Epidemiology, antibiotic susceptibility, and serotype distribution of *Streptococcus pneumoniae* associated with invasive pneumococcal disease in British Columbia – A call to strengthen public health pneumococcal immunization programs

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M Bigham, DM Patrick, E Bryce, et al. Epidemiology, antibiotic susceptibility and serotype distribution of *Streptococcus pneumoniae* associated with invasive pneumococcal disease in British Columbia – A call to strengthen public health pneumococcal immunization programs. Can J Infect Dis 2003;14(5):261-266.

BACKGROUND: This study examined the epidemiology, antibiotic susceptibility and serotype distribution of *Streptococcus pneumoniae* associated with invasive pneumococcal disease (IPD) in British Columbia.

METHODS: Six hospitals and one private laboratory network participated in a prospective, sentinel laboratory based surveillance study of IPD, between October 1999 and October 2000. At each site, *S pneumoniae* isolates were collected and epidemiological data were gathered using a structured questionnaire, for all cases of IPD meeting the study case definition. Isolates were serotyped and tested for antimicrobial susceptibility. Bivariate associations were analyzed and multivariate logistic regression was used to identify independent risk factors associated with hospitalization or death.

RESULTS: One hundred three reports and isolates were collected. Seventy-nine per cent of cases were community-acquired, 64% required hospitalization and 5% died. Cases with one or more assessed risk factor for IPD and of female sex were independent variables associated with hospitalization or death. One-third of isolates had reduced penicillin susceptibility and 96% of these represented serotypes contained in the 23-valent pneumococcal polysaccharide vaccine (PPV-23). Overall, 89% of serotypes identified are included in the PPV-23 vaccine and 88% of isolates from children under five years of age are found in the 7-valent pneumococcal conjugate vaccine (PCV-7). Forty-one per cent of cases qualified for publicly funded pneumococcal vaccine and 34% of eligible persons were vaccinated.

CONCLUSIONS: Overall, pneumococcal serotypes associated with IPD in this study closely matched serotypes included in PPV-23 products currently licensed in Canada. Most serotypes associated with IPD in children under five years of age are included in a recently licenced PCV-7. One third of isolates demonstrated reduced penicillin susceptibility, most involving serotypes included in PPV-23. Effective delivery of current public health immunization programs using PPV-23 and extending protection to infants and young children using the PCV-7 will prevent many cases of IPD.

Key words: *Antibiotic susceptibility; Immunization; Serotype; Streptococcus pneumoniae*

Streptococcus pneumoniae (pneumococcus) is a leading cause of invasive bacterial infections, including septicemia and meningitis, as well as non-invasive infections such as community-acquired pneumonia and acute otitis media (1-3). The highest rates of invasive pneumococcal disease (IPD) are seen in children under two years of age, in whom it is currently the leading cause of invasive bacterial disease in Canada and the United States (3,4). IPD is also a leading cause of illness and death among the elderly and persons having underlying chronic medical conditions (1,2,5). Overall, IPD accounts for more deaths in Canada and the United States than any other vaccine-preventable bacterial disease (6,7).

Data from the Canadian National Centre for Streptococcus indicate the proportion of invasive pneumococcal isolates with reduced penicillin susceptibility increased from 5.5% to 15.2% between 1992 and 2000 (8). The Canadian Bacterial Surveillance Network has documented a similar trend of decreasing susceptibility to penicillin and to other antibiotics among pneumococcal isolates recovered from invasive, respiratory and other sites, between 1988 and 2001 (9).

The high population burden of IPD and adverse consequences of increasing antimicrobial resistance of pneumococcus causing IPD give new impetus to public health prevention programs that better exploit the potential benefits of pneumococcal immunization (1,2,10). Only within the past five years has British Columbia, along with other Canadian provinces and territories, begun to offer 23-valent pneumococcal polysaccharide vaccine (PPV-23) through public health immunization programs, according to recommendations of the National Advisory Committee on Immunization (NACI).

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Study funding provided through the British Columbia Centre for Disease Control

Received for publication August 27, 2002. Accepted May 27, 2003

Épidémiologie, sensibilité aux antibiotiques et distribution sérotype de Streptococcus pneumoniae associé à la maladie pneumococcique invasive en Colombie-Britannique - Un appel pour renforcer les programmes d'immunisation pneumococcique de santé publique.

CONTEXTE : Cette étude a porté sur l'épidémiologie, la sensibilité aux antibiotiques et la distribution sérotype de Streptococcus pneumoniae associé à la maladie pneumococcique invasive (MPI) en Colombie-Britannique.
MÉTHODES : Six hôpitaux et un réseau de laboratoire privé ont participé à une étude de surveillance de contrôle en laboratoire sur la MPI entre octobre 1999 et octobre 2000. À chaque site, on a collecté des isolats de S pneumoniae et consigné des données à l'aide d'un questionnaire structuré se rapportant à tous les cas de MPI qui correspondaient à la définition de l'étude de cas. On a sérotypé et testé les isolats afin de mesurer leur sensibilité antimicrobienne. On a analysé des associations bidimensionnelles et on a utilisé une régression logistique multidimensionnelle pour identifier les facteurs de risque indépendants associés à des cas d'hospitalisation ou de décès.
RÉSULTATS : On a collecté 103 rapports et isolats. 79 % des cas ont été acquis dans la communauté, 64 % ont nécessité une hospitalisation et 5 % ont entraîné la mort du patient. Les cas présentant un facteur de risque évalué ou plus de MPI et chez les patients de sexe féminin étaient des variables indépendantes associées à une hospitalisation ou un décès. Un tiers des isolats avaient une sensibilité réduite à pénicilline et 96 % de ceux-ci représentaient des sérotypes contenus dans le vaccin antipneumococcique polysaccharide 23-valent (VAP-23). Dans l'ensemble, 89 % des sérotypes identifiés sont compris dans le vaccin VAP-23 et on trouve 88 % des isolats d'enfants de moins de cinq ans dans le vaccin conjugué antipneumococcique 7-valent (VCA-7). On a vacciné 41 % des cas qualifiés pour recevoir le vaccin antipneumococcique financé par les deniers publics et 34 % des personnes admissibles.
CONCLUSIONS : Dans l'ensemble, les sérotypes pneumococciques associés aux MPI dans cette étude correspondaient étroitement à ceux compris dans les produits VAP-23 autorisés présentement au Canada. On retrouve la plupart des sérotypes associés aux VAP chez les enfants de moins de cinq ans dans un VCA-7 récemment autorisé. Un tiers des isolats affichait sensibilité réduite à la pénicilline, la plupart portant sur des sérotypes compris dans le VAP-23. L'application efficace des programmes d'immunisation actuels de santé publique utilisant le VAP-23 et la protection élargie des nourrissons et des jeunes enfants avec du PCV-7 préviendront de nombreux cas de MPI.

NACI recommends immunization using PPV-23 for all persons 65 years of age and older, and for those two to 64 years of age with health conditions placing them at higher risk of IPD or its complications (2,5). Further benefits may accrue after provinces/territories introduce a 7-valent pneumococcal conjugate vaccine (PCV-7) that was licensed in Canada in June 2001, into routine universal infant immunization programs. This vaccine has demonstrated potential to decrease acute or recurrant otitis media associated with antibiotic-resistant pneumococcus; reduce carriage and spread of resistant pneumococci in community settings; and decrease antibiotic use (11).

We report on a one year, prospective, sentinel laboratory-based study of IPD in British Columbia, Canada. The objectives were to characterize the epidemiology, antibiotic susceptibility and serotype distribution of *S pneumoniae* associated with IPD, and viewed in the context of existing and future public health prevention strategies.

METHODS

A prospective, laboratory-based surveillance study of IPD in British Columbia was undertaken between October, 1999 and October, 2000. Six sentinel surveillance hospitals and one private laboratory network participated in the study. Sites were recruited through the British Columbia chapter of the Canadian Association of Medical Microbiologists, which has representatives from hospital laboratories across the province. Participating sites were nonrandomly selected to be as representative as possible of a wide range of patient demographics and diverse geographic locations from both hospital- and community-based laboratories throughout British Columbia. Hospital sites included two large tertiary referral hospitals in the Vancouver area (one of which is also the referral laboratory for pneumococcal isolates from across the province); a large urban tertiary hospital on Vancouver Island; the provincial children's hospital in Vancouver; and two regional referral hospitals that each serve communities of about 100,000 persons along with their respective surrounding rural regions in the interior of the province. The participating private laboratory network is one of two private community laboratory networks primarily serving urban communities in southwestern British Columbia and Vancouver Island. The British Columbia chapter of the Canadian Association of Medical Microbiologists estimated that these sites process more than 50% of all invasive pneumococcal isolates from British Columbia (Dr E Bryce, Vancouver Hospital and Health Science Centre: personal communication, April 2001).

The study case definition for IPD included laboratory confirmed IPD, with recovery of *S pneumoniae* from a normally sterile site (eg, blood, cerebrospinal fluid). Isolates related to acute otitis media and pneumococcal pneumonia without bacteremia were excluded. *S pneumoniae* isolates were identified using standard methods and forwarded to the National Centre for Streptococcus in Edmonton, Alberta for capsular serotyping, and the Microbiology Research Laboratory at University of Manitoba in Winnipeg, Manitoba for antimicrobial susceptibility testing. Minimum inhibitory concentrations (MICs) were determined to the following antimicrobials: penicillin, ceftriaxone, cefuroxime, levofloxacin, moxifloxacin, erythromycin, clindamycin, tetracycline, sulfamethoxazole trimethoprim, linezolid, and vancomycin. MICs were determined in accordance with guidelines published by the National Committee for Clinical Laboratory Standards, using a microbroth dilution method (12). *Streptococcus pneumoniae* ATCC 49619 (NCCLS, USA) was used for weekly quality control on each panel configuration.

At hospital sites, the infection control practitioner completed an enhanced surveillance form for each isolate of pneumococcus meeting the study case definition. This form indicated the clinical presentation, location of the patient five days before specimen collection, the patient's underlying health status, important risk factors for IPD (as defined by NACI [5]), pneumococcal immunization status (as recorded in the hospital medical record or where possible, obtained from the family doctor) and outcome of the infection episode. Primary sources of documentation of confirmed pneumococcal immunization (eg, public health or physician records) were not checked to confirm immunization status reported by infection control practitioners. For isolates from the private laboratory group, the medical microbiologist or designate attempted to contact the physician who submitted the specimen, to obtain the necessary data.

Sentinel sites forwarded isolates and surveillance forms to the British Columbia Centre for Disease Control. Isolates were

excluded from the study if they were unaccompanied by a surveillance form, did not satisfy the case definition for IPD, or represented a second isolate from the same individual within one month.

All data were electronically coded and recorded, and analyses conducted with SPSS 10 (SPSS Inc, USA). Frequency distributions were evaluated for each major outcome variable. Contingency table analyses of categorical data were conducted using Mantel-Haenszel method, Pearson's χ^2 statistic and Fisher's exact test to explore the relationship between parameters such as immunization status and indications for immunization (ie, age and risk factors), as well as serotype distribution and antimicrobial susceptibility. Forward stepwise logistic regression, analyzing on dependent variables found to be significant (P<0.05) in bivariate analyses, was used to identify independent risk factors associated with severe clinical outcomes; ie, death, or hospitalization (as a surrogate of severe disease).

RESULTS

One hundred three reports and accompanying isolates associated with IPD were received between October, 1999 and October, 2000. Seventy-five of 103 (73%) isolates were collected during the six month period between January and June, 2000. Most isolates (99 of 103) were recovered from blood, while three were recovered from cerebrospinal fluid.

Patient characteristics are depicted in Table 1. Persons under five years of age, and over 65 years of age together represented 65 of 103 (63%) cases: 39 (38%) were under five years of age, while 26 (25%) were 65 years and over.

Eighty-one of 93 (87%) infections occurred in people who were living in the community five days before specimen collection. Sixty-six (64%) of invasive infections led to hospitalization and there were five deaths. Thirty-nine of 103 (38%) persons had one or more underlying medical illnesses known to increase the risk of IPD and representing an indication for immunization, yet among the 32 eligible persons with recorded age, risk factor and immunization status, only 11 (34%) were vaccinated. Only eight of 15 (53%) persons 65 years and older and three of the 17 (18%) under 65 years of age with recorded risk factors, were vaccinated.

Pre-existing risk factors for IPD were associated with more severe clinical outcomes (ie, hospitalization or death). Severe outcomes affected 37 (34 hospitalizations and three deaths) of 39 persons (95%) with risk factors compared with 34 (32 hospitalizations and two deaths) of 64 persons (53%) without underlying medical illness (P<0.001; OR=16.3; 95% CI: 3.6-73.5). Men were less likely to be hospitalized or die than women (P=0.04, OR 0.38; 95% CI: 0.15-0.97). On logistic regression analysis, having one or more of the assessed risk factors and female sex were independently associated with hospitalization or death.

Table 2 compares 81 cases in whom immunization status was reported, with respect to underlying indications for immunization (important comorbidity or age 65 years and older). IPD caused by serotypes contained in PPV-23 was less commonly identified among immunized persons than IPD due to pneumococcal serotypes not included in this vaccine (P=0.022, OR=0.096; 95% CI: 0.009-1.023).

Table 3 depicts antibiotic resistance profiles of 93 isolates tested. One-third of isolates were penicillin resistant. Thirteen per cent (4 of 31) of the intermediate and high level resistant penicillin isolates were also resistant to erythromycin. All seven high level penicillin-resistant isolates had high level resistance to sulfamethoxazole-trimethoprim (S/T), while only 9.7% (7 of 62) penicillin sensitive isolates had reduced susceptibility to S/T (P<0.001). All seven high level penicillin resistant isolates had reduced susceptibility to cefuroxime (MIC≥2), compared with none of 62 penicillin sensitive isolates (P<0.001).

TABLE 1
Characteristics of 103 cases of invasive pneumococcal disease

			Number	Percent
Sex				
Women			41	39.8
Men			62	60.2
Age group				
<2 years			20	19.4
2-4 years			19	18.4
5-12 years			4	3.9
13-50 years			18	17.4
51-64 years			13	12.6
≥65 years			26	25.2
Not specified			3	2.9
Location at time of onset of infection*				
Acute care facility			6	5.8
Long term care			6	5.8
Community			81	78.7
Not recorded			10	9.7
Clinical presentation				
Bacteremia			51	49.5
Bacteremia and pneumonia			46	44.7
Meningitis			5	4.8
Other			1	1.0
Risk factors				
No risk factors			64	62.1
One or more of the following:			39	37.9
Asplenia			2	1.9
Chronic heart/lung disease			17	16.5
Cirrhosis			10	9.7
Renal disease			3	2.9
Diabetes			3	2.9
Immunosuppression			10	9.7
Immunization status by risk factor and age				
<65 years	≥1 Risk Factors	Immunized	3	3.8
		Unimmunized	14	17.7
	No Risk Factors	Immunized	4	5.1
		Unimmunized	43	54.4
≥65 years	≥1 Risk Factors	Immunized	7	8.9
		Unimmunized	6	7.5
	No Risk Factors	Immunized	1	1.3
		Unimmunized	1	1.3
Outcome				
Hospitalization			66	64.1
Death			3	2.9
Hospitalization and death			2	1.9
Neither hospitalization nor death			32	31.1

**Location of the patient in the five days prior to specimen collection*

TABLE 2
Comparison of subjects by reported pneumococcal immunization status

	Immunized number (%)	Unimmunized number (%)	Statistical significance*/comment
Overall (n=103)	16 (16)	65 (63)	immunization status unreported in 22 (21%)
Age			
≥ 65 years (n=15)	8 (53)	7 (47)	P<0.001, OR=9.3 (2.6-33.6)
<65 years (n=64)	7 (11)	57 (89)	
Sex			
Women (n=32)	11 (34)	21 (66)	P=0.008, OR=0.2 (0.07-0.7)
Men (n=49)	5 (10)	44 (90)	
Risk factors			
≥1 (n=32)	11 (34)	21 (66)	P=0.008, OR=4.6 (1.4-15.0)
None (n=49)	5 (10)	44 (90)	
Hospitalized or died			
Yes (n=60)	16 (27)	44 (73)	P=0.008, OR=15.9
No (n=21)	0	21 (100)	
IPD caused by serotype in PPV-23†			
Yes (n=49)	11 (22)	38 (78)	P=0.052, OR=0.096 (0-1.41)
No (n=4)	3 (75)	1 (2)	
Reduced penicillin susceptibility			
Yes (n=22)	4 (18)	18 (82)	NS
No (n=47)	10 (21)	37 (79)	

**P-value and Mantel-Haenszel common odds ratio with 95% CI; †Excluding isolates with unknown serotype and from persons <2 years of age; NS Not significant (P>0.05)*

TABLE 3
Antibiotic resistance of 93 pneumococcal isolates

Antibiotic	MIC 90*	Intermediate Resistance† (%)	Resistant‡ (%)
Penicillin	1	25.8	7.5
Clindamycin	0.06	1.1	3.2
Ceftriaxone	0.25	1.1	0
Cefuroxime	2	4.3	6.5
Vancomycin	0.5	0	0
Moxifloxacin	0.25	0	0
Levofloxacin	1	0	0
Tetracycline	0.25	0	4.3
Sulfamethoxazole trimethoprim	2	7.5	9.7
Linezolid	1	0	0
Erythromycin	0.5	2.2	8.6

**MIC90 minimum inhibitory concentration (μg/ml) of the antibiotic for 90% of the isolates tested; †Intermediate resistance: MIC 0.12-1μg/ml; ‡Resistant: MIC >1 μg/ml*

Table 4 summarizes the serotype distribution for 92 isolates. Overall, 82 of the 92 (89%) serotypes identified are included in PPV-23. Sixty-four of 71 (90%) isolates from persons two years and older are included in PPV-23. Among unimmunized persons two years of age or older, 38 of 39 (97%) cases were caused by serotypes included in PPV-23 (not shown). Sixty-six of 92 (71.7%) typed isolates are represented in PCV-7. Sixteen of 18 (89%) typed isolates recovered from patients under two years of age are included in PCV-7. Among unimmunized persons under two years of age, 15 of 17 (88%) were caused by serotypes represented in PCV-7 (not shown).

Twenty-five of 26 (96%) typed isolates with reduced penicillin susceptibility are represented in PPV-23. Three serotypes: 14, 9V and 19F, comprised 85% of all isolates with reduced penicillin susceptibility.

DISCUSSION

Almost two-fifths of cases occurred in children under five years of age. Population based studies have demonstrated a high burden of IPD in this age group (3,4,10,13-15). Young children derive less benefit than adults from PPV-23 and this vaccine is not recommended for use in children under two years of age (4,16,17). However, 88% of infections among children under five years of age in this study were caused by serotypes included in PCV-7. A high protective efficacy of up to 94% is reported for PCV-7 against childhood IPD caused by vaccine-containing serotypes (3,18-21), and population based studies reveal that a high proportion of childhood isolates associated with IPD in Canada and the United States are included in PCV-7 (3-5). In Canada, PCV-7 is recommended by NACI, both in routine universal infant immunization programs for children under 24 months of age, and in catch-up programs for high risk children under five years of age (5). By mid-2003, only three provinces/territories (Alberta, British Columbia, Nunavut) have decided to include this vaccine in their routine universal infant immunization program.

One-third of isolates associated with IPD had reduced susceptibility to penicillin, with increased resistance among this subset of *S pneumoniae* to other important antibiotics used both in community (eg, erythromycin or S/T) and hospital settings (eg, cefuroxime) (22). The proportion of invasive pneumococcal isolates with reduced penicillin susceptibility documented in this study is over twice that reported by the National Centre for Streptococcus during a similar period, (April, 1999 to March, 2000) for invasive pneumococcal isolates submitted from across Canada (8). There is no apparent explanation for this finding. Other evidence indicates no difference in clinical presentation, morbidity or mortality between invasive penicillin sensitive and nonsusceptible pneumococcus in children under 18 years of age, that might otherwise have suggested a detection or testing bias (23).

TABLE 4
Pneumococcal Serotypes

Serotype *in PPV-23 vaccine †in PCV-7 vaccine	Number (%) All ages‡	Number (%) <2 years age	Number (%) ≥2 years age	Number (%) <5 years age	Number (%) with reduced penicillin susceptibility (MIC ≥0.12 μg/ml) Yes	 No
3 *	4 (4.3)	—	4 (5.6)	—	—	3
4 *†	12 (13.0)	2 (11.1)	10 (14.1)	5 (15.2)	—	11
6A	5 (5.4)	—	3 (4.2)	1 (3.0)	1 (25)	3
6B*†	4 (4.3)	3 (16.7)	1 (1.4)	3 (9.1)	1 (25)	3
7F*	1 (1.1)	—	1 (1.4)	—	—	
9V*†	7 (7.6)	1 (5.6)	6 (8.5)	2 (6.1)	5 (100)	
11A*	3 (3.3)	—	3 (4.2)	—	—	3
12F*	3 (3.3)	—	3 (4.2)	—	—	2
13	1 (1.1)	—	1 (1.4)	—	—	1
14*†	19 (20.7)	5 (27.8)	14 (19.7)	9 (27.3)	14 (78)	4
18C*†	9 (9.8)	3 (16.7)	6 (8.5)	7 (21.2)	—	7
19A*	1 (1.1)	—	1 (1.4)	—	1 (100)	
19F*†	10 (10.9)	2 (11.1)	7 (9.9)	3 (9.1)	3 (43)	4
20*	1 (1.1)	—	1 (1.4)	—	—	1
22F*	3 (3.3)	1 (5.6)	2 (2.8)	2 (6.1)	1 (33)	2
23B	2 (2.2)	1(5.6)	1 (1.4)	1 (3.0)	—	2
23F*†	5 (5.4)	—	5 (7.0)	—	—	5
34	1 (1.1)	—	1 (1.4)	—	—	1
35A	1 (1.1)	—	1 (1.4)	—	—	1
Total	92 (100)	18 (100)	71 (100)	33 (100)	26 (33)	53

‡*Includes three isolates with unknown age*

Public health efforts in many jurisdictions are aimed at reducing antibiotic prescribing by primary care providers, which has been shown to be a significant determinant of pneumococcal antimicrobial resistance (9,24,25). Coherent with such community-based initiatives, most cases of IPD in this study were community-acquired. Pneumococcal vaccination may also prevent or slow the emergence of antimicrobial resistance in pneumococcus causing IPD (26,27). Antimicrobial resistance in isolates causing IPD among children under five years age in both the United States and Canada occurs most frequently in serotypes included in PCV-7 (3,15).

Persons with one or more assessed risk factors were much more likely in this study to have been hospitalized or die than persons with no identifiable risk factor. Although all persons 65 years and older, and persons two years of age and older with one or more risk factors for IPD, are eligible for publicly funded PPV-23 in British Columbia, almost two-thirds of eligible persons in this study had not been vaccinated. More comprehensive PPV-23 coverage of eligible persons may have prevented IPD in some of these cases. Reported efficacy of PPV-23 against IPD is 50% to 80% among high risk, older children, high risk adults and seniors (1,3,5,14,17,20,28-31).

We cannot readily explain sex as an independent factor for hospitalization or death on logistic regression. Although univariate analyses showed insignificant differences in age or reported risk factors between sexes, women were significantly more likely to have been immunized than men (P=0.008), suggesting that important, unreported comorbidities may have been more prevalent in females.

This study had several limitations. Since it was not population based, we can draw no inferences about the population burden of IPD or the population coverage of pneumococcal vaccine among eligible persons. Lacking a control group of persons unaffected by IPD, we also cannot assess the protective efficacy of vaccination or the predictors of invasive disease. There are no reliable population uptake data for pneumococcal vaccine in British Columbia to evaluate vaccine effectiveness. Recently implemented public health electronic vaccination registries in British Columbia should improve future ascertainment and validation of both case and population immunization status. We also cannot readily compare our findings with historical British Columbia IPD surveillance, due to a change in reportable IPD case definition in January 2000, which changed the definition from pneumococcal meningitis only to one closely resembling that employed in this study. Reporting was nonuniform throughout the course of the study, with higher case reporting between January and June of the year 2000. Several factors could account for this: true seasonality of IPD; incomplete reporting in the earlier study phase or improved reporting after the case definition of reportable IPD was broadened in January, 2000; or a testing bias associated with increased incidence and enhanced surveillance for other respiratory infectious diseases, such as influenza or respiratory syncytial virus, that peak during winter and early spring. Interestingly, while 103 cases of IPD were identified through this study, over the same period of time, only 76 cases of IPD were reported through passive reporting in the provincial communicable disease surveillance system.

In conclusion, this prospective, sentinel laboratory based study of IPD identified a high proportion of community acquired IPD, one third affecting children under five years of age. Severe IPD, requiring hospitalization or causing death, occured more commonly in persons with one or more assessed risk factors for IPD. One-third of isolates tested showed reduced susceptibility to penicillin. Most serotypes associated with IPD among persons two years of age or older in this study are represented in PPV-23, while most serotypes of isolates from children under two years age are included in PCV-7. Almost two-thirds of persons who were eligible for publicly funded pneumococcal vaccine, were unimmunized. These findings further support public health objectives to maximize pneumococcal vaccine uptake in currently eligible groups and to expand deployment of pneumococcal vaccines in programs for infants and children under five years of age.

ACKNOWLEDGEMENTS: The authors acknowledge and thank Doug Ruisaard, British Columbia Centre for Disease Control, for assistance with data manipulation; Chuck Palteil, British Columbia Centre for Disease Control and Steve Marion, UBC Centre for Disease Control, Vancouver, British Columbia, for assistance with data analysis; Daryl Hoban and Lorraine Palatnick, Health Sciences Centre, Microbiology Research Laboratory, University of Manitoba, Winnipeg, Maniboba, for antimicrobial susceptibility testing of isolates; Marguerite Lovgren, National Centre for Streptococcus, Provincial Laboratory of Public Health for Northern Alberta, Edmonton, Alberta, for serotyping isolates; Susan Roman, for assistance in gaining participation of a private community laboratory network in this study; and Pam Kibsey, British Columbia Chapter, Canadian Association of Medical Microbiologists for site support in Capital Health Region, Victoria, British Columbia.

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