PhD thesis

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# 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 3

Paper 3 is a whole population observational cohort study of antimicrobial prescriptions among children under three years of age in Iceland. Eleven consecutive Icelandic birth-cohorts 2005–2015 were followed from birth until three years of age. Children who imigrated to Iceland after birth were excluded. Follow-up time was censored on death, emigration, or end of the study period (December 31, 2016). Due to short follow-up time, the 2016 birth-cohort was not included in the analysis.

Data regarding outpatient antimicrobial prescriptions was obtained from the National Drug Prescription Registry, which has been previously described (Table ??). Data on primary care visits for respiratory tract infections was collected from the Primary Care Registry using the ICD-10 codes shown in Table ??. If a prescription was filled within three days of a documented physician visit by the same child, then the prescription and the visit were linked. Because data from the Primary Care Registry was only available through December 31, 2015, the portion of the analysis partaining to the linked data was restricted to that date. Population demographical data was acquired from Statistics Iceland (<https://www.statice.is/>).

The data was analysed descriptively over calendar-time, and from a cohort perspective. 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)). The descriptive analysis included all children under three years of age in Iceland. Based on a previously published study, all filled antimicrobial prescriptions was classified into one of six categories; first and second line penicillins, first and second generation macrolides, cephalosporins, and others (Youngster et al. [2017](#ref-Youngster2017)). The proportion of prescriptions within each category was calculated by calendar-year. Five diagnostic-groups were defined based on primary care ICD-10 diagnoses, and the proportion of cases resulting in an antimicrobial prescription was calculated per calendar-year. The groups were Acute upper respiratory infections (J00-J06), Influenza and pneumonia (J09-J18), Other acute lower respiratory infections (J20-J22), AOM (H65, H66 and H72) and Other viral infections (B34).

Birth-cohorts were compared individually or grouped by vaccine eligibility. In the individual birth-cohort analysis, each birth-cohort was compared to the 2010 cohort – the last vaccine non-eligible cohort. Birth-cohorts 2011–2015 were grouped as vaccine-eligible cohorts (VEC), and birth-cohorts 2005–2010 as vaccine non-eligible cohorts (VNEC). The incidence rate () of antimicrobial prescriptions per 100 person-years was calculated in six-month age-brackets for each birth-cohort and 95% confidence intervals estimated using the Wald method (Kirkwood and Sterne [2003](#ref-Kirkwood2003)). Incidence rate ratios () between the VNEC and the VEC were estimated and 95% confidence intervals calculated assuming Poisson variance. The cumulative proportion of children who had filled at least one antimicrobial prescription by three years of age was calculated and compared between the VEC and VNEC using the test of homogeneity. The cumulative number of prescriptions by three years of age per child was categorized as <1, 1–4, 5–9, 10–14 and ≥ 15 prescriptions, and the ratio between VNEC and VEC was calculated for each category. The 2014 and 2015-cohorts were excluded from the cumulative analyses, as they did not have the full three-year follow-up time.

The Andersen-Gill time-to-event model was fitted to the individual level data (Andersen and Gill [1982](#ref-Andersen1982)). It was used to estimate the hazard ratio () of antimicrobial prescription between the study birth-cohorts, which were included in the model as a categorical variable. The effect of age was accounted for by setting age as the model’s underlying measurement of time and stratification by gender allowed for independent baseline hazards. The number of previous antimicrobial prescriptions was included in the model and its relationship allowed to be non-linear by means of restricted cubic splines. Lin and Wei ([1989](#ref-Lin1989)) robust sandwich variance estimates were included to account for successive prescriptions filled by the same child.

The impact of PHiD-CV10 on outpatient antimicrobial prescriptions was estimated as 1 – (the hazard ratio between the last vaccine eligible and vaccine non-eligible cohorts) × 100%. The impact on each successive prescription was also estimated. Finally, the mean number of antimicrobial prescriptions for each gender and vaccine-cohort was calculated as a function of age using the generalized Nelson-Aalen estimate. This was used to estimate the absolute number of prevented antimicrobial prescriptions during the first seven years of the intervention by adding together the expected number of prescriptions per child using the VNEC estimate of the mean and subtracting the expected number of prescriptions per child using the VEC estimate of the mean. The absolute rate reduction was calculated by dividing this estimate with the number of person-years at-risk in the VEC. A sub-analysis was performed to estimate the vaccine impact against AOM-associated antimicrobial prescriptions. The same regression methodology was applied to a subset of the prescriptions which were linked to a primary care physician visit with a diagnosis of AOM. Vaccine impact was similarly estimated as 1 – (the hazard ratio between the last vaccine eligible cohort and the reference cohort) × 100%

# Results

## Paper 1

# Discussion

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