Impact of 7 - Valent Pneumococcal Conjugate Vaccine on Invasive Pneumococcal Disease in Children in Toronto and Peel Regions, Ontario, Canada

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Abstract

Background: Recent studies have documented an increased relative incidence of non-vaccine serotypes (NVS) of ***Streptococcus pneumoniae*** **(SPN)** causing **invasive pneumococcal disease (IPD)** since the introduction of PCV7, in particular 19A. Little is known about the impact of PCV7 on IPD in Ontario since inclusion in the universal immunization schedule (UIS) in January, 2005.

Methods: SPN IPD isolates from children below 18 years of age from Toronto, Canada, are submitted to The Toronto Invasive Bacterial Diseases Network. 908 isolates submitted before (1995 to 2004) and 80 submitted after (2006 to 2007) introduction of PCV7 were compared for serotype and IPD rates. 838 isolates submitted prior to, and 76 submitted post PCV7 introduction were compared for penicillin (Pen) susceptibility using Clinical Laboratory Standards Institute breakpoints for oral Pen.

Results: The proportion of IPD due to NVS increased from 17% before to 57.5% after PCV7 introduction. IPD rates declined post PCV7 introduction, from 11 to 4.3 per 100,000 children per year. IPD due to VS fell from 8.4 to 1.6 per 100,000 per year, that due to NVS increased from 1.9 to 2.5 per 100,000, and NVS 19A increased from 0.3 to 0.8 per 100,000. Overall, there was no change in Pen nonsusceptibility (NS) or resistance (R). Among NVS 19A isolates, Pen NS fell from 77% to 36% (p=0.013) after PCV7 introduction, with no change in Pen R.

Conclusion: Since the addition of PCV7 to the Ontario UIS in 2005:
1. IPD rates have fallen among children below 18 years of age.
2. IPD rates due to NVS have increased, in particular to serotype 19A, but there has been no increase in Pen NS or R.
3. Ongoing surveillance is needed in Canada to monitor serotype trends in IPD and to assess serotype match of future candidate PCVs with serotypes causing IPD.

Background and Objectives

In 2002, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the routine childhood vaccination schedule in some Canadian provinces and territories, with most including it by 2005.

Recent North American studies have documented an increased relative incidence of pneumococcal disease due to non-vaccine serotypes (NVS) since the introduction of PCV7, in particular 19A.[1-3]

The objective of this study was to document the change in serotype distribution of *Streptococcus pneumoniae* (SPN) isolates in Ontario following introduction of PCV7.

We were also interested to know what extra SPN serotype cover would be obtained if Ontario were to adopt the 9 or 13-valent pneumococcal conjugate vaccines.

Methods

- The Toronto Invasive Diseases Bacterial Network (TIBDN) is a collaboration of all hospitals, microbiology laboratories, infection control practitioners, physicians and public health units serving the population of metropolitan Toronto and Peel Regions (population 3.7 million). All SPN isolates causing IPD in Toronto and Peel regions are submitted to TIBDN.
- Isolates causing invasive pneumococcal disease (IPD) in children below 18 years of age pre (1995 to 2004) and post (2006 to 2007) introduction of PCV7 were compared for serotype distribution, IPD rates and penicillin susceptibility.
- A case of IPD was defined as a compatible clinical presentation along with laboratory isolation of SPN from a normally sterile site (e.g. blood, cerebrospinal fluid, or less commonly, joint, pleural, or pericardial fluid).
- Isolates were categorized as susceptible (S; MIC ≤0.06μg/ml), intermediate (I; MIC 0.12 to 1μg/ml), resistant (R; MIC ≥2μg/ml), or nonsusceptible (NS; MIC ≥0.12μg/ml) using current Clinical Laboratory Standards Institute (CLSI) breakpoints for oral Pen V.[4]
- Raw data were entered into an Excel spreadsheet and subsequently analyzed using Stata 8 for Windows (Stata Corporation, USA) and EpiInfo Version 6. Proportions were compared by χ^2 or Fisher's Exact tests. All hypothesis tests were two-tailed, and P ≤0.05 was considered significant.

Results

- The proportion of SPN causing IPD in children that were VS dropped from 76.1% pre to 37.5% post PCV7 introduction (P <0.0001; see Table 1)
- The most common serotype causing IPD post PCV7 was NVS 19A (17.5% of IPD), which also increased the most (2.4% of IPD isolates pre PCV7; P<0.0001).
- The largest reduction was observed in serotype 14 (from 30.2% to 6.2%, P <0.0001), which was also the most common serotype pre PCV7.

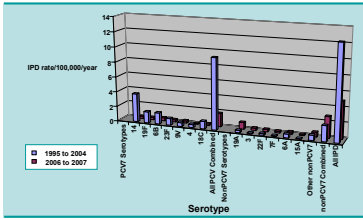
Table 1. TIBDN SPN isolates in children with IPD, Toronto and Peel, before (1995 to 2004) and after (2006 to 2007) introduction of PCV7.

	1995 to 2004 n (% of IPD)	2006 to 2007 n (% of IPD)	IPD rate per 100,000: 1995 to 2004	IPD rate per 100,000: 2006 to 2007	Rate Reduction; P
PCV7 Serotypes					
14	**274 (30.2)**	**5 (6.2)**	**3.8**	**0.3**	**3.5; P <0.0001**
19F	**108 (11.9)**	**5 (6.2)**	**1.5**	**0.3**	**1.2; P <0.0001**
6B	**108 (11.9)**	**6 (7.5)**	**1.5**	**0.4**	**1.1; P=0.0001**
18C	**74 (8.1)**	**3 (3.8)**	**1**	**0.2**	**0.8; P=0.0002**
23F	**64 (7.0)**	**5 (6.2)**	**0.9**	**0.3**	**0.6; P=0.01**
9V	34 (3.7)	4 (5.0)	0.5	0.3	0.2; NS
4	29 (3.2)	2 (2.5)	0.4	0.1	0.3; NS
All PCV Combined	**691 (76.1)**	**30 (37.5)**	**9.5**	**1.8**	**7.7; P <0.0001**
NonPCV7 Serotypes					
19A	**22 (2.4)**	**14 (17.5)**	**0.3**	**0.9**	**-0.6; P=0.004**
3	10 (1.1)	5 (6.2)	0.1	0.3	-0.2; NS
22F	14 (1.5)	5 (6.2)	0.2	0.3	-0.1; NS
7F	10 (1.1)	4 (5.0)	0.1	0.2	-0.1; NS
6A	37 (4.1)	5 (6.2)	0.5	0.3	0.2; NS
15A	5 (0.6)	2 (2.5)	0.07	0.12	-0.05; NS
Other nonPCV7 *	56 (6.2)	11 (13.8)	0.7	0.6	
nonPCV7 combined	**154 (17.0)**	**46 (57.5)**	**2.1**	**2.8**	**-0.7; NS**
NT	5 (0.6)	0 (0)			
ND	58 (6.4%)	4 (5.0%)	0.7	0.2	
Total	**908**	**80**	**12.5**	**4.9**	**7.6; P <0.0001**

* Serotypes that each contribute less than 2% to the total of IPD isolates during both time periods studied
NT nontypeable isolates; ND serotyping not done; NS P value not significant

- IPD rate fell significantly post PCV7 introduction, from 12.5 to 4.9 episodes per 100,000 children per year (Table 1 and Figure 1).
- The largest decrease in IPD rate was observed for VS 14, from 3.8 to 0.3 per 100,000 per year.
- The largest increase in IPD rate in children was observed for NVS serotype 19A, from 0.3 to 0.9 per 100,000 children per year.

Figure 1. IPD rates in children, Toronto and Peel, 1995 to 2004 and 2006 to 2007



* All non-PCV7 serotypes with individual frequency <2% during 2002 to 2007.

Table 2. IPD focus in children, Toronto and Peel, before (1995 to 2004) and after (2006 to 2007) introduction of PCV7.*

	1995 to 2004 n (% of IPD)	2006 to 2007 n (% of IPD)	IPD rate per 100,000: 1995 to 2004	IPD rate per 100,000: 2006 to 2007	Rate Reduction: P
Bacteremia no focus	**419 (46)**	**19 (24)**	**5.8**	**1.2**	**4.6; P <0.0001**
Pneumonia	**225 (24.8)**	**35 (44)**	**3.1**	**2.1**	**1; P=0.04**
Otitis media/bacteremia	**101 (11.1)**	**7 (9)**	**1.4**	**0.4**	**1; P=0.0005**
Meningitis	**87 (9.6)**	**8 (10)**	**1.2**	**0.5**	**0.7;P=0.008**
Septic arthritis	**16 (1.8)**	**0**	**0.2**	**0**	**0.2; P=0.039**
Soft tissue infection	13 (1.4)	0	0.2	0	0.2; NS
Sinusitis	9 (1)	2 (3)	0.12	0.12	0; NS
Empyema	5	1	0.07	0.06	0.01; NS
URTI/bacteremia	4	0	0.06	0	0.06; NS
Peritonitis	4	0	0.06	0	0.06; NS
Cellulitis	**1**	**3**	**0.01**	**0.18**	**-0.17; P=0.02**

*Foci with 2 or less cases in either time period include mastoiditis, pericarditis, osteomyelitis, endocarditis, tonsilitis, and subdural empyema.
NS P value not significant

- Pen R was detected in 48 (5.7%) of 832 IPD isolates tested from 1995 to 2004 with no significant change in 2006 to 2007, when 4 (5.73%) of 76 tested were Pen R.
- Pen NS was detected in 144 (17%) the isolates tested from 1995 to 2004 and 17 (22%) of the isolates tested from 2006 to 2007 (P=0.29).
- Among NVS 19A isolates, Pen NS fell from 77% to 36% (p=0.013) after PCV7 introduction, with no change in pen R.
- Amoxycillin resistance was rare, and there was no significant difference in susceptibility of isolates to amoxycillin between 1995 to 2004 and 2006 to 2007.
- Of the 5 amoxycillin resistant isolates during 1995 to 2004, 4 were VS 19F and 1 was NVS 6A.
- All 3 amoxycillin nonsusceptible isolates during 2006 to 2007 were NVS 19A.

Table 3. Amoxycillin susceptibility among IPD isolates in children, Toronto and Peel, 1995 to 2004 and 2006 to 2007

	Year Group		
Amoxycillin Susceptibility	**1995 to 2004 n (%)**	**2006 to 2007 n (%)**	**P**
Susceptible (MIC ≤2μg/ml)	836 (98.8)	75 (96)	0.09
Intermediate (MIC 4μg/ml)	5 (0.6)	1 (1.3)	0.41
Resistant (MIC ≥8μg/ml)	5 (0.6)	2 (2.6)	0.11
Total number tested	846	78	

Conclusions

- Introduction of PCV7 in Ontario has resulted in a significant decrease in IPD in children in Toronto and Peel. Most of this decrease is in cases of bacteremia without focus.
- We have documented a significant increase in nonvaccine serotype 19A causing IPD in children.
- There has been no increase in penicillin resistance or nonsusceptibility in SPN isolates causing IPD in children in Toronto and Peel since the introduction of PCV7.
- Of SPN isolates causing IPD in children in Toronto since 2006, PCV7 covers 37.5% of isolates. The 9-valent vaccine would provide no extra coverage, but the13-valent PCV would cover 72.5% (35% more than PCV7) of all IPD isolates since 2006.
- Ongoing surveillance is needed to monitor serotype trends in IPD and to assess serotype match of future candidate PCVs with serotypes causing IPD.

References

1. Singleton RJ, Hennessy TW, Bulkow LR, Hammitt LL, Zulz T, Hurlburt DA et al. Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage.[see comment]. JAMA. 2007;297:1784-92.
2. Pichichero ME, Casey JR. Emergence of multiresistant serotype 19A pneumococcal strain not included in the 7-valent conjugate vaccine as an otopathogen in children. JAMA. 2007;298:1772-8.
3. Messina AF, Katz-Gaynor K, Barton T, Ahmad N, Ghaffar F, Rasko D et al. Impact of the pneumococcal conjugate vaccine on serotype distribution and antimicrobial resistance of invasive Streptococcus pneumoniae isolates in Dallas, TX, children from 1999 through 2005. Pediatr Infect Dis J. 2007;26:461-7.
4. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing: Eighteenth Informational Supplement. CLSI document S100-18.* Wayne, PA: Clinical Laboratory Standards Institute; 2008.
5. Image acknowledgement; Centres of Disease Control and Prevention (CDC): Public Health Image Library (PHIL)

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