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

Data was collected from multiple whole population registries and a single hospital registry. The study period was from January 1, 2005 until December 31, 2017. All data was identifiable down to the individual level based on national identification numbers, which are issued to every Icelandic resident at birth or when granted residency. A national identification number is not reused upon the death, and each individual receives one and only one number over the course of their lifetime. Data was sent from the various registries to the Directorate of Health for processing, where it was linked using national identification numbers, before being anonymized and subsequently released to the study group. Anonymization was accomplished by creating a study identification number during the linking process, which is generated directly from the national identification number in a reproducible fashion. The mapping key is kept by the Directorate of Health, and not accessible by the study authors.

The data underlying this study is observational in nature, but benefits from several factors. Electronic medical records have been ubiquitous in Iceland during the study period. The same electronic medical record software, Saga, has been used by all health-care providers and institutions throughout the study period. The International Classification of Diseases, 10th revision (ICD-10), is the only diagnostic coding system which has been in use during the whole study period. All medical procedures have been coded with the NOMESCO Classification of Surgical Procedures (NCSP). Drugs are classified 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.

### Landspitali University Hospital inpatient registry

Landspitali University Hospital is the only tertiary hospital in Iceland, and encompasses Children’s Hospital Iceland – the only paediatric hospital in Iceland.  
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 was 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 were extracted from the inpatient registry for specific papers. These smaller data-sets were delivered directly to the study authors and 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 pediatric 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 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 registry collected and maintained by the Icelandic Directorate of Health from 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. This means that the NDPR does not contain information on prescriptions that were never filled by the patient. This also means that 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 the robustness and coverage of the NDPR. The submission to the NDPR has been automated electronically and coupled with the process by which drugs are dispensed at the pharmacies, essentially excluding the possibility of a filled prescription not being registered.

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*). Primary care centers use the same electronic medical record system and use the ICD-10 diagnostic coding system. The Directorate of Health maintains a registry on all primary care visits within the Icelandic healthcare system. Extensive maintenance and restructuring has been ongoing since early 2016, with no new data added to the registry since December 31, 2015. From this registry the all visits and phone-calls 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 maintains the National Vaccine Registry (NVR). All vaccine doses administered within the healthcare system are systematically recorded in the electronic health record at the time of administration. This record is reviewed and updated regularly, and vaccinations received elsewhere 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.

### Reimburcement database of the Icelandic Health Insurance

The Icelandic healthcare system is a single-payer system with a single government run healthcare insurance. All permanent citizens are covered. Each healthcare visit is associated with a nominal out-of-pocket fee, with the rest of the visit covered by the 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. 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 maintains a reimbursement database which details the nature and number of procedures performed. 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).