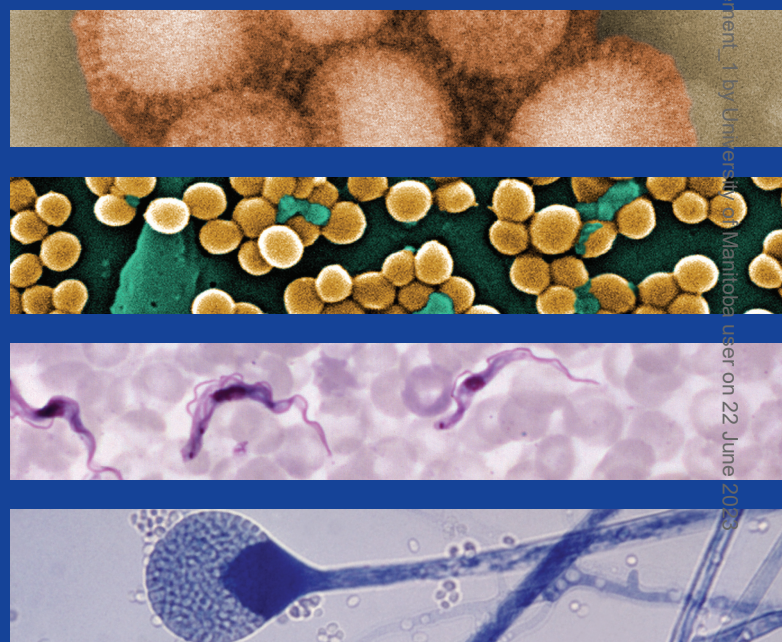


Journal of Antimicrobial Chemotherapy

Supplement 1

Streptococcus pneumoniae Serotyping and Antimicrobial Susceptibility: Assessment for Vaccine Efficacy in Canada After the Introduction of PCV-13: 10 Years of SAVE (2011-2020)



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***Streptococcus pneumoniae* Serotyping and Antimicrobial Susceptibility: Assessment for Vaccine Efficacy in Canada After the Introduction of PCV-13: 10 Years of SAVE (2011–2020)**

Edited by

Athanassios Tsakris

Department of Microbiology, Medical School, University of Athens, Athens, Greece

James Hurley

Grampians Health, Ballarat, Victoria, Australia

Melbourne Medical School, University of Melbourne, Melbourne, Australia

Alan Johnson

Journal of Antimicrobial Chemotherapy, Birmingham, UK

Russell Lewis

Department of Molecular Microbiology, University of Padua, Padua, Italy

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Preface

*Corresponding author. E-mail: atsakris@med.uoa.gr

Streptococcus pneumoniae continues to be a major cause of morbidity and mortality worldwide, associated with invasive (e.g. bacteraemia, meningitis) and non-invasive (e.g. community-acquired respiratory tract) infections. Invasive pneumococcal disease (IPD) is an ongoing threat to global health, with severe socio-economic impacts, and MDR *S. pneumoniae* is a potentially emerging concern amongst IPD.

This Supplement to the *Journal of Antimicrobial Chemotherapy* (JAC) comprises five articles that provide a comprehensive examination of the changing patterns of antimicrobial resistance, serotype distribution, genotypic relatedness and virulence of invasive *S. pneumoniae* isolates obtained across Canada over a 10 year period of the SAVE study. SAVE is an ongoing, annual, national study between the Canadian Antimicrobial Resistance Alliance (CARA) and the National Microbiology Laboratory, focused on characterizing invasive isolates of *S. pneumoniae* obtained across Canada. Some very interesting findings of this national survey, covering the period between 2011 and 2015, have been published in a previous supplement of JAC (Vol. 73, Suppl 7, July 2018).

Although the 14 138 invasive isolates of the current study exhibited consistent *in vitro* susceptibility, and the vaccine coverage of MDR pneumococcal serotypes was high, the increasing diversity of serotypes observed among the MDR isolates over time has shown the ability of the pathogen to evolve rapidly. Additionally, PCV15 and PCV20 pneumococcal vaccines, compared with PCV13, covered more IPD isolates, both overall or when stratified by patient age, region, sex, individual antimicrobial resistance phenotypes or MDR phenotype.

The data presented highlight the evolution of *S. pneumoniae* under the pressure of vaccination and antimicrobial usage, as well as the vaccine coverage against IPD strains. Therefore, the

articles allow clinicians and researchers to view the current status of invasive pneumococcal infections in Canada with, potentially, an insight into both national and global trends. Finally, the survey underlines the need for continued genomic surveillance of *S. pneumoniae* in order to monitor the appearance of new and evolving lineages.

Athanasios Tsakris^{1*}

James Hurley^{2,3}

Alan Johnson⁴

Russell Lewis⁵

¹Department of Microbiology, Medical School, University of Athens, Athens, Greece

²Grampians Health, Ballarat, Victoria, Australia

³Melbourne Medical School, University of Melbourne, Melbourne, Australia

⁴Journal of Antimicrobial Chemotherapy, Birmingham B1 3NJ, UK

⁵Department of Molecular Microbiology, University of Padua, Padua, Italy

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Transparency declarations

None to declare.

***Streptococcus pneumoniae* serotyping and antimicrobial susceptibility: assessment for vaccine efficacy in Canada after the introduction of PCV13**

George G. Zhanel^{1*}, Joseph P. Lynch III² and Heather J. Adam^{1,3}

¹Department of Medical Microbiology and Infectious Diseases, Max Rady College of Medicine, University of Manitoba, Room 543-745, Bannatyne Avenue, Winnipeg, Manitoba R3E 0J9, Canada; ²Division of Pulmonary, Critical Care Medicine, Allergy, and Clinical Immunology Department of Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave, Room 37-131 CHS, Los Angeles, CA 90095, USA; ³Clinical Microbiology, Shared Health, MS673-820 Sherbrook Street, Winnipeg, Manitoba R3A 1R9, Canada

*Corresponding author. E-mail: ggzhanel@pcsinternet.ca

Background: *Streptococcus pneumoniae* continues to be an important bacterial pathogen associated with invasive (e.g. bacteraemia, meningitis) and non-invasive (e.g. community-acquired respiratory tract) infections worldwide. Surveillance studies conducted nationally and globally assist in determining trends over geographical areas and allow comparisons between countries.

Objectives: To characterize invasive isolates of *S. pneumoniae* in terms of their serotype, antimicrobial resistance, genotype and virulence and to use the serotype data to determine the level of coverage by different generations of pneumococcal vaccines.

Methods: SAVE (*Streptococcus pneumoniae* Serotyping and Antimicrobial Susceptibility: Assessment for Vaccine Efficacy in Canada) is an ongoing, annual, national collaborative study between the Canadian Antimicrobial Resistance Alliance (CARE) and the National Microbiology Laboratory, focused on characterizing invasive isolates of *S. pneumoniae* obtained across Canada. Clinical isolates from normally sterile sites were forwarded by participating hospital public health laboratories to the Public Health Agency of Canada—National Microbiology Laboratory and CARE for centralized phenotypic and genotypic investigation.

Results: The four articles in this Supplement provide a comprehensive examination of the changing patterns of antimicrobial resistance and MDR, serotype distribution, genotypic relatedness and virulence of invasive *S. pneumoniae* obtained across Canada over a 10 year period (2011–2020).

Conclusions: The data highlight the evolution of *S. pneumoniae* under pressure by vaccination and antimicrobial usage, as well as vaccine coverage, allowing both clinicians and researchers nationally and globally to view the current status of invasive pneumococcal infections in Canada.

Streptococcus pneumoniae is a genetically diverse, potentially antimicrobial-resistant (AMR) pathogen whose main ecological niche is the nasopharynx, frequently resulting in asymptomatic carriage in young children.^{1–6} *S. pneumoniae* is transmitted by direct contact with contaminated respiratory droplets or secretions, with carriage serving as an important risk factor for horizontal transmission.^{3,4} *S. pneumoniae* (pneumococcus) can cause invasive pneumococcal disease (IPD) but is also well known as the most common and important bacterial cause of acute upper respiratory tract infections (e.g. otitis media, sinusitis) as well as lower respiratory tract infections.^{1–7} IPD more commonly occurs in children less than 2 years of age, adults over 65 years, adults with comorbid conditions and in immunocompromised individuals.^{3,4,6,7–10} Infections caused

by *S. pneumoniae* result in frequent antimicrobial consumption, contributing to the selection of AMR and MDR phenotypes.^{3–6,8,9}

The pneumococcal genome demonstrates considerable plasticity, with individual strains varying by up to 10%.⁴ *S. pneumoniae* may possess conjugative transposons that confer AMR as well as MDR phenotypes with resistance to antimicrobial classes including β -lactams, macrolides, lincosamides, tetracyclines, sulphonamides and even fluoroquinolones.^{4,5,8,9} The unusually large number of ISs can account for up to 5% of the pneumococcal genome.⁴ The pneumococcal genome may contain numerous copies of direct-repeat DNA elements, providing recombination hotspots that help account for the genetic variability between strains.⁴ In addition, this organism serves as a model organism for natural transformation, being able to take

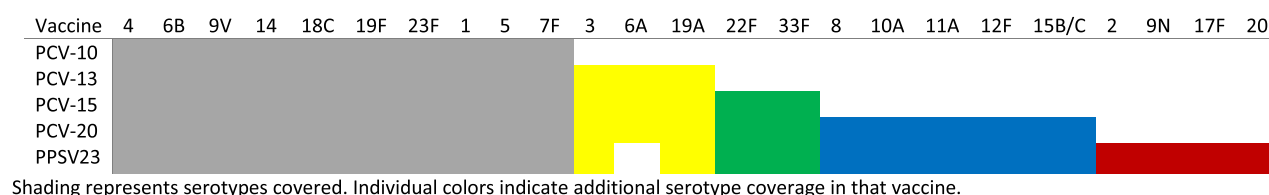


Figure 1. Serotypes contained in various conjugated and polysaccharide vaccines. Shading represents serotypes covered. Individual colours indicate additional serotype coverage in that vaccine. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

up exogenous DNA and utilize homologous recombination to incorporate this DNA into its genome.⁴ Transformation is known to be responsible for alterations in PBPs conferring reduced susceptibility and/or resistance to penicillins and cephalosporins.^{4,9,11}

S. pneumoniae resistance to penicillin and MDR rates are variable across the globe.^{4,11–14} The first MDR pneumococcus was identified in South Africa in 1977.^{4,14} Subsequently, a number of MDR pneumococcal lineages with resistance to three or more antimicrobials have been reported to be circulating worldwide.¹⁴ AMR pneumococcal infections are associated with a substantial burden in terms of morbidity, mortality and healthcare resource utilization.¹⁴ In addition, pneumococcal infections that are AMR are associated with worse patient outcomes resulting from a significantly greater risk of in-hospital death due to pneumonia.¹⁴

The pneumococcal polysaccharide capsule is the most important virulence factor possessed by *S. pneumoniae*. Approximately 100 pneumococcal serotypes have been elucidated on the basis of their polysaccharide capsular antigens, which are categorized according to the unique glycan components and linkages that constitute the capsular polysaccharide of each serotype.^{5,8} Different serotypes have been associated with colonization, mucosal diseases such as otitis media and pneumonia, IPD, severe outcomes, AMR and MDR.^{3–8,10–13} Only a small proportion of the 100 serotypes are associated with the majority of IPD worldwide.^{5,8} Different serotypes arise from point mutations as well as the ease with which *S. pneumoniae* takes up DNA from its surroundings. Each serotype has the ability to elicit type-specific protective immunity, and this characteristic is the basis for phenotypic typing of *S. pneumoniae* isolates using the Quellung reaction.^{5,6}

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) was licensed in 1983 and is still in use today, covering serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F (Figure 1).^{3,12,15} This vaccine is recommended by various national bodies including the Canadian National Advisory Committee on Immunization (NACI) for routine preventative use in a variety of individuals at high risk for IPD.¹⁵ The 7-valent pneumococcal conjugate vaccine (PCV7), which covers serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, was introduced in Canada between 2002 and 2005 to prevent cases of IPD. This conjugate vaccine dramatically reduced the prevalence of vaccine serotypes through active vaccination and herd immunity; however, the introduction of this vaccine was associated with a subsequent increase in non-vaccine serotypes, notably 19A, leading to the introduction of PCV13 (covering serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F)

(Figure 1).^{3,4,7,12} It should be mentioned that conjugate vaccines comprise capsular polysaccharides chemically coupled to proteins that increase their immunogenicity in young children, who do not respond well to polysaccharide antigens alone. Since 2010, in Canada as in many Western countries, PCV13 has been recommended for use in young children and high-risk individuals.¹⁵ More recently PCV13 has been recommended in immunocompromised adults as well as all adults 65 years of age and older.¹⁵ Thus, with the increased use of PCV13 in Canada in the early 2010s, we hypothesized that certain individual non-vaccine serotypes would increase as a cause of IPD and hence we started the SAVE study (*Streptococcus pneumoniae* Serotyping and Antimicrobial Susceptibility: Assessment for Vaccine Efficacy in Canada). In addition, we hypothesized that successful emerging non-vaccine serotypes would be AMR and MDR, clonal in nature and have the potential to increase overall rates of IPD in Canada. Recently, higher valency pneumococcal conjugate vaccines, PCV15 and PCV20, have been studied and introduced to the market in several countries including Canada.^{16–19} With the successful development of these newer conjugate vaccines (i.e. PCV15 and PCV20), the CDC Advisory Committee of Immunization Practices (ACIP) has provided recommendations for use in adults in the USA and thereafter Canadian recommendations followed (Figure 1).¹⁹

Clinical microbiology laboratories provide rapid detection of susceptible and resistant organisms for individual patients. Surveillance studies conducted nationally and/or globally can assist in determining resistance trends over time and over specific geographic areas, patient demographics and allow comparisons between countries. Such routine surveillance studies, despite their limitations and inherent biases, contribute to our understanding of the ongoing evolution of antimicrobial resistance. SAVE is an ongoing (2011 to present), annual, national study focused on characterizing invasive isolates of *S. pneumoniae* obtained across Canada after the introduction of PCV13. The SAVE study is possible due to a collaboration between the Canadian Antimicrobial Resistance Alliance and Public Health Agency of Canada—National Microbiology Laboratory. We previously published a Supplement in the *Journal of Antimicrobial Chemotherapy* after the initial 5 years of the SAVE study (2011–2015) where we reported on 6207 invasive isolates of *S. pneumoniae*.^{20–23} The articles in SAVE 2011–2015 provided an examination of the changing patterns of invasive *S. pneumoniae* obtained across Canada over a 5 year period. This Supplement documents 10 years of the SAVE study (2011–2020) where 14 138 invasive isolates of *S. pneumoniae* and patient demographics were evaluated. The articles in this Supplement provide a comprehensive examination of the changing

patterns of invasive *S. pneumoniae* obtained across Canada over a 10 year period.^{24–28}

In the first article, Alford et al.²⁵ introduce SAVE, describe the methodology of the study and review the changing antimicrobial susceptibility patterns of invasive *S. pneumoniae*. Alford et al.²⁵ report that although invasive pneumococcal isolates collected in Canada from 2011 to 2020 generally exhibited consistent *in vitro* susceptibility to commonly tested antimicrobial agents, small but significant differences in the percentage of isolates susceptible to 4 of the 13 agents tested were observed across the 10 year study: chloramphenicol (−4.4% difference), trimethoprim/sulfamethoxazole (−3.9%), penicillin (non-meningitis breakpoint, +2.7%) and ceftriaxone (meningitis breakpoint, +2.7%; non-meningitis breakpoint, +1.2%). In addition, invasive isolates from specimens other than blood or CSF exhibited greater rates of resistance. They reported a significant association between geographical region and antimicrobial resistance to all antimicrobials except trimethoprim/sulfamethoxazole, as well as concurrent resistance to any one of the antimicrobials and penicillin or clarithromycin.

In the second article, Adam et al.²⁶ analyse serotype evolution, particularly AMR and MDR *S. pneumoniae* serotypes, over time. They report that the overall rate of MDR *S. pneumoniae* was 6.6% (902/13 712) in SAVE. Although there was no change in the MDR rate across the complete study years, the proportion of isolates demonstrating an MDR phenotype decreased significantly between 2011 and 2015 and was followed by a significant increase from 3.9% in 2016 to 9.4% in 2020. MDR was observed in 44 serotypes, with serotypes 15A and 19A predominating; however, a significant increase in the diversity of MDR serotypes occurred from 2011 to 2020, with serotypes 4 and 12F representing increasing proportions of MDR strains in the later study years. The most common MDR pattern was resistance to clarithromycin, clindamycin and doxycycline.²⁶ Adam et al. concluded that although current vaccine coverage of MDR *S. pneumoniae* in Canada is high, the increasing diversity of serotypes observed among the MDR isolates highlights the ability of *S. pneumoniae* to rapidly evolve.

In the third article, Golden et al.²⁷ investigated the lineages and genomic antimicrobial resistance of 10 pneumococcal serotypes commonly collected in Canada during the five most recent years of the SAVE study (2016–2020). They used WGS to identify AMR determinants, virulence genes of interest, MLST sequence types and global pneumococcal sequence clusters (GPSCs). The investigated serotypes represented four of the most prevalent international lineages causing non-vaccine serotype pneumococcal disease in the PCV13 era: GPSC3 (serotypes 8/33F), GPSC19 (22F), GPSC5 (23A) and GPSC26 (12F). Of these lineages, GPSC5 isolates were found to consistently possess the most AMR determinants. Commonly collected vaccine serotypes 3 and 4 were associated with GPSC12 and GPSC27, respectively. However, a more recently collected lineage of serotype 4 (GPSC192) was highly clonal and possessed AMR determinants. Golden et al. concluded that due to continuous and ongoing evolution continued genomic surveillance is required to monitor new and evolving lineages of *S. pneumoniae* in Canada, including resistant GPSC5 and GPSC162.²⁷

In the final article, Schellenberg et al.²⁸ compared the number and proportion of IPD isolates collected in Canada from 2011 to 2020, belonging to serotypes covered by PCV10, PCV13, PCV15,

PCV20 and PPSV23 vaccine formulations. They reported that PCV15 and PCV20 provided significantly greater coverage of IPD isolates than PCV10 and PCV13, in all age groups, all geographical regions and in AMR phenotypes including MDR but not XDR strains. PCV13 vaccine coverage was ~31% with non-PCV13 serotypes 22F and 33F (in PCV15) adding ~13% coverage and non-PCV15 serotypes 8, 10A, 11A, 12F and 15B/C (in PCV-20) adding ~19% vaccine coverage. Non-PCV20 serotypes 2, 9N, 17F and 20 (but not 6A) (polysaccharide vaccine PPSV23) represented ~9% of all IPD serotypes. Lastly they reported that individual vaccine coverage varies depending on the year tested, patient age, geographical location and AMR phenotype.²⁸

The articles in this Supplement provide a comprehensive examination of the changing patterns of invasive *S. pneumoniae* obtained across Canada over a 10 year period while discussing vaccine coverage of all strains as well as AMR, MDR and XDR strains. The SAVE study has many strengths, which include the large dataset covering a 10 year timeframe, facilitating a comprehensive study of serotype evolution, AMR and MDR resistance patterns, vaccine coverage as well as genotypic assessment. However, several limitations need to be recognized. First, the SAVE study does not receive or test isolates from two western provinces (British Columbia and Alberta) and thus does not truly represent data from all provinces in Canada. In addition, provinces across Canada are not required to submit all invasive pneumococci to the SAVE study, though most do, with some provinces sending selected isolates depending on their local laboratory capabilities. Lastly, due to the COVID-19 pandemic, the number of isolates received and tested in 2020 was lower than the preceding years and this needs to be evaluated in context of the reduced number of isolates.

Beyond reducing pneumococcal infections, pneumococcal conjugate vaccines offer additional benefits. A variety of strategies have been recommended to combat pathogens and infections that are AMR and MDR including: surveillance, antimicrobial stewardship, infection prevention and control, rapid diagnostics, monoclonal antibodies, vaccination, bacteriophages and alterations in the human microbiome such as fecal microbiota transplants.^{29,30} The use of vaccines including pneumococcal conjugate vaccines in paediatric and adult immunization programmes is associated with reducing AMR.^{29,30} Pneumococcal conjugate vaccines reduce the emergence and spread of AMR directly and indirectly. By reducing pneumococcal infection, including infection caused by resistant strains, pneumococcal conjugate vaccines directly reduce antimicrobial consumption and thus the emergence of and subsequent transmission of AMR *S. pneumoniae*.^{29,30} In addition, less antimicrobial consumption results in less effect on the normal microbiome of the mouth and upper airways, as well as skin, colonic and vaginal microbiomes.^{29,30} Pneumococcal conjugate vaccines can also reduce AMR indirectly through the development of herd immunity thus reducing pneumococcal carriage and patient-to-patient pneumococcal transmission, including that of resistant strains.^{29,30}

So what are the current recommendations for the use of the new higher valency conjugate vaccines PCV15 and PCV20 in adults? In the USA, the ACIP reviewed the epidemiology of pneumococcal disease along with immunological efficacy and safety of the vaccines and provided recommendations for use

in adults.^{16–19} For adults aged ≥ 65 years who have not previously received PCV13 or whose previous vaccination history is unknown, ACIP recommended that patients receive one dose of either PCV15 or PCV20.¹⁹ If PCV15 is administered, it should be followed by a dose of PPSV23. When PCV15 is administered, the recommended time interval between administration of PCV15 and PPSV23 is ≥ 1 year (with a minimum interval of 8 weeks in selected patients at very high risk for IPD).¹⁹ In adults who have only previously received PPSV23, they may receive either PCV15 or PCV20 ≥ 1 year after their last PPSV23 dose. When PCV15 is used in those with a history of PPSV23 administration, it need not be followed by another dose of PPSV23. For adults aged 19–64 years with certain underlying medical conditions or other risk factors who have not previously received PCV13 or whose previous vaccination history is unknown, ACIP recommends administration of one dose of either PCV15 or PCV20.¹⁹ Adults who have only received PPSV23 may receive either PCV15 or PCV20 ≥ 1 year after their last PPSV23 dose. When PCV15 is administered in patients with a history of PPSV23 receipt, it need not be followed by another dose of PPSV23. ACIP stated that in adults who have previously received PCV13 only or both PCV13 and PPSV23, the incremental public health benefits of providing PCV15 or PCV20 have not been evaluated. Used in this fashion, ACIP concluded, based on cost-effectiveness studies, that use of PCV20 alone or PCV15 in series with PPSV23 for adults aged ≥ 65 years was cost-saving.¹⁹ Finally, ACIP stated that because no comparative data are available, it was up to the individual clinician to decide whether to administer PCV20 alone or PCV15 in series with PPSV23 to their adult patients. In Canada, NACI recently released recommendations on the use of PCV15 and PCV20 in adults.³¹ NACI recommended that a single dose of PCV20 be offered to pneumococcal-naïve adults or adults whose pneumococcal vaccination status is unknown who fall into one of three groups: ≥ 65 years old, 50–64 years with risk factors and ≥ 18 years old with immunocompromising conditions.³¹ In contrast to the US ACIP group, the NACI in Canada recommended that PCV15 followed by PPSV23 may be offered but only as an alternative in the above three adult groups if PCV20 is not available.³¹ NACI's rationale for recommending a single dose of PCV20 versus the PCV15 followed by PPSV23 strategy was that vaccination programme feasibility, vaccine acceptability and uptake may be superior with a single dose of PCV-20.³¹ NACI recommended that PCV20 be offered to adults ≥ 65 years old who have been immunized previously with PPSV23 alone, or PCV13 and PPSV23, if it has been at least 5 years from the last pneumococcal vaccine dose. In addition, NACI recommended that PCV20 be offered to adults ≥ 65 years old who have been immunized previously with PCV13 alone, if it has been 1 year since the last dose. It is clear that with the available data and the current ACIP and NACI recommendations many unanswered questions remain regarding optimal pneumococcal vaccination in adults, including the following: Which vaccine offers better protection, a single dose of PCV20 or PCV15 in series with PPSV23? Would patients who receive a single dose of PCV20 benefit from a subsequent dose of PPSV23 (1 year or more after PCV20)? With the introduction of PCV20, what role should the non-conjugate polysaccharide vaccine PPSV23 have going forward? Should patients be boosted, and if so when and with which vaccine? Will PCV15 and PCV20 be more clinically effective than PCV13 versus

serotype 3? Serotype 3 is possibly the most problematic serotype, coined the 'sugar coated killer' for its thick protective capsular polysaccharide associated with high patient morbidity and mortality.³² The answers to these questions require careful study and consideration.

Our current arsenal of pneumococcal vaccines includes PCV10, PCV13 and PPSV23. In addition, we now have the recently introduced higher valency conjugate vaccines PCV15 and PCV20.^{16–19} Looking beyond PCV15 and PCV20, what is the future of pneumococcal vaccines? We know that the currently available pneumococcal vaccines are not able to protect against non-vaccine (NV) serotypes as well as *S. pneumoniae* serotypes that do not have a capsule. What is driving the NV serotype evolution? *S. pneumoniae* is very capable of acquiring new genetic material from other pneumococci or other *Streptococcus* spp. via transformation and recombination.^{4,9,11,33} This phenomenon along with capsular switching as well as mutations in capsular polysaccharide biosynthesis leads to the emergence and subsequent spread of NV serotypes as well as emergence of non-encapsulated, non-typable pneumococci.^{4,9,11,33} Thus, with the continued evolution increasing the prevalence of serotypes that are AMR and MDR, there continues to be a need to develop new pneumococcal vaccines. These new pneumococcal vaccines would ideally exhibit broader serotype coverage, induce mucosal and systemic immunity, hinder primary intranasal colonization and provide clinical protection from both pneumococcal pneumonia as well as IPD.³³

A variety of pneumococcal proteins are being investigated as potential vaccine candidates, including pneumococcal surface protein A (PspA), pneumolysin, pneumococcal surface protein C and pneumococcal surface adhesin A.³³ These protein-based vaccines consist of highly conserved proteins providing potential for broad serotype coverage.³² Protein-based vaccines such as PspA offer potential for a universal serotype-independent vaccine. Researchers are investigating a variety of pneumococcal vaccine platforms.³³ It should be noted that the current pneumococcal vaccines are administered by intramuscular injection, which is associated with poor induction of mucosal immunity.³³ In addition, antigens may be poorly immunogenic, requiring suitable adjuvants or delivery systems to deliver them through the oral, nasal or mucosal routes in order to facilitate the enhancement of antigen uptake and prolong antigen availability.³³ Therefore, the use of suitable adjuvants and delivery vehicles will be critical to effective vaccine development. Lastly, microparticles and nanoparticles that serve as pneumococcal antigen delivery vehicles are being investigated.³³

This Supplement documents 10 years of the SAVE study (2011–2020) where 14 138 invasive isolates of *S. pneumoniae* were evaluated. The articles in this Supplement provide a comprehensive examination of the changing patterns of invasive *S. pneumoniae* obtained across Canada over a 10 year period. The data highlight the evolution of *S. pneumoniae* AMR and MDR, serotype distribution, genotypic relatedness, virulence under pressure by vaccination and antimicrobial usage, as well as vaccine coverage allowing both clinicians and researchers nationally and globally to view the current status of invasive pneumococcal infections in Canada.

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Disclaimer

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