

Comparison of antimicrobial resistance and serotype patterns in *Streptococcus pneumoniae* from blood cultures and respiratory specimens in Canadian hospitals from the CANWARD study (2007–23)

Heather J. Adam ^{1,2*}, Alyssa R. Golden ³, Irene Martin³, Melanie R. Baxter¹, Ross J. Davidson⁴, James A. Karlowsky^{1,2} and George G. Zhanel¹

¹Department of Medical Microbiology and Infectious Diseases, Max Rady College of Medicine, University of Manitoba, Room 543-745 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E 0J9; ²Clinical Microbiology, Diagnostic Services, Shared Health, MS673-820 Sherbrook Street, Winnipeg, Manitoba, Canada R3A 1R9; ³National Microbiology Laboratory, Public Health Agency of Canada, 1015 Arlington Street, Winnipeg, Manitoba, Canada R3E 3M4; ⁴Queen Elizabeth II Health Sciences Centre, Dalhousie University, 5788 University Avenue, Halifax, Nova Scotia, Canada B3H 1V8

*Corresponding author. E-mail: hadam@sharedhealthmb.ca

Objectives: To compare the antimicrobial resistance and serotype patterns in *Streptococcus pneumoniae* collected from blood cultures and respiratory specimens in Canada from 2007 to 2023.

Methods: *S. pneumoniae* isolates were submitted from Canadian hospitals as part of the ongoing national surveillance study, CANWARD. Antimicrobial susceptibility testing was performed by the CLSI broth microdilution method. Serotypes were determined using WGS and/or the Quellung method.

Results: Of the 3111 *S. pneumoniae* isolates collected, 1103 (35.5%) were from blood cultures and 2008 (64.5%) were from respiratory specimens. The most common serotypes overall were 3, 19A, 22F and 11A. Serotypes 4, 5, 7F, 8, 12F, 14, 19A and 22F were more frequently identified ($P \leq 0.01$) among blood culture isolates, while 6C, 7C, 11A, 19F, 21, 23A, 23B, 23F, 31, 34, 35B, 35F and non-typeable strains were more commonly recognized ($P \leq 0.03$) among respiratory isolates. Susceptibility rates were significantly lower in respiratory isolates than blood culture isolates for penicillin, ceftriaxone, clarithromycin, clindamycin and doxycycline ($P \leq 0.03$). Overall, 8.3% of isolates were MDR/XDR; rates increased over the course of the study ($P = 0.004$). MDR/XDR rates were higher in respiratory isolates (10.5%) than in blood culture isolates (5.8%) ($P < 0.0001$). Serotypes 19A (40.6%) and 15A (27.6%) were predominant in the MDR/XDR isolates.

Conclusions: *S. pneumoniae* from respiratory specimens demonstrated lower antimicrobial susceptibilities and higher MDR rates compared with isolates from blood cultures. Significant differences in the serotypes isolated from blood culture and respiratory specimens were observed. A greater proportion of isolates from blood cultures were serotypes covered by current pneumococcal vaccines.

Introduction

Streptococcus pneumoniae has a significant impact on public health worldwide as the causative agent of invasive pneumococcal disease (IPD) and a common cause of respiratory infections, including community-acquired pneumonia (CAP) and acute otitis media. An estimated 3.7 million episodes of severe pneumococcal disease occurred worldwide in children in 2015.¹ The annual incidence rates of IPD in Canada were consistently between 9.1 and 10.9/100 000 population for 2009–19, with a potentially COVID public health measure-impacted rate of 5.9/100 000 reported for 2020.² IPD rates were highest

for children <1 year and 1–4 years of age as well as individuals older than 60 years.² *S. pneumoniae* is the leading cause of CAP, being identified in a recent study as the causative agent of CAP in 33–50% of cases that had an established aetiology.³ Mortality rates of 8.3% were recently reported for hospitalized adults with IPD and noninvasive all-cause pneumonia in the USA.⁴

S. pneumoniae infections frequently require antibiotic therapy. Due to the high worldwide prevalence of penicillin-non-susceptible *S. pneumoniae*, it has been recognized as a priority pathogen by the WHO for new antibiotic development.⁵ Globally, *S. pneumoniae* was the fourth leading pathogen contributing to the burden of

antimicrobial resistance in 2019 contributing to >250 000 deaths associated with antimicrobial resistance.⁶

Vaccines are effective at reducing pneumococcal disease. There are two types of pneumococcal vaccines available: the 23-valent polysaccharide vaccine PNEUMOVAX®23 (PPSV23) and the pneumococcal conjugate vaccines (PCVs). PPSV23 includes 23 pneumococcal serotypes and has been available since 1983 but is only effective for adults.⁷ The conjugate vaccines are effective for children and adults. The introduction of the first pneumococcal conjugate vaccine, Prevnar®, a 7-valent pneumococcal vaccine (PCV7), into routine infant immunization programs in the early 2000s resulted in significant reductions of IPD.⁸ A 13-valent pneumococcal conjugate vaccine, Prevnar®13 (PCV13), replaced PCV7 in routine infant immunization programs largely in response to the significant rise in the incidence of serotype 19A, which was frequently MDR.⁹ Currently, VAXNEUVANCE™, a 15-valent pneumococcal conjugate vaccine (PCV15), and PREVNAR20™, a 20-valent pneumococcal conjugate vaccine (PCV20), are recommended for children and adults in Canada.¹⁰ In 2024, CAPVAXIVE®, a 21-valent conjugate vaccine with different serotype coverage from the sequentially developed previous conjugate vaccines was recommended for use in adult pneumococcal immunization programs in Canada.¹¹ PPSV23 had been recommended for use in adults following a dose of PCV15 as an alternative to vaccination with PCV20;¹⁰ however, vaccination with PCV20 or PCV21 are now preferred.¹¹

The purpose of this study was to compare the antimicrobial resistance and serotype patterns in *S. pneumoniae* collected from blood cultures and respiratory specimens in Canada from 2007 to 2023 as part of the CANWARD study. This study expands upon an earlier report on *S. pneumoniae* from the CANWARD study.¹²

Materials and methods

Bacterial isolates

Between January 2007 and December 2023, 3111 *S. pneumoniae* isolates from blood and respiratory cultures were collected by the annual CANWARD surveillance program. CANWARD is an ongoing national Public Health Agency of Canada-PHAC/Canadian Antimicrobial Resistance Alliance partnered surveillance study evaluating pathogen prevalence and antimicrobial resistance in bacterial pathogens isolated from patients attending tertiary care hospitals across Canada.¹³ Participating hospital sites submitted their first 100 respiratory isolates and the first 10 blood isolates per month, for 10 months, each study year. Isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) where the *S. pneumoniae* identifications were confirmed by MALDI-TOF mass spectrometry (Bruker Daltonics, Billerica, MA, USA) and bile solubility, as required, and isolates were stocked for further testing.

The CANWARD surveillance study receives annual approval by the University of Manitoba Research Ethics Board (H2009:059).

Antimicrobial susceptibility testing

As previously described,¹³ antimicrobial susceptibility testing was performed by broth microdilution using in-house prepared 96-well microtitre panels in accordance with CLSI methods.¹⁴ MICs were interpreted based on CLSI breakpoints.¹⁵ Here 2939 isolates had complete antimicrobial susceptibility testing profiles for the MDR analysis. MDR was defined as resistance to three or more classes of antimicrobials, represented by

penicillin, clarithromycin, clindamycin, doxycycline, levofloxacin, trimethoprim/sulfamethoxazole and vancomycin. For the MDR analysis, penicillin resistance was defined using the CLSI breakpoint for oral penicillin V (MIC ≥ 2 mg/L). Isolates resistant to five or more of the antimicrobial classes included in the MDR definition were considered XDR.¹⁶

Serotyping

Isolates collected from 2007 to 2022 were serotyped by the Quellung reaction,¹⁷ with pool, group, type and factor commercial antisera (SSI Diagnostica; Statens Serum Institut, Copenhagen, Denmark). From late 2022 onwards, *S. pneumoniae* were sequenced using the Illumina platform and serotypes were identified directly from whole-genome data using the WADE pipeline (<https://github.com/phac-nml/wade>). Isolates that were non-typeable by WGS were confirmed by Quellung reaction. Serotypes 15B and 15C were grouped as 15B/C due to the reported reversible switching between serotypes.^{18,19}

Statistical analysis

Differences in antimicrobial susceptibility rates, MDR/XDR rates, serotypes and patient demographics between *S. pneumoniae* isolates from respiratory specimens and blood cultures were assessed for significance ($P \leq 0.05$) using a two-tailed Fisher's exact test. Changes in serotype proportion, antimicrobial susceptibility and MDR rates throughout the study were assessed for statistical significance ($P \leq 0.05$) using the Cochran-Armitage test for trend. Based on the test limitations, the Cochran-Armitage test for trend analysis could not be performed on portions of the datasets with low annual isolate counts (counts of <5 in >20% of data points) for a particular parameter.

Results

Of the 3111 *S. pneumoniae* isolates collected as part of CANWARD 2007–23, 1103 (35.5%) were obtained from blood cultures while 2008 (64.5%) were from respiratory specimens. A comparison of the demographic characteristics of patients from whom *S. pneumoniae* was isolated from blood cultures and respiratory cultures is presented in Table 1. Male patients accounted for 55.5% of blood culture isolates and 61.7% of respiratory isolates ($P=0.0009$). Blood culture isolates were collected at a higher rate than respiratory isolates from children 0 to <2 years of age ($P=0.0003$). A significantly greater number of blood culture isolates than respiratory isolates were received from sites in central Canada ($P=0.0003$). A significantly greater number of respiratory isolates compared with blood culture isolates were received from sites in eastern Canada ($P<0.0001$).

There were 57 serotypes identified in the *S. pneumoniae* collected as part of the CANWARD study. Five serotypes were uniquely observed with single isolates from blood culture specimens (9A, 9L, 11F, 12A, 25F). Ten serotypes were observed only for respiratory isolates: 10B, 10F, 11D, 18B, 28F, 41F (each, $n=1$), 6D, 17A (each, $n=2$), 37 ($n=3$) and 35C ($n=4$). Figure 1 displays the proportion of *S. pneumoniae* isolated from blood and respiratory isolates for serotypes of which >30 isolates were identified in the entire dataset. Overall, the most commonly observed serotypes were 3 ($n=275$, 8.8%), 19A ($n=248$, 8.0%), 22F ($n=189$, 6.1%), 11A ($n=181$, 5.8%), 23A ($n=138$, 4.4%), 15B/C ($n=133$, 4.3%), 6C ($n=119$, 3.8%), 15A ($n=115$, 3.7%), 19F ($n=111$, 3.6%) and 9N ($n=109$, 3.5%). The 10 most common serotypes isolated from blood cultures (representing 59.4% of isolates, $n=655$) in order of descending frequency were 19A, 3, 22F,

Table 1. Demographic characteristics of patients with *S. pneumoniae* collected from blood and respiratory specimens as part of the CANWARD study (2007–23)

Characteristic	Blood culture isolates (n=1103)	Respiratory isolates (n=2008)	P ^a
Biological sex, n (%)			0.0009
male	612 (55.5)	1238 (61.7)	
female	491 (44.5)	770 (38.3)	
Age group, years, n (%)			
0–<2	69 (6.3)	68 (3.4)	0.0003
2–<6	71 (6.4)	97 (4.8)	NS ^b
6–<18	51 (4.6)	95 (4.7)	NS ^b
18–<50	287 (26.0)	502 (25.0)	NS ^b
50–<65	274 (24.8)	543 (27.0)	NS ^b
≥65	351 (31.8)	703 (35.0)	NS ^b
Region, n (%)			
western Canada ^c	459 (41.6)	801 (39.9)	NS ^b
central Canada ^d	553 (50.1)	870 (43.3)	0.0003
eastern Canada ^e	91 (8.3)	337 (16.8)	<0.0001

^aP value determined using Fisher's exact test^bNS, not statistically significant^cWestern Canada includes the provinces of British Columbia, Alberta, Saskatchewan and Manitoba^dCentral Canada includes the provinces of Ontario and Quebec^eEastern Canada includes the provinces of New Brunswick and Nova Scotia

4, 7F, 12F, 8, 9N, 11A and 15B/C. Comparatively, the 10 most common serotypes isolated from respiratory specimens (representing 58.1% of isolates, $n=1166$) in order of descending frequency were 3, 11A, 19A, 23A, 22F, 15B/C, 6C, 19F, 15A, 23B and 35B (serotypes rank ordered as 10 and 11 listed as both $n=79$). The top 10 serotypes by specimen source are presented visually in Figure S1 (available as [Supplementary data](#) at JAC Online).

The annual serotype distribution of blood and respiratory isolates and the overall comparison of serotypes by specimen source are detailed in Table S1. Serotypes that were identified significantly more frequently for blood culture isolates than for respiratory isolates included: 4, 5, 7F, 8, 12F, 14, 19A and 22F. Serotypes that were identified significantly more frequently for respiratory isolates than for blood culture isolates included: 6C, 7C, 11A, 19F, 21, 23A, 23B, 23F, 31, 34, 35B, 35F and non-typeable isolates. Few serotypes were identified in sufficient annual numbers to allow for trend analysis. Of those with sufficient datapoints, an increasing trend in prevalence of serotype 9N was observed $P<0.0001$ overall (blood and respiratory isolates combined) while no significant trends were observed for serotype 3, 11A, 22F or 23A.

The percentages of *S. pneumoniae* isolates (stratified as all, blood culture and respiratory), from the entire CANWARD study (2007–23) and the most recent study year (2023), that had a serotype covered by PCV13, PCV15, PCV20, PCV21 and PPSV23 are presented in Table 2. The highest percentage of isolates covered by the vaccines by specimen type was observed for PPSV23

and blood culture isolates (77.8% for all years and 85.7% in 2023, respectively). The percentage of isolates with serotypes included in PCV21 was significantly greater than PPSV23 overall and for respiratory isolates ($P<0.0001$) over the course of the study although no significant differences were observed for the 2023-year subset. The percentage of isolates with serotypes included in PPSV23 was significantly greater than PCV20 overall ($P<0.0001$), for blood culture isolates ($P=0.001$) and for respiratory isolates ($P=0.009$). Similarly, the percentage of isolates with serotypes included in PCV20 was significantly greater than PCV15 ($P<0.0001$) and PCV15 included a significantly greater number of isolates than PCV13 ($P<0.0001$) for all specimen sources (all, blood and respiratory). There was no significant difference in the percentage of isolates with vaccine-included serotypes between the most recent study year (2023) and the entire study dataset (2007–23) for any of the vaccines.

The antimicrobial susceptibilities of *S. pneumoniae* isolates from blood cultures and respiratory specimens, overall and by year, are presented in Table 3. Susceptibility rates were significantly lower in *S. pneumoniae* isolates from respiratory specimens compared with blood culture isolates for penicillin (oral and meningitis breakpoints, $P<0.0001$; non-meningitis breakpoints, $P=0.03$), ceftriaxone (meningitis breakpoint, $P=0.006$), clarithromycin ($P=0.02$), clindamycin ($P=0.0003$) and doxycycline ($P<0.0001$). A trend of decreasing ceftriaxone susceptibility (meningitis breakpoint) was observed overall over the course of the study, from 98.8% in 2007 to 90.9% in 2023 ($P<0.0001$). Decreasing susceptibility trends were also observed for clarithromycin overall and specifically for the blood culture isolates ($P=0.01$ and $P=0.007$, respectively), with susceptibility rates decreasing overall from 80.7% in 2007 to 69.1% in 2023 and 87.3% in 2007 to 71.4% in 2023 for the blood culture isolates. Similarly, decreasing susceptibility trends were observed for doxycycline overall and specifically for respiratory isolates ($P=0.04$), with susceptibility rates decreasing overall from 88.8% in 2007 to 83.6% in 2023 and 87.4% in 2007 to 82.4% in 2023 for respiratory isolates. No other significant trends were observed for other antimicrobials and specimen sources for which the trend analysis could be performed [penicillin (IV, non-meningitis overall), clindamycin (overall and respiratory isolates) and trimethoprim-sulfamethoxazole (all sources)].

The overall and annual rates of MDR and/or XDR in *S. pneumoniae* isolates from blood and respiratory specimens are listed in Table 4. Overall, 8.6% of the isolates were MDR/XDR. MDR/XDR rates in the respiratory isolates (10.0%) were significantly higher than the rates in blood culture isolates (5.8%) ($P<0.0001$). The subsets of MDR (7.5% versus 4.6%, $P=0.002$) and XDR (2.6% versus 1.3%, $P=0.02$) were identified at significantly higher rates in respiratory isolates compared with blood culture isolates. Trend analysis demonstrated significant increases in MDR/XDR *S. pneumoniae* from 2007 to 2023 for all isolates ($P=0.004$) and for the respiratory ($P=0.03$) subset. The same trend was observed for the MDR subset of all *S. pneumoniae* ($P=0.005$).

MDR and/or XDR was observed in 26 serotypes of the *S. pneumoniae* isolates overall (17 in blood culture isolates and 22 in respiratory isolates). The serotype distribution of MDR/XDR *S. pneumoniae* isolates in the CANWARD study (2007–23), overall and by specimen source, are displayed in Figure 2. The

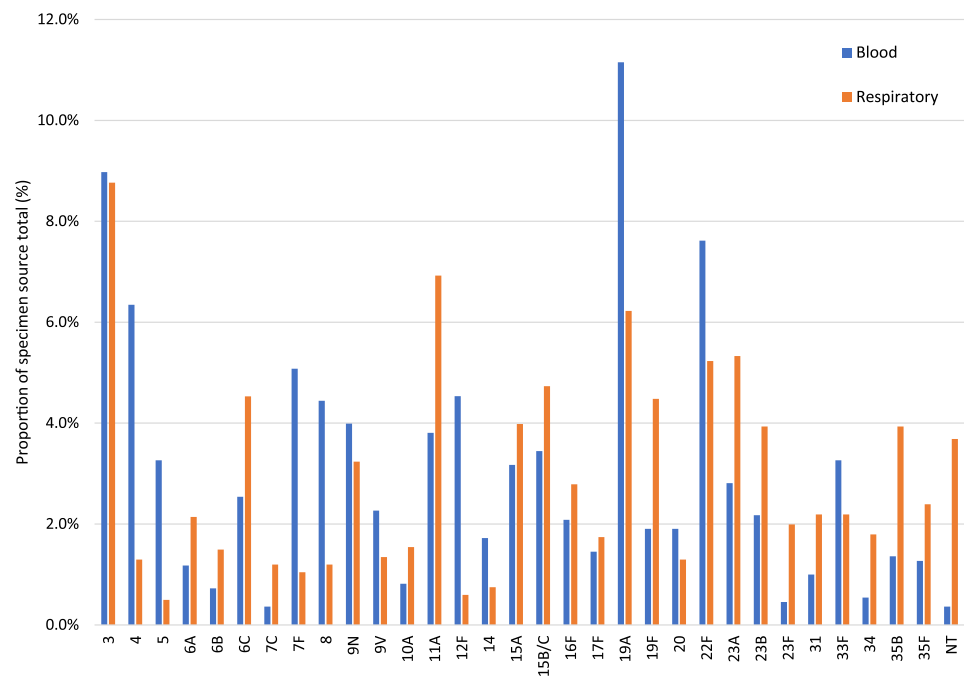


Figure 1. Proportion of *S. pneumoniae* isolated from blood and respiratory specimens by serotype ($n > 30$) in the CANWARD study, 2007–23. Serotypes for which <30 isolates were collected between 2007 and 2023 include: 6D (2; 0 Blood, 2 Respiratory), 7C (28; 4 Blood, 24 Respiratory), 9A (1; 1 Blood, 0 Respiratory), 9L (1; 1 Blood, 0 Respiratory), 10B (1; 0 Blood, 1 Respiratory), 10F (1; 0 Blood, 1 Respiratory), 11B (5; 1 Blood, 4 Respiratory), 11D (1; 0 Blood, 1 Respiratory), 11F (1; 1 Blood, 0 Respiratory), 12A (1; 1 Blood, 0 Respiratory), 13 (14; 5 Blood, 9 Respiratory), 17A (2; 0 Blood, 2 Respiratory), 18B (1; 0 Blood, 1 Respiratory), 18C (25; 7 Blood, 18 Respiratory), 21 (30; 2 Blood, 28 Respiratory), 22A (3; 1 Blood, 2 Respiratory), 25F (1; 1 Blood, 0 Respiratory), 28A (16; 4 Blood, 12 Respiratory), 28F (1; 0 Blood, 1 Respiratory), 29 (5; 2 Blood, 3 Respiratory), 33A (5; 4 Blood, 1 Respiratory), 35A (9; 2 Blood, 7 Respiratory), 35C (4; 0 Blood, 4 Respiratory), 37 (3; 0 Blood, 3 Respiratory), 38 (21; 11 Blood, 10 Respiratory) and 41F (1; 0 Blood, 1 Respiratory).

Table 2. Proportion of *S. pneumoniae* isolates collected from blood and respiratory specimens as part of the CANWARD study with serotypes contained in the pneumococcal conjugate vaccines

Percentage of isolates by specimen source/year(s)					
All		Blood culture isolates		Respiratory isolates	
	2007–23	2023	2007–23	2023	2007–23
Vaccine	($n=3111$)	($n=55$)	($n=1103$)	($n=21$)	($n=2008$)
					($n=34$)
PCV13	35.5	40.0	43.7	57.1	30.9
PCV15	44.1	41.8	54.6	61.9	38.3
PCV20	59.8	67.3	71.6	85.7	53.3
PCV21	73.2	69.1	74.9	52.4	72.3
PPSV23	64.7	69.1	77.8	90.5	57.5
					55.9

predominate serotypes among the MDR/XDR isolates were 19A ($n=78$, 40.6%) and 15A ($n=53$, 27.6%). Serotype 9V was identified more frequently among MDR/XDR blood culture isolates compared with respiratory isolates (13.3% versus 2.6%, $P=0.003$). Serotypes 19F and non-typeable isolates were identified more frequently among MDR/XDR respiratory isolates compared with blood culture isolates (10.9% versus 0%, $P=0.005$ and

9.9% versus 0%, $P=0.009$, respectively). The percent of MDR/XDR *S. pneumoniae* that were serotypes covered by PCV13, PCV15, PCV20, PCV21 and PPSV23 overall were 53.2%, 56.0%, 58.7%, 65.5% and 60.0%, respectively. For the blood/respiratory isolates, the percent of isolates with serotypes covered by PCV13, PCV15, PCV20, PCV21 and PPSV23 were 61.7%/50.5%, 65.0%/53.1%, 70.0%/55.2%, 76.6%/62.0% and 71.7%/56.3%, respectively. For both the blood culture and respiratory isolates, the most common resistance pattern/serotype combinations were MDR 15A resistant to clarithromycin, clindamycin and doxycycline and XDR 19A resistant to clarithromycin, clindamycin, doxycycline, penicillin and trimethoprim/sulfamethoxazole, as detailed in Table S2.

Discussion

S. pneumoniae causes significant morbidity and mortality in the very young, elderly and immunocompromised patients as the causative agent of IPD and a leading cause of respiratory infections.^{1–4} The purpose of this study was to compare the demographics, serotypes and antimicrobial susceptibility rates of *S. pneumoniae* isolates collected from blood cultures and respiratory specimens of patients in Canadian hospitals between 2007 and 2023. A review of the demographic parameters demonstrated that respiratory isolates were collected significantly more frequently from male patients than from female patients.

Table 3. Annual antimicrobial susceptibility testing results for S. pneumoniae collected from blood and respiratory specimens as part of the CANWARD study (2007–23)

CANWARD study year	% susceptible by specimen source (overall/blood/respiratory)									
	Penicillin (oral, penicillin V and IV, meningitis) (n = 2954)	Penicillin (IV, non-meningitis) (n = 2954)	Ceftriaxone (meningitis) (n = 2989)	Ceftriaxone (non-meningitis) (n = 2989)	Clarithromycin (n = 2987)	Clindamycin (n = 2987)	Doxycycline (n = 2986)	Levofloxacin (n = 2987)	SXT ^a (n = 2997)	Vancomycin (n = 2981)
2007	79.8/86.0/76.7	97.7/99.1/97.0	98.8/99.5/98.4	99.7/100/99.5	80.7/87.3/77.3	94.1/96.7/92.8	88.8/91.5/87.4	99.4/100/99.1	86.3/88.4/85.2	100/100/100
2008	80.8/83.3/80.0	98.8/99.1/98.7	97.0/99.1/96.4	99.2/100/99.9	80.2/86.0/78.5	91.3/93.0/90.8	85.3/89.4/84.1	98.6/100/98.2	82.5/85.5/81.7	100/100/100
2009	88.7/9.7/86.3	100/100/100	97.5/99.1/96.4	99.1/100/97.9	83.7/88.9/77.9	96.6/98.1/94.7	88.2/91.7/84.2	99.5/99.1/100	91.1/96.3/85.3	100/100/100
2010	84.5/83.5/85.6	97.7/98.2/97.1	98.1/98.2/98.1	99.1/98.2/100	76.9/73.1/80.8	94.3/94.4/94.2	90.6/90.7/90.4	99.1/99.1/99.0	79.7/78.7/80.8	100/100/100
2011	83.5/91.5/79.7	97.8/98.3/97.6	94.5/96.6/93.5	98.4/100/97.6	76.9/76.3/77.2	89.0/89.8/88.6	84.6/88.1/82.9	98.9/98.3/99.2	85.2/91.5/82.1	100/100/100
2012	89.0/92.0/88.0	97.0/92.0/98.7	94.9/93.8/95.5	100/100/100	76.5/77.1/76.1	90.4/91.7/89.8	86.0/91.7/83.0	98.5/97.9/98.9	89.0/89.6/88.6	100/100/100
2013	84.5/92.5/78.2	98.3/100/97.0	96.1/98.8/94.1	98.9/100/98.0	72.9/68.8/76.2	92.8/96.3/90.1	84.0/87.5/91.2	97.1/98.7/96.0	83.9/84.8/83.2	100/100/100
2014	87.1/90.5/85.7	99.3/100/99.0	94.6/97.6/93.3	100/100/100	77.4/83.3/75.0	92.5/95.2/91.3	85.6/95.2/81.7	100/100/100	82.1/82.9/81.7	100/100/100
2015	79.7/95.3/72.2	100/100/100	98.5/100/97.8	100/100/100	66.2/65.1/66.7	91.7/95.3/90.0	82.7/88.4/80.0	100/100/100	83.5/81.4/84.4	100/100/100
2016	85.5/91.7/82.7	99.1/100/98.8	99.1/100/98.8	100/100/100	76.1/77.8/75.3	92.3/97.2/90.1	89.7/94.4/87.7	100/100/100	88.9/91.7/87.7	100/100/100
2017	83.3/87.0/80.9	100/100/100	95.6/97.8/94.1	100/100/100	79.8/82.6/77.9	90.4/91.3/89.7	88.6/91.3/86.8	100/100/100	85.1/82.6/86.8	100/100/100
2018	81.5/90.5/76.6	100/100/100	94.1/95.2/93.5	100/100/100	79.0/83.3/76.6	90.8/97.6/87.0	80.7/88.1/76.6	99.2/100/98.7	89.9/88.1/90.9	100/100/100
2019	77.5/82.9/73.3	95.0/97.1/93.3	91.3/91.4/91.1	96.3/97.1/95.6	77.5/71.4/82.2	88.8/82.9/93.3	86.3/80.0/91.1	100/100/100	77.5/77.1/77.8	100/100/100
2020	83.8/90.0/80.0	98.8/100/98.0	95.0/93.3/96.0	100/100/100	71.3/76.7/68.0	87.5/90.0/86.0	80.0/86.7/76.0	100/100/100	88.8/90.0/88.0	100/100/100
2021	80.6/85.7/79.3	94.4/100/93.1	86.1/85.7/86.2	100/100/100	77.8/85.7/75.9	91.7/100/89.7	77.8/85.7/75.9	100/100/100	75.0/85.7/72.4	100/100/100
2022	85.1/87.5/82.6	100/100/100	93.6/95.8/91.3	100/100/100	87.2/87.5/87.0	97.9/100/95.7	91.5/95.8/87.0	100/100/100	80.9/79.2/82.6	100/100/100
2023	87.3/95.2/82.4	98.2/100/97.1	90.9/95.2/88.2	100/100/100	69.1/71.4/67.6	92.7/100/88.2	83.6/85.7/82.4	100/100/100	81.8/81.0/82.4	100/100/100
2007–23	82.8/88.1/79.9	98.4/99.1/98.1	96.6/97.8/95.9	99.4/99.7/99.2	78.1/80.5/76.7	92.4/94.8/91.1	86.4/90.1/84.4	99.2/99.5/99.0	84.8/83.9/86.5	100/100/100
P ^a (2007–23)	NA ^c /NA ^c /NA ^c	NS ^b /NA ^c /NA ^c	< 0.0001 ^f /NA ^c /NA ^c	NA ^c /NA ^c /NA ^c	0.011 ^f /NS ^b /NA ^c	NS ^b /NA ^c /NS ^b	0.041 ^f /NA ^c /NA ^c	NA ^c /NA ^c /NA ^c	NS ^b /NS ^b /NS ^b	NA ^c /NA ^c /NA ^c
P ^a (Blood versus Resp.)	<0.0001	0.03	0.006	NS	0.02	0.0003	<0.0001	NS	NS	NS

^aSXT, trimethoprim/sulfamethoxazole.
^bCalculated using the Cochran–Armitage test for trends.
^cNA, not available; isolate counts were <5 in >20% of data points, therefore, the Cochran–Armitage test for trend analysis could not be performed.
^dNS, not statistically significant.
^eSignificance of the difference between total study susceptibility rates (2007–23) of blood culture isolates and respiratory isolates calculated using Fisher’s exact test.
^fI, decreasing trend in susceptibility rate.

Previous studies have shown higher pneumococcal carriage rates in men than women,²⁰ which may result in a higher frequency of respiratory infections. The current study also demonstrated that significantly more *S. pneumoniae* isolates were collected from blood cultures than respiratory specimens in children <2 years of age. The high burden of IPD among young children has been well documented.^{1,2,8}

Notable differences in the serotypes identified from blood culture and respiratory isolates were observed in this study. Serotypes 4, 7F, 8, 19A and 22F were predominant (included in the top 10) from blood cultures and isolated significantly more frequently from that specimen source than from respiratory isolates. These serotypes have been reported to have high invasive disease potential in studies comparing serotypes associated with nasopharyngeal carriage and those associated with IPD in the USA^{21,22} and Portugal.²³ However, serotypes 19A and 22F were also predominant serotypes identified from respiratory specimens in our study. Similarly, serotype 3 is considered a serotype with high invasive potential but was identified among the top 10 serotypes for both the blood culture and respiratory isolates. Sá-Leão et al. reported heterogeneous disease potential for some serotypes, including serotypes 3, 19A and 22F, with specific clones demonstrating increased invasive potential,²³ which may partially explain why a number of serotypes were associated with both specimen sources in our study. Serotypes 6C, 19F, 23A and 35B were predominant (included in the top 10) among respiratory isolates and were detected more frequently from that specimen source than from blood culture isolates in our study. These serotypes have been reported to have a lower invasive disease potential and to be associated with nasopharyngeal carriage.^{21–23} Serotypes 11A and 15B/C are associated with nasopharyngeal carriage but were isolated among the top 10 serotypes from both blood culture and respiratory isolates, although notably, serotype 11A was significantly more common among the respiratory isolates. Heterogeneous invasive potential has also been reported for serotype 11A.²³

Although few serotypes were observed in sufficient annual frequencies to allow for trend analysis, the proportion of isolates with serotype 9N was found to increase over the course of the study (2007–23) while no trends were observed for serotypes 3, 11A, 22F and 23F. The increase in serotype 9N has been previously reported in Canadian IPD isolates.²⁴ Notably, serotype 9N was one of the most common non-PCV13 serotypes reported from adults with IPD in the WHO-commissioned Pneumococcal Serotype Replacement and Distribution Estimation (PSERENADE) project.²⁵ PPSV23 and the newly available PCV21 provide coverage of serotype 9N; it will be important to monitor if use of PCV21 reverses this trend in future years. The continued predominance of serotype 3, despite its inclusion in all conjugate vaccine formulations, has been noted worldwide^{25,26} and is postulated to be due to lower vaccine effectiveness for serotype 3.²⁷ While serotype 22F is included in PCV15, PCV20 and PCV21, these conjugate vaccines have only been recently introduced in Canada so we would not anticipate that they would have yet impacted the serotype distribution of circulating *S. pneumoniae* strains.

Antimicrobial susceptibility rates for penicillin, ceftriaxone, clarithromycin, clindamycin and doxycycline were significantly lower in respiratory isolates compared with blood culture isolates. Similarly, penicillin, macrolide and tetracycline resistance

rates were found to be higher in non-IPD isolates than IPD isolates in a multicentre evaluation of *S. pneumoniae* from adults in the USA.⁴ While *S. pneumoniae* usually only transiently infects a patient during a case of IPD, pneumococcal carriage in the nasopharynx is often long term. A longer duration of nasopharyngeal carriage of *S. pneumoniae* provides a greater risk of antibiotic exposure, resulting in a fitness advantage to maintaining resistance mechanisms,²⁸ and supports the observations presented herein. The susceptibility rates of the *S. pneumoniae* isolated from respiratory specimens in our study were comparable to the rates described for Canadian isolates by the Canadian Respiratory Organism Surveillance Study (CROSS)²⁹ conducted a decade earlier (1997–2002), except for a notable increase in the resistance rates for clarithromycin, clindamycin and doxycycline in the contemporary dataset. The susceptibility rates of the invasive *S. pneumoniae* isolates in this study were similar to those reported for IPD isolates collected between 2011 and 2020 in Canada³⁰ with slightly greater susceptibility rates observed in the CANWARD study for penicillin (IV, meningitis), clarithromycin and clindamycin. The overall decreasing trends in clarithromycin and doxycycline susceptibility rates observed in this study are partially attributable to the predominant 15A and 19A MDR isolates, which most commonly display resistance to both clarithromycin and doxycycline. The association of serotypes 12F, 15A, 19A and 22F with macrolide resistance has been previously discussed.¹² MDR rates were significantly higher in respiratory isolates than in blood culture isolates. The Mohanty et al. study from the USA reported similar MDR rates, 5.0% for IPD and 12.3% for non-IPD isolates,⁴ to those reported in this study, 5.8% for blood culture and 10.0% for respiratory isolates. An increasing trend of MDR/XDR was observed throughout the study years (2007–23) for isolates from all sources and specifically for the respiratory isolates. The MDR rates for respiratory isolates of *S. pneumoniae* have been significantly increasing for many years as this trend was observed in the earlier Canadian study (CROSS) starting in 1997.²⁹

Overall and for both specimen sources, the most common MDR serotypes were 15A and 19A. Differences by specimen source among the MDR isolates were noted for other serotypes with serotypes 19F and non-typeable MDR isolates being exclusively identified in respiratory isolates and MDR serotype 9V being more commonly identified in blood culture isolates. The emergence of MDR 15A and 19A has been consistently described in international studies.^{24,31,32}

A greater proportion of blood culture isolates had serotypes covered by vaccines compared with respiratory isolates. This observation was expected as this study covered a time period in which multiple vaccines were developed and implemented as part of public health programs to address the predominantly circulating serotypes causing IPD. The significant increases in the proportion of isolates targeted by the higher-valency conjugate vaccines, compared with PCV13, observed in this study were comparable with those reported globally as part of the PSERENADE project.²⁵ The proportion of MDR isolates with serotypes contained in PCV13 and PCV15 was greater than the vaccines' coverage of serotypes in all of the *S. pneumoniae* isolates. Conversely, PCV20, PCV21 and PPSV23's coverage of serotypes for all *S. pneumoniae* isolates in the study was greater than the proportion of MDR isolates with serotypes included in those vaccines. The additional serotypes

Table 4. Annual rates and trend analysis of MDR and XDR *S. pneumoniae* collected from blood and respiratory specimens as part of the CANWARD study (2007–23)

Isolate Source/MDR Phenotype	Percentage MDR or XDR by year ^a																	P ^b	% 2007–23
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023		
All																			
MDR/XDR	6.5	9.5	3.4	7.1	11.5	10.1	7.8	10.4	8.3	7.7	8.8	11.8	12.5	16.3	13.9	2.1	14.5	0.004†	8.6
MDR	5.5	7.2	3.0	3.8	7.1	6.1	5.0	6.9	6.8	7.7	6.1	10.1	8.8	15.0	8.3	2.1	12.7	0.005†	6.5
XDR	0.9	2.4	0.5	3.3	4.4	4.0	2.8	3.5	1.5	0	2.6	1.7	3.8	1.3	5.6	0.0	1.8	NA ^c	2.1
Blood																			
MDR/XDR	3.8	7.1	2.8	5.6	10.2	8.3	2.5	4.9	4.7	0	8.7	7.1	17.1	13.3	14.3	4.2	9.5	NA ^c	5.8
MDR	3.3	6.2	2.8	2.8	6.8	0	1.3	4.9	2.3	0	6.5	7.1	14.3	13.3	14.3	4.2	9.5	NA ^c	4.6
XDR	0.5	0.9	0	2.8	3.4	8.3	1.3	0	2.3	0	2.2	0	2.9	0	0	0	0	NA ^c	1.3
Respiratory																			
MDR/XDR	7.8	10.3	4.2	8.7	12.2	10.7	11.9	12.6	10.0	11.1	8.8	14.3	8.9	18.0	13.8	0	17.6	0.03†	10.0
MDR	6.6	7.4	3.2	4.8	7.3	8.0	7.9	7.8	8.9	11.1	5.9	11.7	4.4	16.0	6.9	0	14.7	NS ^d	7.5
XDR	1.2	2.8	1.1	3.8	4.9	2.7	4.0	4.9	1.1	0	2.9	2.6	4.4	2.0	6.9	0	2.9	NA ^c	2.6

^aA total of 2939 isolates had complete antimicrobial susceptibility testing profiles for the MDR analysis. The number of isolates per year was 635 in 2007 (212 Blood; 423 Respiratory), 503 in 2008 (113 Blood; 390 Respiratory), 203 in 2009 (108 Blood; 95 Respiratory), 212 in 2010 (108 Blood; 104 Respiratory), 182 in 2011 (59 Blood; 123 Respiratory), 99 in 2012 (24 Blood; 75 Respiratory), 180 in 2013 (79 Blood; 101 Respiratory), 144 in 2014 (41 Blood; 103 Respiratory), 133 in 2015 (43 Blood; 90 Respiratory), 117 in 2016 (36 Blood; 81 Respiratory), 114 in 2017 (36 Blood; 81 Respiratory), 119 in 2018 (42 Blood; 77 Respiratory), 80 in 2019 (35 Blood; 45 Respiratory), 80 in 2020 (30 Blood; 50 Respiratory), 36 in 2021 (7 Blood; 29 Respiratory), 47 in 2022 (24 Blood; 23 Respiratory) and 55 in 2023 (21 Blood; 34 Respiratory).

^bP < 0.05 indicates statistical significance in annual percentage of MDR/XDR and MDR rates according to the Cochran–Armitage test for trend.

^cNA, not available; isolate counts were <5 in >20% of data points, therefore, the Cochran–Armitage test for trend analysis could not be performed.

^dNS, not statistically significant.

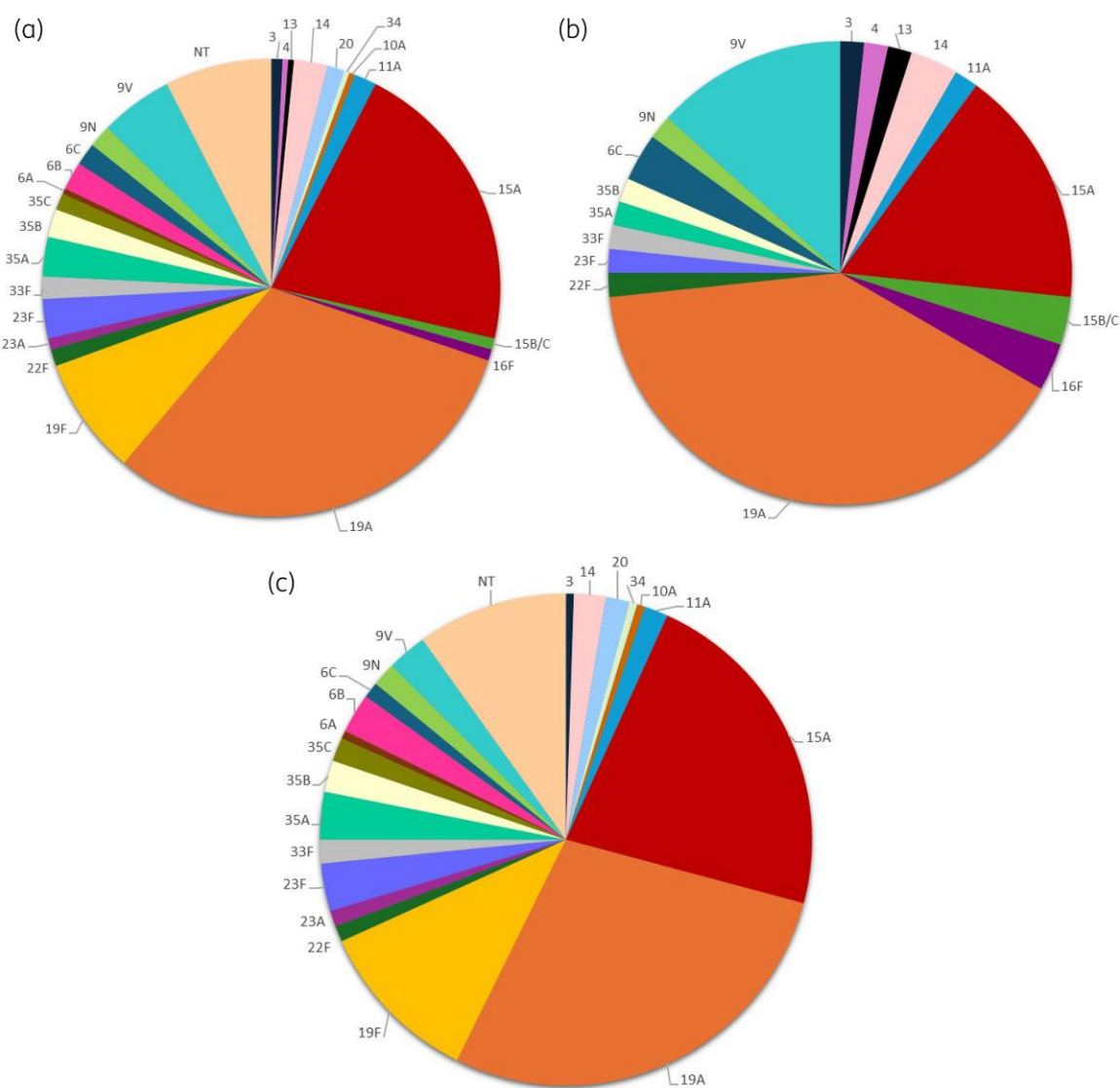


Figure 2. Serotype distribution of MDR/XDR *S. pneumoniae* isolates in the CANWARD study, 2007–23. a) All MDR/XDR isolates (n=252), b) MDR/XDR isolates from blood culture isolates (n=60), c) MDR/XDR isolates from respiratory isolates (n=192).

included in PCV20 and PPSV23, compared with PCV15, were common (>15%) in the overall dataset but uncommon (<5%) among the MDR isolates. While PCV21 does not provide coverage for some of the common MDR isolates, notably those with serotype 19F and 9V, it is the only currently available vaccine that provides coverage for serotype 15A, which is predominant among the MDR isolates. The inclusion of 15A in PCV21 is a significant development in the fight against antimicrobial resistance, particular MDR, in *S. pneumoniae*.

The previously described limitations of the CANWARD study in regards to evaluating antimicrobial resistance and serotype patterns in *S. pneumoniae* remain relevant.¹² Notably, the study only collects the first 100 respiratory isolates each year and the first 10 blood isolates per month (January–October), which may not fully capture seasonal variation of pneumococcal disease and may be impacted by regional IPD outbreaks. The identity and annual number of contributing sites has varied slightly throughout the

study, which may impact the distribution of pneumococcal isolates submitted. However, replacement participating sites were specifically selected with an intent to maintain the geographical representation of the study.

Overall, this study highlighted numerous differences between Canadian isolates of *S. pneumoniae* from blood cultures and respiratory specimens. The noted differences between specimen sources and observed trends in serotype prevalence, decreased antimicrobial susceptibilities and increasing MDR rates support both ongoing pneumococcal surveillance as well as further development of pneumococcal vaccines.

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CANWARD data can also be found at www.can-r.ca, the official website of the Canadian Antimicrobial Resistance Alliance (CARA).

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Transparency declarations

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Disclaimer

The opinions expressed in this paper are those of the authors, and do not necessarily represent those of Avir Pharma Inc., Iterum Therapeutics, Merck Canada Inc., Paladin Labs, Pfizer, Sandoz Canada, Shionogi Inc., Sunovion Pharmaceuticals Canada Inc., Venatorx Pharmaceuticals Inc., Verity Pharmaceuticals and Xediton Pharmaceuticals Inc.

Supplementary data

Figure S1 and Tables S1 and S2 are available as [Supplementary data](#) at JAC Online.

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