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# Vaccine Coverage of PCV-13, PCV-15 and PCV-20 against Antimicrobial-nonsusceptible and Multidrug-resistant *Streptococcus pneumoniae* (SAVE 2011-2020)

A.R. GOLDEN[1], H.J. ADAM[2,3], M. BAXTER[2], I. MARTIN[1], W. DEMCZUK[1], M.R. MULVEY[1,2], J.A. KARLOWSKY[2,3], G.G. ZHANEL[2], and the CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE (CARA)

[1]Public Health Agency of Canada - National Microbiology Laboratory (PHAC-NML), [2]University of Manitoba, and [3]Shared Health, Winnipeg, Manitoba, Canada

Dr. Alyssa Golden
National Microbiology Laboratory
Public Health Agency of Canada
Winnipeg, MB, Canada R3E 3R2
alyssa.golden@phac-aspc.gc.ca

## Introduction

The pneumococcal conjugate vaccine Prevnar®, covering multiple *Streptococcus pneumoniae* serotypes of concern, has reduced systemic infections and recurrent upper respiratory tract infections in children [1, 2]. The 13-valent pneumococcal conjugate vaccine (PCV-13, serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) is currently recommended for routine prevention of invasive pneumococcal disease (IPD) in Canada [3].

Two new conjugate vaccines have been developed: PCV-15 (PCV-13 serotypes plus 22F and 33F) and PCV-20 (PCV-15 serotypes plus 8, 10A, 11A, 12F and 15BC). As of late 2021, the United States Advisory Committee on Immunization Practices now recommends using PCV-15 or PCV-20 in PCV-naïve adults ≥65 years or >18 years with certain underlying conditions [4]. PCV-15 and PCV-20 have also recently received approval by Health Canada for the prevention of IPD and IPD/CAP, respectively, in adults ≥18 years [5].

It is critical to understand the spread and evolution of these novel vaccine serotypes as PCV-15/PCV-20 formulations become the standard of care across North America. Therefore, the purpose of this study was to compare the proportion of IPD isolates collected in Canada from 2011 to 2020 that demonstrated a PCV-13, PCV-15 or PCV-20 serotype.

## Materials and Methods

### Isolate Collection

In collaboration with CARA, selected Canadian public health laboratories and PHAC-NML, the SAVE study collected 14,138 invasive isolates of *S. pneumoniae* from 2011 to 2020. *S. pneumoniae* isolated from sterile sites are forwarded from the Canadian public health laboratories [Canadian Public Health Laboratory Network (CPHLN)] to the Public Health Agency of Canada – National Microbiology Laboratory (PHAC-NML). After permission of the submitting CPHLN sites (as detailed in the acknowledgments), the *S. pneumoniae* isolates were forwarded to CARA.

### Serotyping

Serotyping was performed using the Quellung reaction with pool/group/type/factor commercial antisera (SSI, Copenhagen) with supplementary molecular serotyping by PCR multiplex as described: (http://www.cdc.gov/ncidod/biotech/strep/pcr.htm).

### Antimicrobial Susceptibility Testing

Susceptibility testing was performed using custom designed in-house manufactured antimicrobial susceptibility panels according to CLSI methods [6]. MICs were determined by the broth microdilution method, which was performed in adherence to all CLSI practices and quality control measures and interpreted utilizing CLSI criteria [6, 7]. Multidrug/extensive-drug resistance (MDR/XDR) was defined as resistance to 3 or more/5 or more antimicrobial classes, respectively.

### Statistical Analysis

Statistical significance ($P<0.05$) of coverage differences was assessed using the two-tailed Fisher's exact test, or chi-squared test in the case of a large sample size (>5000 isolates).

## Results

The Canadian Antimicrobial Resistance Alliance (CARA) has studied the contribution of PCV-13, PCV-15 and PCV-20 serotypes to IPD prevention across Canada, revealing significant differences in patient subgroups and over time **(Figure 1)**.

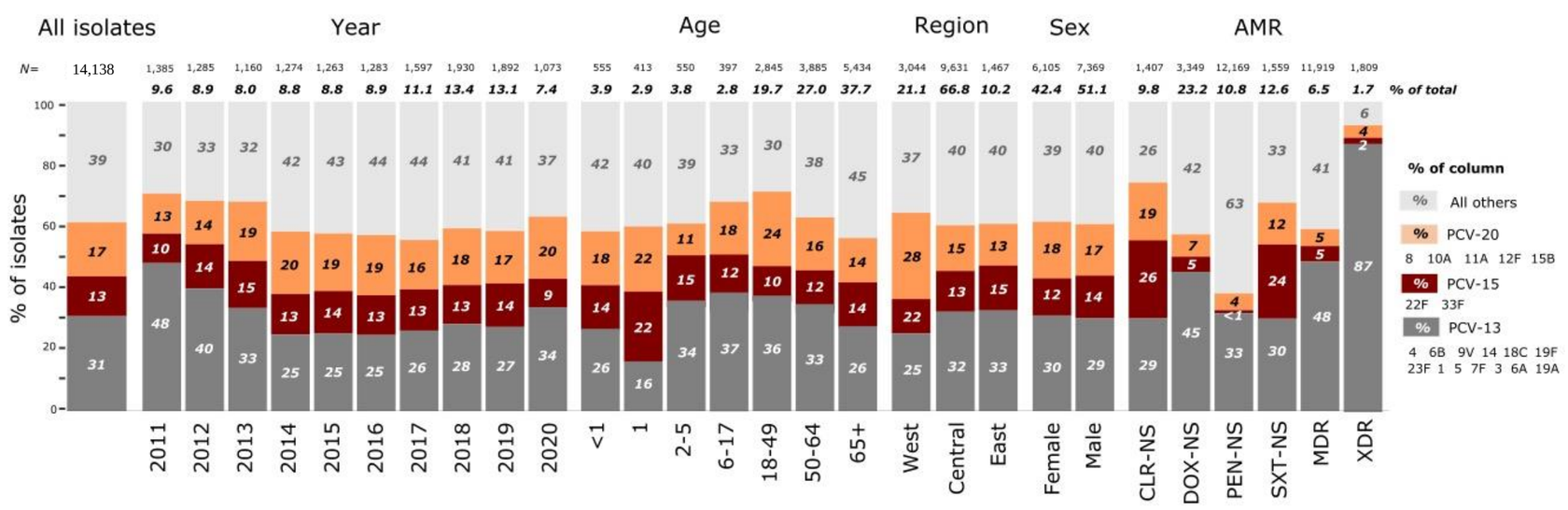


***Figure 1: Graphical representation of differences between PCV-13/PCV-15 and PCV-15/PCV-20 coverage in all isolates, by age group, and resistance phenotype. Numbers on bars indicate percentages.***

CLR, clarithromycin; DOX, doxycycline; PEN, penicillin (oral penicillin V breakpoints - nonsusceptible MIC ≥0.12 mg/L); SXT, trimethoprim-sulfamethoxazole; NS, nonsusceptible; MDR, multidrug-resistant (resistant to 3 or more antibiotic classes); XDR, extensively drug resistant (5 or more classes).

Each higher-valency PCV accounted for a higher proportion of IPD isolates than the preceding formulation, both overall and by demographic category (age group, region and sex) **(Table 1)**. A significantly higher proportion of clarithromycin-, doxycycline- and SXT-nonsusceptible and MDR IPD isolates in Canada were serotypes contained in PCV-15 and PCV-20 compared to PCV-13. Coverage of XDR isolates was not significantly different across the vaccine formulations.

***Table 1: Proportion of invasive S. pneumoniae isolates demonstrating PCV-13, PCV-15 or PCV-20 serotype, by demographic category.***

| Category (n) | Proportion of isolates with vaccine serotype, n (%) | | | *P*-value | |
|---|---|---|---|---|---|
| | PCV-13 | PCV-15 | PCV-20 | 13vs15 | 15vs20 |
| **All SPN (14138)** | 4334 (30.7) | 6155 (43.5) | 8624 (61.0) | <0.0001 | <0.0001 |
| **Age Group** (years) | | | | | |
| 0 - <1 (369) | 97 (26.3) | 148 (40.1) | 214 (58.0) | <0.0001 | <0.0001 |
| 1 - <2 (412) | 66 (16.0) | 156 (37.9) | 245 (59.5) | <0.0001 | <0.0001 |
| 2 - <6 (550) | 187 (34.0) | 269 (48.9) | 333 (60.5) | <0.0001 | <0.0001 |
| 6 - <18 (397) | 146 (36.8) | 194 (48.9) | 268 (67.5) | 0.0007 | <0.0001 |
| 18 - <50 (2845) | 1023 (36.0) | 1303 (45.8) | 1992 (70.0) | <0.0001 | <0.0001 |
| 50 - <65 (3884) | 1291 (33.2) | 1742 (44.9) | 2428 (62.5) | <0.0001 | <0.0001 |
| >65 (5436) | 1426 (26.2) | 2215 (40.7) | 2984 (54.9) | <0.0001 | <0.0001 |
| **Region** [a] | | | | | |
| Western Canada (3045) | 763 (25.1) | 1102 (36.2) | 1950 (64.0) | <0.0001 | <0.0001 |
| Central Canada (9626) | 3094 (32.1) | 4363 (45.3) | 5787 (60.1) | <0.0001 | <0.0001 |
| Eastern Canada (1467) | 477 (32.5) | 690 (47.0) | 887 (60.5) | <0.0001 | <0.0001 |
| **Sex** | | | | | |
| Female (6107) | 1830 (30.0) | 2673 (43.8) | 3691 (60.4) | <0.0001 | <0.0001 |
| Male (7368) | 2279 (30.9) | 3162 (42.9) | 4507 (61.2) | <0.0001 | <0.0001 |

[a] Western Canada includes Saskatchewan and Manitoba; Central Canada includes Ontario and Quebec; Eastern Canada includes Newfoundland and Labrador, Nova Scotia, Prince Edward Island and New Brunswick.

***Table 2: Proportion of invasive S. pneumoniae isolates demonstrating PCV-13, PCV-15 or PCV-20 serotype, by resistance phenotype.***

| Resistance Phenotype (n) | Proportion of isolates with vaccine serotype, n (%) | | | *P*-value [a] | |
|---|---|---|---|---|---|
| | PCV-13 | PCV-15 | PCV-20 | 13vs15 | 15vs20 |
| **All SPN (14138)** | 4334 (30.7) | 6155 (43.5) | 8624 (61.0) | <0.0001 | <0.0001 |
| Clarithromycin-nonsusceptible (3352) | 955 (28.5) | 1831 (54.6) | 2481 (74.0) | <0.0001 | <0.0001 |
| Doxycycline-nonsusceptible (1407) | 634 (45.1) | 705 (50.1) | 808 (57.4) | 0.0082 | <0.0001 |
| Penicillin-nonsusceptible [a] (1558) | 516 (33.1) | 527 (33.8) | 584 (37.5) | NS | 0.0362 |
| SXT-nonsusceptible (1808) | 537 (29.7) | 968 (53.5) | 1200 (66.4) | <0.0001 | <0.0001 |
| MDR (902) | 433 (48.0) | 481 (53.3) | 532 (59.0) | 0.0268 | 0.0176 |
| XDR (215) | 188 (87.4) | 192 (89.3) | 202 (94.0) | NS | NS |

[a] Oral penicillin V breakpoints (nonsusceptible MIC ≥0.12 mg/L); NS, not significant; SXT, trimethoprim-sulfamethoxazole.

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## Conclusions

1. Investigational higher-valency PCVs provided significantly greater serotype coverage overall, and for patients in all age groups, regions and both genders (*P*<0.0001).
2. In general, a significantly higher proportion of antimicrobial-nonsusceptible and MDR IPD isolates in Canada are serotypes contained in PCV-15 and PCV-20 compared to PCV-13 (*P*≤0.0362).
3. Coverage of penicillin-nonsusceptible isolates was not significantly higher for PCV-15 in comparison to PCV-13. This is likely because serotypes 22F and 33F are not commonly associated with penicillin resistance [8].
4. Serotype coverage of XDR isolates did not significantly differ between PCV-13, PCV-15 and PCV-20.