Author's response to reviews

Title: The persisting burden of invasive pneumococcal disease in HIV patients: an observational cohort study

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Author's response to reviews: see over
Re: ‘The persisting burden of invasive pneumococcal disease in HIV patients: an observational cohort study’; MS: 7390548375846608

Dear Editor:

Thank you and the reviewers for reading our study and providing expert insights. We too hope that the manuscript is of value to the field. We found the comments helpful in strengthening the quality of our study.

We have addressed the comments individually below. As suggested, we have also analyzed our serotype results within the context of our local childhood vaccination program with PCV7.

We appreciate the constructive feedback and hope that you will find our revised manuscript of interest to the readers of BMC Infectious Diseases.

Sincerely,

Reed Siemieniuk

Dan Gregson

M. John Gill

1. The incidence of invasive pneumococcal disease (IPD) between 2000 and 2010 in a regional HIV population in Southern Alberta, Canada. : the sentence is not fully correct since observation ends at 1st January 2010 and also Figure 1 refer till 2009. Please, better define and/or revalue the studied period, in all Sections of the article.

We agree and have clearly defined the study period (January 1st, 2000 to January 1st, 2010) in all sections of the manuscript.

2. The authors should give a better definition of pneumococcal pneumonia since a pneumococcal aetiology can’t be diagnosed just by isolation from a sputum sample; the authors could differentiate e.g., a proved diagnosis from a presumptive/strongly suggested diagnosis (e.g. ref. to: DM Musher Streptococcus pneumoniae; Chapter 200 in “Principle and Practice on Infectious Diseases”, Mandell, Douglas, Bennet Eds, 7th Edition). Moreover clinical, radiological and laboratory criteria to support the diagnosis of pneumococcal pneumonia should be added.

We absolutely agree that pneumococcal pneumonia cannot be and indeed were not diagnosed solely on isolation from a sputum sample. In our population,
sputum samples were only deemed diagnostic if there was strong clinical/radiological suspicion of pneumonia and a good quality sample obtained. To provide clarity, we have add the following qualifying statement in the methods section:

“Sputum and BAL samples were obtained because of strong clinical suspicion for lower respiratory tract infection, generally associated with radiologic evidence and severe illness”

3. All risk factors for IPD - included into the analysis - should be listed and defined

We have added the following statement to address this suggestion:

“These risk factors included gender, age group (≤30, 31-45, 46-60, or ≥61), race (white, Aboriginal, black, or other), education (< high school or ≥ high school), a smoking history (if >1 month), alcohol abuse (>9 drinks/week for females, >14 drinks/week for males), IDU (at any time), nadir CD4 cell count (≤200, 201-500, or >500/µL), co-trimoxazole use, frequency of PPV-23 administration (never, < every 5 years, or ≥ every 5 years), history of active tuberculosis (any clinical event), history of a common HIV-associated pulmonary disease (mycobacterium avium complex or pneumocystis jiroveci pneumonia), asthma, COPD, or Hepatitis C.”

4. In the nested case-control study other relevant analyzed variables should be stated (e.g. COPD, asthma and other relevant factors for pneumococcal infection)

The reviewer makes the suggestion that perhaps variables other than those controlled for could explain the findings in our nested case-control analysis. We agree and have chosen 4 factors a priori to evaluate for between-group differences: nadir CD4, COPD, asthma, and hepatitis C. We did not find any significant difference between cases and controls for these variables, which highlights the clinical similarity between cases and controls and strengthens the analysis. We have added the following statement to the methods section:

“Differences in nadir CD4 count, a history of COPD, asthma, and hepatitis C were also evaluated.”

And to the results:

“No significant differences in nadir CD4, history of COPD, asthma, or hepatitis C were identified between groups (data not shown).”

5. There were 46 episodes of IPD; of these, 7 had positive sputum or BAL samples. There were 22 episodes of illness where S. pneumoniae was isolated from sputum or BAL only”. The kind of IPD and of “other” pneumococcal “illness” should be explained: e.g. bacteremic pneumonia? Meningitis? Non bacteremic pneumonia?
Sinusitis? Otitis? It is known that pneumococcal vaccine doesn’t give a good protection for e.g. otitis

The reviewer correctly highlights the fact that IPD is a diverse entity defined as isolation of S. pneumoniae from a normally sterile site, including all of the sites mentioned above. As we outline in the Microbiology subsection of the results, S. pneumoniae was isolated from the blood, pleural fluid, and ascitic fluid in our study. As mentioned, there were no cases isolated from the CSF, sinuses, or other sites.

6. **It could be relevant to report and analyze CD4 count and viremia during each single pneumococcal event and to insert these data into the multivariate analysis in Table 1**

We agree that CD4 and HIV viral load may play a role in the acquisition of pneumococcal disease. Many of the patients in our study had more than one incident of pneumococcal disease; at times this was a recurrence within the same year and other times there was a new incident years later. We analyze human and clinical factors associated with developing pneumococcal disease one or more times. In this context, it would not be helpful to evaluate CD4 or viral load at the time of infection because some patients would have multiple different measurements and furthermore, the comparative group did not have any incidents of pneumococcal disease.

The question of whether certain risk factors predispose a person to pneumococcal disease at different CD4 counts or viral loads is an interesting one, but cannot be addressed in this study.

7. **“Microbiology”: this Section is quite confusing and must be elucitated extensively. E.g. How many isolates were recovered from all pneumococcal diseases and from each single patients? How many isolates have been serotyped from sterile sites, from BAL and from other sites? How many strains have been serotyped in total:50 or 55?**

This was indeed unclear. In total, 50 strains were included in the final analysis. Although 55 incidents were identified, some of these were duplicates in that the same patient had a BAL and sterile site sample serotyped during the same incident. We have clarified and altered the “Microbiology” subsection to reflect this information.

8. **"Risk factors": this section should be clarified regarding significance of risk factors; identified risk factors are significant for what? IPD? Pneumonia? All pneumococcall diseases? Please, improve description of the regression and multivariate analysis.**

In this section, we provide accompanying p-values for risk factors associated
with the development of all pneumococcal disease. Risk factors for pneumococcal pneumonia and IPD were similar (as seen in table 1). We thank the reviewer for the suggestion and have edited the section for clarity:

“...were all independently associated with developing any pneumococcal disease in the multivariate analysis (table 1). Risk factors were similar for pneumococcal pneumonia and IPD.”

9. **Table 2 is cited in the text, but it is not present!**

The citation to table 2 has been removed from the text.

10. **The relevance of the section “Hospitalization” should be pointed out and then discussed: e.g. why non invasive pneumococcal diseases required hospitalization?**

As the study our study evaluates the burden of pneumococcal disease in our HIV-infected cohort, we feel that an important measure of disease burden lies in hospitalization data. In order to clarify the importance of hospitalization data, we have added the following to the discussion:

“Hospitalization is associated with a higher degree of severity and increased costs of care: proven pneumococcal disease usually required in-patient care. There is a high disease burden associated with pneumococcal disease in HIV-positive patients,...”

11. **“In 1946 HIV-patients with 11,099 years of follow up...”: did you mean “In 1946 HIV-patients with 11,099 persons/years of follow up”? Please check the term in abstract and in all Sections.**

Yes. We have changed this to read 11,099 person-years of follow-up.

12. **“COPD” abbreviation is not defined**

COPD is now defined in the abstract and text.

13. **“The total number of days each patient was in “active care” at the clinic was measured from the initial visit until the patient moved, died, or was lost to follow-up”: please, better define the follow up period.**

We have cleared up the follow-up period with the following statement:

“The follow-up period was measured from the initial HIV-care visit until the patient moved, died, was disconnected from care, or until January 1st, 2010; this was used to calculate incidence rates [14].”

14. **Add p values into Table 1**
We agree that p-values can be helpful for defining significance and indeed had considered adding p-values to table 1 as the reviewer suggests. However as the table is already very large we have only included the confidence intervals to define significance in the table. Within the text of the manuscript however, we have included p-values for risk factors associated with all pneumococcal disease.

15. **Figure 2: legend/title should report the source of isolates: as stated in Results Section, those 50 strains were isolated just from sterile sites and BAL.**

We have added the following statement to the figure legend:

“40 of there were isolated from a sterile site only, 4 from bronchoalveolar lavage (BAL) only, and 6 from both a sterile site and BAL.”

16. **apart from PCV-7, please discuss also regarding PCV-13. Is it already introduced into the paediatric vaccinal schedule in Calgary?**

PCV13 only entered routine childhood immunization schedules after the study period in our region, but we agree this is an important consideration for future trends and have added in the discussion:

“Further shifts may occur as the 13-valent vaccine was introduced into routine care in our region in 2010.”

17. **Rewrite the study comparing what happens in pre-PCV7 era (2000-2002), immediately after PCV7 introduction (2002-2004) and when PCV7 coverage reached high values (2005-2010).**

We agree that it is important to evaluate serotype trends in the context of routine childhood immunization and, as suggested, have analyzed trends over the study period and added in the following sentences.

“We also evaluated serotype trends over the course of the study period in the context of routine childhood immunization with PCV7, which was introduced in 2002 [15]. Before the introduction of PCV7 (January 1st, 2000 to December 31st, 2001), 1 of 4 incidents was due to a serotype covered by PCV7. In the immediate period after the introduction of PCV7 (January 1st, 2002 to December 31st, 2004), 2 of 9 (22%) were PCV7 serotypes. After PCV7 was well established in our community (January 1st, 2005 to January 1st, 2010), 2 of 37 (5.4%) isolates were PCV7 serotypes; which represents a non-significant decrease compared to the period prior to 2005 (P=0.10).”

We also discuss these findings later:
“Our results suggest that in adult HIV populations, there may be a trend away from serotypes included in the routine childhood vaccinations.”

18. More details on vaccination schedule used (ie, how many doses of PPV-23) are required

We thank the reviewer for the comment and have added the following:

“Patients were immunized with two doses of PPV-23 five years apart and with a repeat dose every five years based on clinical discretion.”

19. Discussion has to be re-written considering benefits of PCV7 and potential benefits of PCV13.

We completely agree that there may be indirect benefits to HIV-positive populations from routine childhood immunizations. In our discussion, we outline the fact that relatively few of the infections were due to PCV7 serotypes and suggest childhood immunization as an explanation for this. We also agree that PCV13 may have further benefits given its increased serotype coverage. To this end, we write the following:

“We found that PCV7 would have covered only 10% of serotyped infections seen in our population over the last decade. A serotype shift after the implementation of a childhood immunization program is a plausible explanation for this low incidence as this has been described in HIV patients elsewhere, as well as the Calgary-area population [10,12]. Our results suggest that in adult HIV populations, there may be a trend away from serotypes included in the routine childhood vaccinations. Further shifts may occur after PCV13 was introduced into routine care in our region in 2010. Many of the serotypes observed in our study would be included in PCV13, suggesting that a secondary reduction in pneumococcal disease among HIV-positive adults is possible.”