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Title	The epidemiology of invasive pneumococcal disease in older adults from 2007-2014 in Ontario, Canada; a population based study
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Reviewer 1	Caroline Quach MD MSc
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General comments (author response in bold)	Abstract: 1. Please provide a methodology that explains the study design, setting, outcomes, and statistical analysis used. **Added to line 19-20**. Introduction: 2. On lines 36-37, the authors say that since the introduction of PCV7 in childhood immunization programs, childhood rates of IPD have declined. Although it is true that there was a decline in the incidence initially, most jurisdictions were seeing an increase in childhood IPD rates after the first few years of implementation, due to serotype replacement. Was it the authors' intention to say that the incidence of IPDs due to PCV7 serotypes has been declining since the PCV7 program introduction? If such is the case, please modify. **Change has been made to reflect it is only the PCV7 serotypes that decreased**. 3. On lines 37-39, when talking about impact of PCV on nasopharyngeal carriage, it should be specified that this is true mainly for the CRM197-based vaccines. PCV10 does not seem to decrease NP carriage. Please modify. **Change has been made to reflect this**. Methods: 4. It would be easier to follow if the methods section was divided in sub-sections with headings. **Changed**. 5. Lines 66 and after: What happens when the same case is captured both by the PHOL surveillance system and TIBDN? Is there a way to ensure that the same case is not represented twice in the surveillance program? **All reporting of serotype data for TIDBN is done through that group. The data is then shared with PHO. In this way, duplicate cases are removed and any additional cases are added to provincial reporting system** **-added clarification line 78-79**. 6. Line 76: How was the vaccination information retrieved? How valid is this information? This needs to be detailed in the methods section. **Local public health unit captured this information. Based on hand held records, not verified. Added clarification to line 86-88. Also added to limitations (immunization records not verified)**. 7. How complete is the PHOL+TIBDN surveillance program felt to be? Any validation ever done on the % of IPD isolates sent to PHOL? **Since IPD is a reportable disease in Ontario – we believe that the data set is very complete. Please see results section – of the 3825 cases during the study period, 72.6% had serotyping information documented. Further data – lim et al – this reference was also added to manuscript**. Results: 8. Line 112: The sentence starting with "When viewed as a trend over time by all PCV13 serotypes" – I would suggest rewording as: When analyzing trends over time, the incidence of IPD due to PCV13 serotypes significantly increased (…). It would make the sentence easier to understand. **Modified as requested**. 9. Line 114, the next sentence should also be clarified. It took me a while to understand that "serotypes unique to PCV13" actually meant those in PCV13, not in PCV7 (or 10). Please modify. **Modified as requested**. 10. Line 117: The authors describe the trend for certain serotype, starting in 2011 – with the implementation of PCV13. It would be interesting to discuss the trend for these serotypes during the PCV7- and 10-era as well. **For PCV 7 please see publication by Lim et al. Since PCV10 was only a program for 13 months, therefore inadequate time for possible changes in serotype distribution.** 11. Given the availability of data, knowing when which vaccine program was implemented, it would have been interesting to see the time lag between implementation and impact on serotypes circulating in the elderly population. PCV7 was implemented in 2005; this surveillance unfortunately only starts in 2007. PCV10 was implemented in 2009: was anything seen after the implementation – although used for a very short period? PCV13 was implemented in 2010: is there a sense as to how long after a decrease in PCV13, not 7 serotypes was observed? Could regression discontinuity be used to formally test the impact of the childhood vaccination program on the incidence in the elderly population? This information would be key to help policy-making on PCV13 use in the adult population. **This was done as requested. Added to methods (line 100-104) and results section (line 136-7)**. Interpretation: 12. Line 147: there is a period just before a comma. **Deleted comma**. 13. Figure 1 is truncated in my document at year 2011 and the legend is not visible. **Changed as requested**.

Reviewer 2	Jane Buxton MBBS, MHSc
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General comments (author response in bold)	1. The research question is not clear. Were the researchers a priori interested in herd immunity or was this a descriptive analysis and a finding of the analysis? **Please see line 18 and 55 – we were interested a priori in herd immunity**. Abstract 2. Briefly provide possible explanation(s) for results and provide any recommendation and the importance of the findings (the so what?) **Added**. 3. Reference needed line 42 (i.e. for Whitney). **Added**. 4. Define PPV, line 51- defined in Abstract but not in text. **Added**. 5. No mention of pneumococcal pneumonia infections secondary to influenza. **We did not look at this and with our current surveillance system not able to therefore added to limitations**. 6. Typo "population projects" line 87 projections. **Changed**. 7. More detail in the method section for statistical methodology, which covariates included in model and how, which comparisons made, etc. **Ask Kenny. Added into methods (Line 100). No additional covariates since our data is aggregated**. 8. Line 97 / States no significant trends overall in incidence over time and refers to figure 1. Please provide regression results; Figure 1 does not provide enough information. Was the analysis performed for all age groups combined or were each vaccine type assessed for the breakdown of each of the age groups? **Analysis is by serotype but combined age groups. We did separate by age groups but trends were the same, therefore not separated in the interest of space. p-value added**. 9. Discrepancy in line 110 (72.6% had serotyping documented) and line 194 (Seventy-three percent did NOT have serotyping information). **Changed**. 10. Is serotyping more likely in cases hospitalized i.e. more severe disease? Do certain sero types cause more severe disease or particular clinical presentations? **No association found then analysis was re run to look at serotypes by hospitalization status**. 11. Line 147 punctuation (.,). **Comma deleted**. 12. Avoid using acronyms for those which only appear once or twice in text e.g. a. Line 168 NACI; b. Line 170 ACIP; c. Line 185 use Vaccine Effectiveness instead of VE (only appears twice). **Have taken out acronyms listed (NACI and ACIP). Taken out VE**. 13. Line 194-196: Consider providing evidence to address the limitation that missing information might introduce bias (based on the data, does it seem likely that it is biased?) and how this bias might change the results (towards or away from your null). 14. Some years appear higher rates of particular types – e.g. 2010 – why was this- was it a severe influenza year? **Reviewed this – the 2009/2010 year was not particularly bad influenza year. 2010/2011 was a worse year. We reviewed IPD data and did not find a difference in cases by flu year**. 15. Provide more conclusions regarding the importance of this research. **Added**. 16. Are there any other possible explanations for observed results not addressed in this research and could be investigated in the future? **Based on the literature – herd immunity is the most likely explanation. Additional investigation – and specifically ongoing surveillance over time would be helpful**. 17. Figure 1 covers two pages, difficult to read. **Changed**. 18. Aim for self-contained tables and figures; define acronyms and subtypes (ex. What does NVP ST mean? Additional PCV13 ST? etc.). **Changed**. 19. Define IPD in Table 2 title. **Changed**. 20. Consider re-arranging data in Table 2 to make more reader friendly. **Modified**. 21. PCV13 ST Rate missing from Figure 2 graphs. If intentional, provide reasoning. **Modified**. 22. Likely will be dealt with at editorial stage but lines on graphs not clear when printed in black and white. **Modified**.
Reviewer 3	Dr. George Zhanel
Institution	Max Rady College of Medicine, Department of Medical Microbiology and Infectious Diseases, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Man.
General comments (author response in bold)	1. Why do the authors believe that serotype 3 decreased, other studies consistently do not report a decline of this serotype? **Related to circulating serotypes. Added to manuscript – line 184-6**. 2. Can the authors comment at all on the efficacy of PCV10 reduction apart from PCV 7 and PCV 10? Specifically did PCV10 account for any of the reduction of serape 19A (in vitro data suggest that it might). **Data on herd immunity is based on products that have CRM 197 – which the PCV-10 product does not include. Therefore, we did not have any evidence to hypothesize that PCV10 would impact serotype distribution. Also program was in place for a short period (13 months)**. 3. Do the authors believe that further reductions in IPD in individual >= 65 years of age is best achieved by enhancing PPV23 immunization or PCV13 vaccination in adults >= 65 or both ? They do show that there is still considerable IPD in patients >= 65 despite herd immunity. **The authors believe a combination of actions are needed but we considered further explanation/exploration out of scope for the paper**. 4. The authors also need to further describe what they mean on lines 204/205 about working towards higher valency conjugate vaccines. **We would like to see vaccine development with either a conserved portion of S. pneumonia or a conjugate vaccine with more than 13 serotypes. Added to manuscript**.