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Factors affecting antimicrobial resistance among colonising *Streptococcus pneumoniae* in rural Alaska villages over 10 years

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Background

Streptococcus pneumoniae (“pneumococcus”) is the most common bacterial pathogen causing otitis media and the major bacterial pathogen for sinusitis, bronchitis and community-acquired pneumonia (1). Meningitis, septicaemia and other sterile site infections caused by pneumococcus are defined as invasive pneumococcal disease (IPD) (1). The reservoir for pneumococci is the nasopharynx of humans (1). There are over 90 different pneumococcal capsular serotypes, which differ in their potential of causing invasive disease, disease severity and likelihood of carriage (2). In 2001, the first pneumococcal conjugate vaccine (PCV7) was included in the US childhood vaccine schedule. Use of PCV7 has decreased the IPD burden and the carriage of PCV7 serotypes, while an increase of non-vaccine serotypes has been seen (3).

Pneumococcal resistance to antimicrobials has increased over time, complicating empiric treatment choices. Factors affecting resistance include antibiotic use and the introduction of pneumococcal conjugate vaccines for children. We studied pneumococcal nasopharyngeal colonization in 4 rural Alaskan villages annually for 10 years to evaluate factors related to antimicrobial resistance.

Methods

Every spring, from 1998–2004 and 2008–2010, nasopharyngeal swabs (NPS) were obtained for pneumococcal culture, serotyping and susceptibility testing from voluntary participants of all ages (n = 1,850). Information on antibiotic use, pneumococcal vaccination status and living conditions was collected. Comparisons were made over time using the Cochran–Armitage trend test.

Results

Over the 10-year study period, 3,908 of 11,330 participants (34.5%) NPS were positive for pneumococcus.

An average of 61% (1,133/1,850) of village residents participated per year. Colonization prevalence among children <5 years varied between 42 and 76%, and between 21 and 46% in the group ≥5 years.

The colonisation rates of pneumococcus decreased over time from 30 to 47% during 1998–2004 to 25–26% during 2008–2010 (all ages). With the exception of serotype 19F isolates (n = 9, 2009; n = 2, 2010), no PCV7 serotypes were observed from 2008 to 2010. The highest prevalence serotypes in 2010 were non-vaccine serotypes 19A, 6C and 35F. The number of 19A carriage isolates increased from 1 (0.35%) in 1998 to 50 (12.5%) in 2010. Serotype 6C increased from 3 (1.7%) in 1998 to 35 (8.8%) in 2010 and serotype 35F increased from 8 (2.8%) in 1998 to 39 (9.8%) in 2010.

The 5 most commonly used antibiotics in these 4 villages in 1998–2010 were amoxicillin (33%), trimethoprim–sulfamethoxazole (tri/sulfa) (16%), azithromycin (11%), penicillin G (8%) and ceftriaxone (6%). The mean number of antibiotic courses used was 1.04 per person (all ages) per 6 months during the respiratory season in 1998, decreasing to 0.34 per person per 6 months in 2010. The mean numbers of antibiotic courses used were 0.81 (persons ≥5 years) and 2.22 (<5 years) per person per 6-month-period during the respiratory season in 1998, decreasing to 0.26 (≥5 years) and 0.87 (<5 years) respectively in 2010.

In 2002, 59% of the children in the 4 villages were up-to-date for their age with PCV7, increasing to 65% in 2003 and 74% in 2004. During the later years, an average

of 83% (2008), 73% (2009) and 80% (ranging from 76 to 100% in the different villages in 2010) of all the children were age-appropriately vaccinated.

Among children <5 years of age, a significant decrease in the number of pneumococcal isolates fully resistant to penicillin was observed ($n = 20$, 26.3% in 1998 to $n = 6$, 5.4% in 2010, $p < 0.0001$), while isolates demonstrating intermediate susceptibility to penicillin increased significantly ($n = 13$, 17% in 1998 to $n = 32$, 28.6% in 2010, $p < 0.0001$). In the age group ≥ 5 years, there was also a significant decrease in isolates fully resistant to penicillin ($n = 23$, 10.9% to $n = 12$, 4.2%, $p < 0.0001$), while a significant increase was observed in intermediate susceptible isolates ($n = 27$, 12.7% to 48, 16.7%, $p = 0.005$).

A significant decreasing trend over time (1998–2010) for pneumococcal isolates non-susceptible to erythromycin was seen in the age group ≥ 5 years ($n = 25$, 11.8% to $n = 24$, 8.4%, $p = 0.002$), while no significant trend could be seen among children <5 years ($p = 0.33$). A decreasing trend over time (1998–2010) was seen for all villages separately, except for in one village (referred to as “village C”), where a significant increasing trend over time is seen ($p < 0.0001$). Another exception was “village A”, where a significant increase of non-susceptible isolates was seen in the years 2004–2010 ($p = 0.007$). This increase was no longer significant when removing the effect of serotype 19A ($p = 0.06$).

With regard to non-susceptibility of pneumococcal carriage isolates to tri/sulfa, a significant decreasing trend over time of pneumococcal isolates was seen both among children <5 years, ($n = 44$, 58% in 1998 to $n = 32$, 28.6% in 2010, $p < 0.0001$) and in the age group ≥ 5 years ($n = 52$, 24.5% to $n = 42$, 14.6% $p < 0.0001$). In village A, a significant increase of non-susceptible ($p < 0.0001$), intermediate susceptible ($p = 0.03$) and resistant isolates ($p < 0.0001$) to tri/sulfa was seen in 2008–2010. When removing the effect of serotype 19A during these years, the increase was no longer significant ($p = 0.06$).

With regard to non-susceptibility to tetracycline, a significant decreasing trend over time (1998–2010) was observed both among children <5 years ($n = 16$, 21% to $n = 8$, 7%, $p = 0.003$), as well as in the age group ≥ 5 years ($n = 18$, 8.5% to $n = 11$, 3.8%, $p = 0.004$).

A significant decreasing trend over time (1998–2010) was observed for non-susceptible isolates to ceftriaxone among children <5 years ($n = 15$, 19.7% to $n = 3$, 2.7%, $p < 0.0001$) and for the age group ≥ 5 years ($n = 19$, 9% to $n = 8$, 2.8%, $p < 0.0001$).

Of the serotype 19A isolates; 93.6% demonstrated intermediate susceptibility and 3.67% demonstrated resistance to penicillin, 24.8% were non-susceptible to erythromycin, 13.3% had intermediate susceptibility against tri/sulfa and 60.6% were fully resistant to tri/sulfa. About 1.83% were non-susceptible to tetracycline, while only 1.38% were non-susceptible to ceftriaxone. The increased frequency and tendency of being resistant to serotype 19A in 2008–2010 was an important factor contributing to increased antibiotic resistance, with a more pronounced effect in some villages.

Conclusions

This study demonstrates that increases in an antimicrobial-resistant strain can quickly reverse an overall trend of decreasing resistance among carriage isolates despite high vaccine coverage and declining antibiotic use in the population. These findings highlight the importance of local surveillance of both carriage and IPD isolates for pneumococcal resistance and serotypes after conjugate vaccine introduction.

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