Author's response to reviews

**Title:** Invasive Pneumococcal Infections Among Persons With and Without Underlying Medical Conditions: Implications for Prevention Strategies

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**Author's response to reviews:** see over
The Editor,

**BMC Infectious Diseases**

Melissa Norton, MD
BioMed Central Ltd,
Middlesex House,
34-42 Cleveland Street,
London W1T 4LB, UK.

June 10, 2008

Dear Dr. Norton,

Enclosed is a revised version of our manuscript titled “Invasive Pneumococcal Infections Among Persons With and Without Underlying Medical Conditions: Implications for Prevention Strategies” (MS: 2062356805195363), which we would like to resubmit for publication in the *BMC Infectious Diseases* in the category of research article. We appreciated the reviewers’ comments and have made the requested changes. Detailed responses to all of the reviewers’ comments are included in point-to-point format. We have incorporated the suggestions in the text when appropriate.

Thank you for considering this paper for *the BMC Infectious Diseases*. Please address correspondence regarding this manuscript at the address below.

Sincerely yours,

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Responses to reviewers’ comments

**Reviewer 1:** Paul William Roche

**Reviewer's report:**

This is a valuable examination of invasive pneumococcal infections in adults without underlying medical conditions, for whom pneumococcal immunisation with PPV23 is usually not recommended.

The authors make use of comprehensive population based data, health care registries and vital statistics to assess all cause, in-hospital mortality. The recognition that 47% of adults 18 to 64 year with IPI did not qualify for PPV23 immunisation because they did not have a recognised co-morbidity is an important finding and provides a rationale for extending universal pneumococcal immunisation to the over 50 year age group. The cost effectiveness of this approach would need to be examined.

This manuscript could be published without revision

**RESPONSE:**

**No revision performed.**

**Reviewer 2:** Angel Vila-Corcoles

**Reviewer's report:**

General comments

In this study, the authors investigated all episodes of invasive pneumococcal infections (bactereaemias and meningitis) identified by Finnish microbiology laboratories during 1995-2002 and evaluate the incidence and mortality of invasive pneumococcal disease according to age groups, sex and with various underlying medical conditions among the Finnish population.

In the study design, the authors have linked different data sources including the National Infectious Disease Register (NIDR), the National Cancer Registry, the National Social Insurance Institution (KELA), the National Hospital Discharge Register (HILMO) and NIDR (HIV infection).

This reviewer believes that the strength of the paper lies not in its design, which is inherently limited, but in the opportunity to compare the results (basically incidence rates and lethality) with data previously reported in other settings. I believe that the paper could be published after a minor revision, and that this
journal provides an appropriate forum. If approved for publication, I would hope for a little revision based on the following discussion.

Minor comments.

1.- This study describes a number of cases and incidence rates of invasive pneumococcal diseases in Finnish all-age population. Although the authors make a special emphasis on the population of working-age adults, the Study population was really all-age inhabitants, so the title does not reflect the true content of the paper. I believe that the title should be changed to reflect the content more accurately

RESPONSE:
The title is changed to: “Invasive Pneumococcal Infections Among Persons With and Without Underlying Medical Conditions: Implications for Prevention Strategies”

2.- In the Results section of the abstract, the sentences are too long and it is difficult for readers to understand well some phrases. I suggest this paragraph be rewritten using shorter sentences, clearly separated by points.

RESPONSE:
Revised as suggested.

3.- I suggest changing the term IPI (invasive pneumococcal infections) for IPD (invasive pneumococcal disease) throughout the manuscript. The abbreviation IPD is commonly used in articles about pneumococcal infections and it is more familiar to readers than IPI, which is not generally used.

RESPONSE:
Revised as suggested.

4.- Invasive pneumococcal infections represent only 15-25% of overall pneumococcal infections. Thus, although invasive disease is the most severe manifestation of the pneumococcal infections, it represents very incompletely the overall burden of pneumococcal disease and this concern should be adequately commented on in the Discussion.
RESPONSE:

We have added the following sentence on pages 12-13, 1st paragraph:

“Furthermore, although IPD is the most severe manifestation of pneumococcal infections, it represents only a small proportion of the overall burden of pneumococcal disease.”

5.- in the Statistical analysis section, the authors should describe more extensively the method that they used to select the variables in their multivariable analysis

RESPONSE:

The following sentence was added to the Statistical analysis section on page 6:

“Piecewise exponential hazard regression model [14] was used in age-group 18-64 years to assess the risk of death with underlying medical conditions for which PPV23 is currently recommended in Finland (Appendix 1, Table 2), controlling also for other medical underlying conditions, the type of IPD presentation, age and sex.”

6.- In the Discussion section, the authors says: "In Finland, the coverage of PPV23 among the elderly and high risk groups is about 3%. This coverage is very small. Could the authors provide some explanation for this data?

RESPONSE:

There have not been any large campaigns to the general public and risk groups concerning PPV23. To our knowledge, only small risk groups such as persons with HIV infection and splenectomised patients are actively vaccinated. Some regional vaccination campaigns targeting elderly persons in context with influenza vaccination have been conducted.

We added the following sentence on page 14, 2nd paragraph:

Despite of the existing vaccine recommendation, PPV23 is not included in the government-funded national vaccination program, and the expense is covered by the treating clinical unit or the individual. Two clinical trials have been conducted in Finland to assess the efficacy of PPV23 against pneumonia [33, 34]. The conflicting results from these trials regarding the efficacy in the aged of PPV23 against mainly serologically diagnosed pneumococcal pneumonia, or pneumonia in general, probably have also had a major influence on the vaccination coverage.
7.- Two large studies on pneumococcal vaccine effectiveness were conducted among Finnish people in the 1990s (Koivula et al, Am J Med 1997; Honkanen et al, Vaccine 1999). I think that these two studies should be mentioned in the Introduction or in the Discussion and referenced in the Bibliography, because they are related to some concerns mentioned in the Discussion of this paper.

RESPONSE:
Please, see the previous comment (#6).

8.- Do the authors have data on serotype distribution of cases? This data could be very interesting to evaluate the serotype coverage of both 7-valent and 23-valent vaccines and to estimate the potential impact of pneumococcal vaccination programs in the Finnish study population, as is mentioned in the Discussion.

RESPONSE:
Unfortunately, we do not have serotype data that can be linked reliably and with reasonable effort on the individual level to cases in the present study. We have previously published data on serotype distribution by age-groups and vaccine-group coverage in our study population (Klemets et al, Scand J Infect Dis 2008, in press, reference #25) and among IPD cases with nosocomial pneumococcal bacteremia from the same cohort (Lyytikäinen et al, Arch Int Med 2007: 167(15); 1635-40).

No revision in the manuscript.

9.- In my opinion, the “conclusion” is not adequate. It says “Routine childhood immunisation with PCV7 has not yet been introduced in Finland. However, increasing evidence has been accumulating about the substantial indirect effects of childhood PCV7 immunisation in reducing rates of adult pneumococcal disease in the U.S. and elsewhere...”

Although I agree with this sentence, in my opinion it can not be the conclusion of this study because it is not supported by the data provided in the study. The aim of the study was to know the incidence of invasive pneumococcal disease among the Finnish population, but it did not assess pneumococcal vaccine impact for different indications. Thus, I suggest moving this paragraph into the Discussion and rewriting a more balanced “Conclusion” based on data provided by the study. For example: “.... The burden of invasive pneumococcal infections is high
in Finland, not only in young children and elderly people, but also in working age people without high-risk conditions. In the general population of non-elderly adults, two-thirds of invasive infections and one half of fatal cases occur in persons without a recognised PPV23 indication. Thus, policy makers should consider alternative prevention strategies to reduce the burden of pneumococcal disease among the overall population.”

RESPONSE:
Revised as suggested. The following Conclusion was added on pages 15-16:

“In addition to young children and elderly persons, the burden of invasive pneumococcal infections is also substantial among working-age persons without high risk conditions. In the general population of non-elderly adults, two-thirds of invasive infections and one half of fatal cases occur in persons without a recognised PPV23 indication. Policymakers should therefore consider additional prevention strategies to reduce the burden of pneumococcal disease in the overall population.”

Reviewer 3: Ake Ortqvist

Reviewer's report:
This paper provides interesting data concerning the morbidity and mortality in IPI among working-age adults in Finland. It is a well-performed study and I have only a few comments.

Minor Essential Revisions
Abstract, Conclusions: I would suggest changing "consider alternative prevention strategies..." to "consider additional prevention strategies...."

RESPONSE:
Revised as suggested.

Discussion:
- The average annual incidence of IPI during the 8-year period was 10.6/100.000 inhabitants for all age groups and approximately 22/100.000 (my calculation) for those 65 years of age or above. These figures are very low - for all inhabitants approximately two thirds and for persons 65+ about half of the incidence seen in Sweden (which in turn, compared to many other countries, e.g. the US is low). It is unlikely that the "true" incidence in Finland is so much lower than that in Sweden. The authors should discuss this finding and the possible reasons for it,
e.g. low blood culturing frequency or antibiotic treatment before cultures are performed. It might also be worthwhile to study if there are large discrepancies in incidence of IPI between different regions, indicating varying practices. Further, the authors should discuss what the implications for their results would be if the "true" incidence was 15 instead of 10 /100,000 and especially if the major part of these "missing" patients were elderly or were working-age group patients with indication for vaccination with PPV23.

**RESPONSE:**

We have added the following sentences on page 12:

“Although our estimates from national laboratory-based surveillance are representative of the entire population of Finland, the observed IPD incidence was low compared with reports from some other European countries [22-24], and the United States [1], our previous report from Finland found that the overall average annual incidence of IPD increased by 35.1% during a 8-year study period and increased in all adult age groups. [25]. In that study temporal increase and higher regional IPD rates were significantly associated with higher blood culturing rates suggesting that the true incidence of IPD may be higher.”

- p.10, 2nd para, 2nd sentence; Wasn't it 9% CFP during the first week and not 9% of all deaths occurring during the first week?

**RESPONSE:**

We have corrected this error as suggested.

- p.12, 1rst para, last sentence; early antibiotic treatment without previous blood cultures may also be an explanation for the low incidence of IPI among HIV+ patients.

**RESPONSE:**

We agree and have added the following part of a sentence on page 12, 2nd paragraph:

“The relatively low rate of IPD among persons infected with HIV in Finland may reflect good access to antiretroviral therapy, early antibiotic treatment without blood cultures and use of prophylactic antibiotics among those with low CD4+ T cell count.”

- p.14, Conclusions; Although data from the US of an indirect herd immunity in adults due to vaccination of children with PCV7 are persuasive, the "evidence" is weak. So far the experience in US is what we have. Some preliminary reports
from other countries (Spain, Portugal) where vaccination with PCV7 also is quite widespread have not been as positive. So, it's not for sure that an introduction of PCV7 in children in Finland would result in a reduction of IPI also in adults. Maybe other dosages, or vaccination schedules, with PCV10 or PCV13 may become equally attractive as alternative or additional strategies for pneumococcal vaccination of adults?

RESPONSE:

We consider this comment relevant and added one reference from Spain and Portugal, respectively. On the other hand, there are also some positive preliminary reports from the U.K and Norway. The following sentence and references from Spain, Portugal, Norway and the U.K. were added on page 15, 2nd paragraph:

“Routine childhood immunisation with PCV7 has not yet been introduced in Finland. However, increasing evidence has been accumulating about the substantial indirect effects of childhood PCV7 immunisation in reducing rates of adult pneumococcal disease in the U.S. and elsewhere [40, 41], although early reports from some European countries have had inconsistent results [42-45]”

Discretionary Revisions:

Results:

- Mortality, p.8, 1st para, last sentence; Were there patients hospitalised as long as 90 days?

RESPONSE:

The patients were hospitalised for variable periods. We have reported both total case fatality proportion within the defined periods, as well as the in-hospital case fatality proportion for those who were still hospitalised at each specific point of time. In many studies only the in-hospital CFP has been reported and we included this for enabling comparisons. We have corrected the sentence:

“The in-hospital case-fatality proportions (CFPs) within 7, 28 and 90 days were 8%, 10% and 11%, respectively. “

In total 22 cases died during hospitalisation between day 29 and 90 (range from 29 to 77 days).