The potential impact of the 13-valent conjugate pneumococcal vaccine on antibiotic resistance in pneumococci

S Nzenze, K Klugman, S Madhi

Introduction

Streptococcus pneumoniae strains associated with antibiotic non-susceptibility have spread globally since their first description in the late 1960s.1 Although a number of antibiotic non-susceptible clones of S. pneumoniae (ANSP) have been identified, international clones with high-level penicillin non-susceptibility (PNSP) have predominantly been limited to a few of the 93 different pneumococcal serotypes.2,3 In particular, PNSP and other ANSP strains of S. pneumoniae, prior to the era of pneumococcal conjugate vaccines (PCVs), have been associated with serotypes that commonly colonise the nasopharynx of young children. These include serotypes 6A, 6B, 9V, 14, 18C, 19A, 19F and 23F.4,7 Examples thereof include recent data from South Asia where, with pre-introduction of PCV, more than 90% of invasive pneumococcal isolates were associated with penicillin resistance, and 50% with high resistance to third-generation cephalosporins.5 The serotype distributions of PNSP included 6B, 14, 19F and 23F.6 Among 10 Latin American countries, there was a 38% overall prevalence of penicillin non-susceptibility among pneumococcal isolates. The highest penicillin resistance was recorded in the Dominican Republic and Mexico, with increasing resistance being observed in Colombia and Brazil.8 Up to 80% of PNSP in Brazil was also associated with serotypes 6A, 6B, 14, 19A, 19F and 23F.7

However, there is geographic variability in the epidemiology of serotypes associated with antibiotic non-susceptibility, even in the absence of PCV. An example of this includes the identification of antibiotic-resistant strains prevailing as serotypes not included in either a 7-valent (PCV7) or 13-valent (PCV13) formulation. Among these are reports by Porat et al from Israel, in which penicillin non-susceptible strains from middle-ear fluid pneumococcal isolates have been identified with serotypes 15B/C, 21, 33F and 35B.10 Antibiotic-resistant clones of pneumococci usually evolve as a single serotype, these clones may subsequently become encapsulated as another serotype.5,11,12
a specific antibiotic-resistant clone of pneumococcus.12,13 The factors associated with evolution of antibiotic resistance in pneumococci, mechanisms by which isolates acquire resistance, and the global distribution of resistant strains, were recently reviewed.14

Another major contributor to the emergence of antibiotic resistance among pneumococci involves pressure of antibiotic exposure.15,16 This includes suboptimal antibiotic use of certain classes of antibiotics, and the emergence of ANSP clones.17,18 Dagan et al recently reported an increase in serotype 19A from acute otitis media cases in Israel, in the absence of immunisation with PCV, which was due to the emergence and expansion of two new, multidrug-resistant clones. This was temporarily associated with the increased use of azithromycin, and frequent use of oral cephalosporins.19 The association of macrolide and azalide use with antibiotic susceptibility to S. pneumoniae isolated from children is also evident in other studies, including one in Ethiopia, where use of azithromycin, for the treatment of trachoma, increased the prevalence of resistance to azithromycin from 6.3% to 62.3% within one year.20 Similarly, a study of Greek children attending day-care centres in the presence of widespread PCV7 immunisation, reported on the dissemination of erythromycin-resistant and multidrug-resistant pneumococci associated with nasopharyngeal colonisation. Erythromycin and multidrug resistance were also significantly associated with exposure to macrolides in the previous three months, 90% of which involved clarithromycin and selected cephalosporins.21,22

Elsewhere, the use of cotrimoxazole prophylaxis in human immunodeficiency virus (HIV)-infected individuals has also contributed to the emergence of cotrimoxazole-resistant strains, as well as resistance implicating other antibiotic classes.23,24 Although cotrimoxazole prophylaxis has been associated with a modest reduction (7%) in the prevalence of pneumococcal nasopharyngeal colonisation, the risk of colonisation with cotrimoxazole-resistant pneumococci increased within six weeks of commencing prophylaxis (RR: 3.2, 1.3-7.8, p-value = 0.04).25 In addition, infants receiving cotrimoxazole prophylaxis also had an increased risk of colonisation with clindamycin-non-susceptible pneumococci (RR: 1.6, 1.0-2.6, p-value = 0.04), although the prevalence of non-susceptibility to other antibiotic classes remained unchanged.25

Further evidence of antibiotic use being associated with emergence of antibiotic resistance is the observation that the prevalence of PNSP has decreased in some countries following rationalisation of antibiotic use.26 However, this strategy of rationalising antibiotic use, to contain the emergence and spread of antibiotic-resistant pneumococci, remains challenging to implement in most settings. A much more dramatic and sustained decline in the prevalence of antibiotic-resistant pneumococci associated with colonisation and pneumococcal disease has been observed following the widespread introduction of PCV in many industrialised countries.27-30 In addition, PCV immunisation, in combination with reduced antibiotic exposure, has had an additive effect on reducing the prevalence of colonisation by ANSP.31

A detailed review of the experience of PCV7 in relation to pneumococcal antibiotic resistance was undertaken recently by Dagan and Klugman.9 The action of PCV against invasive and mucosal infections may have a dual effect on reducing the prevalence and incidence of antibiotic-resistant pneumococcal disease. In addition to the direct effect of PCV-targeting serotypes most commonly associated with antibiotic resistance, PCV further contributes in reducing the prevalence of antibiotic non-susceptible strains, by reducing the use of antibiotics. An initial vaccine efficacy trial in the USA reported a reduction of 35 antibiotic prescriptions per 100 fully vaccinated children in the first 3.5 years of life, or 1.4 million antibiotic prescriptions per year.25 This included a 5.4% (CI 4.0-6.7%) reduction in antibiotic prescriptions, as well as a 12.6% (CI 9.6-15.6%) reduction in use of “second-line” antibiotics in PCV recipients.32 In another randomised control study, children who received a 9-valent PCV (PCV9) formulation reported a 17% reduction in antibiotic use.33 The decline in the use of most classes of antibiotics has been even more dramatic in the USA than that observed in vaccine efficacy trials. This included a 41.9% reduction in antibiotic prescriptions for acute otitis media between 1997 (pre-vaccine) and 2004 (post-vaccine).34 Van Effelterre et al also observed a 36% overall reduction in antibiotic use, including a 41% reduction in amoxicillin use, and a 53% reduction in ceftriaxone use, seven years after the introduction of PCV7 in the USA.35

The 7-valent (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) PCV, which also confers cross-protection against serotype 6A, has been highly efficacious and effective in reducing colonisation by these serotypes, as well as subsequently almost eliminating transmission thereof within communities in industrialised settings.36,37 In addition, as PCV7 includes the serotypes commonly associated with ANSP prior to the PCV era, there have been dramatic declines in the incidence of ANSP disease among PCV-vaccinated and unvaccinated individuals in some countries, with widespread PCV7 immunisation coverage.30,38,39 These studies corroborated the findings of an earlier clinical trial from South Africa which reported that a PCV9 reduced invasive pneumococcal disease (IPD) due to PNSP by 67% and cotrimoxazole-resistant strains by 56%, and showed a 56% reduction in IPD from any drug-resistant pneumococci.38 Similarly, in Gambian children, PCV9 recipients at 16 months were less likely to be colonised with isolates resistant to tetracycline and cotrimoxazole (RR: 0.90 and 0.95 respectively, p-value = 0.05).40 A randomised controlled study in day-care attendees also reported that toddlers vaccinated with PCV had a reduced risk of subsequent nasopharyngeal colonisation by antibiotic-resistant strains of pneumococci. In addition, the younger siblings of PCV-vaccinated toddlers were also less likely to be subsequently colonised by antibiotic-resistant strains.41,42 A specific example of the effectiveness of PCV immunisation in reducing ANSP illness comes from the USA, where a decrease...
was observed in the incidence of IPD due to PNSPs by 57% (decrease from 6.3 to 2.7 cases per 100,000) and multi-drug-resistant strains by 59% (decrease from 4.1 to 1.7 cases per 100,000). The study also showed a reduction in ANSP disease in individuals not vaccinated with PCV7, through induction of “herd immunity”. Although the magnitude of decrease in PNSP IPD was greatest in children less than two years of age (81%, 70.3 to 13.1 cases per 100,000), a 49% decline in PNSP IPD was also observed among adults who were 65 years of age and older (16.4 to 8.4 cases per 100,000). However, there was an increase in incidence of IPD caused by the non-vaccine serotype 19A among children under two years (2.0 to 8.3 per 100,000). This increase in serotype 19A IPD was more recently attributable to a primary increase in ANSP strains, while the incidence of IPD from serotype 19A antibiotic-susceptible strains has increased to a lesser extent. However, the initial decline in the prevalence of ANSP associated with the residual burden of IPD three years following the introduction of PCV7 (2001-2004) in the USA has, more recently (2005-2007), been associated with a significant rebound in the prevalence of ANSP. This increase in prevalence of ANSP has involved multiple classes of antibiotics, and in particular, middle-ear isolates in children under five years of age.

Further evidence of the impact of PCV7 immunisation in reducing invasive disease due to antibiotic-resistant strains of pneumococci includes data from Canada. Tyrrell et al reported that in addition to an overall 61% reduction in IPD in Canada following PCV7 introduction, the prevalence of PNSP among invasive isolates decreased, from 14% in 2000, to 4.6% in 2006. In addition, IPD associated with erythromycin non-susceptibility also showed a downward trend, from 8.8% to 5.8%, across the same period. In contrast, in the Canary Islands, the prevalence of erythromycin resistance did not change following PCV introduction, although the prevalence of IPD associated with penicillin non-susceptibility decreased, from 87.3% in the pre-vaccine era, to 13.8% in 2003 (p-value < 0.001). However, by 2006, there was a rebound to 41.7% of IPD in Canary Islands being associated with PNSP, which included an increase in disease due to serotypes 3, 6A, 15 and 19A.

The reduction in vaccine-serotype pneumococcal disease beyond the age group targeted for immunisation resulted from the effectiveness of PCV7 in reducing the colonisation of vaccine serotypes in vaccinated children. Young children are the major source of pneumococcal transmission in industrialised and possibly low-income settings, despite the high prevalence of colonisation in adults from these communities. Therefore, containment of colonisation by antibiotic-resistant serotypes in young children may result in the interruption of transmission, and consequently, lower risk of disease from these serotypes in unvaccinated community members. However, conversely, there has been a parallel increase in colonisation by non-vaccine serotypes in both the vaccinated, and unvaccinated, parts of the population, similar to that observed in initial randomised controlled trials.

Although some non-PCV7 serotypes may be less virulent, less likely to cause IPD, and less often associated with ANSP, these serotypes may subsequently acquire virulence factors associated with disease-causing potential, and encapsulate pneumococcal clones associated with antibiotic resistance. In addition, there have been serotype epidemiological shifts in which antibiotic-resistant clones of pneumococci are being identified. Primary among these in the USA has been an increase in incidence of colonisation and disease due to antibiotic-resistant 19A, against which the inclusion of serotype 19F in PCV7 does not elicit cross-protection. The increase in serotype 19A illness has been evident in vaccinated and unvaccinated individuals, and has been associated with an increase in nasopharyngeal colonisation, acute otitis media, and IPD. Increases in serotype 19A, which was temporally associated with the introduction of PCV7, have also been described elsewhere, such as in Spain and Canada. Consequently, serotype 19A, which was an important serotype associated with nasopharyngeal colonisation and IPD in children during the pre-PCV introduction, has emerged as a major associated with IPD and ANSP following PCV7 immunisation.

The change in epidemiology of serotypes associated with antibiotic-resistant strains of pneumococci may be due to immunological pressure induced by vaccination against select serotypes. However, such changes may also occur in the absence of any vaccine-induced immunological pressure. Examples thereof include an increase in disease associated with serotype 19A antibiotic-resistant strains, which occurred in the absence of PCV introduction in some countries. In addition to immunological pressure, emergence of antibiotic-resistant strains may continue to increase, due to ongoing antibiotic pressure. This has been highlighted by Van Effeltere et al, who reported that an increase in IPD associated with antibiotic-resistant strains of serotype 19A was associated with a temporal increase (180%) in azithromycin use, despite a decrease in use of other classes of antibiotics during that time. Through mathematical modelling, Van Effeltere et al were able to show that antibiotic pressure contributed to a greater extent the increase in serotype 19A disease, rather than the PCV7 immunisation programme. The increase in serotype 19A illness observed in the USA was almost exclusively associated with an increase in serotype 19A ANSP, whereas the incidence of serotype 19A illness associated with penicillin-susceptible strains remained constant. However, the increase in serotype 19A ANSP disease has also been identified as relating to a capsular switch from a PCV7 serotype. Moore et al reported that the initial emergence of ANSP in the USA was predominantly associated with the clonal expansion of an ANSP strain that was previously identified with serotype 4 in the pre-PCV era. More recently, Bruggeman et al reported that the global expansion of ANSP serotype 19A was associated with the capsular switch from serotype 4 in the USA.

The gradual shift in serotype epidemiology associated with ANSP from PCV7 serotypes (65% initially) to non-vaccine
serotypes (63%), although predominantly involving serotype 19A (19%), has also involved increases in other non-PCV7 serotypes. Antimicrobial resistance rates, including multidrug resistance, among non-PCV7 serotypes from respiratory tract isolates increased 25-32% between 2000-2004 in the USA. By 2007, seven years post-PCV7 introduction, 53% of PNSP IPD isolates were serotype 19A.

Serotypes included in PCV13, and not in PCV7, include serotypes 1, 3, 5, 6A, 7F and 19A. In addition, there is 100% immunological cross-reactivity with serotype 6C from inclusion of serotype 6A in PCV13, compared to only 20% immunological cross-reactivity from inclusion of serotype 6B in PCV7.

Serotype 6C, which was recently identified and previously grouped under serotype 6A, has emerged as the main serotype associated with serogroup 6 disease in the USA post-PCV7. There has been 164% increase in serotype-6C illness post-PCV7 introduction in the USA, from 0.22 cases per 100 000 in 1999, to 0.58 cases per 100 000 in 2007. In addition, in 2007, a third of serotype-6C isolates were penicillin non-susceptible.

Reduced antibiotic susceptibility to serotype 6C has also been reported in Brazil, where 18.8% of serotype 6C isolates were non-susceptible to penicillin. However, the impact of PCV 13 on the prevalence of antibiotic-resistant pneumococci and the spectrum of serotypes may vary geographically, in part possibly depending on the prevailing patterns of serotypes associated with nasopharyngeal colonisation and antibiotic resistance prior to the introduction of PCV. Those serotypes that are already associated with antibiotic-resistant clones prior to the introduction of PCV13 are likely to have a selective advantage in becoming the more dominant serotypes associated with antibiotic-resistance post-introduction of PCV13. In Spain, there was a decrease in IPD due to PCV7 serotypes, and an increase in non-vaccine serotypes associated with PNSP. A study of Portuguese children attending day-care centres, while demonstrating a decline in the carriage of antibiotic-resistant pneumococci by PCV7 serotypes, showed a parallel gradual increase in the prevalence of antibiotic resistance of other serotypes (6A, 10A, 15A/C, 19A, 23A, 33F). The overall prevalence of colonisation with ANSP remained the same prior to, and after, the introduction of PCV7 in Portugal.

Pulse-field gel electrophoresis indicated that the ongoing high prevalence of antibiotic-resistant pneumococcal colonisation represented replacement of the original resistant strains by other clonal types of drug-resistant pneumococci. This suggests that “replacement” serotypes associated with antibiotic resistance may be composed of pre-existing, and newly emerging, pneumococcal-resistant strains. The latter is possibly caused by ongoing antibiotic pressure. This could be a reason for the observation in Portuguese children. Further evidence of the likely geographic variability of the impact of PCV against ANSP colonisation and pneumococcal disease was found among Aboriginal children in Australia. Although pneumococcal vaccination was associated with a modest overall decline in colonisation by pneumococci (82% in 2003 vs. 76% post-PCV7 introduction in 2005), the diversity of serotypes associated with ANSP post-PCV7 introduction persisted. The serotypes most commonly associated with penicillin non-susceptibility in the PCV7-era, in descending order, included 19A, 19F, 6B, 16F, 11A, 9V and 23B. In addition, the most common serotypes associated with azithromycin-resistant strains (5% overall) were 23B, 17F, 9N, 6B, 6A, 11A and 23F. Some of these serotypes were already causing significant ANSP disease in the pre-vaccine era. For example, serotypes 19A and 16F accounted for 34% and 7% of PNSP serotypes, respectively, prior to PCV7 introduction, and increased to 38% and 19% of PNSP, respectively, following PCV7 immunisation.

Based on the above, it would appear that the greatest potential of PCV to reduce the prevalence and incidence of antibiotic-resistant pneumococcal colonisation and disease is likely to require a combination of vaccine introduction, and the judicious use of antibiotics. Supporting this is the experience from France, where a national programme for the judicious use of antibiotics was started in 2001, and which was followed by the introduction of PCV7 in 2003. Despite a high prevalence of PNSP (52%) pre-introduction of PCV7 compared to in Portugal (24%), by 2005, there was a rapid decline in the prevalence of PNSP to 38% following the introduction of PCV7 in France, compared to no change in the prevalence of PNSP in Portugal. Results from the study indicated that the prevalence of colonisation with PNSP was greatest (16.2%) in children who had not been vaccinated with PCV7, but who had received antibiotics in past three months, and lowest (4.6%) in children who had received PCV7, and not received any last antibiotics in the last three months.

Based on the comparable immunogenicity of the additional serotypes included in PCV13 to those in PCV7, it is anticipated that the effectiveness of PCV13 against IPD, due to the additional serotypes, may be similar to that observed with PCV7 against the homologous serotypes. Surveillance data for the USA, which introduced PCV7 in 2000, suggest that by the year 2007, there was almost complete elimination of PCV7 serotype disease, and 64% of remaining IPD was caused by the additional non-PCV7 serotypes included in PCV13. In particular, 95% of IPD were now caused by serotypes 3, 7F and 19A.

It is expected that PCV13 vaccination will result in a decrease in colonisation and disease associated with those additional serotypes included in PCV13 which commonly colonise the nasopharynx (e.g. 6A and 19A), and are associated with PNSP. In addition, PCV13 immunisation is also expected to bring about a further reduction in antibiotic use than that observed with PCV7, which itself may positively influence a reduction in the prevalence and emergence of ANSP. However, nasopharyngeal colonisation and pneumococcal disease,
due to non-PCV13 serotypes associated with antibiotic non-susceptibility, are likely to persist in the PCV13 era, and may include the emergence of other single, or multiple, ANSP serotypes. Non-PCV13 serotypes, including serotypes 6C, 15A, 23A and 35B, already account for 40% of PNS isolates in the USA prior to 13 immunisation.57 Bettinger et al, in a study in Canada, also reported an increase in number of ANSP associated with serotype 22F post-PCV7 introduction, which is not included in PCV13.38 Similarly, a diversity of ANSP non-PCV13 serotypes, such as 35B, 33F, 21 and 15B/C, have also been described in Israel prior to PCV introduction.10

In conclusion, PCV13 is likely to bring about further gains in reducing the burden of disease from ANSP. In particular, PCV13 will reduce disease against 19A, emerging as an important ANSP disease-causing pneumococcal serotype following PCV7 immunisation. However, it is unlikely that immunisation with PCV13 will provide comprehensive control of disease from ANSP. This would require a pneumococcal vaccine that targets the prevention of nasopharyngeal colonisation by the vast majority of serotypes with disease-causing potential. The prevention of viral infections, due to respiratory syncytial virus, influenza A/B viruses and other viruses, may contribute in controlling ANSP, by reducing antibiotic usage. Although, the burden of ANSP is likely to be reduced following widespread use of PCV13, empiric treatment of pneumococcal disease may need to continue with selection of antibiotic classes and doses aimed at treating ANSP, as these strains are unlikely to be eliminated completely through PCV vaccination alone.

Declaration

There was no external funding of this project.

SAN: There was no conflict of interest.

SAM and KPK: Speakers’ bureau, have in the past received honoraria, served as part-time consultants and received grant support from GSK and Pfizer.

Ethics approval was not required.

References


