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

## Data collection and sources

During the study period from January 1, 2005 to December 31, 2017, all data were collected from multiple whole population registries, and from a single hospital registry. All data were identifiable down to an individual level usingnational identification numbers, which are issued to every Icelandic inhabitant, either at birth or when granted residency. Each individual receives one and only one number over the course of their lifetime, and national ID numbers are permanently retired at time of death. The Directorate of Health processed all data sent from the various registried, linking them to specific national identification numbers, and then anonymizing before releasing to the study group. Anonymization was accomplished by creating a study identification number during the linking process, generated directly from the national identification number in a reproducible fashion. The mapping keywas kept by the Directorate of Health, and not accessible to study authors.

The data underlying this study are observational in nature, but enhanced and supported by several factors. Not only are all medical records in Iceland stored electronically, but the same software, Saga, has been used by all health-care providers and institution throughout the entire study period. Likewise, the International Classification of Diseases, 10th revision (ICD-10), is the only diagnostic coding system in use in Iceland during the study period. Furthermore all medical procedures have been coded with the NOMESCO Classification of Surgical Procedures (NCSP), and drugs are classified exclusively using the Anatomical-Therapeutic-Chemical (ATC) classification system of the World Health Organization.

In the following sub-chapters, each registry providing study data will be reviewed: (how about listing each of the registries here, or each kind of data that were collected?- just as a kind of transitional sentence and summary)

### Landspitali University Hospital inpatient registry

Landspitali University Hospital is the sole tertiary hospital in Iceland, and encompasses Children’s Hospital Iceland – Iceland's the only paediatric hospital. (No new paragraph here...)It also functions as a primary and secondary hospital for the capital area, serving 65% of the Icelandic population. In 2017, the total number of hospital beds in Iceland totaled 1,050 (Gobierno de España, Ministerio de Industria, and Instituto para la Diversificación y Ahorro de Energía IDAE [2017](#ref-OECD2017)). Of those, 687 were at Landspitali University Hospital. The inpatient registry contains information on all emergency department and outpatient visits, and all hospital admissions to Landspitali University Hospital. For the period of January 1, 2005 to December 31, 2017, data were extracted on all unplanned acute-care visits and hospital admissions with ICD-10 discharge diagnoses compatible with respiratory infections (see Table 1).

Table 1 The International Classification of Diseases, 10th revision codes used in the current study

|  |  |
| --- | --- |
| ICD-10 code | Disease |
| A40 | Streptococcal sepsis |
| A41 | Other sepsis |
| A48 | Other bacterial diseases, not elsewhere classified |
| A49 | Bacterial infection of unspecified site |
| B00 | Herpesviral [herpes simplex] infections |
| B08 | Other viral infections characterized by skin and mucous membrane lesions, not elsewhere classified |
| B33 | Other viral diseases, not elsewhere classified |
| B34 | Viral infection of unspecified site |
| B95 | Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere |
| B96 | Other bacterial agents as the cause of diseases classified elsewhere |
| G00 | Bacterial meningitis,not elsewhere classified |
| H65 | Nonsuppurative otitis media |
| H66 | Suppurative and unspecified otitis media |
| H70 | Mastoiditis and related conditions |
| H72 | Perforation of tympanic membrane |
| H73 | Other disorders of tympanic membrane |
| J00 | Acute nasopharyngitis [common cold] |
| J01 | Acute sinusitis |
| J02 | Acute pharyngitis |
| J03 | Acute tonsillitis |
| J04 | Acute laryngitis and tracheitis |
| J05 | Acute obstructive laryngitis [croup] and epiglottitis |
| J06 | Acute upper respiratory infections of multiple and unspecified sites |
| J09 | Influenza due to certain identified influenza viruses |
| J10 | Influenza due to other identified influenza virus |
| J11 | Influenza due to unidentified influenza virus |
| J12 | Viral pneumonia, not elsewhere classified |
| J13 | Pneumonia due to Streptococcus pneumoniae |
| J14 | Pneumonia due to Hemophilus influenzae |
| J15 | Bacterial pneumonia, not elsewhere classified |
| J16 | Pneumonia due to other infectious organisms, not elsewhere classified |
| J17 | Pneumonia in diseases classified elsewhere |
| J18 | Pneumonia, unspecified organism |
| J20 | Acute bronchitis |
| J21 | Acute bronchiolitis |
| J22 | Unspecified acute lower respiratory infection |
| J32 | Chronic sinusitis |
| J36 | Peritonsillar abscess |
| J40 | Bronchitis, not specified as acute or chronic |
| J85 | Abscess of lung and mediastinum |
| J86 | Pyothorax |
| J90 | Pleural effusion, not elsewhere classified |
| N30 | Cystitis |
| N39 | Other disorders of urinary system |
| R05 | Cough |
| R50 | Fever of other and unknown origin |

Additionally, any visit or hospital admission associated with NCSP procedural codes in Table 2) were extracted.

Table 2 NOMESCO Classification of Surgical Procedures codes used in the current study

|  |  |
| --- | --- |
| NCSP code | Description |
| EMB 00 | Excision of lesion of tonsil or adenoid |
| EMB 10 | Tonsillectomy |
| EMB 15 | Intracapsular destruction of tonsils |
| EMB 20 | Adenotonsillectomy |
| EMB 30 | Adenotomy |
| EMB 99 | Other excision on tonsils and adenoids |
| EMW 99 | Other operation on tonsil or adenoids |
| DCA 10 | Paracentesis of tympanic membrane |
| DCA 20 | Insertion of ventilating tube through tympanic membrane |
| DCW 00 | Removal of ventilating tube from tympanic membrane |

The data included the date of the visit, date of hospital discharge, hospital length of stay, the departments involved and a detailed breakdown of costs associated with the visit. A separate unique identification number was provided for each individual visit or hospital admission.

Several smaller data-sets pertaining to specific papers were extracted from the inpatient registry, and delivered directly to the study authors. These lesser data-sets were not linked to the main study data. For paper I, all doses of ceftriaxone administered at the Children’s Hospital Iceland between January 2009 and December 2015 were extracted from the hospital’s medication administration system using the ATC code J01DD04. Any ICD-10 diagnostic code associated with the visit or hospital admission in which ceftriaxone was administered, was extracted from the inpatient registry. Importantly, this included all ICD-10 codes, not only those in Table 1. The aggregate number of yearly visits to the the paediatric emergency department of Children’s Hospital Iceland 2008-2015 was also obtained for use in paper I. Paper VI required synthetic controls used within a time-series analysis framework. The aggregate monthly number of acute-care visits and hospital admissions for several sub-chapters of the ICD-10 diagnostic coding system (Table 3)) were obtained for 22 different age-groups.

Table 3 NOMESCO Classification of Surgical Procedures codes used in the current study

|  |  |
| --- | --- |
| ICD-10 code | Description |
| A10-B99 | Certain infectious and parasitic diseases |
| C00-D48 | Neoplasms |
| D50-89 | Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism |
| E00-99 | Endocrine, nutritional and metabolic diseases |
| G00-G99 | Diseases of the nervous system |
| H00-99 | Diseases of the eye and adnexa, Diseases of the ear and mastoid process |
| I00-99 | Diseases of the circulatory system |
| K00-99 | Diseases of the digestive system |
| L00-99 | Diseases of the skin and subcutaneous tissue |
| M00-99 | Diseases of the musculoskeletal system and connective tissue |
| N00-99 | Diseases of the genitourinary system |
| P00-99 | Certain conditions originating in the perinatal period |
| Q00-99 | Congenital malformations, deformations and chromosomal abnormalities |
| R00-99 | Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified |
| S00-T99 | Provisional assignment of new diseases of uncertain etiology |
| U00-99 | Injury, poisoning and certain other consequences of external causes |
| V00-Y99 | External causes of morbidity |
| Z00-99 | Factors influencing health status and contact with health services |

Data from the inpatient registry was used in papers I, IV, V and VI.

### The national drug prescription registry

The national drug prescription registry (NDPR) is a whole population archive, collected and maintained by the Icelandic Directorate of Health since January 1, 2005. It contains information on all filled drug prescriptions in Iceland. All pharmacies are required by law to collect data on each filled prescription and submit to the NDPR. An important distinction must be made between a filled prescription and a prescription. The NDPR receives information if and when a prescription is filled. It does not contain information on prescriptions that were never filled by the patient. All prescriptions contained within the NDPR were paid for and received by the patient. Extensive validation and error testing has been performed by the Directorate of Health to ensure robust and thorough coverage by the NDPR. Automated electronic submissions, coupled with tightly controlled processes by which pharmacies dispense drugs, has essentially excluded the possiblity of any filled prescriptions escaping registration.

All prescriptions within the ATC therapeutic subgroup “J01” (Antibacterials for Systemic Use), “J07” (Vaccines), “S01” (Opthalmologicals) and “S02” (Otologicals) were extracted for the period from January 1, 2005 to December 31, 2017. The chemical subgroups used in the study are shown in Table 4)

Table 4 Anatomical Therapeutic Chemical codes used in the current study

|  |  |
| --- | --- |
| ATC chemical subgroup code | Description |
| J01A | Tetracyclines |
| J01B | Amphenicols |
| J01C | Beta-lactam antibacterials, penicillins |
| J01D | Other beta-lactam antibacterials |
| J01E | Sulfonamides and trimethoprim |
| J01F | Macrolides, lincosamides and streptogramins |
| J01G | Aminoglycoside antibacterials |
| J01M | Quinolone antibacterials |
| J01R | Combinations of antibacterials |
| J01X | Other antibacterials |
| J07A | Bacterial vaccines |
| J07B | Viral vaccines |
| J07C | Bacterial and viral vaccines |
| J07X | Other vaccines |
| S01A, S02A | Anti-infectives |
| S01C, S02C | Anti-inflammatory agents and anti-infectives in combination |

### The Primary Care Database

In the Icelandic healthcare system, primary care is provided by family medicine physicians at neighborhood based centers (*Heilsugæsla*). All primary care centers use the same electronic medical record system as well as the ICD-10 diagnostic coding system. The Directorate of Health maintains a registry on all primary care visits within the Icelandic healthcare system. With extensive maintenance and restructuring ongoing since early 2016, no new data added to the registry since December 31, 2015. From this registry, data onall visits and phone consultations with diagnostic codes compatible with respiratory tract infections were extracted for the period January 1, 2005 to December 31, 2015 (Table 1).

### The National Vaccine Registry

The Icelandic Directorate of Health also maintains the National Vaccine Registry (NVR). All vaccine doses administered within the healthcare system are systematically recorded in an individual's electronic health record at the time of administration. This record is reviewed and updated regularly, and vaccinations received elsewhere are included. The NVR collects this information from all electronic health records in the country. All administered vaccine doses with ATC codes “J07AL” (Pneumococcal vaccines) were extracted for the period of January 1, 2005 to December 31, 2017.

### Reimbursement database of the Icelandic Health Insurance

The Icelandic healthcare program is a single-payer system with one government-run healthcare insurance administration, under which all permanent citizens are covered. Each healthcare visit requires a nominal out-of-pocket fee, with the rest of the visit covered by insurance. Healthcare providers are either salaried governmental employees, or independent practitioners who are reimbursed on a per case basis according to pre-determined negotiations with Icelandic Health Insurance administration. To receive pay for services, physicians must submit a reimbursement form, detailing the nature of the visit and any procedures performed, using pre-specified procedural codes. Icelandic Health Insurance agency maintains a reimbursement database which details the nature and number of procedures performed. A record of all otolaryngological procedures performed on the middle ear and tonsils were extracted from the reimbursement database for the period from January 1, 2005 to December 31, 2017, using the procedural codes in Table 5)

Table 5 Reimbursement codes used in the current study

|  |  |
| --- | --- |
| Reimbursement code | Description |
| 5500601 | Myringotomy, one or both ears, under local anesthetic |
| 5500602/55Q0602+55Z0602 | Placement of tympanostomy, one ear (local anesthetic/general anesthesia) |
| 5500603/55Q0603+55Z0603 | Placement of tympanostomy tube, one ear, and myringotomy, both ears (local anesthetic/general anesthesia) |
| 5500604/55Q0604+55Z0604 | Removal of tympanostomy tube, one ear (local anesthetic/general anesthesia) |
| 5501001/55Q1001+55Z1001 | Placement of tympanostomy tube, both ears (local anesthetic/general anesthesia) |
| 5501002/55Q1002+55Z1002 | Removal of tympanostomy tube, both ears (local anesthetic/general anesthesia) |
| 5501201/55Q1201+55Z1201 | Adenoidectomy (local anesthetic/general anesthesia) |
| 5501301/55Q1301+55Z1301 | Adenoidectomy and placement of tymponstomy tube or myringotomy, one or both ears (local anesthetic/general anesthesia) |
| 5501801/55Q1801+55Z1801 | Tonsillectomy with or without adenoidectomy (local anesthetic/general anesthesia) |
| 5501802/55Q1802+55Z1802 | Tonsillectomy with or without adenoidectomy - performed with laser (local anesthetic/general anesthesia) |
| 5501901/55Q1901+55Z1901 | Tonsillectomy, with or without adenoidectomy, and tympanostomy or myringotomy (local anesthetic/general anesthesia) |
| 5501902/55Q1902+55Z1902 | Tonsillectomy, with or without adenoidectomy, and tympanostomy or myringotomy - performed with laser (local anesthetic/general anesthesia) |
| 5502002/55Q2002+55Z2002 | Myringoplasty with patch (local anesthetic/general anesthesia) |

## Paper 1

# Results

## Paper 1

A total of 117,250 visits to the Children’s Hospital for any indication were recorded from 2008 to 2015. S easonal variation in the number of these visits was apparent, with an increase in visits during the winter months of October through March compared with that in April through September. The total number of visits grew steadily from 12,229 in 2008 to 14,502 in 2015. During the same period, 4,624 children <4 years of age visited the Children’s Hospital 6,232 times for the treatment of 4,994 distinct episodes of AOM, of which 531 episodes were treated with ceftriaxone. The number of children <18 years of age living within the Children’s Hospital’s referral region was stable during the study period decreasing from 62,067 in 2008 to 61,798 in 2015. The number of children <4 years of age in the same region increased from 13,562 in 2008 to 14,644 in 2011 and then decreased again to 13,272 in 2015. Raw incidence rates of total visits, visits for AOM and parenteral ceftriaxone use are shown.

# Discussion

Gobierno de España, Turismo y Comercio Ministerio de Industria, and Instituto para la Diversificación y Ahorro de Energía IDAE. 2017. *Health at a Glance 2017*. Health at a Glance. OECD. doi:[10.1787/health\_glance-2017-en](https://doi.org/10.1787/health_glance-2017-en).