake rate of PCV7 in this latter population is unavailable. PCV13 replaced PCV7 in December 2010. The vaccines are administered to infants at 2, 6 and 12 months [10]. Irish data for quarter four 2012, estimates that 92% of children aged 24 months had received three doses of PCV [11]. It was hoped that PCV13 would reduce carriage and infection caused by these additional serotypes some of which were reported to have increased following PCV7 introduction [5–7]. Furthermore, it was anticipated that PCV13 would augment the positive effects of PCV7 on AMR, particularly through the eradication of 19A, an important source of resistance among pneumococci [5,7,12]. Unfortunately, the positive effects of conjugate vaccines may be offset by increased non-vaccine type (NVT) pneumococci, i.e. non-vaccine serotypes replacement [12].

It has been demonstrated that different pneumococcal serotypes have varying propensity to cause different infections or to be asymptomatically carried, i.e. colonisation [4]. On-going surveillance is crucial given this variation and particularly in the era of conjugate vaccines to detect the early emergence of possible replacement serotypes. Data on pneumococcal serotypes associated with invasive disease in Ireland has been available for several years [13–15]. However, given the impact that other pneumococcal infections have on health and the link between carriage and disease, surveillance of carriage isolates and isolates causing NII is fundamental.

Following introduction of PCV7 and PCV13 we surveyed pneumococcal serotypes and antimicrobial susceptibilities from carriage and NII in an Irish paediatric hospital. Additionally, we compared trends in serotype distribution and antimicrobial resistance between isolates collected after PCV introduction to isolates collected the year prior to the introduction of PCV7.

2. Materials and methods

2.1. Isolate collection and storage

The study was performed in Temple Street Children's University Hospital, an acute paediatric hospital in Dublin. The 131-bed hospital provides primary and secondary care to the surrounding area, with national tertiary referral services. From January 2007 to December 2007 and January 2009 to December 2012, pneumococcal isolates from carriage sites and isolates recovered from specimens used to diagnose non-invasive infections were collected. Carriage isolates were from nasopharyngeal swabs and aspirates, nasal specimens and throat swabs. The majority of nasal specimens were part of pre-operative screens taken before upper airway surgery (e.g. cleft palate repair) to guide antibiotic prophylaxis. Pneumococci were screened for in nasal/nasopharyngeal specimens using 5% sheep's blood with overnight incubation at 37 °C (5% CO_2) in the presence of an optochin disc. Pneumococci from throat specimens were considered carriage [16]. The NII included conjunctivitis, non-bloodstream infection lower respiratory tract infection (nbLRTI) and otitis media (OM). Conjunctivitis specimens were obtained from conjunctiva swabs. nbLRTI specimens included bronchial alveolar lavages, endotracheal aspirates and sputum. OM specimens were from spontaneous ontological drainage. The child's gender and age were recorded but PCV7/13 vaccination status and prior antibiotic use was unknown. Ethical approval was obtained from the ethics committee at Temple Street Children's University Hospital. Collected pneumococci were stored in 1:3 glycerol (nutrient broth containing 0.5% glucose and 10% glycerol) horse serum storage medium at −70 °C.

2.2. Serotyping

Pneumococci retrieved from storage from 2007 and 2009–2012 were cultured overnight at 37 °C (5% CO_2) and were serotyped by PCR as previously described [17]. The standard capsular reaction test using the chessboard system using antiserum from the Statens Serum Institut (Copenhagen, Denmark) was used to confirm the PCR result or to identify serotypes not detected by PCR. Two different pneumococcal colonies were selected separately for PCR. Additionally, any morphologically distinct colonies were picked separately for capsular reaction to determine if multiple serotypes were present in the same clinical specimen. Serotypes 15B and 15C were classified as 15B/C as inter-conversion can occur between these serotypes [18]. Isolates typed as serotypes 6A, 6B by slide co-agglutination were subject to additional PCR [19,20] to confirm the slide co-agglutination result. These PCRs also detects serotype 6C and 6D.

2.3. Antimicrobial susceptibility testing

Isolates were tested for susceptibility to penicillin, cefotaxime, tetracycline, erythromycin, clindamycin and levofloxacin using the Etest method (BioMerieux). Susceptibility was interpreted using Clinical Laboratory Standards Institute (CLSI) guidelines [21]. Oral penicillin and the non-meningitis interpretative breakpoints were used to define isolate susceptibility to penicillin and cefotaxime, respectively. Isolates were considered antimicrobial resistant (AMR) if they were non-susceptible to at least one of the antimicrobials and included isolates with intermediate susceptibility. Multi-drug resistant isolates (MDR) were defined as resistant to three antimicrobials or more, excluding isolates with intermediate susceptibility.

2.4. Statistical analysis

Proportions were compared using the two tailed Fishers exact test using the GraphPad QuickCalcs website http://www.graphpad.com/quickcalcs/contingency1/ (accessed February 2014). A p-value of less than 0.05 was considered significant.

3. Results

3.1. Rate of isolation and patient characteristics 2009–2012

From January 2009 to December 2012, 339 pneumococci from 336 children (mean age 39 months) were isolated from carriage sites and NII. Three different children had two different pneumococcal serotypes isolated at the same time from a carriage site (serotypes 3 and 18C), conjunctivitis (serotypes 11A and 16F) and nbLRTI (serotypes 6B and 19F). The number of isolates collected from each anatomical site from 2009, 2010, 2011 and 2012 respectively was as follows: carriage, $n = 18$, $n = 48$, $n = 39$, $n = 30$; conjunctivitis, $n = 10$, $n = 30$, $n = 23$, $n = 21$; nbLRTI, $n = 12$, $n = 28$,