PhD thesis

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2018-11-05

# Preamble

Placeholder

# Introduction

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## 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 2 is a whole-population observational cohort study that followed all children born in Iceland between January 1, 2005 and December 31, 2015, from birth until three years of age, death or end of the study period. All primary care visits in which an ICD-10 diagnostic code of suppurative otitis media (H66) was recorded were included. Any visits occuring within 30 days of a previously documented visit by the same child were excluded from the main analysis.

Data were obtained from the Primary Care Registry of the Icelandic Directorate of Health, and included all ICD-10 codes associated with the visit, as well as the date of the visit, age and gender of the child, and physician identification number. The study identification number used to identify unique individuals is directly derived from the national indentification numbers issued to each individual by the government. Individuals who had immigrated to Iceland after birth were excluded. Demographic population data was obtained from Statistics Iceland.

Cohorts were defined based on year of birth, or vaccine eligibility. Birth-cohorts 2005–2010 were grouped as vaccine non-eligible cohorts (VNEC) and birth-cohorts 2011–2015 as vaccine eligible cohorts (VEC). 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 [@-rms] and epiR (Stevenson et al. [2017](#ref-R-epiR)).

Crude incidence rates () were calculated per 100 person-years at risk for each birth cohort, stratified by four-month age brackets. The individual time at-risk was carefully constructed to exclude the 30 days following each recorded otitis media visit. This avoided the period previously designated as outside the study's time parameters. Crude incidence rate ratios () between VNEC and VEC were calculated, and confidence intervals estimated, assuming Poisson variance.

In the subset of children who had full follow-up time, the number of children who experienced episodes of otitis media were tabulated and the distribution between VNEC and VEC compared using the test of homogeneity, Additionally, the crude risk ratio between the VEC and VNEC of experiencing 0, 1–4, or >5 episodes of otitis media before three years of age was calculated.

The Andersen-Gill extension of the Cox regression model for repeated events was used to model data on the individual level, and to account for censoring of follow-up time (Andersen and Gill [1982](#ref-Andersen1982)). To correct for successive visits by the same individual, Lin and Wei’s sandwich variance estimates were used (Lin and Wei [1989](#ref-Lin1989)). From this model, the hazard ratio (HR) of otitis media visits between each birth-cohort and the last vaccine non-eligible cohort was caclulated. The impact of PHiD-CV10 on otitis media visits was calculated using 1 – (HR between the last vaccine-eligible birth cohort and the last vaccine non-eligible cohort).

The HR between VNEC and VEC was calculated for each number of previous otitis media visits, and the mean number of episodes as a function of age was estimated from the model using the generalized Nelson-Aalen estimator (Cook and Lawless [2007](#ref-Cook2007)). To determine the number of otitis media episodes prevented in the first five years of the vaccination, each child’s follow-up time was multiplied by the Nelson-Aelen estimate of the mean number of episodes. The absolute reduction in the incidence rate was then calculated by dividing the estimated number of prevented episodes with the total person-time of the VEC.

# Results

## Paper 1

# Discussion

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