PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Bacterial meningitis in Finland, 1995-2014: a population-based observational study
AUTHORS	Polkowska, Aleksandra; Toropainen, Maija; Ollgren, Jukka; Lyytikainen, Outi; Nuorti, Pekka

VERSION 1 - REVIEW

REVIEWER	Eric Thelin Karolinska Institutet, Sweden University of Cambridge, UK
REVIEW RETURNED	20-Jan-2017

GENERAL COMMENTS	Abstract: Objectives: Major: I lack a hypothesis in the ”Objective”. Did you believe that there would be different trends of different bacterial origins following vaccinations? Abstract: Conclusions: Minor: “The documentation of changes in causative organisms and age distribution for meningitis cases are important for re-evaluating clinical guidelines for empiric antibiotic therapy” I don’t think this belongs in the Conclusion in the Abstract as you don’t provide any information about antibiotic therapy or guidelines in the Abstract, instead it is well suited for the general conclusion of the manuscript. General comment minor: Wouldn’t it be more interesting to study trends over age group (Like in Table 3) but for specific bacteria as this better would show if the vaccination programs had been effective or not? General comment minor: There is a lot of text about the dynamic frequency of different serotypes of bacteria. Considering that you have a lot of other tables and figures for this information, and that you obviously consider it important in the manuscript, I think this information belongs in Table form and not in running text Table 2 Minor: The first part of Table 2 is Figure 1. I think it is redundant to show them twice, and I prefer the Figure (perhaps with the data as supplementary information?). Table 2 Minor: The different age spans make it difficult to adequately interpret the mean annual incidence. If you only look at that, it looks like it is almost only kids <2 years that are affected by bacterial meningitis, while this is clearly not the case as the mean age for all your patients is a lot higher. I suggest that you try to normalize the groups somehow or insert an adjustment for the number of cases in this Table (if you decide to keep this part of the Table, see previous comment).

	Figure 2: Minor: Please provide information on what “PCV10” is in the Figure. Discussion: The discussion was very well written and really interprets the findings in an adequate way. To be honest, I don’t think your “limitation” to include only culture positive cases is an actually limitation as it decreases the false-positive rate of cases in this study, but I like how you tackle the issue with potential negative CSF cultures in the Discussion. Good job! Ethical consideration: Is it possible to include the ethical reference number (which I believe is a necessity for all medical studies in Finland, including population cohort studies like the current)? Perhaps this study doesn’t need a formal ethical application like the authors suggest. Summary: While this study perhaps mostly re-inforce already known concepts of meningitis in modern countries, it is well written and provides important information about meningitis epidemiology from a nation-wide approach. It does however give important information suggesting that vaccination programs really helps. I recommend minor revision correcting some minor issues

REVIEWER	Jacob Bodilsen Department of Infectious Disesases, Aalborg University Hospital, Aalborg, Denmark
REVIEW RETURNED	20-Jan-2017

GENERAL COMMENTS	Manuscript ID: bmjopen-2016-015080. Review of manuscript: ’Bacterial meningitis in Finland, 1995-2014: a population-based observational study’. Dear editor and authors Thank you for inviting me to review this very interesting manuscript. The authors report of incidences of cerebrospinal fluid (CSF) culture-positive bacterial meningitis notified to the National Infectious Diseases Register (NIDR) in Finland from 1995 to 2014. They identified a total of 1361 cases of bacterial meningitis with *S. pneumoniae* and *N. meningitidis* as the predominating pathogens. Results showed year-to-year variations in incidences of these two pathogens with a substantial decrease when the entire study period was examined. The incidences of the other pathogens were more or less constant. A sub-analysis of case fatality of patients with bacterial meningitis in 2004-2009 vs. 2010-2014 remained

	unchanged at approximately 10%. General considerations: I think the data are useful and the information contributes to our general understanding of the epidemiology of bacterial meningitis in Northern Europe. Considering the aims of the study I do not think that the data are essential in developing or revising treatment guidelines as e.g. empiric antibiotic therapy is hardly going to change unless data on antibiotic susceptibility patterns are also available and reported. Maybe the manuscript could benefit from more focus on the interesting secular trends in incidences of pneumococcal (variations before pneumococcal vaccinations were implemented in 2010) and meningococcal meningitis? Completeness (or lack thereof) of notifications of culture-positive cases of bacterial meningitis to the NIDR should be discussed. There is some redundancy in the text, tables and figures in the results section. Some references may be omitted. Please mention existence or not of a national guideline for antibiotic treatment of bacterial meningitis and adjunctive dexamethasone treatment during the study period? There is also a need for minor language revision. Minor specific revisions: 1. Please present data as n/N (%) throughout the abstract and manuscript instead of just percentages. Incidence rates should be specified as x.xx/100,000/year. Please be consistent in the order of presenting the data, e.g. incidence rates followed by n/N (%) or vice versa. 2. I do not think that it is appropriate to suggest a linear yearly decline in incidences (e.g.: abstract, results section, lines 4-6) as they clearly vary from year to year for most of the pathogens - as the authors also show in Table 1 and Figure 2. 3. Page 3, third point in 'Strengths and limitations'. Impact of conjugate vaccine for *H. influenzae*.: This is not addressed in the study as the vaccine was introduced in 1986 in Finland (ref. 15) and the study period begins in 1995 and incidences remain consistently very low throughout. Regarding effect of 10-valent pneumococcal vaccine: Incidences clearly decline in small children as reported in the results section, but overall incidence of pneumococcal meningitis only has a substantial decrease in 2014 (Table 1 and Figure 2). Interestingly, there is also considerable secular variation in pneumococcal incidences before the introduction pneumococcal vaccine in 2010. Maybe these aspects can be discussed?

	4. Do the authors have access to antibiotic susceptibility results of isolated pathogens? 5. Page 4, line 28. I do not think that references 10+12 are appropriate in this context. 6. I think reference 15 was published in 1992 and not 2016? 7. Are data complete for all variables (specimen date, date of birth, sex and personal identity) in all notified cases? 8. Was there an association between year of implementation of dexamethasone in treatment guidelines (if this is recommended in Finland?) and case-fatality proportions? 9. Page 5, lines 41-43. 'Case definitions' states that case fatality is actually categorised as 30-day case fatality rate. This term could be used more consistently throughout the paper as it provides a more accurate measure of mortality. Most patients admitted with bacterial meningitis undergo lumbar puncture within 1-2 days so it seems reasonable to use day of CSF culture as T0? 10. Page 6, lines 6-7. Pathogen specific annual incidence rates. Was a form of standardisation performed (direct or indirect)? If not and data are readily available maybe this could be done to better compare variations in incidence rates? 11. Comparisons of overall median age at the beginning and end of the study period seems rather trivial given the decrease in incidence of meningococcal meningitis and is not very useful clinically, nor in designing clinical guidelines and is too crude a measure for vaccination strategies. The data can be omitted or just mentioned once in the results section. 12. Page 7, lines 22-24. It seems more appropriate to mention ranges of incidence rates of overall meningitis after the reported mean incidence (page 7, line 10). 13. Page 7, line 26. There is a slight discrepancy in case fatality (30-day?) proportion in the study period 2004-2009 (10% vs. 10.6%)? 14. Page 9, Table 2. Age category. I would prefer if results were reported first as median and thereafter IQR in the next line. Maybe 'means' could be omitted as the variation of age can be ascertained by the IQRs. 15. I think Table 3 can be omitted (please see comment 2). Statistical analysis used should be reported in the Table header if it is decided to keep it in the manuscript. 16. The data in Table 1 is presented well in Figure 2. Maybe Table 1 can be omitted or reported in supplementary material? Maybe the y-axis could be labelled as incidence rate/100,000/year. I know it is almost always reported in yearly incidence rates but I prefer it to be

	specified. 17. Given the information in Table 2 it seems like figure 1 is redundant (more appropriate as supplementary material)? 18. Some of the age groups have very low absolute number of deaths (e.g. 4 and 3 deaths among children and adolescents) and it seems a little optimistic to report case fatality percentages with decimals? 19. Please consider displaying incidence rates of pneumococcal and meningococcal meningitis in different age groups during the study period in figures instead, 1 figure for each pathogen with calendar year on the x-axis and incidence rates on the y-axis with different lines representing different age groups (a lot of incidence rates may confuse the reader)? 20. Page 15, line 44 does not really make sense. Maybe it can be rephrased: 'Overall incidence rates of listeria meningitis were without significant variations throughout the study period and ranged from 0.04-0.21/100,000/year'? Or something like that. 21. Page 16, lines 12-17. I think the decrease in incidence in children during the study period 1995-2014 was due to a decrease in meningococcal and pneumococcal disease (vaccination and secular trends) and not because of *H. influenzae* vaccination implemented in 1986. Please see comment 3. 22. Page 16, lines 26-46. Maybe this part could be rewritten and presented in a shorter and more accurate way summarising that secular trends have been observed frequently (e.g. in the US) as well as successful implementations of conjugate group C meningococcal vaccines (e.g. in England – who were the first as far as I know, the Netherlands etc.) with both declines in clinical cases and carriage (herd immunity)? Lines 46-50 can be omitted. 23. Page 17, lines 23-28. Pregnancy and older age hardly explains the higher incidence in men vs. women – quite the contrary. Are men more often immunosuppressed in Finland? No references examining alcoholism and risk of listeria meningitis instead of reference 29? 24. Page 18, lines 28-32. Maybe McMillan *et al*, CID, 2001 is a more useful reference for timing and cause of death in bacterial meningitis than reference 39?

REVIEWER	Matthias G. Vossen Medical University of Vienna Austria
REVIEW RETURNED	31-Jan-2017

GENERAL COMMENTS	In their well written manuscript the authors present the results of a

	retrospective study, documenting the incidence development of the most common bacterial meningitis pathogens in Finland during 1995 to 2014. They describe that the mainstay of bacterial meningitis is caused by Streptococcus pneumoniae and Neisseria meningitides. A reduction of meningitis incidence observed by the authors is mainly driven by a reduction of meningitis cases caused by these bacteria. Although an overall reduction of cases could be observed, the case fatality rate remained unchanged from 2004 to 2014. The manuscript raises some minor questions: - Could the authors elaborate on the “secular” trends and their proposed impact on meningitis? - The authors offer an explanation attempt for the higher incidence of Listeria monocytogenes meningitis in men than in women, however, it would be nice if they could discuss this finding to a greater extent and maybe offer a hypothesis what the predisposing factors may be in the case of Listeria monocytogenes, as smoking is a logical predisposition for invasive pneumococcal disease, but surely not for meningitis with listeria. - It might be interesting to see the meningitis rate in young adults (18-25y), as the group 18-49 shows the most cases and young adults would be the “classic” meningococcal meningitis patient and the median age is described to be 18 years. - The authors describe a serotype switch to non-Hib serotypes causing Haemophilus influenza meningitis. Was there an increase in non-PCV10 serotypes for pneumococcal meningitis? Minor corrections: - Page 3. Line 26 typo: “underestimated” - Reference 30: Please add a “last accessed on” date

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Eric Thelin
Institution and Country: Karolinska Institutet, Sweden; University of Cambridge, UK
Competing Interests: None declared

Abstract: Objectives: Major: I lack a hypothesis in the ”Objective”. Did you believe that there would be different trends of different bacterial origins following vaccinations?
This was an evaluation of national surveillance data, thus no formal hypothesis testing was performed. In addition, according to STROBE guideline, listing the hypothesis is not required in the abstract.

Abstract: Conclusions: Minor: “The documentation of changes in causative organisms and age distribution for meningitis cases are important for re-evaluating clinical guidelines for empiric antibiotic therapy” I don’t think this belongs in the Conclusion in the Abstract as you don’t provide any information about antibiotic therapy or guidelines in the Abstract, instead it is well suited for the general conclusion of the manuscript.
We revised the conclusions as follows:
“Ongoing epidemiological surveillance is needed to identify trends, evaluate serotype distribution, assess vaccine impact and to develop future vaccination strategies.” (Page 2, lines 22-23; in the Revision version of the manuscript, after hiding markups)

General comment minor: Wouldn’t it be more interesting to study trends over age group (Like in Table 3) but for specific bacteria as this better would show if the vaccination programs had been effective or

not?
We changed Table 1 to show trends over age groups and pathogens. (Page 8)

General comment minor: There is a lot of text about the dynamic frequency of different serotypes of bacteria. Considering that you have a lot of other tables and figures for this information, and that you obviously consider it important in the manuscript, I think this information belongs in Table form and not in running text.
The information on main serotypes was kept in the text body, since it was not feasible to combine data on three different pathogens in one table.

Table 2 Minor: The first part of Table 2 is Figure 1. I think it is redundant to show them twice, and I prefer the Figure (perhaps with the data as supplementary information?).
We removed the information on incidence rates from Table 2 and moved these data to Table 1. In Table 1 the absolute number of cases is also presented. Figure 1 shows proportions (not incidence rates) of bacterial meningitis cases caused by each pathogen in specific age-groups during the study period 1995-2014. (Table 1: page 8, Figure 1: page 10)

Table 2 Minor: The different age spans make it difficult to adequately interpret the mean annual incidence. If you only look at that, it looks like it is almost only kids <2 years that are affected by bacterial meningitis, while this is clearly not the case as the mean age for all your patients is a lot higher. I suggest that you try to normalize the groups somehow or insert an adjustment for the number of cases in this Table (if you decide to keep this part of the Table, see previous comment).
The data shown are age-group specific incidence rates (thus age span does not affect the ability to compare the data,) calculated as number of cases per person-years at given age span. To add information on the disease burden, we added the number of cases to modified Table 1. Division to smaller age groups would negatively affect the ability to visually present data and to calculate the trends (because of small numbers or lack of cases in strata). (Table 1, page 8)

Figure 2: Minor: Please provide information on what “PCV10” is in the Figure.
We added a legend for “10-valent pneumococcal conjugate vaccine (PCV10)”. (Page 13)

Discussion: The discussion was very well written and really interprets the findings in an adequate way. To be honest, I don’t think your “limitation” to include only culture positive cases is an actually limitation as it decreases the false-positive rate of cases in this study, but I like how you tackle the issue with potential negative CSF cultures in the Discussion. Good job!
Thank you.

Ethical consideration: Is it possible to include the ethical reference number (which I believe is a necessity for all medical studies in Finland, including population cohort studies like the current)? Perhaps this study doesn’t need a formal ethical application like the authors suggest.
According to the National Institute of Health and Welfare, no ethical review was required for this study. We revised the Ethical consideration section as follows:
“Data used in the analysis were collected as a part of national routine surveillance which falls under the existing mandate of THL. No formal Institutional Review Board (IRB) review was required for this study. Personal identifiers were removed after linkage with vital status data“. (Page 6, lines 13-15)

Summary: While this study perhaps mostly re-inforce already known concepts of meningitis in modern countries, it is well written and provides important information about meningitis epidemiology from a nation-wide approach. It does however give important information suggesting that vaccination programs really helps. I recommend minor revision correcting some minor issues
Thank you.

Reviewer: 2
Reviewer Name: Jacob Bodilsen
Institution and Country: Department of Infectious Disesases, Aalborg University Hospital, Aalborg, Denmark
Competing Interests: None declared

In my opinion the manuscript can be accepted after some revisions and I would happily go through it again. Please see attached file.

Manuscript ID: bmjopen-2016-015080.
Review of manuscript: 'Bacterial meningitis in Finland, 1995-2014: a population-based observational study'.
Dear editor and authors
Thank you for inviting me to review this very interesting manuscript.
The authors report of incidences of cerebrospinal fluid (CSF) culture-positive bacterial meningitis notified to the National Infectious Diseases Register (NIDR) in Finland from 1995 to 2014. They identified a total of 1361 cases of bacterial meningitis with S. pneumoniae and N. meningitidis as the predominating pathogens. Results showed year-to-year variations in incidences of these two pathogens with a substantial decrease when the entire study period was examined. The incidences of the other pathogens were more or less constant. A subanalysis of case fatality of patients with bacterial meningitis in 2004-2009 vs. 2010-2014
remained unchanged at approximately 10%.

General considerations:
I think the data are useful and the information contributes to our general understanding of the epidemiology of bacterial meningitis in Northern Europe. Considering the aims of the study I do not think that the data are essential in developing or revising treatment guidelines as e.g. empiric antibiotic therapy is hardly going to change unless data on antibiotic susceptibility patterns are also available and reported.
The conclusion of the abstract was revised to (please also see response to reviewer 1): "Ongoing epidemiological surveillance is needed to identify trends, evaluate serotype distribution, assess vaccine impact and to develop future vaccination strategies." (Page 2, lines 22-23)

Maybe the manuscript could benefit from more focus on the interesting secular trends in incidences of pneumococcal (variations before pneumococcal vaccinations were implemented in 2010) and meningococcal meningitis?
We added some additional points to the discussion of pneumococcal trends:
"Before the introduction of PCV10 considerable variation in pneumococcal meningitis incidence rates was seen. As there was no major changes in surveillance or diagnostic practices in Finland, these changes may be related to emergence of new serotypes, selective pressure from antibiotic use or natural fluctuation in serotypes [24-26]." (Page 15, lines 23-25)
And meningococcal part:
"Changes in rates of meningococcal disease have also been observed in other countries in Europe and worldwide [16-17]. The reasons for these declines in incidence are not clear but may be related to population immunity to circulating strains, changes in colonizing organisms in the nasopharynx or increasing use of influenza vaccine. Also changes in behavioral risk factors such as lower prevalence of smoking or crowding, might contribute [18-19]. (Page 15, lines 11-15)
We deleted sentence from line 43- 44.
We propose keeping lines 46-50, since one of our aims was to provide information for developing future prevention strategies.

Completeness (or lack thereof) of notifications of culture-positive cases of bacterial meningitis to the

NIDR should be discussed.
The completeness of the national surveillance system has not been comprehensively evaluated in Finland, however is assumed to be high (close to 100%) because of electronic reporting of cases directly from the clinical microbiology laboratories to the National Infectious Disease Register.

There is some redundancy in the text, tables and figures in the results section. Some references may be omitted.
Please mention existence or not of a national guideline for antibiotic treatment of bacterial meningitis and adjunctive dexamethasone treatment during the study period?
In Finland, standard guidelines for antibiotic treatment of septic infections, including bacterial meningitis are available (http://www.kaypahoito.fi/web/kh/suositukset/suositus?id=nak04784&suositusid=hoi50032). We know that adjunctive dexamethasone treatment was previously widely recommended but there are no published clinical data on the prevalence of its use.
We added some additional point to the discussion:
“Because of lack of clinical data we could not assess the potential impact of treatment changes, such as dexamethasone use, on case fatality.” (Page 17, lines 3-4).

There is also a need for minor language revision.

Minor specific revisions:
1. Please present data as n/N (%) throughout the abstract and manuscript instead of just percentages. Incidence rates should be specified as x.xx/100,000/year. Please be consistent in the order of presenting the data, e.g. incidence rates followed by n/N (%) or vice versa.
We added the information on denominator and numerator as suggested, except when they were provided in the text. The presentation of incidence rates was revised to xx/100,000 person-years.

2. I do not think that it is appropriate to suggest a linear yearly decline in incidences (e.g.: abstract, results section, lines 4-6) as they clearly vary from year to year for most of the pathogens - as the authors also show in Table 1 and Figure 2.
The analysis does not suggest that the trend is necessarily exactly linear, but we assessed what the trend would be if we modeled the data by using linear model. So, this is a compact approximate way of describing the trend. If there was overdispersion in the data, we used a negative binomial model instead of Poisson regression model. Reference: Held L, Höhle M, Hofmann M. A statistical framework for the analysis of multivariate infectious disease surveillance counts. Stat Model 2005;5:187–99

3. Page 3, third point in ‘Strengths and limitations’. Impact of conjugate vaccine for H. influenzae.: This is not addressed in the study as the vaccine was introduced in 1986 in Finland (ref. 15) and the study period begins in 1995 and incidences remain consistently very low throughout.
Since Hib vaccination was introduced before the study period began, we cannot show before and after comparison. Our statement is based on the observation, that there were only two cases of meningitis caused by the H. influenzae type b during 10 years. This is most likely an effect of the vaccination program.
We revised the sentence to: “The study documents the sustained population impact of infant conjugate vaccination against Haemophilus influenzae type b; and introduction of 10- valent pneumococcal conjugate vaccination on reducing the burden of bacterial meningitis, as well as decline in meningococcal meningitis due to secular trend. (Page 3, lines 6-9)

Regarding effect of 10-valent pneumococcal vaccine: Incidences clearly decline in small children as reported in the results section, but overall incidence of pneumococcal meningitis only has a substantial decrease in 2014 (Table 1 and Figure 2). Interestingly, there is also considerable secular

variation in pneumococcal incidences before the introduction pneumococcal vaccine in 2010. Maybe these aspects can be discussed?
Please see above. The following comment was added.
“Before the introduction of PCV10 considerable variation in pneumococcal meningitis incidence rates was seen. As there was no major changes in surveillance or diagnostic practices in Finland, these changes may be related to emergence of new serotypes, selective pressure from antibiotic use or natural fluctuation in serotypes [24-26].” (Page 15, lines 23-25)

4. Do the authors have access to antibiotic susceptibility results of isolated pathogens?
For the purpose of this study, we did not have access to antimicrobial susceptibility data.
We added this information to the methods: “Antimicrobial susceptibility data were not available” (Page 5, lines 13-14).

5. Page 4, line 28. I do not think that references 10+12 are appropriate in this context.
Removed.
6. I think reference 15 was published in 1992 and not 2016?
Yes, thank you. Corrected. (Currently reference 12)

7. Are data complete for all variables (specimen date, date of birth, sex and personal identity) in all notified cases?
Yes, all data were complete for the above mentioned variables. These variables are required and verified for all notifications in the laboratory-based surveillance system in Finland.

8. Was there an association between year of implementation of dexamethasone in treatment guidelines (if this is recommended in Finland?) and case-fatality proportions?
There is no representative information nor published studies, which would show how widely dexamethasone treatment is used. Also in the routine surveillance data, no clinical information is available. Therefore, assessing the association between dexamethasone and case-fatality proportions is not feasible in this study.
We added additional point to the discussion:
“Because of lack of clinical data we could not assess the potential impact of treatment changes, such as dexamethasone use, on case fatality. (Page 17, lines 3-4).

9. Page 5, lines 41-43. ‘Case definitions’ states that case fatality is actually categorised as 30-day case fatality rate. This term could be used more consistently throughout the paper as it provides a more accurate measure of mortality. Most patients admitted with bacterial meningitis undergo lumbar puncture within 1-2 days so it seems reasonable to use day of CSF culture as T0?
We changed the text to 30-day case fatality proportion. The 30-day case-fatality proportion was calculated for the date of the first positive culture.

10. Page 6, lines 6-7. Pathogen specific annual incidence rates. Was a form of standardisation performed (direct or indirect)? If not and data are readily available maybe this could be done to better compare variations in incidence rates?
Because of considerable variation in rates by age, we showed and analyzed age-stratified incidence rates. Direct standardization would not provide additional information to help interpretation. Additional information on rates in specific age groups and by particular pathogen is now provided in the modified Table 1. (Table 1, page 8)

11. Comparisons of overall median age at the beginning and end of the study period seems rather trivial given the decrease in incidence of meningococcal meningitis and is not very useful clinically, nor in designing clinical guidelines and is too crude a measure for vaccination strategies. The data can be omitted or just mentioned once in the results section.

Reporting changes in the median age is part of descriptive analysis of data. This provides useful information regarding which age groups are currently most affected by meningitis and indicates that future prevention measures should be targeted to older age groups who experience largest burden of disease.

12. Page 7, lines 22-24. It seems more appropriate to mention ranges of incidence rates of overall meningitis after the reported mean incidence (page 7, line 10).
We propose keeping the order of text as in the manuscript, to maintain consistency with other paragraphs and sections.

13. Page 7, line 26. There is a slight discrepancy in case fatality (30-day?) proportion in the study period 2004-2009 (10% vs. 10.6%)?
This difference is because of different time periods used in the analysis. The 30-day CFP for the period 2004-2014 was 10% and for the period 2004-2009 it was 10.6%.

14. Page 9, Table 2. Age category. I would prefer if results were reported first as median and thereafter IQR in the next line. Maybe 'means' could be omitted as the variation of age can be ascertained by the IQRs.
Changed as requested. (Table 2, page 9)

15. I think Table 3 can be omitted (please see comment 2). Statistical analysis used should be reported in the Table header if it is decided to keep it in the manuscript.
We removed table 3 and modified table 1 in such a way that the incidence rates in each 5 year period for each pathogen are stratified by age group and the relative change in rate is presented. Information on statistical analysis method is added as footnote. (Table 1, page 8)

16. The data in Table 1 is presented well in Figure 2. Maybe Table 1 can be omitted or reported in supplementary material? Maybe the y-axis could be labelled as incidence rate/100,000/year. I know it is almost always reported in yearly incidence rates but I prefer it
to be specified.
See response 15. We propose keeping revised Table 1. (Page 8)

17. Given the information in table 2 it seems like figure 1 is redundant (more appropriate as supplementary material)?
We removed columns referring to incidence rates in table 2. Figure 1 does not show not incidence rates but proportions (distribution) of cases in different age groups.

18. Some of the age groups have very low absolute number of deaths (e.g. 4 and 3 deaths among children and adolescents) and it seems a little optimistic to report case fatality percentages with decimals?
We report CFP with one decimal.

19. Please consider displaying incidence rates of pneumococcal and meningococcal meningitis in different age groups during the study period in figures instead, 1 figure for each pathogen with calendar year on the x-axis and incidence rates on the y-axis with different lines representing different age groups (a lot of incidence rates may confuse the reader)?
The information on incidence of different pathogens in different age groups is now added to the Table 1. (Page 8)

20. Page 15, line 44 does not really make sense. Maybe it can be rephrased: 'Overall incidence rates of listeria meningitis were without significant variations throughout the study period and ranged from 0.04-0.21/100,000/year'? Or something like that.

We rephrased it to: “Overall incidence rates of listeria meningitis did not vary significantly during the study period, ranging from 0.04 to 0.21/100,000 person-years (Page 14, lines 17-18)

21. Page 16, lines 12-17. I think the decrease in incidence in children during the study period 1995-2014 was due to a decrease in meningococcal and pneumococcal disease (vaccination and secular trends) and not because of H. influenzae vaccination implemented in 1986.
Please see comment 3.
We changed as follows: “The mean age of cases increased significantly during the study period mainly because of the decrease in incidence in children associated pneumococcal conjugate vaccine program and declining secular trend in meningococcal meningitis.” (Page 15, lines 5-7)

22. Page 16, lines 26-46. Maybe this part could be rewritten and presented in a shorter and more accurate way summarizing that secular trends have been observed frequently (e.g. in the US) as well as successful implementations of conjugate group C meningococcal vaccines (e.g. in England – who were the first as far as I know, the Netherlands etc.) with both declines
in clinical cases and carriage (herd immunity)? Lines 46-50 can be omitted.
Please see response above. Revised text as follows:
“Changes in rates of meningococcal disease have also been observed in other countries in Europe and worldwide [16-17]. The reasons for these declines in incidence are not clear but may be related to population immunity to circulating strains, changes in colonizing organisms in the nasopharynx or increasing use of influenza vaccine. Also changes in behavioral risk factors such as lower prevalence of smoking or crowding, might contribute [18-19]. In some countries, decreases were related to meningococcal vaccination. After the introduction of conjugate serogroup C meningococcal vaccine, vaccine serogroup disease nearly disappeared in England [20] and the Netherlands [21]. Direct and indirect (herd protection) vaccine effects were also reported from other European countries including Spain, Ireland and Belgium [22-23].” (Page 15, lines 11-19)
We deleted sentence from line 43- 44.
We propose keeping lines 46-50, since one of our aim was to provide information for developing future prevention strategies.

23. Page 17, lines 23-28. Pregnancy and older age hardly explains the higher incidence in men vs. women – quite the contrary. Are men more often immunosuppressed in Finland? No references examining alcoholism and risk of listeria meningitis instead of reference 29?
We add additional points to discussion:
“L. monocytogenes meningitis cases were 2.5 times more likely to be men. Higher rates of listeriosis in males have also been observed in other studies [7]. However, the reasons are unknown, but may be related to higher prevalence of underlying conditions, alcoholism among men and liver diseases (including alcoholic cirrhosis) [30].” (Page 16, lines 10-13)

24. Page 18, lines 28-32. Maybe McMillan et al, CID, 2001 is a more useful reference for timing and cause of death in bacterial meningitis than reference 39?
Thank you for the reference. Added to reference list, as suggested. (Currently reference 41)

Reviewer: 3
Reviewer Name: Matthias G. Vossen
Institution and Country: Medical University of Vienna, Austria
Competing Interests: None declared

In their well written manuscript the authors present the results of a retrospective study, documenting the incidence development of the most common bacterial meningitis pathogens in Finland during 1995 to 2014. They describe that the mainstay of bacterial meningitis is caused by Streptococcus pneumoniae and Neisseria meningitides. A reduction of meningitis incidence observed by the authors

is mainly driven by a reduction of meningitis cases caused by these bacteria. Although an overall reduction of cases could be observed, the case fatality rate remained unchanged from 2004 to 2014. The manuscript raises some minor questions:

- Could the authors elaborate on the “secular” trends and their proposed impact on meningitis?
We added some additional points to the discussion of pneumococcal trends:
“Before the introduction of PCV10 considerable variation in pneumococcal meningitis incidence rates was seen. As there was no major changes in surveillance or diagnostic practices in Finland, these changes may be related to emergence of new serotypes, selective pressure from antibiotic use or natural fluctuation in serotypes [24-26].” (Page 15, lines 23-25)
And meningococcal trends:
“Changes in rates of meningococcal disease have also been observed in other countries in Europe and worldwide [16-17]. The reasons for these declines in incidence are not clear but may be related to population immunity to circulating strains, changes in colonizing organisms in the nasopharynx or increasing use of influenza vaccine. Also changes in behavioral risk factors such as lower prevalence of smoking or crowding, might contribute [18-19]. (Page 15, lines 11-15)

- The authors offer an explanation attempt for the higher incidence of Listeria monocytogenes meningitis in men than in women, however, it would be nice if they could discuss this finding to a greater extent and maybe offer a hypothesis what the predisposing factors may be in the case of Listeria monocytogenes, as smoking is a logical predisposition for invasive pneumococcal disease, but surely not for meningitis with listeria.
We added more information on this topic However there is no published studies which would assess the possible reasons for that disproportion in Finland.
“L. monocytogenes meningitis cases were 2.5 times more likely to be men. Higher rates of listeriosis in males have also been observed in other studies [7]. However, the reasons are unknown, but may be related to higher prevalence of underlying conditions, alcoholism among men and liver diseases (including alcoholic cirrhosis) [30].” (Page 16, lines 10-13)

- It might be interesting to see the meningitis rate in young adults (18-25y), as the group 18-49 shows the most cases and young adults would be the “classic” meningococcal meningitis patient and the median age is described to be 18 years.
We agree with purpose. However, dividing to such small age group would make it difficult to assess the trends because of small numbers. Also, we would prefer consistency in age groups throughout the manuscript.

- The authors describe a serotype switch to non-Hib serotypes causing Haemophilus influenza meningitis. Was there an increase in non-PCV10 serotypes for pneumococcal meningitis?
Because of the limited scope of this manuscript we did not assess vaccine impact. This would required more advanced analysis. Study addressing this topic will be probably publish soon by other Finnish study group.

Minor corrections:
- Page 3. Line 26 typo: “underestimated”
Corrected.
- Reference 30: Please add a “last accessed on” date
Added according to suggestions.

VERSION 2 – REVIEW

REVIEWER	Eric Thelin 1: Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK 2: Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
REVIEW RETURNED	14-Mar-2017

GENERAL COMMENTS	The authors have adequately responded to my comments and queries. No further revisions necessary in my opinion.

REVIEWER	Jacob Bodilsen Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark
REVIEW RETURNED	22-Mar-2017

GENERAL COMMENTS	The authors have done a very good job at revising the manuscript and adressed my concerns appropriately. It is very well written and I accept the given arguments when suggested changes were not made. As a final minor comment I think that they should mention that they (with good reason) assume all cases to be notified, but there are no certain way to know this. Maybe consider reporting incidence rates with 1 decimal and case-fatality rates with no decimals. I will leave it up to the Editor to decide this. Thank you for letting me review this very interesting manuscript again and I congratulate the authors on a job well done.

REVIEWER	Matthias G. Vossen Medical University of Vienna, Austria
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	The modifications made to the manuscript have improved its quality, I recommend to accept it for publication.

VERSION 2 – AUTHOR RESPONSE

Our response to the optional comment from Reviewer 2 is as follows.
- Currently, the methods section already provides information about the case ascertainment in the Finnish laboratory-based, electronic surveillance system (page 5, lines 9-32). Because the data on laboratory confirmed cases are transmitted directly from the clinical microbiology laboratories' database to the National surveillance database, the ascertainment of laboratory confirmed cases is near complete. The fact that clinically diagnosed cases are not captured is discussed on page 15 (page 15, lines 15-18). As near comprehensive case ascertainment and very high proportion of bacterial isolates received are strengths of our study, we added the following sentence in the discussion section:
- "Because the data on laboratory confirmed cases are transmitted electronically directly from the clinical microbiology laboratories' database to the national surveillance database, a strength of our

study is comprehensive case ascertainment. In addition, almost all isolates of N. meningitidis, H. influenzae and S. pneumoniae (98%) were available for serotyping/grouping at THL reference laboratory (Page 15, lines 13-15).
- We would like to keep the second decimal in the incidence rate since it is commonly used method of presenting small numbers. Rounding to one decimal would increase error.
- We removed the decimals in case fatality proportion since both denominators and numerators are provided.

VERSION 3 – REVIEW

REVIEWER	Eric Thelin Department of Clinical Neuroscience, Karolinska Insitutet, Stockholm, Sweden Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
REVIEW RETURNED	28-Mar-2017

GENERAL COMMENTS	The authors have adequately addressed my concerns and I think the manuscript is fit for publication.

REVIEWER	Jacob Bodilsen Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark
REVIEW RETURNED	28-Mar-2017

GENERAL COMMENTS	I accept the arguments by the authors.

REVIEWER	Matthias G. Vossen Medical University of Vienna
REVIEW RETURNED	13-Apr-2017

GENERAL COMMENTS	The authors have performed a final retouch of the manuscript. Percent numbers were rounded to full numbers and a statement regarding the strengths of the paper has been added. I see no reason to perform any more changes and recommend acceptance of the manuscript as is. Very good job!