Systematic Review Protocol:

Nasopharyngeal carriage of *Streptococcus pneumoniae* in over 60 year olds: A systematic review and meta-analysis

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1 Background and Objectives

1.1 Background

*Streptococcus pneumoniae*, or the pneumococcus, is the commonest cause of community-acquired pneumonia (CAP) in adults (1-3) and a leading cause of death in elderly (4, 5).

Mucosal colonisation by the pneumococcus is an immunising, often asymptomatic event which leads to protection against subsequent re-colonisation and invasive disease (6,7). The prevalence of nasopharyngeal pneumococcal carriage decreases with age (8), for reasons that are not well understood. Sampling artefact has been suggested as an explanation i.e. that detection method (culture versus molecular methods) or sampling location (nasopharyngeal versus oropharyngeal), alters apparent rates (9, 10). However, current reports of carriage in the elderly (>60 years) reflect a wide population variation using the same methods, ranging from no oropharyngeal/nasopharyngeal colonisation to carriage rates of 27% (11)(12).

Risk factors for colonisation in adults include cohabitation/institutionalisation (8,9,13-15), contact with children <2 years (9, 13,14,16-18) and smoking status (8, 19). The relative importance of these environmental and intrinsic factors are not well defined. Decisions regarding vaccination strategy are informed by knowledge of the protection afforded to the individual and the potential to disrupt transmission between individuals. By 2050, 30% of the European population will be over 65 years old (20). These individuals represent a gap in our knowledge of transmission dynamics. Improving our understanding of risk factors for pharyngeal colonisation will support strategic decisions made by vaccination programmes, and may allow targeted immunisation.

We will perform a systematic literature review and meta-analysis using person-level data in order to examine rates of, and risk factors for, carriage.

1.2 Review objectives

1) What is the upper respiratory tract (oropharyngeal/nasopharyngeal) rate of *Streptococcus pneumoniae* colonisation of people aged over 60 years?

Secondary review question:

2) What are the risk factors for nasopharyngeal and oropharyngeal carriage of *S. pneumoniae*?

1.3 Variables of particular importance

From a preliminary background literature review, we identified the following important risk factors for further analysis:

1. Age
2. Smoking status
3. Comorbidities; specifically asthma and chronic obstructive pulmonary disease
4. Living conditions: lives alone/ with spouse/ with children/ institutionalised
5. Contact with children
6. Recent upper respiratory tract infection
7. Recent vaccination
8. Recent antibiotic use
We will also examine through sub-analysis:
- Socio-economic status (low, medium and high) AND/OR
- Household income (HIC)

1.4 Geographical scope

This review will include all countries identified in the preliminary literature search. However, the environmental differences between these countries will be acknowledged in the later analyses with specific sub-group analysis taking into account country income status.

2. Proposed review method

2.1 Analysis international peer reviewed literature

Two independent reviews of the literature will be performed (Wheeler and Smith) in order to screen for inclusion criteria. Discordance will be resolved by consensus. Articles identified will be assessed for quality using established guidelines.

2.1.1 Search strings

The search was conducted using the MEDLINE and EMBASE literature databases.

Three search strings were utilised, one on microbiological agents, one on carriage and colonisation and one on age. Within each string possible relevant searches are combined using ‘OR’. Similarly separate search strings are combined using AND (ie “Streptococcus pneumoniae” AND “colonisation”)

*The following search strings were used in combination:*

*Streptococcus pneumoniae* [MESH] OR “pneumococcus” [ti] OR “streptococc*” [ti]
AGED [Mesh] OR elderly [ti] OR Limit: 18+ years

Limits

The following limits will be applied:

Publication date: 01/01/1945- present

Language: English (original or translation)

2.1.2 Grey literature and other data sources

Where appropriate we will search relevant websites using a Google search for additional information. These websites include:

- World Health Organisation (WHO): [www.who.int](http://www.who.int)
2.1.3 Reference listings of key references

References will be checked in all included studies and relevant literature will be reviewed.

2.1.4 Selection procedure

Articles will be selected for inclusion using a 3 step approach with the following inclusion/exclusion criteria:

Inclusion and exclusion criteria

Inclusion criteria:
1. Papers published since 1946 as per MEDLINE coverage were considered for inclusion
2. Includes participants >60 years old
3. Nasopharyngeal/oropharyngeal airway carriage of *S. pneumoniae*, carriage being defined by standard validated clinical diagnostic techniques including classical culture or PCR

Exclusion criteria:
1. Hospitalised individuals
2. Active or suspected pneumococcal infection
3. No English version or translation available
4. No full journal article available
5. Lower airway samples including sputum or broncho-alveolar lavage
6. Carriage defined by alternative techniques (ie not classical culture or PCR)

Selection procedure:

Step 1: Screening of title and abstract:
- Two independent reviewers will screen the title and abstract using the inclusion and exclusion criteria. Non-concordance of reviewers will be resolved by consensus
- Articles that will be excluded at this point include; posters, letters to editor, editorials or comments

Step 2: Screening full article:
- Full articles identified in step 1 will be assessed by two independent reviewers.
- Articles will be critically appraised using the STrengthening the Reporting of OBservational studies (STROBE) criteria for epidemiological studies (http://www.strobe-statement.org/) criteria (Appendix 1). Non-concordance of grading will be resolved by consensus
- Examples of exclusion criteria in this stage include: a review not conducted in a systematic way, methods not appropriately described, inappropriate sampling methods (e.g. not upper respiratory airway samples)

2.1.5 Study quality assessment checklists and procedures

We will use the STrengthening the Reporting of OBservational studies (STROBE) criteria to appraise the quality and transparency of methods analysis and reporting of studies, examining:
• Title and abstract
• Introduction- background/rationale, objectives
• Methods- study design, setting, participants, variables, data sources/measurement, bias, study size, statistical methods
• Results- participants, descriptive data, outcome data, main results
• Discussion- key results, limitations, interpretation, generalisability
• Other information- funding

2.1.6 Data extraction and presentation

Data from the appropriate articles will be collated in a spreadsheet. We will present:

• Flow chart of selected studies, and their quality grading (using PRISMA and STROBE templates)
• Listing of studies included for review, and (separately) those from which participant level data could be obtained
• Detailed listing of NP carriage per study (objective 1) with study setting, demographics and population, including:
  o Paper title, main author and institution, journal and publication year
  o Study setting, period
  o Total participants, total number of elderly included, age group recruited
  o Sampling method (NP/OP)
  o Outcome measures (Streptococcus pneumoniae carriage, risk factors)
  o Laboratory methodology
  o Comments
• Funnel plot of selected studies to illustrate potential bias, including statistical test of heterogeneity
• Forest plot with combined estimate of carriage rate
• Estimates of correlation or Odds ratios of nasopharyngeal carriage with pre-selected risk factors (objective 2)
  o If sufficient data are available, we will sub-analyse according to study setting/country as defined by region or estimate of per-capita income
• Multivariate analysis of risk factors to assess for confounding or collinearity

2.1.7 Quality control

The following quality control measures will be put in place:

• All titles and abstracts will be screened by two independent researchers (Smith/Wheeler). Any discrepancies will be discussed until unanimous agreement
• All full texts will be discussed by two researchers, any disagreements that cannot be resolved will be adjudicated by a third researcher (Adler/ Rylance) if necessary

2.1.8 Reproducibility

We will ensure that all search strings and dates of searches are provided to maximise reproducibility. Transparency will be ensured with detailed evidence tables of the data extracted as mentioned above.
2.2 Analysing gaps in information

Authors will be emailed separately to request original data sets for inclusion in the meta-analysis.

Gaps in evidence/ lack of high quality studies will be discussed in the final manuscript. Furthermore, any studies which contain information which we were are unable to incorporate in the final meta-analysis will be included in the narrative discussion.

2.3 Presentation of the results

We will present tables and figures as discussed in 2.1.4

2.4 Deliverables

2.4.1 Report

Our findings will be presented in a formal report answering the pre-defined research questions. The report will be written using the PRISMA checklist as a guide.

We propose the following report outline:

- Abstract
- Background and research question/ objectives
- Methods
  - Search strategy/strings (with date of search)
  - Inclusion/exclusion
  - Flow chart of identified studies
- Results:
  - See 2.1.4
- Discussion:
  - Discussion of results
  - Narrative of papers not included in meta-analysis
  - Gaps in information
  - Conclusion
- Supplementary information
- Glossary of terms/ abbreviations used
- List of references

We intend to submit the completed manuscript by August 2016.

2.4.2 Citation database

Mendley citation database will be used.
2.4.3 Authorship

For each study contributing participant-level data to the meta-analysis, the main contributing author will be included in the authorship list for the meta-analysis. This is agreed on the understanding that ICMJE conditions for authorship are met.

2.5 Process management

There will be an initial full research team meeting to clarify/confirm research objectives, timeline and appropriate evidence tables.

Wheeler/Smith (junior researchers) will meet on a weekly basis to discuss the progress of the project. In addition there will be monthly updates with study lead (Rylance) to discuss any issues.

References:


16) Hamaluba M; Kandasamy R; Ndimah S; Morton R; Caccamo M et al. A Cross-Sectional Observational Study of Pneumococcal Carriage in Children, Their Parents, and Older Adults Following the Introduction of the 7-Valent Pneumococcal Conjugate Vaccine. Medicine: January 2015 - Volume 94 - Issue 1 - p e335


Supplementary Appendices

Appendix 1: STROBE checklist
Appendix 2: PRISMA guidelines
Appendix 1: STROBE statement—checklist of items that should be included in reports of observational studies

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Recommendation</th>
<th>Page No.</th>
<th>Relevant text from manuscript</th>
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<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
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<tr>
<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
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<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
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<tr>
<td><strong>Introduction</strong></td>
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<tr>
<td>Background/rationale</td>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
<td></td>
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<tr>
<td>Objectives</td>
<td>3</td>
<td>State specific objectives, including any prespecified hypotheses</td>
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<tr>
<td><strong>Methods</strong></td>
<td></td>
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<tr>
<td>Study design</td>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
<td></td>
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<tr>
<td>Setting</td>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
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</table>
| Participants | 6 | (a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  
*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | |
| | | | (b) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed  
*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
<table>
<thead>
<tr>
<th>Variables</th>
<th>7</th>
<th>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</th>
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</thead>
<tbody>
<tr>
<td>Data sources/measurement</td>
<td>8*</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
</tr>
<tr>
<td>Bias</td>
<td>9</td>
<td>Describe any efforts to address potential sources of bias</td>
</tr>
<tr>
<td>Study size</td>
<td>10</td>
<td>Explain how the study size was arrived at</td>
</tr>
<tr>
<td>Quantitative variables</td>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
</tr>
</tbody>
</table>
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) Cohort study—if applicable, explain how loss to follow-up was addressed  
Case-control study—if applicable, explain how matching of cases and controls was addressed  
Cross-sectional study—if applicable, describe analytical methods taking account of sampling strategy  
(e) Describe any sensitivity analyses |
| Results | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
(b) Give reasons for non-participation at each stage  
(c) Consider use of a flow diagram |
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<th>Section</th>
<th>Page</th>
<th>Description</th>
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</table>
| Descriptive data              | 14*  | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  

(b) Indicate number of participants with missing data for each variable of interest  

(c) **Cohort study**—Summarise follow-up time (eg, average and total amount)  

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| Outcome data                  | 15*  | **Cohort study**—Report numbers of outcome events or summary measures over time  

Case-control study—Report numbers in each exposure category, or summary measures of exposure  

Cross-sectional study—Report numbers of outcome events or summary measures  

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| Main results                  | 16   | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  

(b) Report category boundaries when continuous variables were categorized  

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period  

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| Other analyses                | 17   | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  

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| Discussion                    |      |  

Key results                   | 18   | Summarise key results with reference to study objectives  

Limitations                   | 19   | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias  

Interpretation                | 20   | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence  

Generalisability              | 21   | Discuss the generalisability (external validity) of the study results  

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| Other information             |      |  

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**Funding**

22. Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
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<tr>
<th>Section/topic</th>
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<th>Checklist item</th>
<th>Reported on page #</th>
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<tbody>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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<tr>
<td>Abstract</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>Abstract</td>
</tr>
<tr>
<td>Introduction</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>Introduction</td>
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<td></td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>Introduction</td>
</tr>
<tr>
<td>Methods</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>Search strategy and selection criteria, Protocol S1</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>Search strategy and selection criteria</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>Search strategy and selection criteria</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>Text S1</td>
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<tr>
<td></td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>Search strategy and selection criteria</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>Not applicable</td>
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<td></td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>Data extraction and analysis</td>
</tr>
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</table>
Risk of bias in individual studies

Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Assessment of study quality