PhD thesis

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# Preamble

I am currently writing my PhD thesis on the impact of pneumococcal vaccination in Iceland. I am writing the thesis in Rstudio using the [bookdown](https://bookdown.org/yihui/bookdown/) package and hosting the thesis on Github. Writing the thesis in Rstudio confers many advantages. Tables and Figures can be created directly within Rstudio, which minimizes additional work associated with manually moving them into a separate writing program – a process both error-prone and labor intensive. All aspects of the writing, typesetting and data analysis are documented and version controlled. The bookdown packages automates the process of exporting the thesis to word, pdf and html formats. The thesis will be open access during the writing process. I believe I will be more motivated if my productiveness – or lack thereof, is held accountable to anyone who wishes to check. I would be grateful for any and all comments on any aspect of the thesis under construction.

# 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

The aim was to evaluate whether the introduction of PHiD-CV10 was associated with a reduction in the incidence of otitis media with treatment failure. Treatment of otitis media with ceftriaxone was used as proxy for treatment failure. Ceftriaxone use for other diagnosis and in older children were used as comparators.

All children under eighteen years of age who visited Children’s Hospital Iceland between January 1, 2008 and December 31, 2015 were included. Data were extracted from Landspitali University Hospital’s inpatient registry. A visit was included if an ICD-10 code of Nonsuppurative otitis media (H65) or Suppurative and unspecified otitis media (H66) was recorded in the medical record, or if a child received one or more doses of ceftriaxone. Ceftriaxone use was systematically extracted from the hospital’s medication administration system using the ATC code J01DD04. All associated ICD-10 diagnoses were then obtained from the inpatient registry. The total number of visits per calendar year regardless of diagnosis was provided by the hospital. Children’s Hospital Iceland’s referral area was defined as a 100km driving distance from the hospital. Population demographic data for the referral area was obtained from Statistics Iceland (www.statice.is).

Pre-vaccine (2008-2011) and post-vaccine (2012-2015) periods were defined based on the year of vaccine introduction. Because hospital visits for otitis media are uncommon in older children, the primary analysis was restricted to children under four years of age. Ceftriaxone use was analysed in three separate diagnostic groups  
A visit was considered to be due to otitis media if an ICD-10 code of Nonsuppurative otitis media (H65) or Suppurative and unspecified otitis media (H66) was recorded. Pneumonia visits were defined based on ICD-10 codes Bacterial pneumonia, not elsewhere classified (J15) or Pneumonia, unspecified organism (J18). Finally, visits associated with ceftriaxone administration that did not fall into either of the above categories were classified together.

The number of ceftriaxone treatment episodes per diagnostic group were aggregated by calendar month. An episode was considered distinct if no ceftriaxone administration was documented in the previous fourteen days. Incidence rates (IR) per 1,000 person-years were calculated by dividing the monthly number of ceftriaxone episodes per diagnostic group by the person-time of children in the referral area.

The IR of OM visits were similarly defined and calculated. If a decrease were to be observed in the number of ceftriaxone treated OM episodes, it could be due to a decrease in the number of OM visits or a decrease in the use of ceftriaxone. To evaluate this, the incidence risk of ceftriaxone treatment per 1,000 OM visits was calculated for the pre- and post-vaccine periods.

Statistical analysis was performed in R version 3.4.4. (R Core Team [2018](#ref-R-base)) using the epiR package (Stevenson et al. [2017](#ref-R-epiR)). Incidence rate ratios (IRR) between the pre- and post-vaccine periods were calculated using the formula

where and are the number of visits or ceftriaxone treatment episodes in the pre- and post-vaccine periods respectively, and and are the number of person-years.

The IRR was estimated independently for each age-strata and the stratum-specific estimates were combined (when appropriate) using the Mantel-Haenszel method (Kirkwood and Sterne [2003](#ref-Kirkwood2003)). The Mantel-Haenszel estimate of the IRR is the weighted mean of the IRR in each stratum. The weight for each stratum is

and the resulting Mantel-Haenszel adjusted IRR is therefore

The 95% confidence interval is derived using the delta method, and has range

where the error factor is and the standard error of the natural logarithm of the is

in which the variance of strata is

Finally, the null hypthesis that was tested by calculating the Mantel-Haenszel test statistic

from which the *P*-value was derived.

Combining sratum-specific estimates is appropriate when the exposure-outcome association is the same in each of the strata, i.e. If true, it follows that

The test of heterogeneity is based on the weighted sum of squares of the above differences, and is calculated as

where is the number of strata. It tests whether the data is congruent with the null hypothesis of no effect modification of the exposure-outcome relationship by strata. The greater the differences is between and , the larger the statistic. If the null hypothesis is rejected, the is not calculated and only the stratum-specific IRR are presented.

## Paper 2

# Results

## Paper 1

# Discussion

Kirkwood, BR, and JAC Sterne. 2003. *Essential medical statistics*. Edited by Fiona Goodgame. 2nd ed. Oxford: Blackwell Science. doi:[10.1002/sim.1961](https://doi.org/10.1002/sim.1961).

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>.