PhD thesis

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# Preamble

Placeholder

# Introduction

Placeholder

## Clinical manifestations of *Streptococcus pneumoniae*

### Acute otitis media

#### Pathogens implicated in acute otitis media

#### Healthcare burden of otitis media

#### Tympanostomy tube procedures

#### Acute otitis media in Iceland

### Pneumonia

#### Pathogens causing pneumonia

#### Healthcare burden of pneumonia

#### Pneumonia in Iceland

### Invasive pneumococcal disease

## Pneumococcal vaccines

### A brief history of pneumococcal vaccination

### Key concepts in pneumococcal vaccine epidemiology

### The impact of pneumococcal conjugate vaccines on otitis media

#### Randomized controlled trials

#### Observational studies

### The impact of pneumococcal conjugate vaccines on pneumonia

### The impact of pneumococcal conjugate vaccines on Invasive pneumococcal disease

## Cost-effectiveness in the context of pneumococcal conjugate vaccination

### Measurement of effectiveness and choice of health outcomes

#### Health outcomes considered

#### Effectiveness of pneumococcal conjugate vaccines

### Estimating resources and cost

# Aims

# Materials and methods

Placeholder

## Data collection and sources

### Statistics Iceland

### Landspitali University Hospital inpatient registry

### The Primary Care Registry

### The National Vaccine Registry

### The National Drug Prescription Registry

### Reimbursement database of Icelandic Health Insurance

## Paper 1

## Paper 2

## Paper 3

## Paper 4

## Paper 5

Paper 5 is a single-centre, individual-level, observational cohort study of paediatric hospitalizations due to diseases commonly caused by *Streptococcus pneumonae*. Eleven consecutive Icelandic birth-cohorts 2005-2015 were followed from birth until three years of age. Immigration and emigration data obtained from Statistics Iceland was used to exclude children who had immigrated to Iceland after birth. Included were all hospital admissions to the Children’s Hospital Iceland from January 1st, 2005 to December 31st, 2016. The Children’s Hospital Iceland is the primary paediatric hospital for approximately 90% of Iceland's population (www.statice.is), and serves as a secondary and tertiary paediatric hospital for the entire country. Data on admissions were collected from Landspitali University Hospital’s patient registry. Microbiological data were extracted from a database maintained by the Department of Clinical Microbiology at Landspitali University Hospital.

Seven diagnostic groups were defined in this paper. Five of these groups represent diseases commonly caused by *Streptococcus pneumoniae*; Invasive pneumococcal disease (IPD), meningitis, sepsis, pneumonia and otitis media. The remaining two groups, upper respiratory tract infections (URTI) and other lower respiratory tract infections (LRTI), were included as comparators. Hospitalization was categorised in one of the paper’s diagnostic groups if the relevant ICD-10 diagnostic code was recorded on the discharge chart, or if the admission was associated with microbiologically-confirmed IPD. Admissions with ICD-10 discharge diagnoses compatible with meningitis (G00) were grouped as meningitis. Those with A40 and A41 diagnoses were grouped as sepsis, with J09-J18, as pneumonia, J20-J22 as LRTI, H65, H66, H70 and H72 as OM, and J01-J06 as URTI (Table 1). A hospitalization was considered to be due to IPD if associated with culture or PCR confirmed *Streptococcus pneumoniae* sampled from joint fluid, bone, cerebrospinal fluid or blood, regardless of ICD-10 discharge diagnosis.

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 "Sepsis",  
 "Pneumonia",  
 "Otitis media and complications",  
 "Acute upper respiratory tract infections",  
 "Acute lower respiratory tract infections",  
 "Invasive pneumococcal disease"  
 ),  
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 "-",  
 "-",  
 "OM",  
 "URTI",  
 "LRTI",  
 "IPD"),  
 definition = c(  
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 "ICD-10 discharge diagnosis of A41 or A42",  
 "ICD-10 discharge diagnosis of J09-J18",  
 "ICD-10 discharge diagnosis of H65, H66, H70 or H72",  
 "ICD-10 discharge diagnosis of J00-J06",  
 "ICD-10 discharge diagnosis of J20-J22",  
 "Microbiologically confirmed pneumococcal infection from normally sterile site, regardless of ICD-10 diagnosis"  
 )  
 ),  
 col.names = c("Diagnostic group", "Abbreviation", "Definition"),  
 caption = "Definitions of the paper's diagnostic groups"  
 )

Table 1 Definitions of the paper’s diagnostic groups

|  |  |  |
| --- | --- | --- |
| Diagnostic group | Abbreviation | Definition |
| Meningitis | - | ICD-10 discharge diagnosis of G00 |
| Sepsis | - | ICD-10 discharge diagnosis of A41 or A42 |
| Pneumonia | - | ICD-10 discharge diagnosis of J09-J18 |
| Otitis media and complications | OM | ICD-10 discharge diagnosis of H65, H66, H70 or H72 |
| Acute upper respiratory tract infections | URTI | ICD-10 discharge diagnosis of J00-J06 |
| Acute lower respiratory tract infections | LRTI | ICD-10 discharge diagnosis of J20-J22 |
| Invasive pneumococcal disease | IPD | Microbiologically confirmed pneumococcal infection from normally sterile site, regardless of ICD-10 diagnosis |

Birth-cohorts were compared either individually, or grouped by vaccine eligibility. In the individual birth-cohort analysis, each birth-cohort was compared to the last vaccine non-eligible cohort, i.e. the 2010 birth-cohort. Birth-cohorts 2011–2015 were grouped as vaccine-eligible cohorts (VEC), and birth-cohorts 2005–2010 as vaccine non-eligible cohorts (VNEC). Statistical analyses were performed in R version 3.4.4. (R Core Team [2018](#ref-R-base)) using the R packages; survival (Therneau [2017](#ref-R-survival)), RMS (Harrell, Jr. [2018](#ref-R-rms)) and epiR (Stevenson et al. [2017](#ref-R-epiR)).

Mean age at hospitalization was calculated for each birth-cohort and diagnostic group. Analysis of variance was used to test whether significant difference existed between cohorts.If an overall difference was identified, the analysis was followed by Tukey’s honest significant difference procedure. The median hospital length of stay was calculated for each diagnostic group, and compared between between cohorts using the Wilcoxon rank sum test. Crude incidence rates () of hospital admissions were calculated for each birth-cohort, diagnostic group and age group, and incidence rate ratios () were calculated between the VNEC and VEC assuming Poisson variance. The proportion of hospitalizations which led to intensive care unit (ICU) stays was calculated by birth-cohort and diagnostic group.

The Kaplan-Meier product limit estimator was used to calculate both event-free survival, as well as event-free survival difference of the VNEC compared to the VEC, for each of the diagnostic groups. Subsequent hospitalizations of the same child with the same discharge diagnosis were excluded from this portion of the analysis. Follow-up time was censored upon emigration or death. Cox regression was used to estimate the hazard ratio of admissions between the VNEC and VEC. To clarify whether potential differences between VNEC and VEC were likely to be due to direct effects of the vaccine, the Cox regression was repeated for two restricted age-ranges; 0-90 days of age and 90 days and older. A sensitivity analysis of potential unmeasured confounding of the hazard ratio was calculated using E-values. An E-value represents the minimum association with both exposure and outcome, which an unmeasured confounder would need to have, to completely explain away the observed association.

# Results

## Paper 1

# Discussion

Harrell, Jr., Frank E. 2018. *Rms: Regression Modeling Strategies*. <https://CRAN.R-project.org/package=rms>.

R Core Team. 2018. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. <https://www.R-project.org/>.

Stevenson, Mark, Telmo Nunes, Cord Heuer, Jonathon Marshall, Javier Sanchez, Ron Thornton, Jeno Reiczigel, Jim Robison-Cox, Paola Sebastiani, and Peter Solymos. 2017. *EpiR: Tools for the Analysis of Epidemiological Data*. <https://CRAN.R-project.org/package=epiR>.

Therneau, Terry M. 2017. *Survival: Survival Analysis*. <https://CRAN.R-project.org/package=survival>.