The epidemiology of invasive pneumococcal disease in older adults from 2007-2014 in Ontario, Canada; a population based study.

Authors: S. Desai[1], M.E. Policarpio[1], K. Wong[1], J.B. Gubbay[2,3], J. Fediurek[1], S.L. Deeks[1,4].

1. Immunization and Vaccine Preventable Diseases Division, Public Health Ontario, Toronto, ON, Canada

2. Public Health Ontario Laboratories, Public Health Ontario, Toronto, ON, Canada

3. Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

4. Dalla Lana School of Public Health, University of Toronto, ON, Canada

Corresponding Author: Shalini Desai

Abstract:

Background: In Ontario, Canada, there has been a sequential introduction of pneumococcal conjugate vaccines (PCV): PCV7, PCV10, PCV13 into the publically funded childhood immunization program since 2005. A 23 valent polysaccharide pneumococcal vaccine (PPV23) has been routinely recommended for adults over 65 years since 1996. This study examines the epidemiology of invasive pneumococcal disease (IPD) in adults 65 years and older in the province after 10 years of routine childhood vaccination.

Methods: IPD is a reportable disease in Ontario, therefore analysis of the surveillance data from 2007 to 2014 was undertaken.

Results: A total of 3825 cases of IPD were reported among adults 65 years and older, for an overall annualized incidence rate of 25.4 cases per 100 000 population. There was a decrease in incidence due to serotypes included in PCV7 (3.0 to 0.7 cases per 100 000 population) ($p<0.001$). For PCV13 serotypes, there was a decrease in incidence between 2011-2014 (9.8 to 5.3 cases per 100 000 population ($p<0.001$)). Serotypes unique to PPV23 and those not included in a vaccine increased from 2.3 to 5.8 cases and 2.4 to 7.2 cases per 100 000 population respectively ($p<0.001$).

Interpretation : After the introduction of PCV into the childhood immunization program, we have shown a decrease in serotype-specific incidence in older adults among those serotypes contained in pneumococcal conjugate vaccines which is likely due to herd immunity. IPD due to unique PPV23 serotypes and those that are not covered by any current vaccine have increased over time.

Key words: pneumococcal disease, immunization, older adults, Canada, herd immunity

Introduction:

Preventing invasive pneumococcal disease (IPD), an important bacterial cause of clinical syndromes such as meningitis, bacteremia and complicated pneumonia, is possible with the use of vaccines. Since the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7), childhood rates of IPD have declined (1-3). A decrease in nasal carriage of pneumococcal vaccine serotypes among individuals vaccinated with conjugate vaccines compared with non-immunized individuals has also been described (4-6). A number of studies have documented a decrease in non-immunized adult incidence of PCV7 serotype IPD due to herd immunity after childhood vaccination (1,2). In a multi-state study reported by Whitney and colleagues, reductions in the incidence of IPD were seen among adults over 20 years of age.

PCV7 was introduced as a publicly-funded routine childhood program for all children born after January 2004 (7) in the province of Ontario (population ~13 million) in January 2005 (8). The program consisted of a four-dose schedule with doses administered at 2, 4, 6 and 15 months of age (7). A 10-valent vaccine (PCV10), replaced PCV7 in October 2009, with a subsequent switch to a 13-valent product (PCV13) in November 2010 (2). With this most recent change, Ontario also modified their routine program for infants to receive a total of three doses (at 2, 4 and 12 months). For high risk infants, a four-dose schedule was continued. In adults, PCV13 has not been used in the publicly-funded program outside of high-risk individuals (9). However, since 1996, adults over the age of 65 have been eligible for a dose of PPV-23 which includes 11 additional pneumococcal serotypes.

We reviewed the epidemiology of IPD in Ontario, Canada in adults 65 years of age and older over an eight-year period to understand whether there were potential herd effects from the routine infant immunization program.

Methods:

All cases of IPD that met the following case definition are reportable within the province of Ontario:

> Clinical evidence of invasive disease with laboratory confirmation of infection which includes isolation of *Streptococcus pneumoniae* or detection of *S. pneumoniae* deoxyribonucleic acid by nucleic acid amplification test from a normally sterile site (e.g., blood, cerebrospinal fluid [CSF], excluding middle ear) (10)

Laboratory results are reported by hospital and private laboratories to public health units. Public health unit staff enter core surveillance data into the integrated Public Health Information System (iPHIS).

The Public Health Ontario Laboratories (PHOL) sends all received isolates of *S. pneumoniae* from sterile sites to the National Microbiology Laboratory (NML) in Winnipeg, Manitoba for serotyping. In addition to public health reporting requirements, there is a population based surveillance program, the Toronto Invasive Bacterial Diseases Network (TIBDN), that collects information on cases of *S. pneumoniae*. There are multiple hospital sites in the greater Toronto area that participate in this program representing approximately 4.6 million residents from Ontario. Specimens as well as case information from these participating sites are sent to the main TIBDN laboratory in Toronto for serotyping. Isolates considered not typeable by TIBDN methods are forwarded onto NML for further serotyping. All IPD serotype results (from PHOL and TIBDN) are entered into iPHIS.

Routine reporting of serotype data to public health began in 2007. Therefore, all cases of IPD reported into iPHIS between January 1, 2007 to December 31, 2014 were extracted for this analysis. We included only individuals 65 years of age and older. Individuals with non-invasive disease or non-residents of Ontario were excluded. Age was further divided into 5 year and 10 year age groupings. Data collected included sex, episode date, serotype, vaccination information, public health unit, and outcome. Specimens with no serotype information were excluded from serotype-specific analysis. Geographic areas were consolidated to seven health regions that were used for geographic analysis.

Serotyping was done using latex pneumococcal antisera (Statens Serum Institute, Denmark) and the capsular swelling Quellung reaction (2).

Cases were grouped according to serotypes and vaccine groups (i.e., PCV7, additional PCV 13, all PCV 13, unique PPV23 and non-vaccine preventable serotypes). PCV7 serotype included 4, 6B, 9V, 14, 18C, 19F and 23F. Additional PCV13 serotypes included 1, 3, 5, 6A 7F and 19A. Unique PPV23 serotypes included: 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F. All other serotypes not included in a vaccine were considered non-vaccine preventable serotypes (NVP).

Incidence rates were calculated using annual population estimates from Statistics Canada (2007-2013) and population projects [2014] obtained through intelliHEALTH Ontario and the Ontario Ministry of Health and Long-Term Care (11,12). Descriptive analyses and Poisson regression, to assess trends over time, were done using SAS (v9.3) and Microsoft Excel (2010). A p value of <0.05 was deemed as significant.

We obtained ethics approval from Public Health Ontario's ethics review board.

Results:

A total of 3,825 cases of IPD occurred in adults 65 years of age and older in the study period. There was a slight female predominance (52.0% of cases). Over the eight year period the overall annual IPD incidence remained relatively stable ranging from a high of 28.0 per 100,000 population in 2012 to a low of 22.9 per 100,000 population 65 years and over in 2014 and there was no significant trends in overall incidence over time (Figure 1). There was geographic variation in the annualized incidence of IPD within the province; the Northwest region had the highest annualized incidence (34.7 per 100 000 population), whereas the Northeast and Southwest regions had the lowest (22.3 and 23.7 per 100 000 respectively). Overall, 66.9% of cases required hospitalization and there was a case fatality ratio of 17.7%.

Age Group:

The overall annualized incidence rate of IPD was 25.4 per 100 000 population 65 years of age and older. When age groups were further subdivided, those 65-74 years of age had an annualized incidence of 18.7 per 100 000. This increased to 26.5 per 100 000 and 50.3 cases per 100 000 in those 75-84 years of age and over 85 years of age, respectively. In each of these groups, males had a higher annualized incidence rate than female, and the ratio remained relatively consistent in each age group (Table 1). When viewed by serotype and age, those in the oldest age group (those over 85 years of age) had significantly more disease due to all serotypes and by vaccine type than those in the younger age groups. (Table 2).

Serotype data:

Of the 3,825 cases during the study period, 2,778 cases (72.6%) had serotyping documented. There was a 20% annual decrease in the incidence of PCV7 included serotypes between 2007 and 2014 from 3.0 to 0.7 cases per 100 000 ($p<0.001$). When viewed as a trend over time by all PCV13 serotypes, there was a significant increase ($p<0.001$) in incidence from 2007 to 2010 (7.0 to 12.0 cases per 100 000) followed by a significant decrease ($p<0.001$) in incidence from 2011 to 2014 (9.8 to 5.3 per 100 000). Limiting the analysis to serotypes that were unique to PCV13 showed a similar trend with a significant increase ($p<0.001$) in rates between 2007 and 2010 4.0 to 9.8 cases per 100 000, with a subsequent significant decrease ($p<0.001$) in incidence to 4.6 cases per 100 000 in 2014. Further serotype-specific analysis showed that within those serotypes included in PCV13, from 2011 to 2014 there was a significant decrease in the incidence per year caused by serotypes 7F (27.9% decrease), 19A (23.0% decrease) and 3 (12.7% decrease).

For serotypes unique to PPV23 there was a significant increase ($p<0.001$) in incidence of cases over the study period, with incidence increasing from 2.3 cases per 100 000 in 2007 to 5.8 cases per 100 000 individuals in 2014. For serotypes not included in any vaccine, there has also been a significant increase

(p<0.001) in incidence between 2007 and 2014 from 2.4 cases per 100 000 to 7.2 per 100 000. Further analysis of unique PPV23 serotypes as well as NVP serotypes by serotype and 10 year age groupings showed the greatest increase in incidence was in the oldest age group. (Figure 2)

Immunization status:

A total of 1223 cases had immunization status documented in iPHIS. Of these, 62.4% were reported as unimmunized. Of the 37.6% (460/1223) that were immunized with at least one dose of pneumococcal containing vaccine, 97% (446/460) received PPV23. Interestingly, 26.5% had illness due to a serotype not covered by PPV23 and 22.6% had unspecified (i.e., unknown or missing) serotypes. Of those 234 cases who had been immunized with PPV23 and who had disease caused by a serotype contained within PPV23, 43.6% (102/234) had received vaccine greater than 5 years prior to illness onset. Among those immunized, 7.8% (36/460) had multiple doses of PPV23 vaccine and 2% (9/460) received a pneumococcal conjugate vaccine.

Interpretation:

We have shown that IPD continues to cause a substantial burden of disease in adults 65 years of age and older in Ontario. Annually, an estimated 3000 IPD cases are reported in Canada as a whole. The highest incidence is in those over 60 years of age (21.9 cases per 100 000 population)(13). An estimated 90% of IPD occurs among adults in the United States (14).When data are further analyzed based on ten year age groupings, it is evident that the greatest burden of disease is in the oldest adults (15,16). This is important as older adults also have a higher case fatality ratio of IPD compared with those in younger age groups (16,17) .

We have also demonstrated that the serotype distribution of IPD has changed over the past eight years. The incidence of NVP serotypes increased over the study period. Our data also show there has been a

decrease in disease caused by serotypes contained within the conjugate vaccines. A universal childhood conjugate pneumococcal vaccination program has been in place throughout the study period., Therefore the changes observed in the rates of IPD disease in those 65 years of age and older are likely due to a herd effect from the childhood program, a decrease in nasal carriage and less exposure to *S. pneumoniae*. This is further substantiated by the serotype-specific changes seen. As described by other groups, prior to the introduction of PCV13 among children, rates of IPD due to serotypes contained within PCV13 vaccine increased in children as well as adults over time (1,18-21). After the PCV13 introduction into the childhood program in November 2010 in Ontario, we observed a decrease in the incidence of serotypes unique to this vaccine among the elderly. This is similar to other reports in the literature with sequential PCV-7/PCV-13 introduction (22-25).

PCV13 was licensed based on an aggregate correlate of protection established for PCV7 vaccine serotypes of 0.35ug/ml as well as opsonophagocytic antibody (OPA) titre of 1:8. Andrews and colleagues (26) measured serotype specific correlates of protection in infants who had received two doses of conjugate vaccine and found that higher cut offs for protection were need for serotypes 1, 3, 7F, 19A and 19F and that an OPA titre of 1:8 was not predictive of protection. Additional evidence from Harboe and colleagues' (22) investigation of the Danish population-based laboratory data has shown that since the introduction of pneumococcal conjugate vaccines, serotype 1 and 3 have not shown a significant change in incidence among those 65 years of age and older while all other serotypes in PCV 13 have. In our study, we observed a statistically significant decrease in the incidence of serotype 3, 7F and 19A and a decreasing trend for 19F. Our data suggests that based on the incidence of disease, current correlates of protection do provide a basis for estimating protection and that all serotypes contained within PCV13 have shown decreasing trends in incidence among the elderly.

PCV13 is a safe and effective vaccine in the elderly. Currently NACI has not recommended that this vaccine be used universally and no province or territory has implemented universal PCV13 programs among persons 65 years of age and older. In contrast, the ACIP has made a recommendation to include PCV-13 in the routine adult schedule (27). Based on our finding, the herd effect afforded by the routine childhood program may be sufficient for those adults who interact with young immunized children. However, this may not be the case for the oldest cohort of adults (those over 85 years of age) or adults who have limited interaction with children.

Interestingly, serotypes unique to PPV23 have increased over our study period. This could be due to poor vaccine effectiveness or poor vaccine coverage. A comparison of meta analyses done by Melegaro and Edmunds (28) showed a vaccine effectiveness (VE) of 50-80% against IPD in older adults. Effectiveness also varied by age of receipt of vaccine as well as additional risk factors. Our observed increase in PPV23 serotype related disease could also be due to a failure to vaccinate. More than 70% of cases reporting in iPHIS did not have documentation of receipt of PPV23 vaccine. Another explanation could be waning immunity as 43% of individuals who had received vaccine, had received it more than 5 years prior to illness onset. Morrill and colleagues (24) describe a national cohort of adults over the age of 50 years in which the percentage of overall cases of pneumococcal infections increased among immunized individuals with greater than 5 or 10 years since immunization. The authors also showed that those vaccinated had significantly fewer episodes of IPD despite poor VE. In Ontario, all adults 65 years and over should routinely receive a single dose of PPV23. Vaccine coverage among adults in Ontario is unknown, as there is no immunization registry in the province. National immunization coverage rates for PPV23 estimate 38.7% (range 34.5-41.5%) of adults 65 years and older receive this vaccine (29). Additional work to promote this vaccine could further decrease the burden of disease due to IPD.

There are several limitations to our study. Although IPD is a reportable disease, there is likely under-reporting. Some cases may not have sought medical attention and some may have received empiric antibiotics without testing. Some variables may also be under-reported, particularly those relating to outcome. Seventy three percent of our cases did not have serotyping information. This would only impact our findings if cases without serotype information were systematically different than those with this information. Our data source did not contain information on risk factors or ethnicity, both of which are known to increase the risk of IPD (23). Finally, as there is no provincial registry for immunization, assessment of immunization status was limited by data provided during case investigation.

Conclusions:

Although the overall incidence of IPD in the elderly has remained relatively stable over time, after the introduction of a childhood pneumococcal conjugate program, we have shown a decrease in serotype-specific incidence among serotypes contained in conjugate vaccines in older adults which is likely due to herd immunity. Disease due to serotypes unique to PPV23 and those that are not covered by any current vaccine have increased over time. Improving adult immunization rates with PPV23, as well as working towards higher valency conjugate vaccines could lead to further control of IPD in older adults.

Funding: none

Conflicts of Interest: JBG has received a research grant from Pfizer Inc. to conduct microbiological surveillance of *Streptococcus pneumoniae*.

Acknowledgements: The authors would like to thank Lennon Li and Jeremy Herring for their assistance with statistical testing and population data as well as Lauren Ramsay for her assistance with formatting and references.

References:

(1) Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein–polysaccharide conjugate vaccine. N Engl J Med 2003;348(18):1737-1746.

(2) Lim GH, Wormsbecker AE, McGeer A, Pillai DR, Gubbay JB, Rudnick W, et al. Have changing pneumococcal vaccination programmes impacted disease in Ontario? Vaccine 2013;31(24):2680-2685.

(3) Kellner JD, Vanderkooi OG, MacDonald J, Church DL, Tyrrell GJ, Scheifele DW. Changing epidemiology of invasive pneumococcal disease in Canada, 1998–2007: update from the Calgary-area Streptococcus pneumoniae research (CASPER) study. Clinical Infectious Diseases 2009;49(2):205-212.

(4) Obaro SK, Adegbola RA, Banya WA, Greenwood BM. Carriage of pneumococci after pneumococcal vaccination. The Lancet 1996;348(9022):271-2.

(5) Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999;180(4):1171-1176.

(6) Gounder PP, Brewster M, Bruce MG, Bruden DJ, Rudolph K, Hurlburt DA, et al. Impact of the Pneumococcal Conjugate Vaccine and Antibiotic Use on Nasopharyngeal Colonization by Antibiotic Nonsusceptible Streptococcus pneumoniae, Alaska, 2000[FIGURE DASH]2010. Pediatr Infect Dis J 2015 Nov;34(11):1223-1229.

(7) Public Health Agency of Canada. Update on Pediatric Invasive Pneumococcal Disease and Recommended Use of Conjugate Pneumococcal Vaccines. 2010; Available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-3/index-eng.php. Accessed Jan/25, 2016.

(8) Statistics Canada. Population by year, by province, and territory. 2015; Available at: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo02a-eng.htm. Accessed Jan/25, 2016.

(9) National Advisory Committee on Immunization (NACI). Statement on the use of conjugate pneumococcal vaccine–13 valent in adults (Pneu-C-13). Can Commun Dis Rep 2013;39:1-52.

(10) Ministry of Health and Long-Term Care. Appendix B: Provincial case definitions for reportable diseases - Pneumococcal disease, invasive. 2014.

(11) Population estimates 2005-2013. Ontario Ministry of Health and Long-Term Care: intelliHEALTH Ontario, Statistics Canada. Date Extracted: July 2014.

(12) Population projections 2014. Ontario Ministry of Health and Long-Term Care: intelliHEALTH, Ontario Ministry of Finance. Date Extracted: March 2014.

(13) Public Health Agency of Canada. Notifiable Diseases On-Line. 2015; Available at: http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/charts.php?c=abs, 2015.

(14) Centers for Disease Control and Prevention (CDC). Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae, 2013 2013.

(15) Ruiz LA, Zalacain R, Capelastegui A, Bilbao A, Gomez A, Uranga A, et al. Bacteremic pneumococcal pneumonia in elderly and very elderly patients: host- and pathogen-related factors, process of care, and outcome. J Gerontol A Biol Sci Med Sci 2014 Aug;69(8):1018-1024.

(16) Song JY, Choi JY, Lee JS, Bae IG, Kim YK, Sohn JW, et al. Clinical and economic burden of invasive pneumococcal disease in adults: a multicenter hospital-based study. BMC Infect Dis 2013 May 4;13:202-2334-13-202.

(17) Lexau CA, Lynfield R, Danila R, Pilishvili T, Facklam R, Farley MM, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA 2005;294(16):2043-2051.

(18) Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. The Lancet 2007;369(9568):1179-1186.

(19) Incidence of invasive pneumococcal disease among children after introduction of a 7-valent pneumococcal conjugate vaccine: a population-based study in Olmsted County, Minnesota. Mayo Clinic Proceedings: Elsevier; 2009.

(20) Meichtry J, Born R, Küffer M, Zwahlen M, Albrich WC, Brugger SD, et al. Serotype epidemiology of invasive pneumococcal disease in Swiss adults: A nationwide population-based study. Vaccine 2014;32(40):5185-5191.

(21) Torné AN, Dias JG, Quinten C, Hruba F, Busana MC, Lopalco PL, et al. European enhanced surveillance of invasive pneumococcal disease in 2010: data from 26 European countries in the post-heptavalent conjugate vaccine era. Vaccine 2014;32(29):3644-3650.

(22) Harboe ZB, Dalby T, Weinberger DM, Benfield T, Mølbak K, Slotved HC, et al. Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. Clinical Infectious Diseases 2014;59(8):1066-1073.

(23) Regev-Yochay G, Paran Y, Bishara J, Oren I, Chowers M, Tziba Y, et al. Early impact of PCV7/PCV13 sequential introduction to the national pediatric immunization plan, on adult invasive pneumococcal disease: A nationwide surveillance study. Vaccine 2015;33(9):1135-1142.

(24) Morrill HJ, Caffrey AR, Noh E, LaPlante KL. Epidemiology of pneumococcal disease in a national cohort of older adults. Infectious diseases and therapy 2014;3(1):19-33.

(25) Bruce MG, Singleton R, Bulkow L, Rudolph K, Zulz T, Gounder P, et al. Impact of the 13-valent pneumococcal conjugate vaccine (pcv13) on invasive pneumococcal disease and carriage in Alaska. Vaccine 2015;33(38):4813-4819.

(26) Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. The Lancet Infectious Diseases 2014;14(9):839-846.

(27) Centers for Disease Control and Prevention. PCV13 (Pneumococcal Conjugate) Vaccine. 2015; Available at: http://www.cdc.gov/vaccines/vpd-vac/pneumo/vac-PCV13-adults.htm. Accessed Jan/2016, 2016.

(28) Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses. Eur J Epidemiol 2004;19(4):353-363.

(29) Public Health Agency of Canada. Vaccine coverage amongst adult Canadians: results from the 2012 adult National Immunization Coverage (aNIC) survey. 2014; Available at: http://www.phac-aspc.gc.ca/im/nics-enva/vcac-cvac-eng.php. Accessed Jan/25, 2016.

Table 1. Annualized age-specific incidence (per 100000 population) of IPD among adults 65 years of age and older by sex, in Ontario, Canada from 2007 to 2014 (n=3822)

Age group	Sex				Total	
	Females		Male			
	No.	Rate (per 100,000 population)	No.	Rate (per 100,000 population)	No.	Rate (per 100,000 population)
65-74 years old	715	16.7	804	20.9	1519	18.7
75-84 years old	688	24.2	642	29.5	1330	26.5
85+ years old	587	45.0	386	60.9	973	50.2

Note: excludes 3 cases of unknown sex

Table 2. Annualized age-specific incidence (per 100 000 population) of IPD among adults 65 years of age and older in Ontario, Canada from 2007 to 2014

	Age group					
Vaccine type	**65-74 years old (rate per 100 000 population)**	**p-value**	**75-84 years old (rate per 100 000 population)**	**p-value**	**85+ years old (rate per 100 000 population)**	**p-value**
All types	18.7	Reference	26.5	<0.001	50.3	<0.001
PCV 7 ST	1.3	Reference	1.6	0.205	4.0	<0.001
Additional PCV13 ST	5.3	Reference	6.8	0.001	12.4	<0.001
PCV-13 ST	6.7	Reference	8.5	0.001	16.5	<0.001
Unique PPV23 ST	3.7	Reference	4.9	0.001	9.0	<0.001
NVP ST	3.4	Reference	5.7	<0.001	10.6	<0.001

IPD Figures

Figure 1. Annual incidence rates of serotype groups by vaccine type overall and among adults 65 years ar

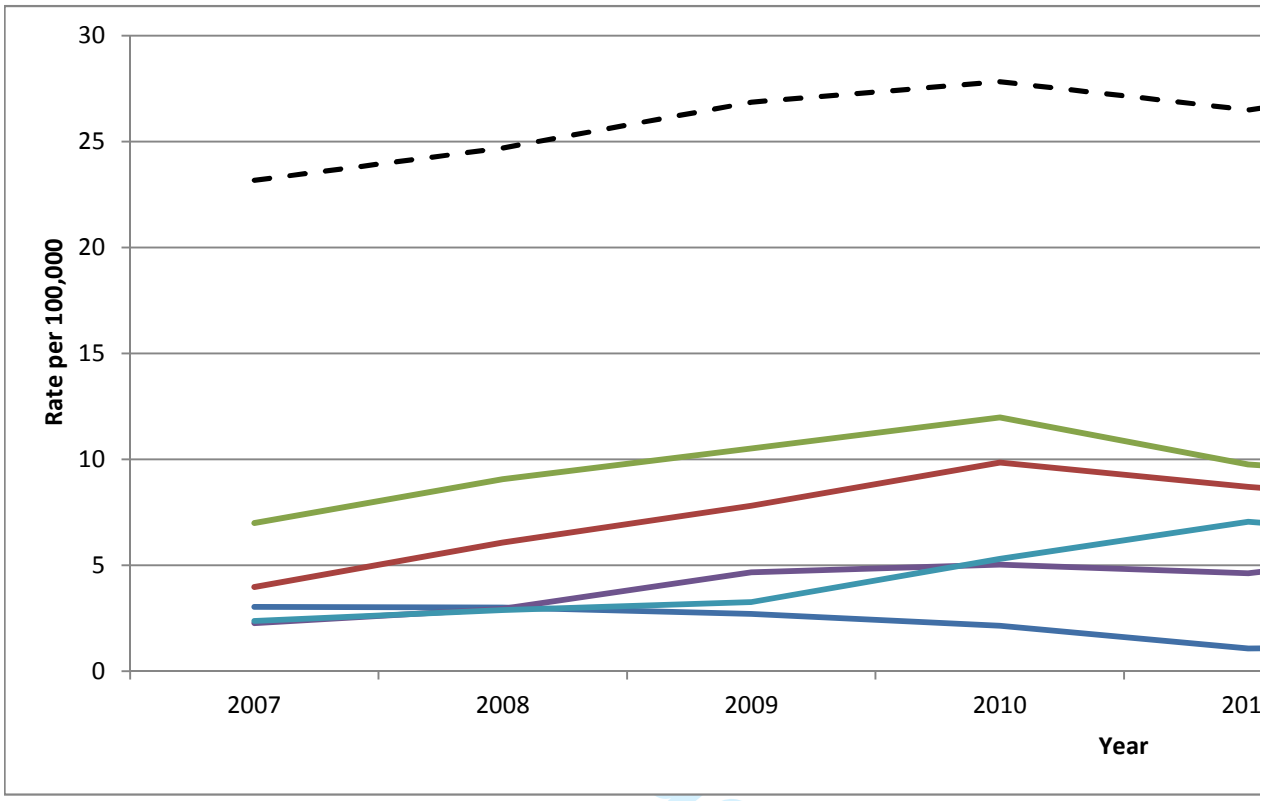
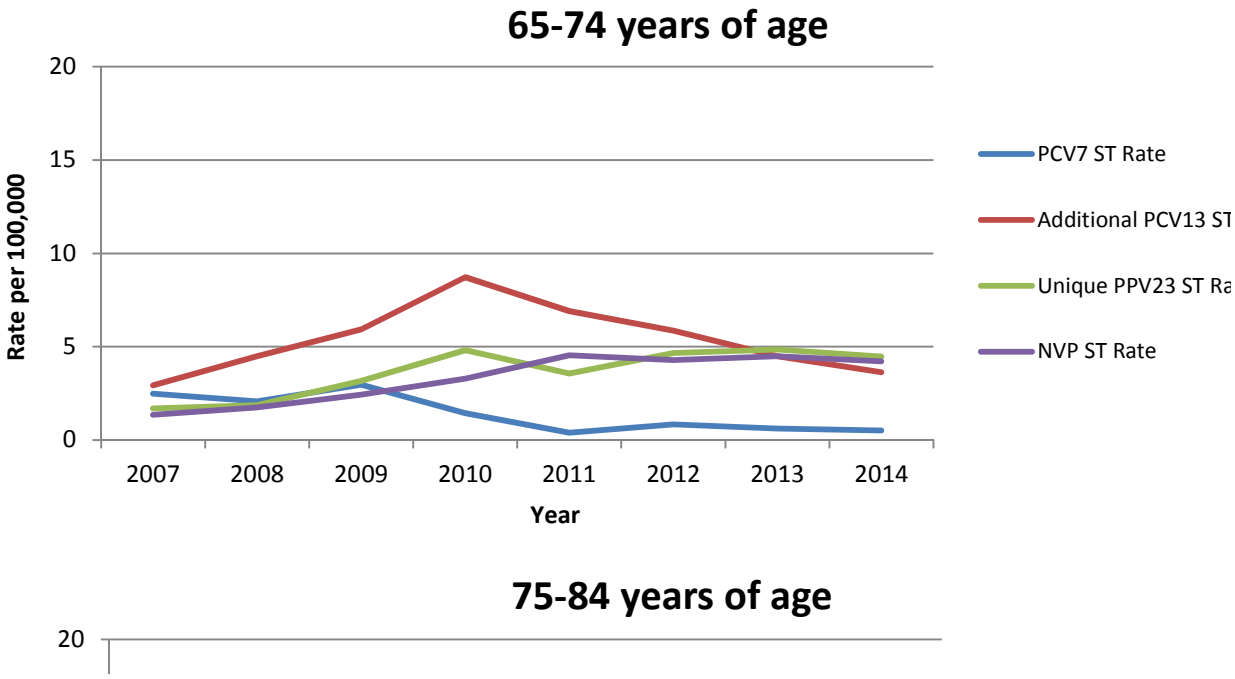
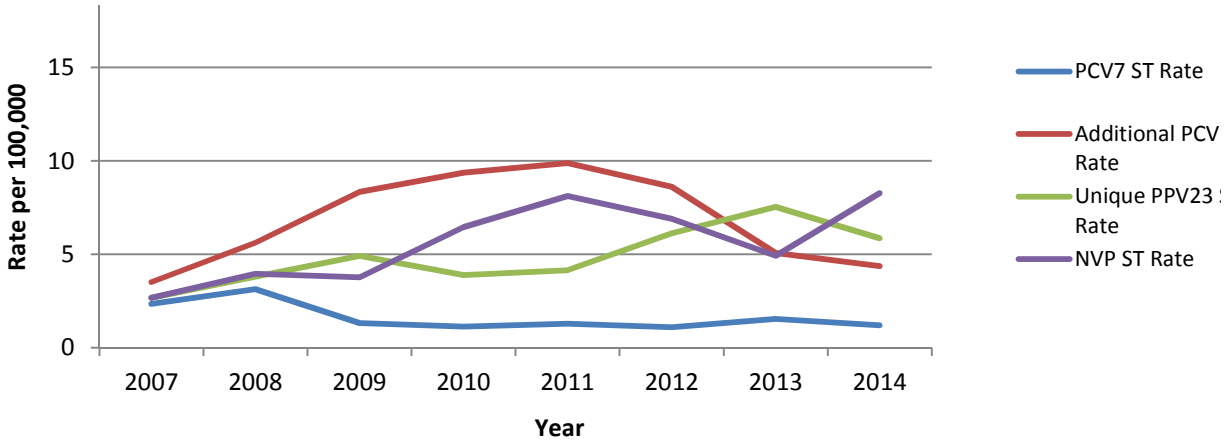
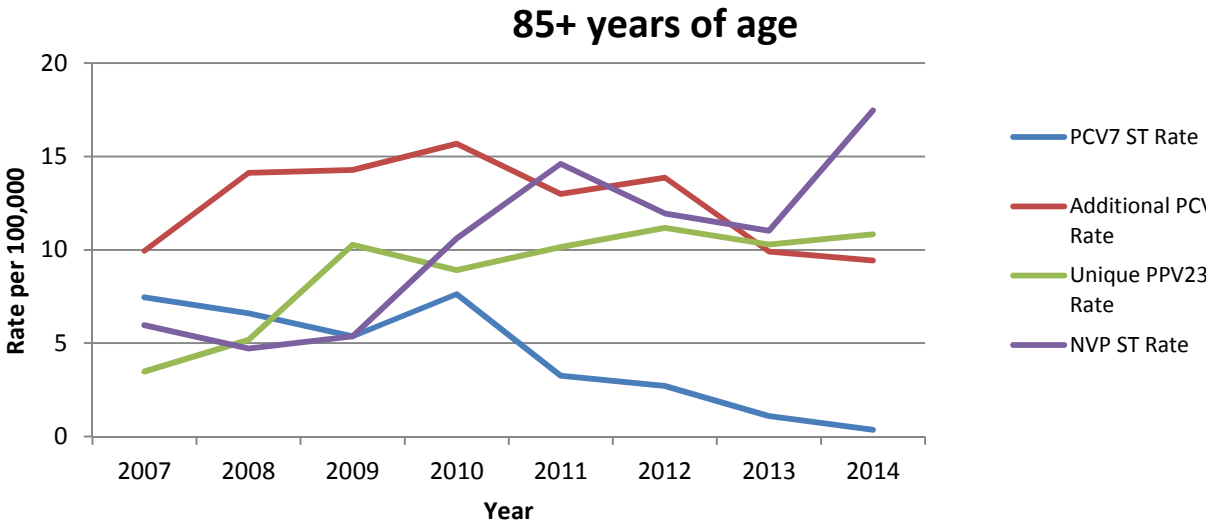


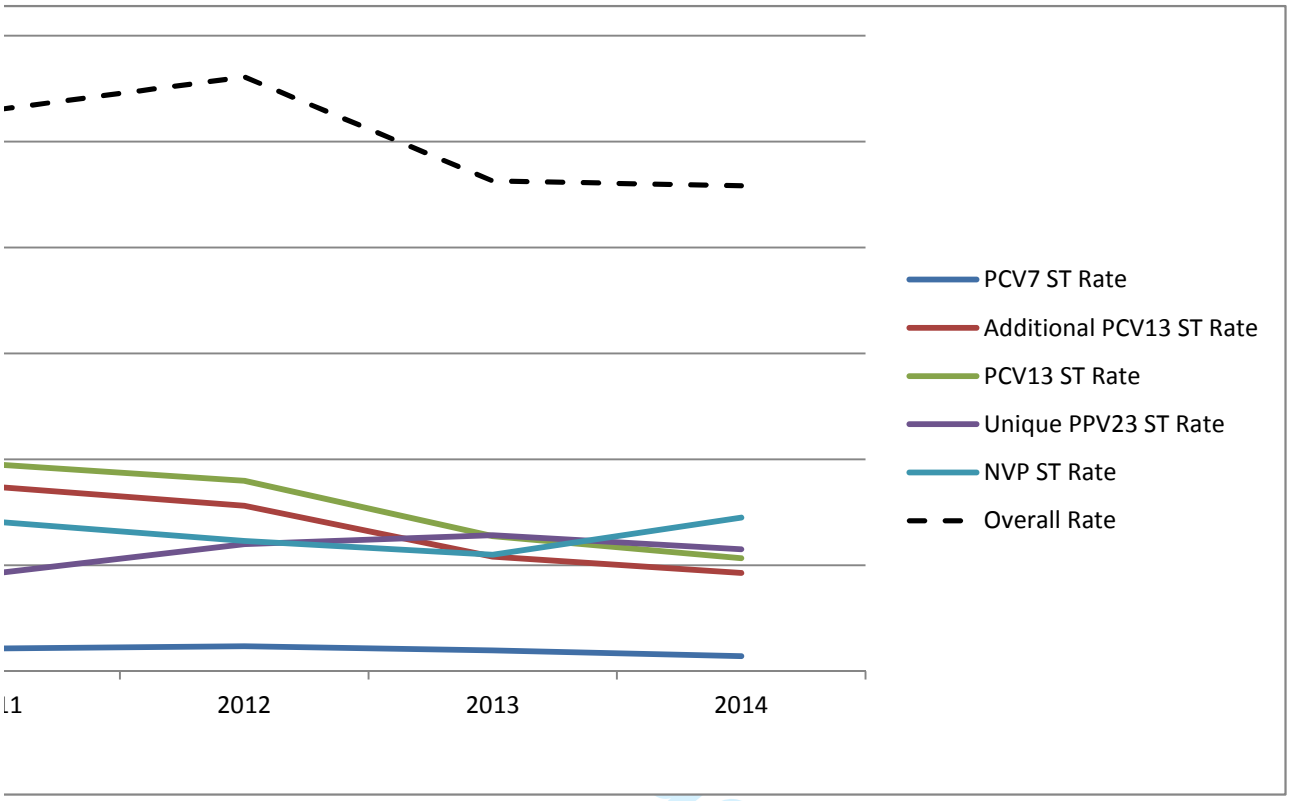
Figure 2. Annual age-specific incidence rates of serotype groups by vaccine type among adults 65 years a







nd older, in Ontario, Canada from 2007 to 2014



nd over (by 10 year groupings) in Ontario, Canada from 2007 to 2014

T Rate

ate

'13 ST

ST

V13 ST

3 ST