PhD thesis

Elías Sæbjörn Eyþórsson

2018-11-22

Table of Contents

[2 Preamble 2](#_Toc530658353)

[3 Introduction 3](#_Toc530658354)

[3.1 Clinical manifestations of *Streptococcus pneumoniae* 5](#_Toc530658355)

[3.1.1 Acute otitis media 6](#_Toc530658356)

[3.1.1.1 Pathogens implicated in acute otitis media 6](#_Toc530658357)

[3.1.1.2 Healthcare burden of otitis media 7](#_Toc530658358)

[3.1.1.3 Tympanostomy tube procedures 7](#_Toc530658359)

[3.1.1.4 Acute otitis media in Iceland 8](#_Toc530658360)

[3.1.2 Pneumonia 8](#_Toc530658361)

[3.1.2.1 Pathogens causing pneumonia 9](#_Toc530658362)

[3.1.2.2 Healthcare burden of pneumonia 10](#_Toc530658363)

[3.1.2.3 Pneumonia in Iceland 11](#_Toc530658364)

[3.1.3 Invasive pneumococcal disease 11](#_Toc530658365)

[3.2 Pneumococcal vaccines 11](#_Toc530658366)

[3.2.1 A brief history of pneumococcal vaccination 11](#_Toc530658367)

[3.2.2 Key concepts in pneumococcal vaccine epidemiology 12](#_Toc530658368)

[3.2.3 The impact of pneumococcal conjugate vaccines on otitis media 13](#_Toc530658369)

[3.2.3.1 Randomized controlled trials 13](#_Toc530658370)

[3.2.3.2 Observational studies 16](#_Toc530658371)

[3.2.4 The impact of pneumococcal conjugate vaccines on pneumonia 16](#_Toc530658372)

[3.2.5 The impact of pneumococcal conjugate vaccines on Invasive pneumococcal disease 16](#_Toc530658373)

[3.3 Cost-effectiveness in the context of pneumococcal conjugate vaccination 16](#_Toc530658374)

[3.3.1 Measurement of effectiveness and choice of health outcomes 16](#_Toc530658375)

[3.3.1.1 Health outcomes considered 16](#_Toc530658376)

[3.3.1.2 Effectiveness of pneumococcal conjugate vaccines 16](#_Toc530658377)

[3.3.2 Estimating resources and cost 16](#_Toc530658378)

[4 Aims 17](#_Toc530658379)

[5 Materials and methods 17](#_Toc530658380)

[5.1 Data collection and sources 17](#_Toc530658381)

[5.1.1 Statistics Iceland 18](#_Toc530658382)

[5.1.2 Landspitali University Hospital patient registry 18](#_Toc530658383)

[5.1.3 The Primary Care Registry 21](#_Toc530658384)

[5.1.4 The National Vaccine Registry 21](#_Toc530658385)

[5.1.5 The National Drug Prescription Registry 21](#_Toc530658386)

[5.1.6 Reimbursement database of Icelandic Health Insurance 22](#_Toc530658387)

[5.2 Impact on otitis media with treatment failure (Paper I) 23](#_Toc530658388)

[5.3 Impact on primary care visits for otitis media (Paper II) 24](#_Toc530658389)

[5.4 Impact on outpatient antimicrobial prescriptions (Paper III) 25](#_Toc530658390)

[5.5 Impact on tympanostomy tube procedures (Paper IV) 27](#_Toc530658391)

[5.6 Impact on respiratory associated hospitalizations (Paper V) 28](#_Toc530658392)

[5.7 Impact and cost-benefit analysis (Paper VI) 29](#_Toc530658393)

[6 Results 31](#_Toc530658394)

[6.1.1 Statistics Iceland 31](#_Toc530658395)

[6.1.2 Landspitali University Hospital patient registry 31](#_Toc530658396)

[6.1.3 The Primary Care Registry 34](#_Toc530658397)

[6.1.4 The National Vaccine Registry 34](#_Toc530658398)

[6.1.5 The National Drug Prescription Registry 36](#_Toc530658399)

[6.1.6 Reimbursement database of Icelandic Health Insurance 38](#_Toc530658400)

[6.2 Paper 1 38](#_Toc530658401)

[7 Discussion 40](#_Toc530658402)

# 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

Table 1 List of abbreviations

|  |  |
| --- | --- |
| Term | Abbreviation |
| Acute otitis media | AOM |
| Anatomical-Therapeutic-Chemical | ATC |
| Community-acquired pneumonia | CAP |
| Confidence intervals | CI |
| Enzyme-linked immunosorbent assay | ELISA |
| Hazard ratio | HR |
| Hospital-aquired pneumonia | HAP |
| Incidence rate | IR |
| Incidence rate ratio | IRR |
| Intensive care unit | ICU |
| International Classification of Diseases, 10th revision | ICD-10 |
| Invasive pneumococcal disease | IPD |
| Leave-one-out cross-validation | LOOCV |
| Lower respiratory tract infection | LRTI |
| National Drug Prescription Registry | NDPR |
| National Vaccine Registry | NVR |
| NOMESCO Classification of Surgical Procedures | NCSP |
| Principal component analysis | PCA |
| Respiratory syncytial virus | RSV |
| Seasonal and trend decompisition using LOESS | STL |
| Tympanostomy tube placement | TTP |
| Upper respiratory tract infection | URTI |
| Vaccine eligible cohorts | VEC |
| Vaccine non-eligible cohorts | VNEC |

*Streptococcus pneumoniae* is a commensal bacterium found in the nasopharynx of humans where it plays an integral role in normal upper respiratory flora. It is also a common pathogen, and one of the most common bacterial causes of disease in humans. In classical medical texts, pneumococcus is described as a Gram-positive lancet-shaped coccus, usually found in pairs. In fact, pneumococcus is *the* Gram-positive coccus, being the first bacteria noted by Christian Gram that retained the dark aniline-gentian violet stain that now bears his name (Gram [1884](#ref-Gram1884)). Pneumococcus was first isolated in 1881 by two microbiologist, George M. Sternberg in the United States and Louis Pasteur in France (Pasteur [1881](#ref-Pasteur1881); Sternberg [1882](#ref-Sternberg1881); Watson et al. [1993](#ref-Watson1993)). The causal association between this newly discovered bacterium and pneumonia was firmly established only five years later (Weichselbaum [1886](#ref-Weichselbaum1886)), and in the following decade, all clinical presentations of pneumococcal infection had been described (Austrian [1981](#ref-Austrian1981)).

The infectious manifestations of pneumococcal disease are, broadly speaking, local infections of the respiratory tract and infections of previously sterile tissue. They range from common to uncommon, and from benign to serious. The most common infectious manifestation of pneumococcus is otitis media (AOM) – an infection of the middle ear. The disease course is benign and rarely results in permanent disability. On the other hand, AOM is the most common reason for physician visit and for antimicrobial prescription in the paediatric population. Antimicrobial consumption is causally related to antimicrobial resistance, a major threat to public health. Recurrent or persistent otitis media is sometimes treated with the surgical placement of tympanic tubes, rendering it the most common surgical procedure in children. Thus, while AOM is a benign disease, it is associated with a large healthcare burden. A potentially more serious manifestation of penumococcal disease is pneumonia, the disease from which pneumococcus gets its name. Pneumonia often requires hospitalization and intravenous antimicrobial treatment, and can lead to permanent disability and death. Pneumococcus can cause invasive infections if it gains access to normally sterile tissue. These includes bacteremia, an infection of the blood, and meningitis, an infection of the meninges. These infectious manifestations are grouped together as invasive pneumococcal disease (IPD). Whilst IPD is extremely uncommon, the consequences can be disastrous. The case-fatality ratio from pneumococcal meningitis in Iceland is estimated at 15.3%. Pneumococcal infections are responsible for a large healthcare burden that spans the range from outpatient to inpatient treatment.

For over a century, scientists have attempted to prevent pneumococcal disease using vaccines with varying results. Pneumococcal vaccine development is complicated by the polysaccharide coating that protects pneumococcus from environmental factors. The polysaccharide capsule acts as an “invisibility cloak” to the human immune system, rendering it unable to detect pneumococcus except through certain patterns in the oligosaccharides contained within the capsule (Tuomanen, Austrian, and Masure [1995](#ref-Epstein1995)). Based on these patterns, pneumococcus has been classified into over 97 different serotypes to date. As the capsule contains only polysaccharides and not proteins, the immune response is T-cell independent and therefore poorly immunogenic, even after being identified by the immune system (Geno et al. [2015](#ref-Geno2015b)). The epidemiology of pneumococcus is dominated by person-to-person transmission of asymptomatic carriage. Because children have no previous immunity to any serotype, they are colonized by pneumococcus more frequently, and each colonization lasts longer (MELEGARO, GAY, and MEDLEY [2004](#ref-Melegaro2004)). This phenomenon is further augmented when multiple immune-naive children congregate, such as in daycare centers and pre-schools (Yagupsky et al. [1998](#ref-Yagupsky1998)). Thus children act as a pneumococcal reservoir for the population, without actually having any clinical disease (Hoshino et al. [2002](#ref-Hoshino2002); Le Polain de Waroux et al. [2014](#ref-LePolaindeWaroux2014); Mosser et al. [2014](#ref-Mosser2014)). Vaccinating children against certain serotypes may therefore lead to a decrease in pneumococcal disease caused by those serotypes in adults. In vaccine epidemiology, this is referred to as herd-effect and is an important consideration for pneumococcal vaccine development. Serotype replacement can also occur, where previously rare serotypes appear and fill the ecological niche vacated by the vaccine serotypes.

Health systems operate under constraints on budgets and resources. Demonstrating vaccine benefit is essential, but not the only factor to consider when making health policy decisions. Cost and resource allocation are also of crucial importance. This is especially complicated in the case of vaccines, because benefits are not seen immediately but rather over time. Benefits occur in both vaccinated and unvaccinated members of the population. The diseases prevented by vaccines have associated expenses which must be accounted for when the expenditures for a vaccine program are evaluated. Cost-effectiveness analysis and cost-benefit analysis are methods developed to measure the ratio between expenditure and benefit, and are used as a tool in making health policy decisions. To adequately perform such an analyses, detailed data on disease incidence and associated costs for the whole population must be available.

Iceland is an independent island nation, isolated in the mid-Atlantic, with a homogeneous population of roughly 330,000 individuals. The first systematic program of vaccination against pneumococcus in Iceland began in April 2011, when the 10-valent pneumococcal *Haemophilus influnzae* protein-D conjugate vaccine (Synflorix, PHiD-CV10) was introduced into the national paediatric vaccination program. The vaccine program entailed two primary doses given at three and five months of age, and a booster dose at twelve months. No catch-up program was undertaken. Prior to the introduction, no systematic vaccination effort had been undertaken in Iceland. As the other Nordic countries, Iceland has a rich legacy of national health-related registers. Detailed individual-level information on vaccine status, outpatient primary care visits, antimicrobial consumption, tympanic tube procedures and hospitalizations are accessible, and linked between registries using national identification numbers. All healthcare costs are available on the individual-level from Icelandic Health Insurance, which is the insurer of all permanent Icelandic residents. This wealth of medical documentation enabled a unique whole-population ecological study examining the impact of systematic pneumococcal vaccination.

## Clinical manifestations of *Streptococcus pneumoniae*

In this chapter the clinical manifestations of pneumococcal disease will be reviewed. The mechanism by which individuals acquire pneumococcus into their normal upper respiratory flora will be discussed, and the association between pneumococcal carriage and disease will be described. Throughout this thesis, attention will be focused on three common clinical presentations of pneumococcal infections; AOM, pneumonia and IPD, including the pathophysiology, natural disease course, and health care burden of each of the presentations.

Pneumococcus has gone by many names since it was first isolated in 1881. It was originally named *Micrococcus pasteuri* by Sternberg (Sternberg [1882](#ref-Sternberg1881)), but by 1920, a scientific consensus was reached that the official name should be *Diplococcus pneumoniae* (Winslow et al. [1920](#ref-Winslow1920)). It was not until 1974 that pneumococcus received its current name, *Streptococcus pneumoniae* (Deibel and Seeley [1974](#ref-Deibel1974)). Because pneumococcus is both a commensal bacterium and a pathogen, its relationship with humans is complex. Most children are colonized by pneumococcus within the first months of life (Leino et al. [2001](#ref-Leino2001a)). The serotype distribution of the initial colonization in a child is influenced by the distribution of serotypes within the child’s family. Over the course of the their lifetime, a child will be colonized by many different serotypes. Their immune system will learn to recognize newly acquired serotypes and will either clear the colonization or maintain an equilibrium in which the serotype is kept within a certain limit of reproduction (Dowling, Sheehe, and Feldman [1971](#ref-Dowling1971); MELEGARO, GAY, and MEDLEY [2004](#ref-Melegaro2004)). In this manner, the contribution of pneumococcus to the human upper respiratory flora is in a state of constant flux. New serotypes enter while the old exit, and the relative density of serotypes changes.

In some cases, the equilibrium between pneumococcus and the host is destabilized, triggering a rapid growth of pneumococcus and resulting in clinical manifestations. It is thought that this is most likely to occur directly following the acquisition of new serotype into the nasopharyngeal flora (Casey, Adlowitz, and Pichichero [2009](#ref-Casey2010)). Because pneumococcus is carried in the nasopharynx, this overgrowth results in infections of adjacent tissue; the sinuses, middle ear and conjunctiva. The pathogenesis of pneumococcal pneumonia is thought to occur through micro-aspiration of upper respiratory secretions, provoking a subsequent rapid proliferation of pneumococcus in the lower respiratory tract. Invasive disease occurs when pneumococcus penetrates the host’s immunological defenses and proliferates in normally sterile tissue. This can occur as a primary event, or can be secondary to infections of the upper or lower respiratory tract. Generally, IPD is considered to encompass meningitis, bacteraemia and septic arthritis. While some may argue that the middle ear is normally sterile, AOM is not considered invasive disease.

### Acute otitis media

Otitis media is an inflammatory state of the middle ear. It is most often caused by a viral or bacterial infection. The clinical presentation of otitis media is variable. Its onset ranges from abrupt to gradual, and its duration from short to protracted. Several categories have been defined to facilitate communication concerning this variability. They are not mutually exclusive, but rather represent a continuum of the disease process. Otitis media can manifest as a acute inflammatory event. This is the classical AOM with which most parents are familiar. AOM can be recurrent, which is defined as AOM occurring three times over a six month period, or four or more times over a twelve month period. Conversely, it can take the form of a chronic low-grade process. The later phenotype includes otitis media with effusion and chronic suppurative otitis media. Otitis media with effusion is defined as the protracted collection of serous fluid in the middle ear. By convention, it is considered to be present if middle ear effusion has been documented to have lasted for three months or longer. It may follow AOM, or be detected without an obvious inciting event. Chronic suppurative otitis media may be thought of as a protracted case of AOM. The child remains sickly and the middle ear is filled with puss. The tympanic membrane often ruptures as a result.

The anatomy of the middle ear is intrinsic to the epidemiology of otitis media, and can elucidate the wide range of presentations described above. The middle ear is located within a recess in the tympanic bone, medially to the tympanic membrane. It communicates with the nasopharynx by means of the Eustachian tube, a thin muscular canal that acts to equalize pressure between the middle ear and the external ear. This communication allows viruses and bacteria in the nasopharynx to gain access to the middle ear which clarifies the association between nasopharyngeal carriage and AOM. The Eustachian tube is anatomically shorter and straighter in children, partly accounting for the much higher risk of middle ear infections in children as compared to adults. It is also much thinner. Because of this, any cause of inflammation in the nasopharynx can lead to a spasm of a child’s Eustachian tube, resulting in the build up of secretions in the middle ear. These secretions provide optimal conditions for bacterial growth and can lead to subsequent otitis media. They can also remain macroscopically uninfected, which, if lasting long enough, would be categorized as otitis media with effusion. The anatomic view also helps to explain the mechanism of the contribution of different risk factors. The cycle of Eustachian tube dysfunction, effusion and increased risk of infection was the catalyst for the development of tympanic tube placements as a treatment for middle ear infections in children. By providing a secondary mechanism by which the middle ear could drain and equalize pressure, the rationale was that propensity for infection would decrease.

#### Pathogens implicated in acute otitis media

Any pathogen that is able to gain access to the middle ear, disrupt the normal function of the Eustachian tube and replicate within the resulting fluid, has the potential to cause otitis media. In upwards of 90% of otitis media cases, the bacteria aspirated from the middle ear fluid will also be found in the nasopharynx (Casey, Adlowitz, and Pichichero [2009](#ref-Casey2010)). The most common bacterial causes of otitis media are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* (Bluestone, Stephenson, and Martin [1992](#ref-Bluestone1992); Casey and Pichichero [2004](#ref-Casey2004); Casey, Adlowitz, and Pichichero [2009](#ref-Casey2010); Ngo et al. [2016](#ref-Ngo2016); Pumarola et al. [2013](#ref-Pumarola2013)). The relative contribution of these three pathogens is remarkably stable between countries and over time. This is likely a consequence of how common they are in the nasopharyngeal flora of children.

A systematic review of studies from 1970-2014 which reported the etiology of otitis media, found that *Streptococcus pneumoniae* caused 30.2% of AOM in Europe (Ngo et al. [2016](#ref-Ngo2016)). In countries that have introduced systematic pneumococcal vaccination, there is evidence to suggest that the microbiology of otitis media has shifted from being predominantly due to pneumococcus to *Haemophilus influenzae* (Block et al. [2004](#ref-Block2004); Van Dyke et al. [2017](#ref-VanDyke2017)). Of the pneumococcal AOM, the prevalence of vaccine serotypes has decreased and non-vaccine serotypes now predominate. Children with otitis media who experience spontaneous rupture of the tympanic membrane have a slightly different distribution of pathogens, with a higher proportion of *Streptococcus pyogenes* and *Staphylococcus aureus* (Chen et al. [2013](#ref-Chen2013); Sonsuwan, Watcharinyanon, and Sawanyawisuth [2016](#ref-Sonsuwan2016)). This could be explained by these pathogens causing a more aggressive infection, or possibly by contamination by bacteria located in the external ear canal. Similarly, coagulase negative staphylococci and *Staphylococcus aureus* are more common in otitis media with effusion (Kim et al. [2013](#ref-Kim2013)). Pneumococcal otitis media is slightly more likely to lead to recurrent otitis media and chronic suppurative otitis media, but is otherwise clinically indistinguishable from otitis media caused by other otopathogens.

#### Healthcare burden of otitis media

The healthcare burden caused by otitis media is disproportionate to its severity. Acute otitis media is the most common reason for physician visit among children, a fact which has been frequently documented in multiple countries. Only focusing on physician visits underestimates the impact of AOM, as some episodes are not reported to physicians but still result in distressing symptoms in children and parental missed days of work. By a child’s third birthday, 60%-80% will have experienced at least one episode of AOM (Kaur, Morris, and Pichichero [2017](#ref-Kaur2017); Teele, Klein, and Rosner [1989](#ref-Teele1989)). Likewise, otitis media is also responsible for the majority of antimicrobial prescriptions, and thus contributes significantly to antimicrobial resistance. Though often benign and self-limiting, AOM can progress to recurrent or chronic infection and require more invasive treatment. Mastoiditis develops in XXX% of cases and will require hospital admission and administration of intravenous antimicrobials. Severe AOM can result in hearing loss and has been estimated to occur XXX%.

#### Tympanostomy tube procedures

For various reasons, parents and clinicians may opt to treat recurrent or chronic otitis media with the placement of a tympanic tube. Tympanic tube procedures are consequently the most common surgical procedure in the paediatric population (Black [1984](#ref-Black1984); Cullen, Hall, and Golosinskiy [2009](#ref-Cullen2009)). Despite their popularity, there is little evidence for the use of tympanostomy tubes for their two most common indications; recurrent otitis media and hearing loss associated with otitis media with effusion (Venekamp et al. [2018](#ref-Venekamp2018); Browning et al. [2010](#ref-Browning2010)). Inconsistent evidence regarding the efficacy of tympanostomy tube procedures is mirrored in the large variation in incidence that is seen both within and between different countries.

In Sweden, the incidence of procedures is low, and was in 1996, estimated to be 10 per 1000 person-years (Florentzson and Finizia [2012](#ref-Florentzson2012)). The incidence was 5.6-6.7 procedures per 1000 person-years in Australia (Spilsbury et al. [2006](#ref-Spilsbury2006)). Even within the United States, there are large variations in the incidence. In 1988, the prevalence rate of tympanostomy tube placements among children younger than eighteen in the United States was estimated to be 13% (95%CI 11%-14%) (Bright et al. [1993](#ref-Bright1993)). In Northern New England alone, the incidence varied between different paediatric surgical areas, from 3.79 to 13.15 procedures per 1000 person-years (Parker et al. [2016](#ref-Parker2016)). The variation can possibly be explained by different thresholds for performing the procedure. By carefully examining the medical records of all children who underwent tympanic tube procedures in five hospitals in New York, Keyhani et al. were able to show that 92% of the procedures would not have been recommended according to the guidelines in force at the time of surgery (Keyhani et al. [2008](#ref-Keyhani2008)).

#### Acute otitis media in Iceland

The incidence AOM, its microbiology, treatment and complications have been evaluated in Iceland. In 1990, a retrospective analysis of two birth-cohorts in a small village in Iceland showed a 66% cumulative incidence of AOM by 24 months of age (Bjarnason, Friðriksson, and Benediktsson [1991](#ref-Bjarnason1991)). A larger study conducted in 1998 used parental questionnaires to estimate the incidence of upper respiratory infections that resulted in antimicrobial treatment and tympanic tube placements among children ages one to six years old (Arason et al. [2002](#ref-Arason2002)). A total of 1030 children were randomly sampled from four geographically separated areas of Iceland and the study achieved a 78% response rate. The study demonstrated high incidence rates of antimicrobially treated AOM for all age-groups, ranging from 1.79 treatment episodes among children one year of age to 0.25 treatment episodes in children six years of age. In this random sample, 58% of all antimicrobial prescriptions were due to AOM. The cumulative incidence of tympanic tube placements was alarmingly high. By one year of age, 23% (95%CI 16%-31%) had already received at least one tympanostomy tube. This proportion exceeded 30% by age two and remained fairly stable thereafter. The study was repeated by the same investigators in 2003 using the exact same cross-sectional random sampling (Arason et al. [2005](#ref-Arason2005)). The proportion of all antimicrobial prescriptions that were due to AOM was almost exactly the same, 57%. Surprisingly, the cumulative incidence of tympanostomy tube placement had slightly increased and was now estimated to be 34%,

### Pneumonia

Pneumonia is defined as the infectious infiltration of the lung parenchyma. Several different classification systems have been proposed to aid in the treatment of pneumonia (Mackenzie [2016](#ref-Mackenzie2016)). Some are based on the anatomical distribution of infectious infiltrates on radiographs, others on the symptomotology and still others on the distribution of risk factors in those being diagnosed with the disease. Each attempts to utilize readily available information to assist in selecting among treatment options and in predicting prognosis. While the ideal classification system would be based on the antimicrobial susceptibility of the causative pathogen, this information is rarely available when treatment decisions are being made. Most commonly, pneumonia is classified by assigning cases based upon the circumstances under which it was diagnosed. Pneumonia is classified as community acquired pneumonia if it is detected in people with limited contact with the healthcare system in the weeks prior to diagnosis. This is the most common type of pneumonia. Remaining pneumonia cases are classified as healthcare associated pneumonia, or hospital-acquired pneumonia if diagnosed during a hospital admission. This simple classification system is remarkably good at predicting antimicrobial resistance in the causative pathogen, and informs the choice of antimicrobial agents.

The mechanism by which pathogens gain access to the lung and replicate there causing infection, is best understood by reviewing the pulmonary anatomy. The pulmonary system has an inverted tree configuration. The trachea acts as the trunk and subdivides into the main-stem bronchi, which lead to the right and left lung, respectively. The respiratory tree further subdivides into lobar and segmental bronchi, each of which supplies an independent anatomical segment of the lung, separated by connective tissue. Each compartment is known as a bronchopulmonary segment, and can be individually infected. Within each bronchopulmonary segment, these branches divide 18-20 more times, their diameter decreasing with every division. The final 16-22 divisions compromise the respiratory bronchioles which lead to the alveoli. To infect the lung, a pathogen must first arrive there. While this may seem like an easy task as gravity aids in the aspiration of upper respiratory secretions, it is, in fact, not a simple matter. As anyone who has experienced “food going down the wrong way” knows, the respiratory tree does not readily tolerate backward flow into the lungs. Irritation of the bronchi results in a cough, a powerful, coordinated neuromuscular response which propels any aspirated material up the respiratory tree. Pathogens are prevented from spreading downwards in a more insidious manner, by a constant flow of mucus from the the terminal bronchioles to the upper respiratory tract. The epithelial lining is covered with cilia, which are tiny hair-like structures that relentlessly sweep the mucus upwards. Even when pathogens overcome this obstacle and progress down the respiratory tree, they are met with a heavy concentration of defensive immune tissue, the amount of which increases with every division of the respiratory tree.

Risk factors of pneumonia are also best explained by referring to the defensive mechanisms employed by the respiratory tree. Processes which interfere with the cough reflex will result in a higher risk of pneumonia. These includes sensory deficiencies present in certain diseases and in the extremes of age, which result in the absence of cough initiation and muscular weakness. Pain associated with fractured ribs can also lead to voluntary suppression of the cough reflex and increases the risk of pneumonia. Another process increases the risk of pneumonia is damage to the respiratory cilia and the resulting stasis of mucus. Cilia damage can result from viral infection or from the inhalation of toxic particles, such as pollution or cigarette smoke, both of which can also cause local immune suppression, further compromising the lung’s defenses.

#### Pathogens causing pneumonia

Any pathogen that is able to gain access to the lung and replicate there, has the potential to cause pneumonia. As is the case of otitis media, the most common bacterial pathogens causing community acquired pneumonia are *Streptococcus pneumoniae*, *Haemophilus influnzae* and *Moraxella catarrhalis* (Rodrigues and Groves [2017](#ref-Rodrigues2017)). Here again, this is most likely to be a function of how common these pathogens are in the upper respiratory flora. Unlike otitis media however, it is exceedingly difficult to determine the causative pathogen in the case of pneumonia (Cilloniz et al. [2016](#ref-Cilloniz2016); Feikin et al. [2017](#ref-Feikin2017)). Ideally, a sample would be taken from the lung itself, but the dangers of such procedures which moreover require highly trained personnel and technical resources, render this option unfeasible. Most studies, therefore, use proxy measures such as sputum, blood cultures and nasopharyngeal swabs. In addition, the inability of children to produce a quality sputum sample exacerbates the difficulties of elucidating the causative pathogen (Rodrigues and Groves [2017](#ref-Rodrigues2017)).

The relative contribution of pathogens varies greatly with the age and risk factor profile. Only a few studies in developed countries have evaluated the distribution of pathogens which cause pneumonia in children, but they consistently demonstrate the importance of viruses in paediatric pneumonia. These results may either indicate that viruses are either the primary etiological factor, or that viruses weaken the respiratory defenses and allow bacterial disease to develop. The considerable heterogeneity in the proportion of pneumonias found to be caused by various pathogens, underscores the importance of study population, time-period and, most importantly, the methods used in determining the causative pathogen (Feikin et al. [2017](#ref-Feikin2017)). A large multicenter study, The Pneumonia Etiology Research for Child Health (PERCH), is underway to clarify the etiology of paediatric pneumonia (Levine et al. [2012](#ref-Levine2012)). Its results have not yet been published. One of the first prospective studies of paediatric pneumonia was undertaken in Chapel Hill, North Carolina, from 1963 to 1971. The study investigated all lower respiratory infections in children, and found most to be caused by respiratory syncytial virus, parainfluenza virus and *Mycoplasma pneumoniae* (Glezen and Denny [1973](#ref-Glezen1973)). The predominance of causative viruses is likely due to the methods, current at the time, used to detect etiology. Following the advent of pneumococcal antibody testing, the recognition of pneumococcus as an important pathogen increased. Using pneumococcal antigens, Paisley et al. found pneumococcus to be a contributor to 19% of paediatric pneumonias from 1978-1979 (PAISLEY et al. [1984](#ref-PAISLEY1984)). In a study conducted in Göteborg, Sweden from 1982-1983, a primitive enzyme-linked immunosorbent assay was used to determine etiology, and found that 13% of paediatric pneumonias were due to *Streptococcus pneumoniae* (CLAESSON et al. [1989](#ref-CLAESSON1989)). In that study, however, antibody testing for pneumococcus was only performed on those who were found to be pneumococcal carriers by nasopharyngeal swap. A few years later, in 1989, a prospective study of paediatric pneumonia in Turku, Finland demonstrated pneumococcus to be a causative pathogen in 38% of cases (Ruuskanen et al. [1992](#ref-Ruuskanen1992)). Another etiological study in Paris in 1992-1994, enrolled 104 consecutive children who presented with pneumonia to a single hospital. Of those, 14% were found to have pneumococcal pneumonia (Gendrel et al. [1997](#ref-Gendrel1997)). In populations where pneumococcal vaccination is universal, two studies on the etiology of paediatric pneumonia have been published. One of these, conducted in the United Kingdom in 2009-2011, found pneumococcus to be causative in 17.4% of cases (Elemraid et al. [2013](#ref-Elemraid2013)). Another is a large prospective study of 2,358 children conducted in 2011-2012 in the United states, which utilized a variety of sampling methods, and detected pneumococcus in only 4% of cases, a result considerably different than all other etiological studies of paediatric pneumonia (Jain et al. [2015](#ref-Jain2015)). The authors’ discussion of possible reasons for this included speculation that low proportion of pneumococcal pneumonia might be due to universal pneumococcal vaccination. All of the above studies identified respiratory syncytial virus to be the most common causative pathogen. Of the bacterial pneumonias, all but one found pneumococcus to be the most common. Their interpretation in complicated by the lack of direct sampling from the lungs. In studies that used strict radiological inclusion criteria and used lung aspiration to determine the etiology, pneumococcal pneumonia was by far the most common pathogen (Gilani et al. [2012](#ref-Gilani2012); World Health Organization Pneumonia Vaccine Trial Investigators’ Group [2001](#ref-WorldHealthOrganization2001)).

While the etiology of adult pneumonia has been more extensively studied, the same challenges are encountered as in the study of children. The estimated proportion of pneumonia cases caused by different pathogens varies between studies. This may represent a true difference in the underlying study populations or may be a result of different study design and methodology. A recent meta-analysis evaluated all published studies of pneumonia etiology in Europe from 1990-2011, and estimated the crude proportion caused by pneumococcus to be 19.3% (Rozenbaum et al. [2013](#ref-Rozenbaum2013)). Seventy-seven studies were included, and inclusion criteria were strict, considering only radiologically confirmed pneumonia. The crude estimate of the proportion of pneumonia caused by *Streptococcus pneumoniae* was 19.3%. After adjusting for several variables using a fixed-effects meta-regression model, the estimated proportion of pneumococcal pneumonia in the average Northern European country was 15%.

#### Healthcare burden of pneumonia

Lower respiratory infections were, in 2016, estimated to cause 2,38 million deaths worldwide and were the sixth leading cause of death (Troeger et al. [2018](#ref-Troeger2018)). Of those deaths, 652,572 (95%CI 586,475-720,612) were estimated to occur among children under five years of age, making lower respiratory infections the leading cause of death in this age-group. Large variations exist in the incidence, morbidity and mortality of pneumonia between countries. Pneumonia disproportionately affects developing countries, which experience over half of the pneumonia associated mortality. Yet pneumonia is still a large healthcare burden in developed countries, and accounts for 3%-18% of all childhood hospital admissions (Madhi et al. [2012](#ref-Madhi2013)). In developed countries, the incidence of pneumonia in children under five years of age is 34-40 cases per 1000 person-years.

#### Pneumonia in Iceland

Paragraph about Icelandic literature and changing epidemiology - Pneumococcal pneumonia prevalence and serotype distribution - Rate of hospitalization, healthcare consumption - Rate of sequelae

### Invasive pneumococcal disease

~ 3 -5 pages - Define different presentations of IPD: meningitis, bacteremia, etc. - Epidemiology, both serotype and age - Risk factors - Burden of disease, health care utilization - Severity - Hospitalization rates, ICU rates - Sequelae - Review of Icelandic literature and changing epidemiology - Meningitis, bacteremia, empyema, joint infection prevalence and serotype distribution - Rate of sequelae

## Pneumococcal vaccines

In this chapter we will review the history of pneumococcal vaccination to better understand the current vaccine climate. Special attention will be paid to the scientific discourse that led to the recognition of the need for conjugating pneumococcal polysaccharides to a protein carrier. Several key concepts in pneumococcal vaccine epidemiology will be discussed, e.g. herd-effect and serotype-replacement. The scientific literature on the impact of pneumococcal conjugate vaccines on AOM, pneumonia and IPD will be reviewed and discussed. Special attention will be paid to issues of study design and statistical methodology and their effect on study interpretation. Randomized controlled trials and observational studies will be reviewed separately. Finally, the evidence will be summarized.

### A brief history of pneumococcal vaccination

The history of pneumococcal vaccination can be roughly divided into three phases; the inactivated (killed) whole-cell vaccines; the polysaccharide vaccines and the conjugated vaccines. It begins in 1911 when Wright and colleagues attempted to use an inoculation of heat-killed pneumococcus to vaccinate South African miners against pneumococcal pneumonia (Wright et al. [1914](#ref-Wright1914)). It should be noted however, that in George Sternberg’s original description of pneumococcus in 1881, he observed that rabbits who were injected with saliva mixed with alcohol and quinine died less frequently than those injected with saliva alone, and were later resistant to re-injection with saliva (Austrian [1999](#ref-Austrian1999a); Sternberg [1882](#ref-Sternberg1881)). Sternberg had inadvertently immunized the laboratory animals against subsequent infection by injecting killed pneumococci, thus proving the concept 30 years before it was first attempted. The 1911 trial by Wright failed to demonstrate efficacy because the significance of serotypes and serotype specific immunogenicity was not known. In the following two decades, several trials using inactivated whole-cell pneumococcal vaccines were published (Cecil [1918](#ref-Cecil1918); Lister [1916](#ref-Lister1916); Lister and Ordman [1936](#ref-Lister1936); Maynard [1913](#ref-Maynard1913)) Due to inconsistencies in study design, the efficacy of whole bacteria pneumococcal vaccines remained fiercely debated at the time, despite some evidence of benefit (Austrian [1999](#ref-Austrian1999a)).

Following discoveries of the immunogenicity of the polysaccharide capsule in the 1920s and 1930 (Dochez and Avery [1917](#ref-Dochez1917); Finland [1931](#ref-Finland1931); Francis and Tillett [1930](#ref-Francis1930); Heidelberger and Avery [1923](#ref-Heidelberger1923); Schiemann and Casper [1927](#ref-Schiemann1927)), inactivated whole-cell pneumococcal vaccines were soon replaced with polysaccharide vaccines. The first clinical trial of a pneumococcal polysaccharide vaccine was conducted in the 1930s on 29,000 adult males in the American Civilian Conservation Corps using a bivalent vaccine (Ekwurzel et al. [1938](#ref-Ekwurzel1938)). With similar methodological problems of previous trials of the inactivated vaccines, the results were debated. A second large trial was conducted in the late 1930s, using a tetravalent polysaccharide vaccine (Macleod et al. [1945](#ref-Macleod1945)). This trial built upon the experience of the previous trials, and was able to show convincing efficacy against pneumococcal pneumonia, leading to the licensure of two hexavalent polysaccharide pneumococcal vaccines in the 1940s. One was formulated for adults and the other for children, each optimized to the serotype distribution within the respective age-group. Unfortunately, these early vaccines fell victim to unfavorable timing; in 1944, Tillet and colleagues showed that bacteraemic pneumococcal pneumonia could be cured by parenteral administration of benzylpenicillin (Tillett, Cambier, and McCormack [1944](#ref-Tillett1943)). With this discovery, the medical community became complacent. The mortality rate of pneumococcal disease decreased sufficiently that there was no longer a perceived need for preventative vaccination. The licenses for the polysaccharide vaccines were withdrawn by the manufacturer due to lack of use (Austrian [1999](#ref-Austrian1999a)). Interest in pneumococcal vaccination re-emerged in the 1950s when it was noted that the mortality benefit of penicillin was not ubiquitous. The elderly and those who had underlying disease did not experience a decrease in their case fatality ratio (Austrian and Gold [1964](#ref-Austrian1964)). This led to a redoubled effort to create a new polysaccharide vaccine. Several large randomized controlled trials were conducted in South Africa in the 1970s (Austrian et al. [1976](#ref-Austrian1976), Smit ([1977](#ref-Smit1977))) and, on the basis of these, a 14-valent pneumococcal vaccine was licensed in the United States in 1977. Its valency was increased to 23 polysaccharides in 1983 (Austrian [1999](#ref-Austrian1999a)).

Early in the development of pneumococcal vaccines, there was an interested in vaccinating children. Two trials were conducted in the early 1980s which tested the use of polysaccharide vaccines in young children. Neither showed benefit (Mäkelä et al. [1981](#ref-Makela1981); Sloyer, Ploussard, and Howie [1981](#ref-Sloyer1981)). This result was not entirely unexpected. In 1937, The first polysaccharide trial conducted in children failed to detect any immunological response (Davies [1937](#ref-Davies1937)). Laboratory studies in the 1930s and 1940s revealed that the reason for this lack of efficacy was due to the thymus independent immune response to purely sacharide antigens. These same studies showed that this could be remedied by adding a protein adjuvant, thus inducing a T-cell response. The strategy of protein conjugation saw its first success in the development of the *Haemophilus influenzae* type b vaccine. Subsequently, several different pneumococcal conjugate vaccines entered phase II and phase III clinical trials in the late 1990s (Austrian [1999](#ref-Austrian1999a)). The first of these to receive licensure was the seven valent pneumococcal conjugate vaccine, licensed in 2000 in the United States. It included the purified polysaccharides of seven serotypes of pneumococcus (4, 9V, 14, 19F, 23F, 18C and 6B) conjugated to CRM197 (PCV7CRM197), a nontoxic variant of the diphtheria toxin. It was shown to be efficacious for IPD, pneumococcal pneumonia and AOM in several randomized trials (Black et al. [2000](#ref-Black2000); Black et al. [2002](#ref-Black2002c); Eskola et al. [2001](#ref-Eskola2001); Fireman et al. [2003](#ref-Fireman2003); O’Brien et al. [2003](#ref-OBrien2003); O’Brien et al. [2008](#ref-OBrien2008)). In the 2000s, higher valency conjugated vaccines were developed and received licensure, based on the randomized trials conducted for the heptavalent conjugated vaccine. They have however been shown to be effective in several cluster randomized trials and observational studies.

### Key concepts in pneumococcal vaccine epidemiology

The epidemiology of pneumococcus is complicated by its relationship with humans. It is both a component of the normal flora of the upper respiratory tract and a common pathogen. Because of the polysaccharide coat, protection against one serotype does not necessarily confer protection against another. If one serotype disappears due to immune recognition, an ecological niche is created which can be filled by different serotype. This process takes place on both the individual and community level. Systematic vaccination programs greatly reduce the prevalence of carriage and disease of the serotypes contained within the vaccine among the vaccinated. If the vaccinated individuals compromise a large enough portion of the population.

### The impact of pneumococcal conjugate vaccines on otitis media

Acute otitis media is still most often caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* despite changes in otopathogens. Prevention of IPD in children and the associated morbidity and mortality was the driving force in the development of pneumococcal conjugate vaccines. However, the public most often associates them with AOM. Most children experience AOM and the dramatic decrease in incidence following pneumococcal conjugate vaccination is what families noticed.

Despite this, AOM is a difficult outcome for trialist as it exists on a continuum. It does not have universally adhered to diagnostic criteria and its signs and symptoms greatly overlap with those of other common diseases. Because AOM is benign and most often self-limited, the probability that a child with AOM is even seen by a physician varies greatly with parental health seeking behavior. Even when AOM is accurately diagnosed it is not possible to ascertain the causative pathogen without invasive sampling, which is not warranted given the benign nature of the disease. This precludes measuring the serotype specific effect of vaccination for most studies - and more importantly, it precludes measuring the effect on pneumococcal AOM.

Thus any estimation of an effect of pneumococcal vaccination will necessarily by diluted by the subjectiveness of AOM diagnosis and the continued lack of protection against other otopathogens. Despite these difficulties, AOM has been associated with pneumococcal vaccination in children from the beginning. It was used as an outcome measure in the earliest trials of the pneumococcal polysaccharide vaccines (Mäkelä et al. [1981](#ref-Makela1981); Sloyer, Ploussard, and Howie [1981](#ref-Sloyer1981)). In the following sub-chapters, the evidence regarding the efficacy and impact of PCV on the otitis media will be reviewed. Randomized controlled trials will be reviewed in greater depth, as they represented the highest quality of evidence of true efficacy. Observational studies will be reviewed more generally.

#### Randomized controlled trials

The first published randomized controlled trial of a pneumococcal conjugate vaccine reported, among other outcomes, the efficacy against AOM (Black et al. [2000](#ref-Black2000)). The study recruited 37,868 children between October 1995 and August 1998 and randomized them to the either PCV7CRM197 or the meningococcus C CRM197 conjugate vaccine. A separate publication from the same trial was published in 2003, and examined the effect of PCV7CRM197 on AOM in more detail using the full data until study completion in April 1999 (Fireman et al. [2003](#ref-Fireman2003)). A visit was considered to be due to the same episode of AOM if the child presented within 21 days of a previous AOM associated visit. Frequent otitis media was then defined as either three episodes within a six month period, or four episodes within a twelve month period. Both the Andersen-Gill extension of the Cox proportional hazards model with robust variance estimation and the binomial test with Klopper-Pearson confidence intervals were used and efficacy was reported as . The estimated vaccine efficacy against otitis media visits was 7.8% (95%CI 5.4%-10.2%). Slightly higher point estimates were found for otitis media episodes, frequent otitis media and ventilatory tube placements (Black et al. [2000](#ref-Black2000); Fireman et al. [2003](#ref-Fireman2003))

The following year the results of two more randomized controlled trials were published (Dagan et al. [2001](#ref-Dagan2001); Eskola et al. [2001](#ref-Eskola2001)). Dagan et al. ([2001](#ref-Dagan2001)) enrolled 264 children ages 12-35 months of age attending eight daycare centers in Beer-Sheva, Isreal. The study employed a block randomized design which stratified the children according to daycare center and age-group. Within each stratified group, children were randomized in blocks of six. The study examined a nine valent pneumococcal CRM197 conjugate vaccine produced by Wyeth-Lederle Vaccines and used the same meningococcal C CRM197 conjugate vaccine as the Black et al. ([2000](#ref-Black2000)) study as a control. The study’s primary endpoint was vaccine-type nasopharyngeal carriage and the secondary endpoint was parent reported respiratory infections. Monthly questionnaires were submitted to parents for one year starting one month after the last per-protocol vaccine dose, and bimonthly thereafter for a total of 18 encounters. Respiratory infections were split into four different categories (Upper respiratory infections, lower respiratory problems, otitis media and other illnesses) and the results were measured in two different ways; episodes per 100 child-months and the proportion of antimicrobial days during the study period. Finally, each category and measurement was compared in children <36 months of age, 36 months of age and older, and overall, resulting in comparisons between the intervention and control. The statistical analysis used and Fischer’s exact contingency table methods but did not account for multiple testing. The study reported an efficacy of 17% (95%CI -2%-33%) for otitis media episodes and 20% (95%CI 14%-26%) antimicrobial treated otitis media, as measured by days spent on antimicrobial. The later does remain statistically significant when the result has been corrected for multiple testing using any standard method.

The later study published in 2001 compared two heptavalent pneumococcal vaccines to a hepatitis B vaccine control (Eskola et al. [2001](#ref-Eskola2001)). The two heptavalent pneumococcal vaccines differed in their use of carrier protein. One was the same vaccine as in the Black et al. ([2000](#ref-Black2000)) study (PCV7CRM197), and the other was a conjugated to meningococcal outer membrane protein complex (PCV7MOMPC). The Eskola et al. ([2001](#ref-Eskola2001)) paper reported comparison of the PCV7CRM197 to the hepatitis B vaccine. The analogous comparison of the PCV7MOMPC was reported in a separate publication (Kilpi et al. [2003](#ref-Kilpi2003)). No head-to-head comparison of the two heptavalent vaccines was ever reported. The study methodology was identical between the two publications as they report different arms of the same study (Eskola et al. [2001](#ref-Eskola2001); Kilpi et al. [2003](#ref-Kilpi2003)).

The study was specifically designed to address the difficulties associated with estimating the effect of pneumococcal vaccination on AOM. A total of 2,497 children were enrolled between December 1995 and April 1997, of which 835 received the PCV7MOMPC vaccine and were therefore not reported in the Eskola et al. ([2001](#ref-Eskola2001)) paper. Children were followed until their last visit at 24 months of age. Of the enrolled children, 95.1% completed full follow-up time and there was no evidence of differential dropout. The study defined beforehand the criteria for what constituted AOM and employed a trained study nurse and physician at each study site. Children were seen at enrollment at two months of age, and periodically assessed thereafter at four, six, seven, twelve, thirteen and 24 months of age. If AOM was diagnosed as defined by the study criteria, myringotomy and aspiration of middle-ear fluid were performed and samples sent for culture. In this way, the study was able to deduce the causative otopathogen. Episodes of AOM were classified as all-cause AOM; culture-confirmed and otopathogen specific AOM; and AOM due to serotypes included in the vaccine. The statistical analysis was again conducted using the Andersen-Gill extension of the Cox proportional hazards model with robust variance estimates and efficacy was reported as . The results were most consistent with a 6% efficacy against all-cause AOM with 95% confidence limits of -4% and 16%. In this case the negative lower confidence limit indicates the data could be consistent with the possibility of a 4% increase in all-cause AOM, given the specified model.

The PCVCRM197 efficacy against culture-confirmed pneumococcal AOM was 35% (95%CI 21%-45%) and was 57% (95%CI 44%-67%) for the seven serotypes included in the vaccine. Similarly, the study demonstrated 57% (95%CI 27%-76%) efficacy against AOM caused by serotype 6A, which is considered a cross-reactive pneumococcal serotype. The study was also one of the first to demonstrate clinically relevant serotype replacement, showing a 33% (95%CI -1%-80%) increase in pneumococcal AOM caused by serotypes not included in the vaccine.

Children who completed the Eskola et al. ([2001](#ref-Eskola2001)) trial and were still living in the study area were invited for a follow-up interview when they were four to five years of age (Palmu et al. [2004](#ref-Palmu2004)). In the extended follow-up trial, the vaccine effectiveness against all tympanostomy tube placements was estimated to be 39% (95%CI 4%-61%). However, this was unblinded study following the unmasking of the original study and there was differential recruitment between the placebo and PCV7CRM197 arms. There was therefore a substantial risk of bias in the study.

The effect estimates for the PCV7MOMPC against culture-confirmed pneumococcal AOM was 25% (95%CI 11%-37%) and was 56% (95%CI 44%-66%) for the seven serotypes included in the vaccine (Kilpi et al. [2003](#ref-Kilpi2003)). However, unlike PCVCRM197, it did not seem to confer protection against cross-reactive serotypes. Interestingly, virtually no effect was seen on all-cause AOM with this vaccine preparation. The effect estimate was -1% (95%CI -12%-10%). These surprising results were not presented in the main text and no explanation was given in the discussion chapter of the paper.

In 2006, Prymula et al. ([2006](#ref-Prymula2006)) reported a randomized study of an eleven valent pneumococcal conjugate vaccine in 4,968 children recruited from paediatric centers in the Czech Republic and Slovakia (Prymula et al. [2006](#ref-Prymula2006)). A strict case definition of otitis media was used and all cases were reviewed by an otolaryngologist. If confirmed, a middle ear fluid sample was obtained by aspiration and sent for culturing. Statistical analysis was completed using Cox proportional hazards models and the Anderson-Gill extension for repeated events.

In 2003, the first paper from a cluster randomized controlled trial of PCV7CRM197 among the Navajo and White Mountain Apache infants was published (O’Brien et al. [2003](#ref-OBrien2003)). In 2008, a retrospective chart review of AOM visits among the participating children was published (O’Brien et al. [2008](#ref-OBrien2008)). The study population was defined as children who had adhered to the study protocol, i.e. a per-protocol analysis. From this population, 944 of the 4,476 eligible children were randomly sampled for chart review. The sample size was restricted for logistical reasons. A rough power analysis which assumed 1.5 years of follow-up time per chart and a baseline incidence of one AOM visit per person-year suggested that a sample of 1,000 children would give 80% power to detect a 15% reduction in the incidence of AOM visits. It is unclear why only 944 children were sampled, given that the power calculation assumed 1,000. Furthermore, it should be noted that the investigators performing the chart review were not blinded to vaccine allocation. This becomes significant when considering that the reviewers had significant leeway in deciding what constituted an AOM visit, and how to categorize the multitude of subjective subgroups considered in the study. Of the 944 children reviewed, only 803 were included for various reasons further limiting the study’s sample. A Poisson regression model was used to estimate the incidence rate ratio between the study arms, and sandwich variance estimates were used to account for the block-randomized design. No difference was found between the PCV7CRM197 arm and the control, with an estimated vaccine efficacy of -0.4% (95%CI -19.4%-15.6%). It is debatable whether this should be considered a randomized controlled trial in light of the methodological flaws discussed above. Even if the study were to be considered randomized, it is unclear how to interpret a study that does not even have 80% power to detect a difference twice as large as the the estimates presented by previous randomized controlled trials.

Table 2 Randomized controlled trials evaluating the efficacy of Pneumococcal conjugate vaccines on otitis media

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Vaccine | Enrollment period | Country | No. of children | Efficacy against Otitis media episodes |
| Black, 2000 & Fireman, 2003 | PCV7 (CRM197) | Oct 1995-Aug 1998 | United States | 37868 | 7.8% (5.4%-10.2%) |
| Dagan, 2001 | PCV9 (CRM197) | Unclear | Isreal | 264 | 17% (-2%-33%) |
| Eskola, 2001 | PCV7 (CRM197) | Dec 1995-Apr 1997 | Finland | 1662 | 6% (-4%-16%) |
| Kilpi, 2003 | PCV7 (MOMPC) | Dec 1995-Apr 1997 | Finland | 1666 | -1% (-12%-10% |
| Prymula, 2006 | PCV9 (HiD) | Oct 2000-Sep 2002 | Czech Republic & Slovakia | 4968 | 33.6% (20.8%-44.3% |
| O’Brien, 2008 | PCV7 (CRM197 | Apr 1997-Aug 2000 | United States | 856 | -0.4% (-19.4%-15.6% |

#### Observational studies

### The impact of pneumococcal conjugate vaccines on pneumonia

~ 2-3 pages - Present evidence of effect on all-cause pneumonia - VT vs. NVT serotypes - Serotype replacement (?) - Herd-effect in adults and non-vaccinated

(Kilpi et al. [2018](#ref-Kilpi2018))

### The impact of pneumococcal conjugate vaccines on Invasive pneumococcal disease

~ 4-6 pages <- largest amount of studies - Present evidence of effect on IPD and subgroups; meningitis, bacteremia etc. - VT vs. NVT - Serotype replacement - Herd-effect

## Cost-effectiveness in the context of pneumococcal conjugate vaccination

~ 3-4 pages - Present overview of literature review and critical analysis. - Recommendations of ISPOR and WHO presented, discuss importance of assumptions and methodology - Introduction to sub-chapters of lit. rev. - Explain how they will be tied in to ISPOR/WHO recommendations

### Measurement of effectiveness and choice of health outcomes

~ 1 page - Shortly explain what is meant by effectiveness and health outcomes - Tie in to ISPOR/WHO

#### Health outcomes considered

~ 2-3 pages - Describe what health outcomes were considered - Tie into actual disease burden known to be caused by pneumococcus

#### Effectiveness of pneumococcal conjugate vaccines

~ 3-4 pages - What effectiveness rationale is used, methods and rationale: critique - Carriage - AOM - Pneumonia - IPD

### Estimating resources and cost

~1 page - Shortly explain what resources and costs mean - Direct vs. indirect - Tie in to ISPOR/WHO

# Aims

The aims of the thesis were to estimate the impact of PHiD-CV10 on various facets of pneumococcal disease, associated healthcare burden, and cost:

1. The incidence of paediatric emergency department visits for otitis media with treatment failure (Paper I)
2. The incidence of otitis media visits to primary care (Paper II)
3. The incidence of outpatient antimicrobial prescriptions (Paper III)
4. The incidence of tymapnostomy tube procedures (Paper IV)
5. The incidence of hospitalizations for respiratory and invasive infections commonly associated with *Streptococcus pneumoniae* (Paper V)
6. Incidence of pneumococcal disease in all age-groups and cost-benefit analysis (Paper VI)

# Materials and methods

## Data collection and sources

During the study period from January 1, 2005 to December 31, 2017, data was collected from multiple whole population registries, and from a single hospital registry. All data was identifiable to individuals by government issued national identification numbers. Each individual receives only one number over the course of their lifetime, and the identification number is permanently retired at the time of death. The Icelandic Directorate of Health processed and anonymized all data from the various registries before releasing it to the study group. A study identifier was created based on the national identification number, which was then removed from the data as part of the anonymization process. The mapping key is kept by the Directorate of Health, and is not accessible to the study group. The study group linked the data from the various registries using both the study identifier and dates of events.

The data underlying this study is observational in nature, and its quality is enhanced by several factors. Not only are all medical records in Iceland stored electronically, but the same software, *Saga*, was used by all health care providers and institutions throughout the 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 classified using the Anatomical-Therapeutic-Chemical (ATC) classification system of the World Health Organization. Continuity between data systems enhanced the quality of results.

In the following sub-chapters, each registry providing study data is reviewed. Statistics Iceland provided data on immigration and emigration, demographic indices and salaries. Diagnostic data was obtained from Landspitali University Hospital’s patient registry and the Primary Care Registry of the Directorate of Health. Pneumococcal vaccination status was collected from the National Vaccine Registry (NVR) and augmented with information on privately purchased vaccine doses obtained from the National Drug Prescription Registry (NDPR). Data regarding antimicrobial prescriptions was also extracted from the NDPR. Finally, reimbursement data for outpatient otolaryngological procedures was obtained from Icelandic Health Insurance.

### Statistics Iceland

Statistics Iceland collects and maintains a large array of economical, social and demographic indices, and provides aggregate data at www.statice.is. For each calendar-year 2005-2017, the number of individuals living in Iceland was collected from Statistics Iceland, stratified by postal-code, gender and age in years. This data was used for the denominator in incidence calculations in all papers. The deciles of salary from 2005-2017 were obtained from Statistics Iceland and used to inform a sensitivity analysis on the cost-benefit of PHiD-CV10 ( [Paper VI](#paper6)). Costs were adjusted for inflation using the National Wage Index of Statistics Iceland. In addition to the aggregate data presented above, individual level information on the immigration and emigration of children zero to four years of age was obtained, anonymized and linked to the other study data.

### Landspitali University Hospital patient registry

Landspitali University Hospital is the sole tertiary hospital in Iceland, and includes Children’s Hospital Iceland – Iceland’s only pediatric hospital. It provides primary and secondary care for the capital area, approximately 65% of the Icelandic population, and tertiary care for the whole population. In 2017, the total number of non-psychiatric curative care hospital beds in Iceland was 732 (www.statice.is). Of those, 669 (91%) were at Landspitali University Hospital. Landspitali’s patient registry records 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 was extracted on all unplanned acute-care visits and hospital admissions with ICD-10 discharge diagnoses compatible with respiratory infections (see Table 3).

Table 3 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 4 were extracted the patient registry.

Table 4 NOMESCO Classification of Surgical Procedures codes used in the current study

|  |  |
| --- | --- |
| NCSP code | Description |
| EMSB00 | Excision of lesion of tonsil or adenoid |
| EMSB10 | Tonsillectomy |
| EMSB15 | Intracapsular destruction of tonsils |
| EMSB20 | Adenotonsillectomy |
| EMSB30 | Adenotomy |
| EMSB99 | Other excision on tonsils and adenoids |
| EMSW99 | Other operation on tonsil or adenoids |
| DCSA10 | Paracentesis of tympanic membrane |
| DCSA20 | Insertion of ventilating tube through tympanic membrane |
| DCSW00 | Removal of ventilating tube from tympanic membrane |

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

Several smaller independent data-sets pertaining to specific papers were extracted from the patient registry. These data-sets were not linked to the main study data.

In [paper I](#paper1), describing the impact of PHiD-CV10 on otitis media with treatment failure, information about all doses of ceftriaxone administered at the Children’s Hospital Iceland between January 2009 and December 2015 was extracted from the hospital’s medication administration system using the ATC code J01DD04. Any ICD-10 diagnostic code associated with a visit or hospital admission in which ceftriaxone was administered, was extracted from the patient registry. Importantly, this included all ICD-10 codes, not only those in Table 3. Also obtained for [paper I](#paper1) was the aggregate number of yearly visits to the pediatric emergency department of Children’s Hospital Iceland 2008-2015.

[Paper VI](#paper6) – a cost-benefit analysis of PHiD-CV10 introduction into the pediatric vaccination program, 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 5) were obtained for 22 different age-groups.

Table 5 The International Classification of Diseases, 10th revision subchapters used to define synthetic conrtrols

|  |  |
| --- | --- |
| 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 patient registry was used in [paper I](#paper1), [paper IV](#paper4), [paper V](#paper5) and [paper VI](#paper6).

### The Primary Care Registry

In the Icelandic healthcare system, primary care is provided by family medicine physicians at 69 neighborhood based centers (*Heilsugæsla*). All primary care centers use the same electronic medical record system, and the same diagnostic coding systems (NCSP, ICD-10) as Landspitali University Hospital and Children’s Hospital Iceland. The Directorate of Health maintains a registry on all primary care visits within the Icelandic healthcare system. From this registry, all physician visits with ICD-10 diagnostic codes compatible with respiratory tract infections were extracted for the period January 1, 2005 to December 31, 2015 (Table 3). From early 2016, extensive maintenance and restructuring of the registry has been ongoing, and no new data has been added since December 31, 2015.

Data from the Primary Care Registry was used in [paper II](#paper2), [paper III](#paper3), [paper IV](#paper4) and [paper VI](#paper6).

### 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 they are administered. This record is reviewed and updated regularly, and vaccinations given in other healthcare facilities 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.

Data from the NVR are used in all papers.

### 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 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 them to the NDPR. An important distinction must be made between a written prescription and a filled prescription. The NDPR receives information if and when a prescription is filled. It does not record information on written prescriptions that were never filled by the patient. Therefore, all prescriptions documented within the NDPR were paid for and received by the patient. Extensive validation and error testing have been performed by the Directorate of Health to ensure the robustness of the NDPR. Automated electronic submissions, coupled with tightly controlled processes by which pharmacies dispense drugs, has essentially excluded the possibility 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 6

Table 6 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 |

Data from the NDPR was used in [paper II](#paper2), [paper III](#paper3) and [paper IV](#paper4).

### Reimbursement database of Icelandic Health Insurance

The healthcare system in Iceland is a single-payer system with one government-run health insurance provider, under which all permanent citizens are covered. Most healthcare visits require a nominal out-of-pocket fee, with the rest of the visit covered by the insurance. There are exceptions to this – for example, visits by children under two years of age are completely 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. Data on 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 7

Table 7 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) |

Data from the reimbursement database was used in [paper IV](#paper4).

## Impact on otitis media with treatment failure (Paper I)

The objective of Paper I 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 a proxy for treatment failure. Ceftriaxone use for other diagnoses and in older children was used as a comparator.

All children under eighteen years of age who visited Children’s Hospital Iceland between January 1, 2008 and December 31, 2015 were included. 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), as previously described in 4.1.1.

Data was extracted from Landspitali University Hospital’s [patient registry](patientregistry). A visit was included in the study if an ICD-10 code of Nonsuppurative otitis media (H65) or Suppurative and unspecified otitis media (H66) was documented in the medical record, or if a child received one or more doses of ceftriaxone. All administered doses of ceftriaxone were systematically extracted from the hospital’s medication administration system using the ATC code J01DD04. The ICD-10 diagnoses associated with the ceftriaxone administrations were then obtained from the patient registry. The total number of visits per calendar year and month regardless of diagnosis was provided by the hospital.

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 (OM) 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; otitis media, pneumonia and other , based on the associated ICD-10 diagnostic codes. Ceftriaxone was considered to be due to OM, if an ICD-10 code of Nonsuppurative otitis media (H65) or Suppurative and unspecified otitis media (H66) were recorded. It was considered due to pneumonia if ICD-10 codes Bacterial pneumonia, not elsewhere classified (J15) or Pneumonia, unspecified organism (J18) were recorded. Visits associated with ceftriaxone administration that did not fall into either of the above categories were classified together as “Other”.

The number of ceftriaxone treatment episodes per diagnostic group was 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 number of person-years accrued by 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 either a decrease in the number of OM visits or a decrease in the use of ceftriaxone. To evaluate this, the incidence risk of ceftriaxone treated OM episodes was calculated per 1,000 OM episodes presenting to Children’s Hospital Iceland for both 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 () were calculated between the pre- and post-vaccine periods, and were estimated independently for each age-strata. The stratum-specific estimates were combined (when appropriate) using the Mantel-Haenszel method and 95% confidence intervals (CI) calculated using the delta procedure (Kirkwood and Sterne [2003](#ref-Kirkwood2003)). The Mantel-Haenszel estimate of the incidence rate ratio () is the weighted mean of the in each stratum. The null-hypothesis that was tested by calculating the Mantel-Haenszel test statistic, from which the *P*-value was derived.

Combining stratum-specific estimates is appropriate when the exposure-outcome association is the same in each of the strata, i.e. The test of heterogeneity assesses whether the data is congruent with the null hypothesis which predicts 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 are presented.

## Impact on primary care visits for otitis media (Paper II)

The objective of Paper II was to evaluate the impact of PHiD-CV10 on the incidence of otitis media in Icelandic children. Paper II 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 occurring within 30 days of a previously documented visit by the same child were excluded from the main analysis.

Data was obtained from the [Primary Care Registry](primarycareregistry) of the Icelandic Directorate of Health. In addition to the diagnosis of otitis media, the data 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 derived from the national identification numbers issued individuals by the government. Those 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 (Harrell, Jr. [2018](#ref-R-rms)) and epiR (Stevenson et al. [2017](#ref-R-epiR)).

Crude IR of OM visits were calculated per 100 person-years at risk for each birth cohort, stratified by four-month age brackets. Following each OM visit, there was a 30 day period in which it was impossible for a visit to be recorded due to the study design. To avoid misclassifying this period, the individual time at-risk was carefully constructed to exclude the 30 days following each recorded otitis media visit. Crude IRR 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 cumulatively experienced 0-12 episodes of OM 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 OM 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 ([1989](#ref-Lin1989)) sandwich variance estimates were used. From this model, the hazard ratio (HR) of OM visits between each birth-cohort and the last vaccine non-eligible cohort was calculated. The impact of PHiD-CV10 on OM visits was defined as 1 – ( between the last vaccine-eligible birth cohort and the last vaccine non-eligible cohort) \* 100%.

The HR between VNEC and VEC was calculated for each number of previous OM 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 [2007b](#ref-Cook2007)). To determine the number of OM episodes prevented in the first five years of the vaccination, each child’s follow-up time was multiplied by the Nelson-Aalen 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.

## Impact on outpatient antimicrobial prescriptions (Paper III)

The objective of Paper III was to estimate the impact of PHiD-CV10 on outpatient antimicrobial prescriptions among children in Iceland. Paper III is a whole population observational cohort study of antimicrobial prescriptions in 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 immigrated to Iceland after birth were excluded. Follow-up time was censored on death, emigration, or the end of the study period (December 31, 2016). Because of shortened 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, as previously described in 4.1.5. Data on primary care visits for respiratory tract infections was collected from the Primary Care Registry using the ICD-10 codes in Table 3. Prescriptions filled within three days of a documented physician visit by the same child were linked. Because data from the Primary Care Registry was only available through December 31, 2015, the portion of the analysis pertaining to the linked data was restricted to that date. Demographic population data was acquired from Statistics Iceland (<https://www.statice.is/>).

Data was analysed both descriptively and from a cohort perspective. Descriptive analysis included all Icelandic children under three years of age during the study period. 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)). Based on a previously published study, all filled antimicrobial prescriptions were classified into one of six categories; first and second line penicillins, first and second generation macrolides, cephalosporins, and finally, 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 five diagnostic-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 either individually, or grouped by vaccine eligibility. In the individual birth-cohort analysis, each birth-cohort was compared to the last vaccine non-eligible cohort, i.e. the 2010 birth-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. Ninety-five percent confidence intervals were 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. The ratio between VNEC and VEC was then calculated for each of these categories. 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 (HR) of antimicrobial prescription between the study birth-cohorts, which were included in the model as a categorical variable. Age was accounted for by defining it as the model’s underlying measurement of time. The model was stratified by gender to allow for independent baseline hazards. The number of previous antimicrobial prescriptions was included in the model, and its effect allowed to be non-linear by means of restricted cubic splines (Cook and Lawless [2007a](#ref-Cook2007a)). Lin and Wei ([1989](#ref-Lin1989)) robust sandwich variance estimates were applied to account for the correlation between 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 last vaccine non-eligible cohort) \* 100%. The impact on each successive prescription was also estimated. Finally, the generalized Nelson-Aalen estimate of the mean number of antimicrobial prescriptions for each gender and vaccine-cohort was calculated (Cook and Lawless [2007b](#ref-Cook2007)). To estimate the absolute number of prevented antimicrobial prescriptions during the first seven years of the intervention, the following formula was utilized; first, the expected number of prescriptions per child was added together by multiplying each child’s follow-up time with the VNEC estimate of the mean number of prescriptions per child. Next, the expected number of prescriptions per child was estimated using the VEC estimate of the mean. Finally, the absolute number prevented was calculated by subtracting the VEC total from the VNEC total. The absolute rate reduction was then calculated by dividing the absolute number prevented, with the number of person-years at-risk in the VEC.

A sub-analysis was performed to estimate the vaccine impact against OM-associated antimicrobial prescriptions. The above described regression methodology was applied to those antimicrobial prescriptions that were linked to a primary care physician visit resulting in a diagnosis of AOM.

## Impact on tympanostomy tube procedures (Paper IV)

The objective of Paper IV was to estimate the impact of PHiD-CV10 on the incidence of tympanostomy tube placements (TTP) among children in Iceland. Paper IV is an individual level observational cohort study of all outpatient TTP procedures in Iceland. The study period is from January 1, 2005 to December 31, 2016. Eleven consecutive birth-cohorts 2005-2015, were followed from birth until five years of age, or end of the study period. Children who immigrated to Iceland after birth were excluded from the analysis. Those children who emigrated were censored from the study on the date of emigration. This allowed for accurate person-year at risk calculations.

Data on outpatient TTP was obtained from the Icelandic Health Insurance reimbursement database, using reimbursement codes compatible with TTP (Table 7). Information regarding inpatient TTP was extracted from Landspitali University Hospital’s patient registry using NCSP codes (Table 4). These data were linked with data on primary care and emergency department visits for otitis media (OM). Data on primary care visits was obtained from the Primary Care Registry, and information regarding emergency department visits was extracted from the hospital’s patient registry. Primary care data was only available until December 31, 2015. A visit was considered to be due to OM if an ICD-10 diagnostic code of Non-suppurative otitis media (H65), Suppurative otitis media (H66), Mastoiditis (H70) or Perforation of tympanic membrane (H72) was recorded. A repeat visit within 30 days was assumed to represent the same episode, and was excluded. Data regarding filled antimicrobial prescriptions was extracted from the National Drug Prescription Registry using ATC code J01 (antibacterials for systemic use).

Cohorts were defined based on year of birth or vaccine eligibility. Birth-cohorts 2005-2010 were classified 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 (Harrell, Jr. [2018](#ref-R-rms)) and epiR (Stevenson et al. [2017](#ref-R-epiR)). Crude incidence rates (IR) of TTP per 100 person-years were calculated for each birth-cohort in 6-month age-groups. Crude incidence rate ratios (IRR) between the VEC and VNEC were calculated, and 95% confidence intervals estimated assuming Poisson variance. The Kaplan-Meier product limit estimate was used to calculate the cumulative proportion of TTP procedures for each birth-cohort, and confidence intervals calculated using the log delta method.

The comparison of the risk of TTP between birth-cohorts was adjusted for two confounders; the number of prior OM diagnoses and the number of prior antimicrobial prescriptions. Among children who had undergone TTP and had the full five year follow-up time, the distribution in the number of previous visits and prescriptions was compared between VNEC and VEC using the test of independence. When adjusting for the number of previous visits, four years was considered full follow-up time due to restricted data. If a significant difference was detected, the risk ratio and absolute risk difference between VEC and VNEC were calculated, stratified by the prior number of visits or antimicrobial prescriptions. Confidence intervals were estimated with the of independence.

A Cox regression model was constructed to accurately account for the influence of age and censored follow-up time. Three separate models were estimated. The first did not adjust for prior OM visits or antimicrobial prescriptions, while the later two did. The Cox regression model using the number of previous OM visits was censored at December 31, 2015 due to restricted data. Each Cox model was stratified by gender. Correlation between repeated observations of the same child was adjusted, using Lin and Wei ([1989](#ref-Lin1989)) sandwich variance estimates. The hazard ratio (HR) of TTP was estimated between each of the study’s birth-cohorts. The vaccine impact of PHiD-CV against TTP was estimated as 1 – (the hazard ratio between the last vaccine eligible cohort and the last vaccine non-eligible cohort) \* 100%.

## Impact on respiratory associated hospitalizations (Paper V)

The objective of Paper V was to estimate the impact of PHiD-CV10 on the incidence of pediatric hospitalizations due to diseases commonly caused by *Streptococcus pneumonae*. Paper V is a single-center, individual-level, observational cohort study of pediatric hospitalizations. Eleven consecutive Icelandic birth-cohorts 2005-2015 were followed from birth until three years of age. Immigration and emigration data obtained from Statistics Iceland was used to exclude children who had immigrated to Iceland after birth. Included were all hospital admissions to the Children’s Hospital Iceland January 1st, 2005 to December 31st, 2016. The Children’s Hospital Iceland is the primary pediatric hospital for approximately 90% of Iceland’s population (www.statice.is), and serves as a secondary and tertiary pediatric hospital for the entire country. Data on admissions was collected from Landspitali University Hospital’s patient registry. Microbiological data was extracted from a database maintained by the Department of Clinical Microbiology at Landspitali University Hospital.

Seven diagnostic groups were defined in this paper. Five of these represent diseases commonly caused by *Streptococcus pneumoniae*; Invasive pneumococcal disease (IPD), meningitis, sepsis, pneumonia and otitis media. The remaining two groups, upper respiratory tract infections (URTI) and other lower respiratory tract infections (LRTI), were included as comparators. Hospitalization was categorized in a diagnostic group, if the relevant ICD-10 diagnostic code was recorded on the discharge chart, or if the admission was associated with microbiologically-confirmed IPD. Admissions with ICD-10 discharge diagnoses compatible with meningitis (G00) were grouped as meningitis. Those with A40 or A41 diagnoses were grouped as sepsis; with J09-J18, as pneumonia; J20-J22 as LRTI; H65, H66, H70 and H72 as OM; and J01-J06 as URTI (Table 8). A hospitalization was considered to be due to IPD if associated with culture or PCR confirmed *Streptococcus pneumoniae* sampled from joint fluid, bone, cerebrospinal fluid or blood, regardless of ICD-10 discharge diagnosis.

Table 8 Definitions of the Paper V’s diagnostic groupings

|  |  |  |
| --- | --- | --- |
| Diagnostic group | Abbreviation | Definition |
| Meningitis | - | ICD-10 discharge diagnosis of G00 |
| Sepsis | - | ICD-10 discharge diagnosis of A41 or A42 |
| Pneumonia | - | ICD-10 discharge diagnosis of J09-J18 |
| Otitis media and complications | OM | ICD-10 discharge diagnosis of H65, H66, H70 or H72 |
| Acute upper respiratory tract infections | URTI | ICD-10 discharge diagnosis of J00-J06 |
| Acute lower respiratory tract infections | LRTI | ICD-10 discharge diagnosis of J20-J22 |
| Invasive pneumococcal disease | IPD | Microbiologically confirmed pneumococcal infection from normally sterile site, regardless of ICD-10 diagnosis |

Birth-cohorts were compared either individually, or grouped by vaccine eligibility. In the individual birth-cohort analysis, each birth-cohort was compared to the last vaccine non-eligible cohort, i.e. the 2010 birth-cohort. Birth-cohorts 2011–2015 were grouped as vaccine-eligible cohorts (VEC), and birth-cohorts 2005–2010 as vaccine non-eligible cohorts (VNEC). 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)).

Mean age at hospitalization was calculated for each birth-cohort and diagnostic group. Analysis of variance was used to test whether significant difference existed between cohorts. If an overall difference was identified, the analysis was followed by Tukey’s honest significant difference procedure. The median hospital length of stay was calculated for each diagnostic group, and compared between cohorts using the Wilcoxon rank sum test. Crude incidence rates () of hospital admissions were calculated for each birth-cohort, diagnostic group and age group, and incidence rate ratios () were calculated between the VNEC and VEC assuming Poisson variance. The proportion of hospitalizations which led to admission to the intensive care unit (ICU) was calculated by birth-cohort and diagnostic group.

The Kaplan-Meier product limit estimator was used to calculate both event-free survival, as well as the event-free survival difference of the VNEC compared to the VEC for each of the diagnostic groups. Subsequent hospitalizations of the same child with the same discharge diagnosis were excluded from this portion of the analysis. Follow-up time was censored upon emigration or death. Cox regression was used to estimate the hazard ratio of admission between the VNEC and VEC. To clarify whether potential differences between VNEC and VEC were likely to be due to direct effects of the vaccine, the Cox regression was repeated for two restricted age-ranges; 0-90 days of age and 90 days and older. A sensitivity analysis of potential unmeasured confounding of the hazard ratio was calculated using E-values (VanderWeele and Ding [2017](#ref-VanderWeele2017)). An E-value represents the minimum association an unmeasured confounder would need to have with both the exposure and the outcome, to completely explain away the observed association.

## Impact and cost-benefit analysis (Paper VI)

The objective of Paper VI was estimate the impact of PHiD-CV10 on pneumonia and invasive pneumococcal disease (IPD) hospitalizations in all age-groups, and calculate the cost-benefit of PHiD-CV10 introduction. Paper VI is a cost-benefit analysis of PHiD-CV10 based on whole population observational data. The study period is from January 1, 2005 to December 31, 2017. The study population included all permanent Icelandic citizens. Cost-benefit was estimated for three disease categories; invasive pneumococcal disease (IPD), pneumonia and otitis media, and was stratified by age-groups; 0-4 years of age, 5-19, 20-39, 40-64, 65-79 and 80+. The data was analysed as a time-series, and incorporated synthetic controls.

Data were extracted from several registries. The impact on otitis media was estimated among children 0-19 years of age. Primary care visits with ICD-10 diagnoses compatible with otitis media (H65, H66, H70, H72) were extracted from the Primary Care Registry. The observation period was restricted to 2005-2015, as the Primary Care Registry has not been updated for 2016 and 2017. The impact on hospitalized pneumonia and IPD was estimated for all age-groups and for the whole study period. Hospitalizations with ICD-10 diagnoses compatible with pneumonia (J09-J18) were obtained from Landspitali University Hospital’s patient registry. Microbiological data were extracted from a database maintained by the Department of Clinical Microbiology at Landspitali University Hospital and linked to the patient registry. A hospitalization was considered to be due to IPD if associated with culture or PCR confirmed *Streptococcus pneumoniae* sampled from joint fluid, bone, cerebrospinal fluid or blood, regardless of ICD-10 discharge diagnosis. The aggregate number of visits and hospitalizations per calendar-month for diagnoses unrelated to *Streptococcus pneumoniae* infections were also extracted from both registries and used as synthetic controls (Table 5).

The cost-benefit analysis was completed in two separate steps. First, the impact of PHiD-CV10 introduction into the pediatric vaccination program in Iceland was estimated. This was accomplished using a previously published Bayesian time-series methodology (Bruhn et al. [2017](#ref-Bruhn2017); Shioda et al. [2018](#ref-Shioda2018a)). The pre-vaccine period was defined as January 1, 2005 to December 31, 2010, and the post-vaccine period as April 1, 2013 to December 31, 2017. For each disease category and age-group, four models of PHiD-CV10 impact were estimated. All were Bayesian Poisson models with observation specific random intercepts to account for over-dispersion (Dvorzak and Wagner [2016](#ref-R-pogit)). Each model utilized the pre-vaccine period to predict the monthly occurrence of the outcome of interest in the post-vaccine period, had the vaccination not occurred.

The simplest model was a time-series without an offset term. Calender-month effects were accounted for using dummy variables. The time-series model used the pre-vaccine period to estimate the trend. It predicted the monthly number of cases of the disease category, assuming the pre-vaccine trend would have continued if the vaccination had not occurred. A second, similar time-series model was also estimated, but included an offset term of all non-respiratory visits. This model used the pre-vaccine period to estimate the relationship between the outcome of interest and all non-respiratory visits. It also predicted the occurrence in the post-vaccine period assuming the relationship would not have changed, had the vaccination not occurred. The third model included synthetic controls as covariates and used Bayesian variable selection to choose which of them to include (Bruhn et al. [2017](#ref-Bruhn2017)). The prior for each synthetic control was set as a Dirac spike with a point-mass at zero. The pre-vaccine period was used to estimate the relationship between the synthetic controls and the outcome of interest, and to select the optimal controls. This relationship was used to predict the trend in the post-vaccine period, had the vaccination not occurred. Finally, a two-step model was fitted, using a seasonal and trend decomposition (STL) and principal component analysis (PCA) (Shioda et al. [2018](#ref-Shioda2018a)). STL was used to extract a smoothed trend for each of the synthetic controls. PCA was then used to extract the first principal component, which was used as a covariate in the final prediction model.

Leave-one-out cross-validation (LOOCV) was used to calibrate the models, using data from the pre-vaccine period. The LOOCV was also used to calculate the average point-wise likelihood for each model, diagnostic category and age-group. The average point-wise likelihoods were used as weights in a Bayesian model stacking procedure, which produced the final stacked model used in the analysis.

# Results

The results of papers I-VI are summarized in their respective subchapters. Because data was collected over a four year period from 2013-2017, and the papers that form this thesis were written and published at different times, the study period and population described in each paper varies slightly. They differ however only marginally from the final data summary described below.

When data from all registries are taken together, individual level information was available for 372,641 Icelandic citizens, of which 183,233 were female and 181,048 were male. Gender was unknown for 8,360 individuals. The full date of birth was known for 363,456 and the birth-year was available for the rest. The median birth-year for the whole study population was 1979 (IQR 1958-1997). Death was registered for 12,308 individuals during the study period.

### Statistics Iceland

Statistics Iceland provided data on the immigration and emigration of all Icelandic children zero to four years of age from 2005-2017. Of the 57,695 Icelandic children born 2005 or later, 5,577 moved to or from the country 6,847 times. The proportion of children in each birth-cohort who moved at least once before five years of age, was consistently 9%-12% of those birth-cohorts who had full follow-up time (birth-cohorts 2005-2012).

### Landspitali University Hospital patient registry

All visits and hospitalizations with ICD-10 diagnostic codes compatible with respiratory infections (Table 3) and procedural codes compatible with tympanostomy tube procedures (Table 4), were extracted from Landspitali’s patient registry. The number of visits and hospitalizations with each of the study’s ICD-10 diagnoses recorded as the first diagnosis, are shown in Table 9.

Table 9 Number of visits or hospitalizations with International Classification of Diseases, 10th revision codes used in the current study as the primary diagnosis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ICD-10 code | Disease | Hospital visits | Hospitalizations | Primary care visits |
| A40 | Streptococcal sepsis | 37 | 135 | 68 |
| A41 | Other sepsis | 370 | 777 | 279 |
| A48 | Other bacterial diseases, not elsewhere classified | 5 | 28 | 10 |
| A49 | Bacterial infection of unspecified site | 123 | 26 | 1,861 |
| B00 | Herpesviral [herpes simplex] infections | 497 | 22 | 2,176 |
| B08 | Other viral infections characterized by skin and mucous membrane lesions, not elsewhere classified | 76 | 1 | 655 |
| B33 | Other viral diseases, not elsewhere classified | 32 | 4 | 106 |
| B34 | Viral infection of unspecified site | 25,601 | 528 | 329,179 |
| B95 | Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere | 12 | 4 | 40 |
| B96 | Other bacterial agents as the cause of diseases classified elsewhere | 5 | 7 | 29 |
| G00 | Bacterial meningitis,not elsewhere classified | 79 | 60 | 3 |
| H65 | Nonsuppurative otitis media | 2,803 | 75 | 38,585 |
| H66 | Suppurative and unspecified otitis media | 11,647 | 244 | 160,086 |
| H70 | Mastoiditis and related conditions | 164 | 86 | 259 |
| H72 | Perforation of tympanic membrane | 1,270 | 233 | 1,947 |
| H73 | Other disorders of tympanic membrane | 67 | 3 | 727 |
| J00 | Acute nasopharyngitis [common cold] | 3,525 | 49 | 124,984 |
| J01 | Acute sinusitis | 4,625 | 113 | 152,076 |
| J02 | Acute pharyngitis | 1,869 | 44 | 124,874 |
| J03 | Acute tonsillitis | 5,019 | 213 | 106,491 |
| J04 | Acute laryngitis and tracheitis | 983 | 38 | 19,288 |
| J05 | Acute obstructive laryngitis [croup] and epiglottitis | 2,738 | 40 | 3,148 |
| J06 | Acute upper respiratory infections of multiple and unspecified sites | 3,649 | 94 | 110,236 |
| J09 | Influenza due to certain identified influenza viruses | 250 | 185 | 9 |
| J10 | Influenza due to other identified influenza virus | 282 | 151 | 699 |
| J11 | Influenza due to unidentified influenza virus | 1,003 | 77 | 34,949 |
| J12 | Viral pneumonia, not elsewhere classified | 206 | 189 | 189 |
| J13 | Pneumonia due to Streptococcus pneumoniae | 129 | 265 | 80 |
| J14 | Pneumonia due to Hemophilus influenzae | 18 | 44 | 34 |
| J15 | Bacterial pneumonia, not elsewhere classified | 2,489 | 1,129 | 1,870 |
| J16 | Pneumonia due to other infectious organisms, not elsewhere classified | 60 | 37 | 62 |
| J17 | Pneumonia in diseases classified elsewhere | 17 | 15 | 38 |
| J18 | Pneumonia, unspecified organism | 8,576 | 4,501 | 66,232 |
| J20 | Acute bronchitis | 2,431 | 297 | 148,963 |
| J21 | Acute bronchiolitis | 2,874 | 707 | 6,178 |
| J22 | Unspecified acute lower respiratory infection | 356 | 55 | 9,425 |
| J32 | Chronic sinusitis | 3,298 | 405 | 52,899 |
| J36 | Peritonsillar abscess | 1,095 | 254 | 1,239 |
| J40 | Bronchitis, not specified as acute or chronic | 893 | 49 | 77,272 |
| J85 | Abscess of lung and mediastinum | 98 | 41 | 24 |
| J86 | Pyothorax | 20 | 62 | 48 |
| J90 | Pleural effusion, not elsewhere classified | 560 | 409 | 599 |
| N30 | Cystitis | 6,112 | 568 | 133,560 |
| N39 | Other disorders of urinary system | 12,901 | 2,868 | 36,154 |
| R05 | Cough | 2,471 | 11 | 83,948 |
| R50 | Fever of other and unknown origin | 3,433 | 557 | 27,121 |

A total of 169,585 records (of 74,740 individuals) were available, of which 135,841 (64,090) were visits to outpatient clinics or emergency departments and 33,744 (20,318) were hospital admissions. The most visits of a single individual was 170 and the most admissions, 31. The number of study procedures performed at Landspitali University Hospital is shown in Table 10.

Table 10 Number of study NOMESCO Classification of Surgical Procedures performed in the current study

|  |  |  |
| --- | --- | --- |
| NCSP code | Description | Number of procedures |
| EMSB00 | Excision of lesion of tonsil or adenoid | 1 |
| EMSB10 | Tonsillectomy | 88 |
| EMSB15 | Intracapsular destruction of tonsils | 2 |
| EMSB20 | Adenotonsillectomy | 101 |
| EMSB30 | Adenotomy | 170 |
| EMSB99 | Other excision on tonsils and adenoids | 2 |
| EMSW99 | Other operation on tonsil or adenoids | 1 |
| DCSA10 | Paracentesis of tympanic membrane | 289 |
| DCSA20 | Insertion of ventilating tube through tympanic membrane | 340 |
| DCSW00 | Removal of ventilating tube from tympanic membrane | 0 |

The age distribution of visits and hospital admissions are shown in Figure 1. Though children and young adults comprise most of the visits due to study diagnoses, older adults make up the largest number of hospitalizations.

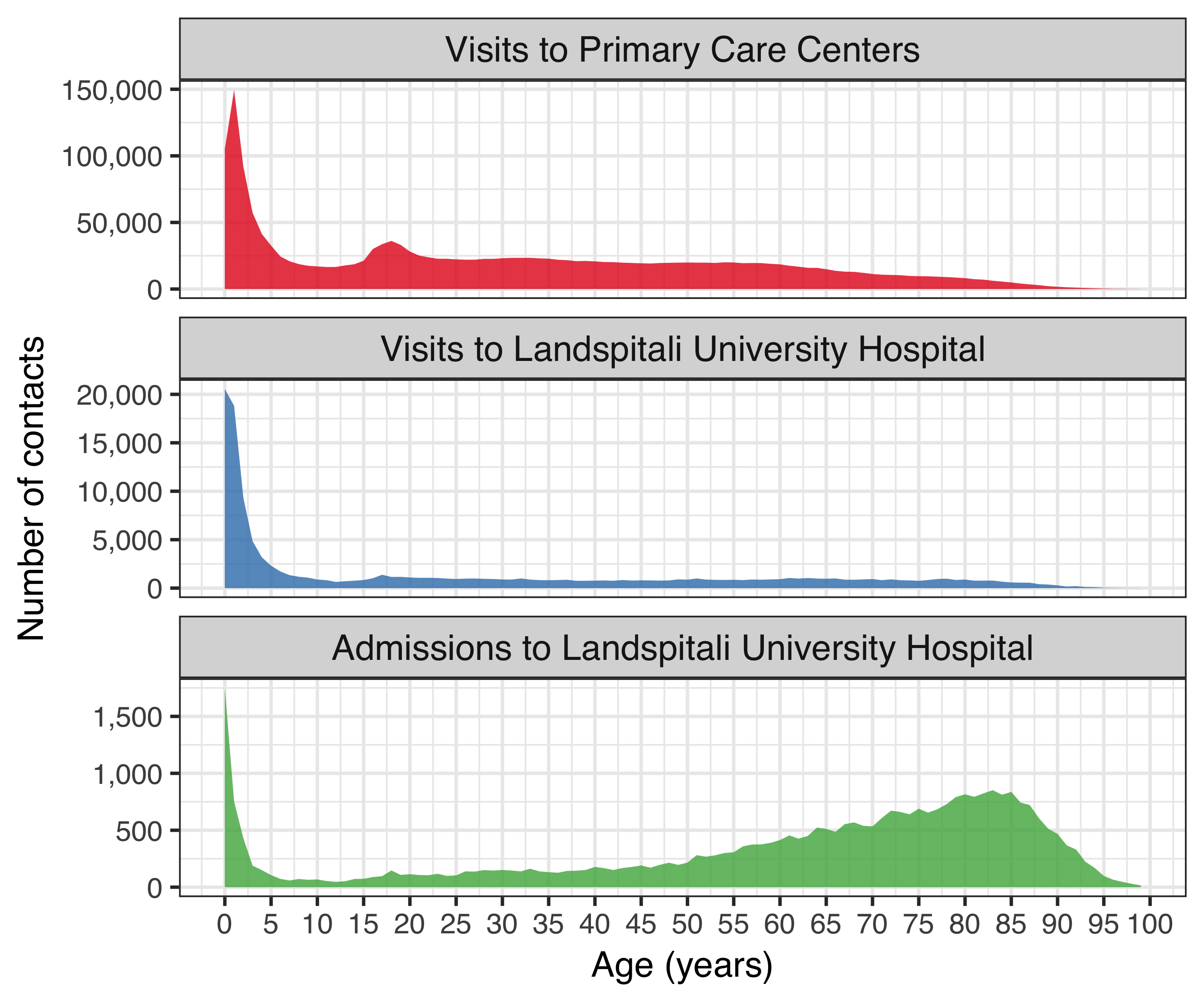


Figure 1 Total number of contacts to Landspitali University Hospital and Primary Care Centers

### The Primary Care Registry

The Primary Care Registry recorded all primary care health contacts for the period 2005-2015. All physician contacts associated with the diagnostic codes listed in Table 3 were extracted for the given period. A total of 1,963,439 separate contacts were recorded between 298,307 individual patients and 1,266 different physicians. The movst visits for a single individual was 212. The distribution in the number of contacts by age can be seen in Figure 1.

### The National Vaccine Registry

The National Vaccine Registry recorded all administered vaccine doses for the period 2005-2017. All recorded pneumococcal vaccine doses were extracted. A total of 110,712 doses of pneumococcal vaccines were administered to 51,601 individuals during the study period. The monthly number of administered doses per age-group and vaccine is shown in Figure 2.

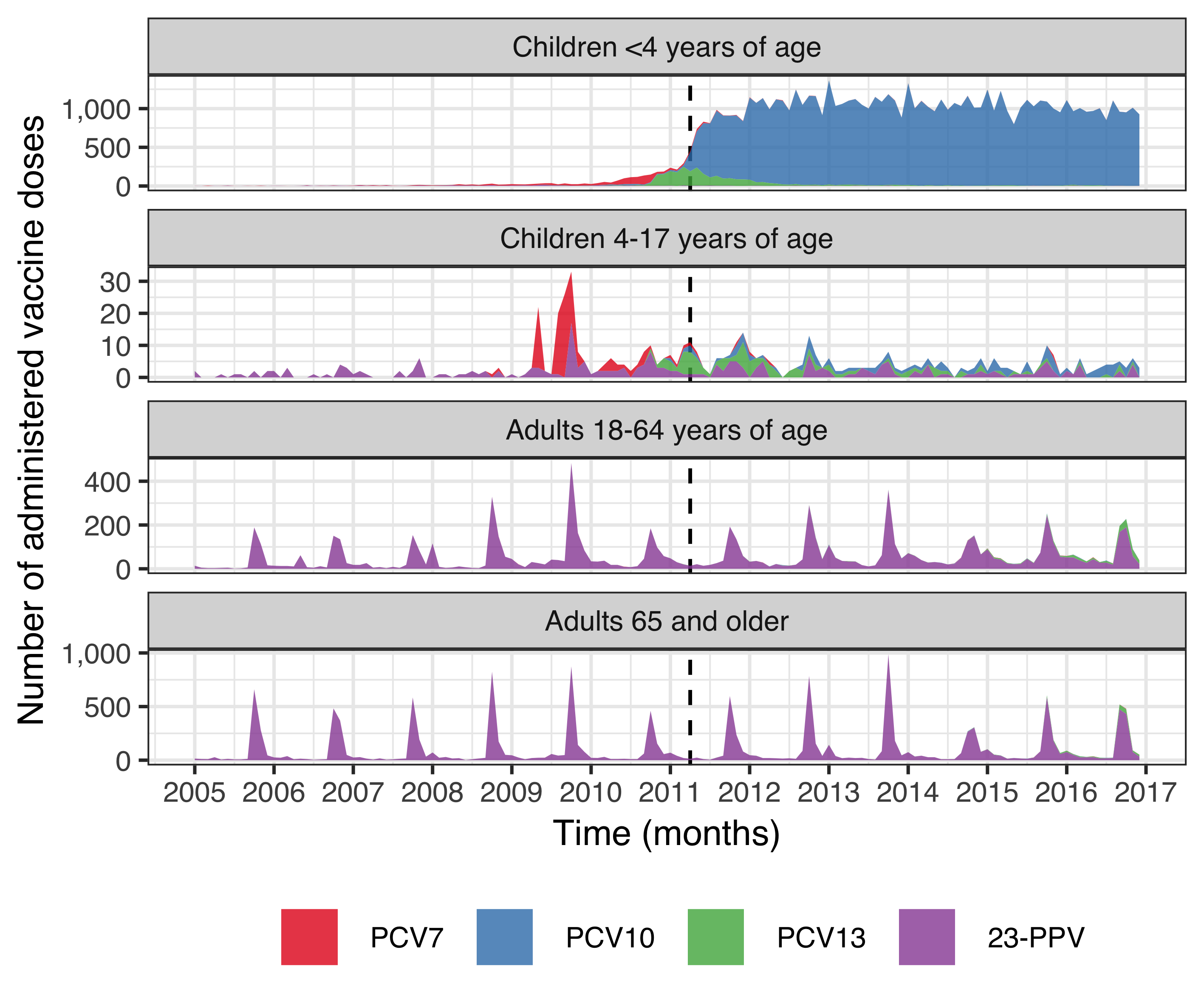


Figure 2 Monthly number of administered pneumococcal vaccine doses by type and age-group

Table 11 shows the number of children in each birth-cohort who had received zero, one, two, and three doses of a pneumococcal conjugate vaccine by four years of age. Children who moved to or from the country before four years of age, were excluded from the table.

Table 11 The number of children in each birth-cohort who has received from zero to three pneumococcal conjugate vaccine doses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Birth-cohort | Zero doses | One dose | Two doses | Three doses |
| 2005 | 4,207 | 10 | 5 | 4 |
| 2006 | 4,278 | 26 | 8 | 3 |
| 2007 | 4,345 | 51 | 18 | 13 |
| 2008 | 4,348 | 140 | 62 | 37 |
| 2009 | 4,292 | 166 | 237 | 87 |
| 2010 | 3,660 | 158 | 336 | 549 |
| 2011 | 260 | 44 | 144 | 3,976 |
| 2012 | 197 | 45 | 154 | 4,059 |
| 2013 | 165 | 41 | 123 | 3,927 |
| 2014 | 131 | 49 | 196 | 3,956 |
| 2015 | 81 | 40 | 442 | 3,404 |

Some children in vaccine non-eligible cohorts received one, two or three doses of pneumococcal conjugate vaccines before four years of age. This generally occured at an older age than children in the vaccine eligible cohorts Figure 3.

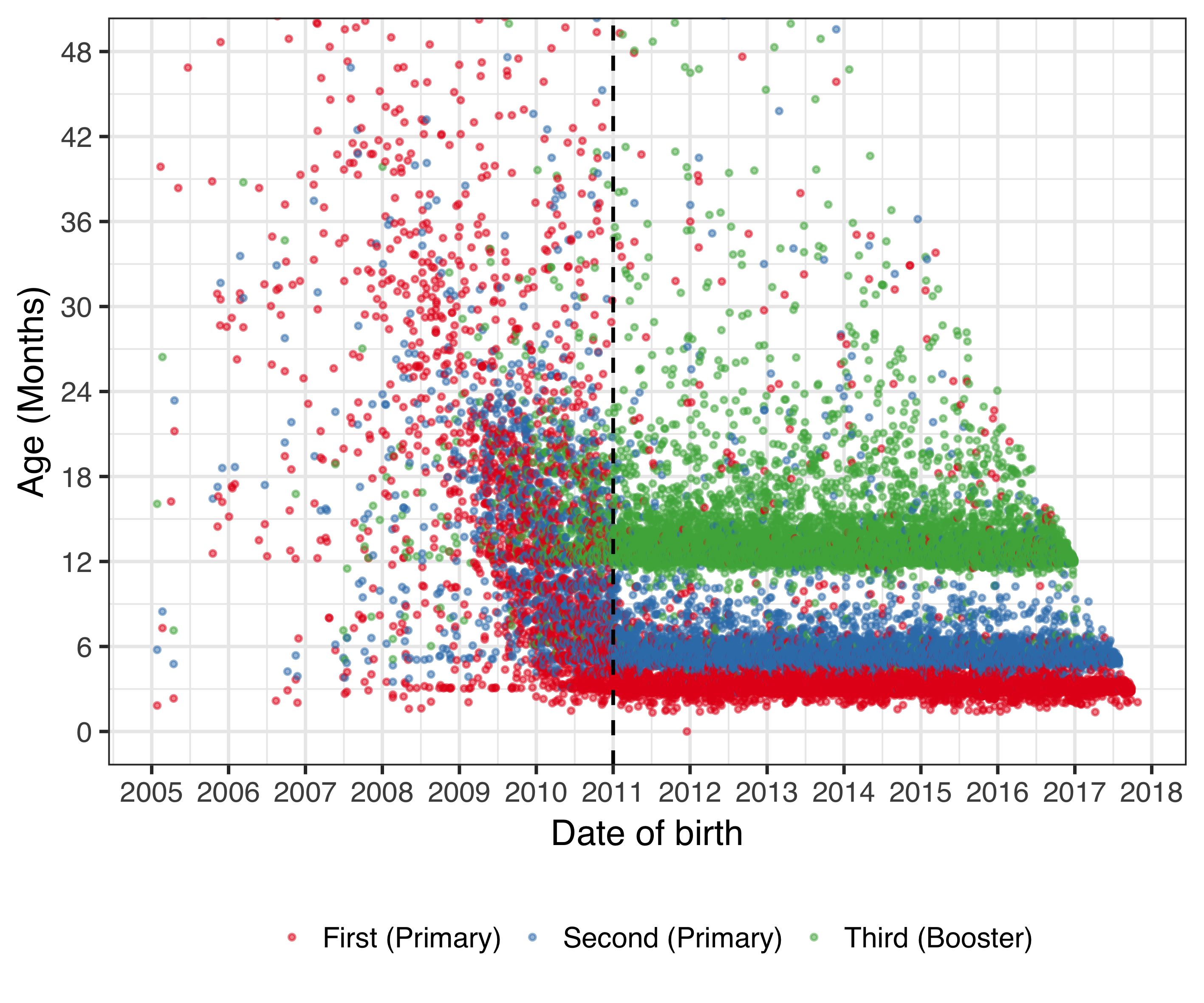


Figure 3 Age at the time of administered pneumococcal vaccine dose by birth date

### The National Drug Prescription Registry

The National Drug Prescription Registry (NDPR) recorded all filled prescriptions from 2005-2017. From this registry, all antibacterials for systemic use (J01), vaccines (J07), opthalmologicals (S01) and otologicals (S02) were extracted. A total of 4,020,624 prescriptions were recorded among 360,560 individuals. The number of prescriptions by therapeutic subgroup of the ATC classification system is shown in Table 12. The highest number of antimicrobial prescriptions filled by a single individual was 336 during the study period.

Table 12 Number of prescriptions by Anatomical Therapeutic Chemical codes used in the current study

|  |  |  |
| --- | --- | --- |
| ATC chemical subgroup code | Description | No of prescriptions |
| J01A | Tetracyclines | 357,498 |
| J01B | Amphenicols | 0 |
| J01C | Beta-lactam antibacterials, penicillins | 1,720,661 |
| J01D | Other beta-lactam antibacterials | 106,757 |
| J01E | Sulfonamides and trimethoprim | 168,045 |
| J01F | Macrolides, lincosamides and streptogramins | 344,098 |
| J01G | Aminoglycoside antibacterials | 71 |
| J01M | Quinolone antibacterials | 135,864 |
| J01R | Combinations of antibacterials | 0 |
| J01X | Other antibacterials | 96,318 |
| J07A | Bacterial vaccines | 9,687 |
| J07B | Viral vaccines | 16,703 |
| J07C | Bacterial and viral vaccines | 496 |
| J07X | Other vaccines | 0 |
| S01A | Anti-infective opthalmologicals | 287,904 |
| S02A | Anti-infective otologicals | 1 |
| S01C | Anti-inflammatory agents and anti-infectives opthalmologicals | 40,315 |
| S02C | Anti-inflammatory agents and anti-infectives otologicals | 25,218 |

The distribution of antimicrobial prescriptions by age is shown in Figure 4.

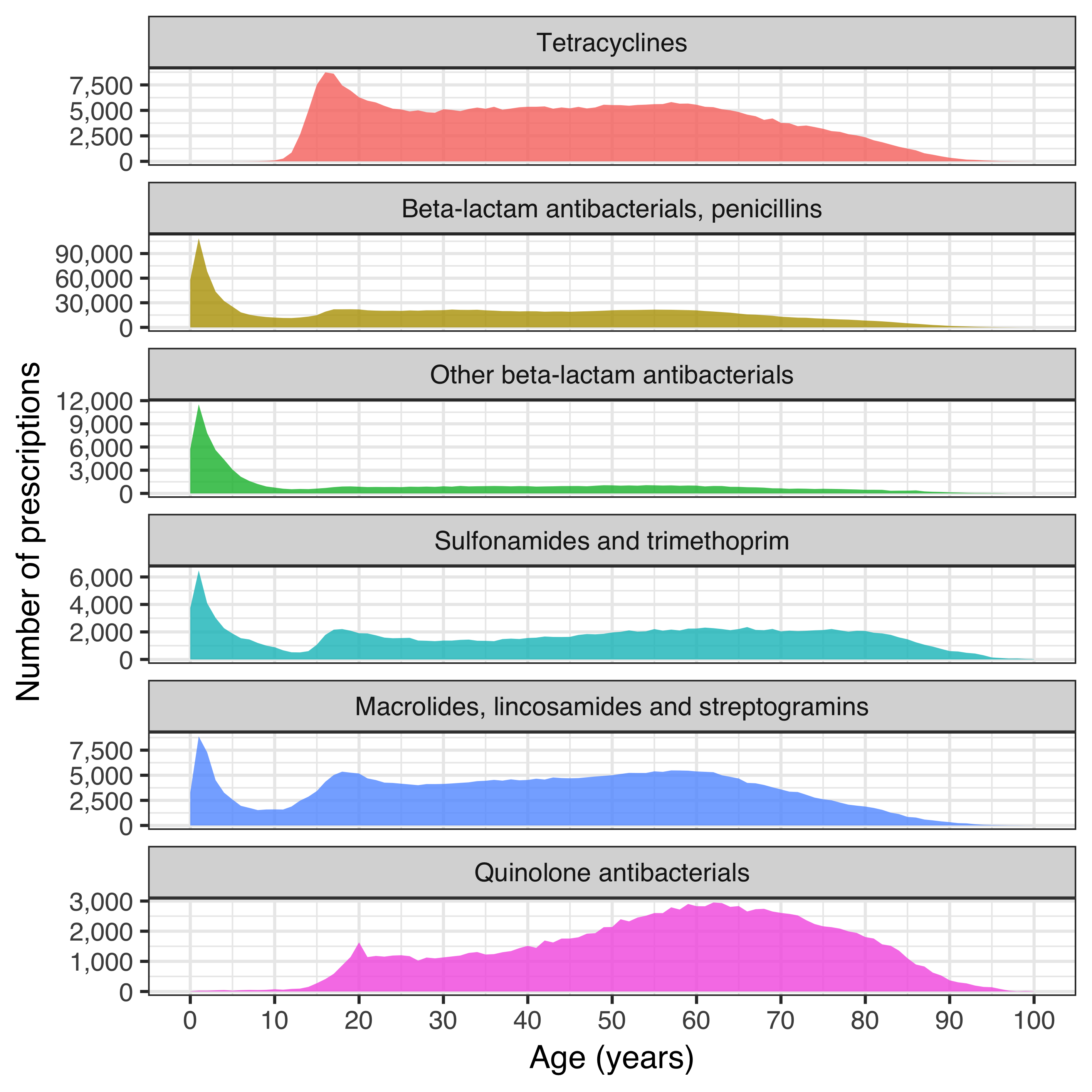


Figure 4 Antimicrobial prescriptions by age

### Reimbursement database of Icelandic Health Insurance

All interactions with independent health care practitioners were recorded in Icelandic Health Insurance’s reimbursement database. From this database, all records of otolaryngological procedures were extracted. A total of 51,814 procedures were recorded among 34,084 individuals.

## Paper 1

The total number of children under eighteen years of age who lived within Children’s Hospital Iceland’s referral region remained stable during the study period, decreasing from 62,067 in 2008 to 61,798 in 2015. The variation was more pronounced in the number of children under four years of age in the same region, which increased from 13,562 in 2008 to 14,644 in 2011, and then decreased to 13,272 in 2015.

During the period January 1, 2008 to December 31, 2015, 103,220 visits were recorded to the Children’s Hospital Iceland. The visits varied over the calendar year, spiking in the winter months and troughing in the summer months Figure 5.

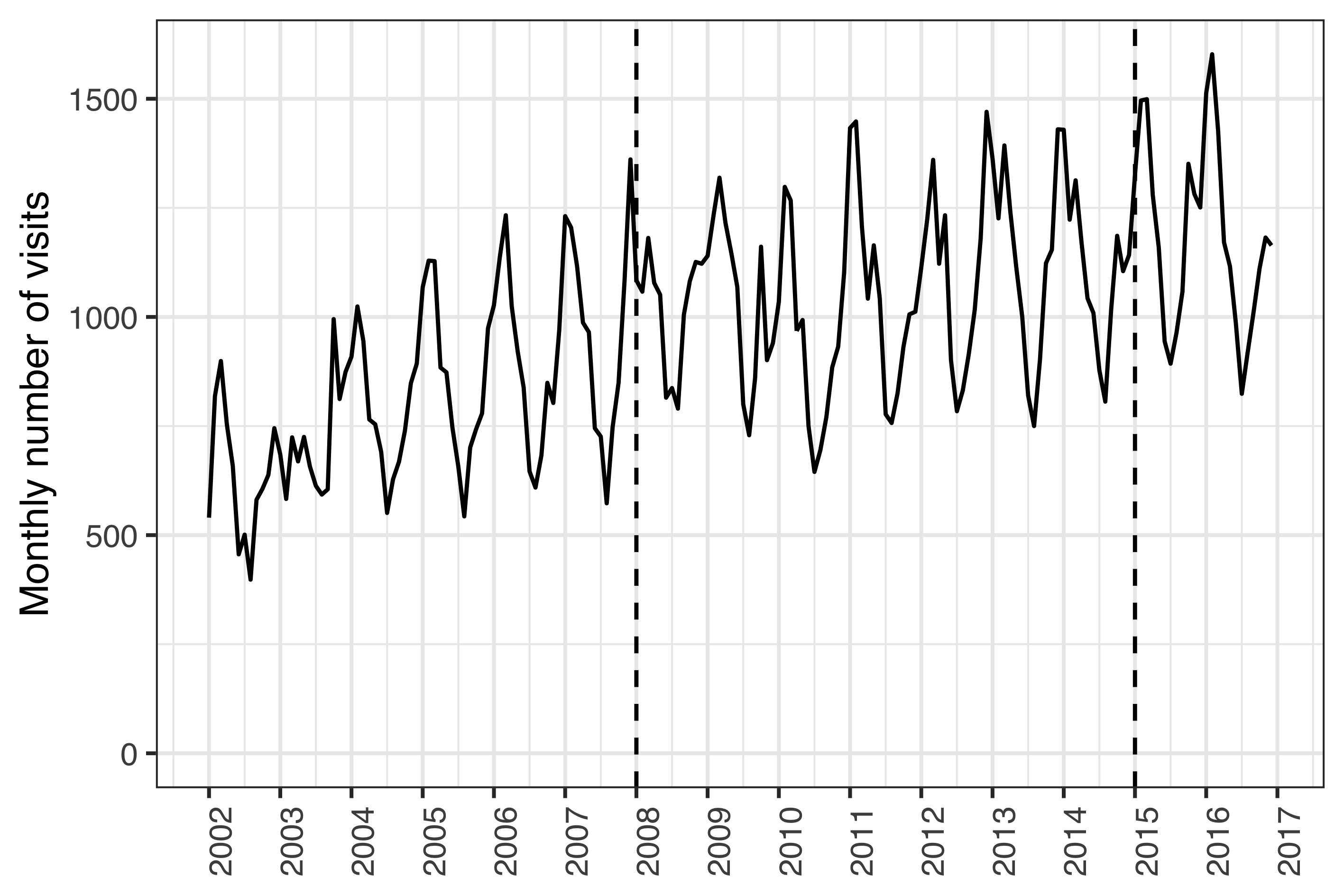


Figure 5 Monthly number of visits to Children’s Hospital Iceland

The total number of visits increased steadily during the study period, from 12,229 in 2008 to 14,502 in 2015. During the same period, 6,232 visits to the Children’s Hospital Iceland for acute otitis media were recorded for 4,624 individual children under four years of age, representing 4,994 distinct episodes. Of those episodes, 531 were treated with one or more doses of ceftriaxone.

47.5 per 1000 person- years in the prevaccine period to an incidence rate of 33.9 per 1000 person-years postvaccine. The effect of vaccine period varied sig- nificantly across age strata precluding Mantel–Haenzel adjustment. The crude overall IRR was 0.86 (95% CI: 0.81–0.91; P < 0.001). A significant decrease in visits was observed only in children 2–3 years of age (IRR 0.71; 95% CI: 0.63–0.80; P < 0.001. A nonsig- nificant trend toward a decrease was observed in other age strata. Children 0–1 and 3–4 years of age visited the Children’s Hospital because of episodes of AOM for a total of only 481 and 396 times, respectively,

Significantly fewer episodes of AOM were treated with ceftriaxone in the postvaccine period compared with those in the prevaccine period (Table 1). The effect was consistent across age strata with an overall Mantel–Haenzel adjusted IRR 0.45 (95% CI: 0.37–0.54; P < 0.001). During the entire study period, only 16 epi- sodes of AOM in children 0–1 year of age, and 20 episodes in chil- dren 3–4 years of age, were treated with ceftriaxone. Age-specific incidence rates and incidence rate ratios are shown in Table 2. The relative risk of treatment with ceftriaxone if presenting to the Chil- dren’s Hospital with AOM decreased significantly after vaccination. The effect was consistent across age strata with a Mantel–Haenzel adjusted relative risk ratio of 0.53 (95% CI: 0.44–0.63; P < 0.001. Episodes of pneumonia treated with ceftriaxone also decreased overall, from 251 treatment episodes in the prevaccine period to 90 in the postvaccine period, with a Mantel–Haenzel adjusted IRR 0.36 (95% CI: 0.28–0.45; P < 0.001. This signifi- cant decrease was observed in all age strata. Ceftriaxone use for other indications in children <4 years of age did not decrease sig- nificantly, with an IRR of 0.92 (95% CI: 0.84–1.02; P = 0.13. Age- specific incidence rates and incidence rate ratios by indication for each vaccine period are shown in Table 2. Quarterly incidence of ceftriaxone treatment episodes by indication is shown in Figure 1.

An overall decrease in incidence rate of ceftriaxone use in children <18 years of age regardless of indication was noted at the Children’s Hospital Iceland after PHiD-CV10 introduction, from 0.93 treatment episodes per 1000 person-years in the prevaccine period to 0.80 in the postvaccine period with a crude overall IRR 0.86 (95% CI: 0.81–0.91; P < 0.001). However, when analyzed by age group, this is exclusively because of a significant decrease in incidence rate of ceftriaxone use in children 0–3 years of age (IRR 0.73; 95% CI: 0.67–0.79; P < 0.001). Ceftriaxone use did not decrease significantly in other age groups, and there was a trend toward increasing use in children 12–17 years of age (Figure 2).

# Discussion

* discuss the completeness of the data, the number of Icelanders in the study data vs. the total number of icelanders.
* discuss the age distribution regarding the number of visits vs hospitalizations.
* discuss the vaccine registry, how no difference is occurring in pneumococcal vaccinations of adults
* discuss how the 2009 and 2010 cohorts received vaccination late, almost like a catch-up.

Andersen, P. K., and R. D. Gill. 1982. “Cox’s Regression Model for Counting Processes: A Large Sample Study.” *The Annals of Statistics* 10 (4): 1100–1120. doi:[10.1214/aos/1176345976](https://doi.org/10.1214/aos/1176345976).

Arason, Vilhjalmur A, Johann A Sigurdsson, Karl G Kristinsson, and Sigurdur Gudmundsson. 2002. “Tympanostomy tube placements, sociodemographic factors and parental expectations for management of acute otitis media in Iceland.” *The Pediatric Infectious Disease Journal* 21 (12): 1110–5. doi:[10.1097/01.inf.0000040702.00373.95](https://doi.org/10.1097/01.inf.0000040702.00373.95).

Arason, Vilhjalmur A., Johann A. Sigurdsson, Karl G. Kristinsson, Linn Getz, and Sigurdur Gudmundsson. 2005. “Otitis media, tympanostomy tube placement, and use of antibiotics.” *Scandinavian Journal of Primary Health Care* 23 (3). Taylor & Francis: 184–91. doi:[10.1080/02813430510031298](https://doi.org/10.1080/02813430510031298).

Austrian, R, R M Douglas, G Schiffman, A M Coetzee, H J Koornhof, S Hayden-Smith, and R D Reid. 1976. “Prevention of pneumococcal pneumonia by vaccination.” *Transactions of the Association of American Physicians* 89: 184–94. <http://www.ncbi.nlm.nih.gov/pubmed/14433>.

Austrian, Robert. 1981. “Pneumococcus: the first one hundred years.” *Reviews of Infectious Diseases* 3 (2): 183–9. doi:[10.1093/clinids/3.2.183](https://doi.org/10.1093/clinids/3.2.183).

———. 1999. “A brief history of pneumococcal vaccines.” *Drugs & Aging* 15 Suppl 1: 1–10. <http://www.ncbi.nlm.nih.gov/pubmed/10690790>.

Austrian, Robert, and J Gold. 1964. “Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia.” *Annals of Internal Medicine* 60: 759–76. doi:[10.7326/0003-4819-60-5-759](https://doi.org/10.7326/0003-4819-60-5-759).

Bjarnason, Skúli, Ingþór Friðriksson, and Jón Benediktsson. 1991. “Tíðni bráðrar miðeyrabólgu hjá börnum á svæði heilsugæslustöðvarinnar Borgarnesi.” *Læknablaðið* 77 (4): 137–40. <http://www.hirsla.lsh.is/lsh/bitstream/2336/90415/1/L1991-04-77-F3.pdf>.

Black, Nick. 1984. “SURGERY FOR GLUE EAR —A MODERN EPIDEMIC.” *The Lancet* 323 (8381): 835–37. doi:[10.1016/S0140-6736(84)92280-3](https://doi.org/10.1016/S0140-6736(84)92280-3).

Black, S, H Shinefield, Bruce Fireman, E Lewis, P Ray, J R Hansen, L Elvin, et al. 2000. “Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group.” *The Pediatric Infectious Disease Journal* 19 (3): 187–95. <http://www.ncbi.nlm.nih.gov/pubmed/10749457>.

Black, Steven B, H R Shinefield, S Ling, J Hansen, Bruce Fireman, D Spring, J Noyes, et al. 2002. “Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia.” *Pediatr Infect Dis J* 21 (9): 810–15. doi:[10.1097/01.inf.0000027926.99356.4c](https://doi.org/10.1097/01.inf.0000027926.99356.4c).

Block, Stan L., James Hedrick, Christopher J. Harrison, Ron Tyler, Alan Smith, Rebecca Findlay, and Eileen Keegan. 2004. “Community-Wide Vaccination with the Heptavalent Pneumococcal Conjugate Significantly Alters the Microbiology of Acute Otitis Media.” *The Pediatric Infectious Disease Journal* 23 (9): 829–33. doi:[10.1097/01.inf.0000136868.91756.80](https://doi.org/10.1097/01.inf.0000136868.91756.80).

Bluestone, C D, J S Stephenson, and L M Martin. 1992. “Ten-year review of otitis media pathogens.” *The Pediatric Infectious Disease Journal* 11 (8 Suppl): S7–11. doi:[10.1097/00006454-199208001-00002](https://doi.org/10.1097/00006454-199208001-00002).

Bright, R A, R M Moore, L L Jeng, C M Sharkness, S E Hamburger, and P M Hamilton. 1993. “The prevalence of tympanostomy tubes in children in the United States, 1988.” *American Journal of Public Health* 83 (7): 1026–8. [http://www.ncbi.nlm.nih.gov/pubmed/8328599 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1694786](http://www.ncbi.nlm.nih.gov/pubmed/8328599%20http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1694786).

Browning, George G, Maroeska M Rovers, Ian Williamson, Jørgen Lous, and Martin J Burton. 2010. “Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children.” *Cochrane Database of Systematic Reviews*, no. 10 (October). doi:[10.1002/14651858.CD001801.pub3](https://doi.org/10.1002/14651858.CD001801.pub3).

Bruhn, Christian A W, Stephen Hetterich, Cynthia Schuck-Paim, Esra Kürüm, Robert J Taylor, Roger Lustig, Eugene D Shapiro, Joshua L Warren, Lone Simonsen, and Daniel M Weinberger. 2017. “Estimating the population-level impact of vaccines using synthetic controls.” *Proceedings of the National Academy of Sciences* 114 (7): 1524–9. doi:[10.1073/pnas.1612833114](https://doi.org/10.1073/pnas.1612833114).

Casey, Janet R, Diana G Adlowitz, and Michael E Pichichero. 2009. “New Patterns in the Otopathogens Causing Acute Otitis Media Six to Eight Years After Introduction of Pneumococcal Conjugate Vaccine.” *The Pediatric Infectious Disease Journal* 29 (November): 1. doi:[10.1097/INF.0b013e3181c1bc48](https://doi.org/10.1097/INF.0b013e3181c1bc48).

Casey, Janet R., and Michael E. Pichichero. 2004. “Changes in frequency and pathogens causing acute otitis media in 1995-2003.” *The Pediatric Infectious Disease Journal* 23 (9): 824–8. doi:[10.1097/01.inf.0000136871.51792.19](https://doi.org/10.1097/01.inf.0000136871.51792.19).

Cecil, R. L. 1918. “RESULTS OF PROPHYLACTIC INOCULATION AGAINST PNEUMOCOCCUS IN 12,519 MEN.” *Journal of Experimental Medicine* 28 (1): 19–41. doi:[10.1084/jem.28.1.19](https://doi.org/10.1084/jem.28.1.19).

Chen, Yi-Jen, Yu-Chia Hsieh, Yhu-Chering Huang, and Cheng-Hsun Chiu. 2013. “Clinical manifestations and microbiology of acute otitis media with spontaneous otorrhea in children.” *Journal of Microbiology, Immunology and Infection* 46 (5). Elsevier Taiwan LLC: 382–88. doi:[10.1016/j.jmii.2013.04.001](https://doi.org/10.1016/j.jmii.2013.04.001).

Cilloniz, Catia, Ignacio Martin-Loeches, Carolina Garcia-Vidal, Alicia San Jose, and Antoni Torres. 2016. “Microbial etiology of pneumonia: Epidemiology, diagnosis and resistance patterns.” *International Journal of Molecular Sciences* 17 (12). doi:[10.3390/ijms17122120](https://doi.org/10.3390/ijms17122120).

CLAESSON, BO A., BIRGER TROLLFORS, INGER BROLIN, MARTA GRANSTRÖM, JØRGEN HENRICHSEN, ULF JODAL, PER JUTO, et al. 1989. “Etiology of community-acquired pneumonia in children based on antibody responses to bacterial and viral antigens.” *The Pediatric Infectious Disease Journal* 8 (12): 856–61. doi:[10.1097/00006454-198912000-00006](https://doi.org/10.1097/00006454-198912000-00006).

Cook, Richard J. (Richard John), and Jerald F. Lawless. 2007a. *The Statistical Analysis of Recurrent Events*. Edited by M Gail, K Krickeberg, J Sarmet, A Tsiatis, and W Wong. New York: Springer Science + Business Media.

———. 2007b. *The statistical analysis of recurrent events*. Springer.

Cullen, Karen A, Margaret J Hall, and Aleksandr Golosinskiy. 2009. “Ambulatory surgery in the United States, 2006.” *National Health Statistics Reports*, no. 11 (January): 1–25. <http://www.ncbi.nlm.nih.gov/pubmed/19294964>.

Dagan, Ron, M Sikuler-Cohen, O Zamir, J Janco, Noga Givon-Lavi, and D Fraser. 2001. “Effect of a conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care center attendees.” *Pediatr Infect Dis J* 20 (10): 951–58. <http://www.ncbi.nlm.nih.gov/pubmed/11642629>.

Davies, John A. V. 1937. “The Response of Infants to Inoculation with Type I Pneumococcus Carbohydrate.” *The Journal of Immunology*.

Deibel, RH, and HW Seeley. 1974. “Family II: Streptococcuceae.” In *Bergey’s Manual of Determinative Bacteriology*, edited by R. E. Buchanan and N. E. Gibbons, 8th ed., 490–517. Baltimore: The William; Wilkins Co.

Dochez, A Lz, and O T Avery. 1917. “The elaboration of specific soluble substance by pneumococcus during growth.” *The Journal of Experimental Medicine*. doi:[10.1084/jem.26.4.477](https://doi.org/10.1084/jem.26.4.477).

Dowling, John N, Paul R Sheehe, and Harry A Feldman. 1971. “Pharyngeal pneumococcal acquisitions in ‘normal’ families: a longitudinal study.” *The Journal of Infectious Diseases* 124 (1): 9–17. <http://www.ncbi.nlm.nih.gov/pubmed/4401272>.

Dvorzak, Michaela, and Helga Wagner. 2016. *Pogit: Bayesian Variable Selection for a Poisson-Logistic Model*. <https://CRAN.R-project.org/package=pogit>.

Ekwurzel, G M, J S Simmons, L I Dublin, and L D Felton. 1938. “Studies on immunizing substances in pneumococci. VIII. Report on field tests to determine the prophylactic value of a pneumococcus antigen.” *Public Health Rep* 53 (42): 1877–93.

Elemraid, Mohamed A., Andrew D. Sails, Gary J.A. Eltringham, John D. Perry, Stephen P. Rushton, David A. Spencer, Matthew F. Thomas, et al. 2013. “Aetiology of paediatric pneumonia after the introduction of pneumococcal conjugate vaccine.” *European Respiratory Journal* 42 (6): 1595–1603. doi:[10.1183/09031936.00199112](https://doi.org/10.1183/09031936.00199112).

Eskola, J, T. Kilpi, A. Palmu, J. Jokinen, J. Haapakoski, E. Herva, A. Takala, et al. 2001. “Efficacy of a pneumococcal conjugate vaccine against acute otitis media.” *N Engl J Med* 344 (6): 403–9. doi:[10.1056/nejm200102083440602](https://doi.org/10.1056/nejm200102083440602).

Feikin, Daniel R., Laura L. Hammitt, David R. Murdoch, Katherine L. O’Brien, and J. Anthony G. Scott. 2017. “The Enduring Challenge of Determining Pneumonia Etiology in Children: Considerations for Future Research Priorities.” *Clinical Infectious Diseases* 64 (suppl\_3): S188–S196. doi:[10.1093/cid/cix143](https://doi.org/10.1093/cid/cix143).

Finland, M. 1931. “SPECIFIC CUTANEOUS REACTIONS AND CIRCULATING ANTIBODIES IN THE COURSE OF LOBAR PNEUMONIA: I. CASES RECEIVING NO SERUM THERAPY.” *Journal of Experimental Medicine* 54 (5): 637–52. doi:[10.1084/jem.54.5.637](https://doi.org/10.1084/jem.54.5.637).

Fireman, Bruce, Steven B Black, Henry R Shinefield, Janelle Lee, Edwin Lewis, and Paula Ray. 2003. “Impact of the pneumococcal conjugate vaccine on otitis media.” 1. 2003/01/25. Vol. 22. The Pediatric infectious disease journal. doi:[10.1097/00006454-200301000-00006](https://doi.org/10.1097/00006454-200301000-00006).

Florentzson, Rut, and Caterina Finizia. 2012. “Transmyringeal ventilation tube treatment: a 10-year cohort study.” *International Journal of Pediatric Otorhinolaryngology* 76 (8). Elsevier Ireland Ltd: 1117–22. doi:[10.1016/j.ijporl.2012.04.013](https://doi.org/10.1016/j.ijporl.2012.04.013).

Francis, T, and W S Tillett. 1930. “Cutaneous reactions in pneumonia. The development of antibodies following the intradermal injection of type-specific polysaccharide.” *The Journal of Experimental Medicine*. doi:[10.1084/jem.52.4.573](https://doi.org/10.1084/jem.52.4.573).

Gendrel, D., J. Raymond, F. Moulin, J. L. Iniguez, S. Ravilly, F. Habib, P. Lebon, and G. Kalifa. 1997. “Etiology and response to antibiotic therapy of community-acquired pneumonia in French children.” *European Journal of Clinical Microbiology & Infectious Diseases* 16 (5): 388–91. doi:[10.1007/BF01726370](https://doi.org/10.1007/BF01726370).

Geno, K. Aaron, Gwendolyn L. Gilbert, Joon Young Song, Ian C. Skovsted, Keith P. Klugman, Christopher Jones, Helle B. Konradsen, and Moon H. Nahm. 2015. “Pneumococcal Capsules and Their Types: Past, Present, and Future.” *Clinical Microbiology Reviews* 28 (3): 871–99. doi:[10.1128/CMR.00024-15](https://doi.org/10.1128/CMR.00024-15).

Gilani, Zunera, Yuenting D. Kwong, Orin S. Levine, Maria Deloria-Knoll, J. Anthony G Scott, Katherine L. O’Brien, and Daniel R. Feikin. 2012. “A Literature Review and Survey of Childhood Pneumonia Etiology Studies: 2000–2010.” *Clinical Infectious Diseases* 54 (suppl\_2): S102–S108. doi:[10.1093/cid/cir1053](https://doi.org/10.1093/cid/cir1053).

Glezen, W. Paul, and Floyd W. Denny. 1973. “Epidemiology of Acute Lower Respiratory Disease in Children.” *New England Journal of Medicine* 288 (10): 498–505. doi:[10.1056/NEJM197303082881005](https://doi.org/10.1056/NEJM197303082881005).

Gram, Christian. 1884. “Ueber die isolierte Fabung der Schizomyceten in Schnitt und Trockenpraparaten.” *Fortschritte Der Medicin* 2: 185–89.

Harrell, Jr., Frank E. 2018. *Rms: Regression Modeling Strategies*. <https://CRAN.R-project.org/package=rms>.

Heidelberger, M, and O T Avery. 1923. “THE SOLUBLE SPECIFIC SUBSTANCE OF PNEUMOCOCCUS.” *The Journal of Experimental Medicine*. doi:[10.1084/jem.40.3.301](https://doi.org/10.1084/jem.40.3.301).

Hoshino, Kazuhiko, Hiroshi Watanabe, Rinya Sugita, Norichika Asoh, Simon Angelo Ntabaguzi, Kiwao Watanabe, Kazunori Oishi, and Tsuyoshi Nagatake. 2002. “High rate of transmission of penicillin-resistant Streptococcus pneumoniae between parents and children.” *Journal of Clinical Microbiology* 40 (11): 4357–9. doi:[10.1128/JCM.40.11.4357](https://doi.org/10.1128/JCM.40.11.4357).

Jain, Seema, Derek J. Williams, Sandra R. Arnold, Krow Ampofo, Anna M. Bramley, Carrie Reed, Chris Stockmann, et al. 2015. “Community-Acquired Pneumonia Requiring Hospitalization among U.S. Children.” *New England Journal of Medicine* 372: 835–45. doi:[10.1056/NEJMoa1405870](https://doi.org/10.1056/NEJMoa1405870).

Kaur, Ravinder, Matthew Morris, and Michael E. Pichichero. 2017. “Epidemiology of Acute Otitis Media in the Postpneumococcal Conjugate Vaccine Era.” *Pediatrics* 140 (3): e20170181. doi:[10.1542/peds.2017-0181](https://doi.org/10.1542/peds.2017-0181).

Keyhani, Salomeh, Lawrence C Kleinman, Michael Rothschild, Joseph M Bernstein, Rebecca Anderson, and Mark Chassin. 2008. “Overuse of tympanostomy tubes in New York metropolitan area: evidence from five hospital cohort.” *BMJ (Clinical Research Ed.)* 337 (5). British Medical Journal Publishing Group: a1607. doi:[10.1136/bmj.a1607](https://doi.org/10.1136/bmj.a1607).

Kilpi, T, Heidi Ahman, J Jokinen, K S Lankinen, A Palmu, H Savolainen, M Gronholm, et al. 2003. “Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate v.” *Clin Infect Dis* 37 (9): 1155–64. doi:[10.1086/378744](https://doi.org/10.1086/378744).

Kilpi, T.M., J. Jokinen, T. Puumalainen, H. Nieminen, E. Ruokokoski, H. Rinta-Kokko, M. Traskine, et al. 2018. “Effectiveness of pneumococcal Haemophilus influenzae protein D conjugate vaccine against pneumonia in children: A cluster-randomised trial.” *Vaccine* 36 (39). The Authors: 5891–5901. doi:[10.1016/j.vaccine.2018.08.020](https://doi.org/10.1016/j.vaccine.2018.08.020).

Kim, Su Jin, Ji Hyun Chung, Ho Min Kang, and Seung Geun Yeo. 2013. “Clinical bacteriology of recurrent otitis media with effusion.” *Acta Oto-Laryngologica* 133 (11). Taylor & Francis: 1133–41. doi:[10.3109/00016489.2013.816442](https://doi.org/10.3109/00016489.2013.816442).

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).

Le Polain de Waroux, Olivier, Stefan Flasche, David Prieto-Merino, and W John Edmunds. 2014. “Age-Dependent Prevalence of Nasopharyngeal Carriage of Streptococcus pneumoniae before Conjugate Vaccine Introduction: A Prediction Model Based on a Meta-Analysis.” Edited by Hiroshi Nishiura. *PLoS ONE* 9 (1): e86136. doi:[10.1371/journal.pone.0086136](https://doi.org/10.1371/journal.pone.0086136).

Leino, Tuija, Kari Auranen, Jukka Jokinen, Maija Leinonen, Päivi Tervonen, and Aino K. Takala. 2001. “Pneumococcal carriage in children during their first two years: important role of family exposure.” *The Pediatric Infectious Disease Journal* 20 (11): 1022–7. doi:[10.1097/00006454-200111000-00004](https://doi.org/10.1097/00006454-200111000-00004).

Levine, Orin S., Katherine L. O’Brien, Maria Deloria-Knoll, David R. Murdoch, Daniel R. Feikin, A. N. DeLuca, Amanda J. Driscoll, et al. 2012. “The Pneumonia Etiology Research for Child Health Project: A 21st Century Childhood Pneumonia Etiology Study.” *Clinical Infectious Diseases* 54 (suppl 2): S93–S101. doi:[10.1093/cid/cir1052](https://doi.org/10.1093/cid/cir1052).

Lin, D. Y., and L. J. Wei. 1989. “The Robust Inference for the Cox Proportional Hazards Model.” *Journal of the American Statistical Association* 84 (408): 1074–8. doi:[10.1080/01621459.1989.10478874](https://doi.org/10.1080/01621459.1989.10478874).

Lister, Frederick Spencer. 1916. “An experimental study of prophylactic inoculation against pneumococcal infection in the rabbit and in man.” *Publication of the South African Institute of Medical Research* 8: 231–87.

Lister, Frederick Spencer, and D Ordman. 1936. “The Epidemiology of Pneumonia on the Witwatersrand Goldfields and the Prevention of Pneumonia and Other Allied Acute Respiratory Diseases in Native Labourers in South Africa by Means of Vaccine.” *Journal of the American Medical Association* 106 (9): 733. doi:[10.1001/jama.1936.02770090069032](https://doi.org/10.1001/jama.1936.02770090069032).

Mackenzie, Grant. 2016. “The definition and classification of pneumonia.” *Pneumonia* 8 (1). Pneumonia: 14. doi:[10.1186/s41479-016-0012-z](https://doi.org/10.1186/s41479-016-0012-z).

Macleod, C M, Richard G Hodges, Michael Heidelberger, and W G Bernhard. 1945. “PREVENTION OF PNEUMOCOCCAL PNEUMONIA BY IMMUNIZATION WITH SPECIFIC CAPSULAR POLYSACCHARIDES.” *The Journal of Experimental Medicine* 82 (6): 445–65. [http://www.ncbi.nlm.nih.gov/pubmed/19871511 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2135567](http://www.ncbi.nlm.nih.gov/pubmed/19871511%20http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2135567).

Madhi, Shabir a, Philippe De Wals, Carlos G Grijalva, Keith Grimwood, Ronald Grossman, Naruhiko Ishiwada, Ping-Ing Lee, et al. 2012. “The Burden of Childhood Pneumonia in the Developed World.” *The Pediatric Infectious Disease Journal* 32 (3): 1. doi:[10.1097/INF.0b013e3182784b26](https://doi.org/10.1097/INF.0b013e3182784b26).

Maynard, G D. 1913. “An enquiry into the etiology, manifestations and prevention of pneumonia amongst natives on the Rand recruited from tropical areas.” *Public South Afr Inst Med Res* 1 (0): 1–101.

Mäkelä, P H, M Leinonen, J Pukander, and P Karma. 1981. “A study of the pneumococcal vaccine in prevention of clinically acute atttacks of recurrent otitis media.” *Reviews of Infectious Diseases* 3 Suppl: S124–32. <http://www.ncbi.nlm.nih.gov/pubmed/6974386>.

MELEGARO, A., N. J. GAY, and G. F. MEDLEY. 2004. “Estimating the transmission parameters of pneumococcal carriage in households.” *Epidemiology and Infection* 132 (3): 433–41. doi:[10.1017/S0950268804001980](https://doi.org/10.1017/S0950268804001980).

Mosser, Jonathan F., Lindsay R. Grant, Eugene V. Millar, Robert C. Weatherholtz, Delois M. Jackson, Bernard Beall, Mariddie J. Craig, Raymond Reid, Mathuram Santosham, and Katherine L. O’Brien. 2014. “Nasopharyngeal carriage and transmission of Streptococcus pneumoniae in American Indian households after a decade of pneumococcal conjugate vaccine use.” *PLoS ONE* 9 (1): 3–10. doi:[10.1371/journal.pone.0079578](https://doi.org/10.1371/journal.pone.0079578).

Ngo, Chinh C., Helen M. Massa, Ruth B. Thornton, and Allan W. Cripps. 2016. “Predominant Bacteria Detected from the Middle Ear Fluid of Children Experiencing Otitis Media: A Systematic Review.” Edited by Sean Reid. *PloS One* 11 (3): e0150949. doi:[10.1371/journal.pone.0150949](https://doi.org/10.1371/journal.pone.0150949).

O’Brien, Katherine L, Lawrence H Moulton, Raymond Reid, Robert Weatherholtz, Jane Oski, Laura Brown, Gaurav Kumar, et al. 2003. “Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial.” *Lancet* 362 (9381): 355–61. doi:[10.1016/S0140-6736(03)14022-6](https://doi.org/10.1016/S0140-6736(03)14022-6).

O’Brien, Katherine L., Angeline B David, Aruna Chandran, Lawrence H Moulton, Raymond Reid, Robert Weatherholtz, and Mathuram Santosham. 2008. “RANDOMIZED, CONTROLLED TRIAL EFFICACY OF PNEUMOCOCCAL CONJUGATE VACCINE AGAINST OTITIS MEDIA AMONG NAVAJO AND WHITE MOUNTAIN APACHE INFANTS.” *The Pediatric Infectious Disease Journal* 27 (1): 71–73. doi:[10.1097/INF.0b013e318159228f](https://doi.org/10.1097/INF.0b013e318159228f).

PAISLEY, JOHN W., BRIAN A. LAUER, KENNETH MCINTOSH, MARY P. GLODE, JULIUS SCHACHTER, and ACAROL RUMACK. 1984. “Pathogens associated with acute lower respiratory tract infection in young children.” *The Pediatric Infectious Disease Journal* 3 (1): 14–19. doi:[10.1097/00006454-198401000-00005](https://doi.org/10.1097/00006454-198401000-00005).

Palmu, Arto A I, Jouko Verho, Jukka Jokinen, Pekka Karma, and Terhi M Kilpi. 2004. “The seven-valent pneumococcal conjugate vaccine reduces tympanostomy tube placement in children.” *The Pediatric Infectious Disease Journal* 23 (8): 732–38. doi:[10.1097/01.inf.0000133049.30299.5d](https://doi.org/10.1097/01.inf.0000133049.30299.5d).

Parker, Devin M., Laura Schang, Jared R. Wasserman, Weston D. Viles, Gwyn Bevan, and David C. Goodman. 2016. “Variation in Utilization and Need for Tympanostomy Tubes across England and New England.” *The Journal of Pediatrics* 179 (December). Elsevier Inc.: 178–184.e4. doi:[10.1016/j.jpeds.2016.08.093](https://doi.org/10.1016/j.jpeds.2016.08.093).

Pasteur, Louis. 1881. “Note sur la maladie nouvelle provoquee par la salive d’un enfant mort de la rage.” 10. Vol. 2. Paris: I’Academie de Medicine. <https://gallica.bnf.fr/ark:/12148/bpt6k408671n>.

Prymula, Roman, Pascal Peeters, Viktor Chrobok, Pavla Kriz, Elena Novakova, Eva Kaliskova, Igor Kohl, et al. 2006. “Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae: A randomised double-blind efficacy study.” *Lancet* 367 (9512): 740–48. doi:[10.1016/S0140-6736(06)68304-9](https://doi.org/10.1016/S0140-6736(06)68304-9).

Pumarola, Felix, Josep Marès, Isabel Losada, Isabel Minguella, Fernando Moraga, David Tarragó, Ulla Aguilera, et al. 2013. “Microbiology of bacteria causing recurrent acute otitis media (AOM) and AOM treatment failure in young children in Spain: Shifting pathogens in the post-pneumococcal conjugate vaccination era.” *International Journal of Pediatric Otorhinolaryngology* 77 (8): 1231–6. doi:[10.1016/j.ijporl.2013.04.002](https://doi.org/10.1016/j.ijporl.2013.04.002).

R Core Team. 2018. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. <https://www.R-project.org/>.

Rodrigues, C. M. C., and H. Groves. 2017. “Community-Acquired Pneumonia in Children: the Challenges of Microbiological Diagnosis.” Edited by Colleen Suzanne Kraft. *Journal of Clinical Microbiology* 56 (3): JCM.01318–17. doi:[10.1128/JCM.01318-17](https://doi.org/10.1128/JCM.01318-17).

Rozenbaum, M. H., P. Pechlivanoglou, T. S. Werf, J. R. Lo-Ten-Foe, M. J. Postma, and E. Hak. 2013. “The role of Streptococcus pneumoniae in community-acquired pneumonia among adults in Europe: a meta-analysis.” *European Journal of Clinical Microbiology & Infectious Diseases* 32 (3): 305–16. doi:[10.1007/s10096-012-1778-4](https://doi.org/10.1007/s10096-012-1778-4).

Ruuskanen, O., H. Nohynek, T. Ziegler, R. Capeding, H. Rikalainen, P. Huovinen, and M. Leinonen. 1992. “Pneumonia in childhood: Etiology and response to antimicrobial therapy.” *European Journal of Clinical Microbiology & Infectious Diseases* 11 (3): 217–23. doi:[10.1007/BF02098083](https://doi.org/10.1007/BF02098083).

Schiemann, O., and W. Casper. 1927. “Sind die spezifisch pracipitablen Substanzen der 3 Pneumokokkentypen Haptene?” *Zeitschrift Fur Hygiene Und Infektionskrankheiten*. doi:[10.1007/BF02176583](https://doi.org/10.1007/BF02176583).

Shioda, Kayoko, Cynthia Schuck-Paim, Robert J. Taylor, Roger Lustig, Lone Simonsen, Joshua L Warren, and Daniel M Weinberger. 2018. “Challenges in estimating the impact of vaccination with sparse data.” *Epidemiology (Cambridge, Mass.)* 4 (5): 1. doi:[10.1097/EDE.0000000000000938](https://doi.org/10.1097/EDE.0000000000000938).

Sloyer, John L, John H Ploussard, and Virgil M Howie. 1981. “Efficacy of pneumococcal polysaccharide vaccine in preventing acute otitis media in infants in Huntsville, Alabama.” *Reviews of Infectious Diseases* 3 Suppl: S119–23. <http://www.ncbi.nlm.nih.gov/pubmed/7280444>.

Smit, Pieter. 1977. “Protective Efficacy of Pneumococcal Polysaccharide Vaccines.” *JAMA: The Journal of the American Medical Association* 238 (24): 2613. doi:[10.1001/jama.1977.03280250039019](https://doi.org/10.1001/jama.1977.03280250039019).

Sonsuwan, Nuntigar, Patcharin Watcharinyanon, and Kittisak Sawanyawisuth. 2016. “What are the leading causative pathogens in acute otitis media with tympanic membrane perforation?” *International Journal of Pediatric Otorhinolaryngology* 90 (November). Elsevier Ltd: 20–22. doi:[10.1016/j.ijporl.2016.08.021](https://doi.org/10.1016/j.ijporl.2016.08.021).

Spilsbury, Katrina, Abdul Latif Kadhim, James B Semmens, Francis J Lannigan, Spilsbury K., Kadhim A.L., Semmens J.B., et al. 2006. “Decreasing rates of middle ear surgery in Western Australian children.” *Archives of Otolaryngology - Head and Neck Surgery* 132 (11): 1216–20. doi:[10.1001/archotol.132.11.1216](https://doi.org/10.1001/archotol.132.11.1216).

Sternberg, G M. 1882. “A fatal form of septicemia in the rabbit produced by subcutaneous injection of human saliva.” Washington: National Board of Health; U.S. Government Printing Office. [https://books.google.is/books?id=YojXubzmx3sC{\&}printsec=frontcover{\&}hl=is{\#}v=onepage{\&}q{\&}f=false](https://books.google.is/books?id=YojXubzmx3sC%7b\&%7dprintsec=frontcover%7b\&%7dhl=is%7b\#}v=onepage{\&}q{\&}f=false).

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>.

Teele, D W, J O Klein, and B Rosner. 1989. “Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study.” *The Journal of Infectious Diseases* 160 (1): 83–94. <http://www.ncbi.nlm.nih.gov/pubmed/2732519>.

Therneau, Terry M. 2017. *Survival: Survival Analysis*. <https://CRAN.R-project.org/package=survival>.

Tillett, W S, M J Cambier, and J E McCormack. 1944. “The Treatment of Lobar Pneumonia and Pneumococcal Empyema with Penicillin.” *Bulletin of the New York Academy of Medicine* 20 (3): 142–78. doi:[10.7326/0003-4819-60-5-759](https://doi.org/10.7326/0003-4819-60-5-759).

Troeger, Christopher, Brigette F Blacker, Ibrahim A Khalil, Puja C Rao, Shujin Cao, Stephanie RM Zimsen, Samuel B Albertson, et al. 2018. “Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016.” *The Lancet Infectious Diseases* 3099 (18): 1–20. doi:[10.1016/S1473-3099(18)30362-1](https://doi.org/10.1016/S1473-3099(18)30362-1).

Tuomanen, Elaine I., Robert Austrian, and H. Robert Masure. 1995. “Pathogenesis of Pneumococcal Infection.” Edited by Franklin H. Epstein. *New England Journal of Medicine* 332 (19): 1280–4. doi:[10.1056/NEJM199505113321907](https://doi.org/10.1056/NEJM199505113321907).

Van Dyke, Melissa K., Jean-Yves Pirçon, Robert Cohen, Shabir A. Madhi, Andrés Rosenblüt, Mercedes Macias Parra, Khalid Al-Mazrou, et al. 2017. “Etiology of Acute Otitis Media in Children Less Than 5 Years of Age.” *The Pediatric Infectious Disease Journal* 36 (3): 274–81. doi:[10.1097/INF.0000000000001420](https://doi.org/10.1097/INF.0000000000001420).

VanderWeele, Tyler J., and Peng Ding. 2017. “Sensitivity Analysis in Observational Research: Introducing the E-Value.” *Annals of Internal Medicine* 167 (4): 268–74. doi:[10.7326/M16-2607](https://doi.org/10.7326/M16-2607).

Venekamp, Roderick P, Paul Mick, Anne GM Schilder, and Desmond A Nunez. 2018. “Grommets (ventilation tubes) for recurrent acute otitis media in children.” *Cochrane Database of Systematic Reviews* (4):CD0047 (4): CD004741. doi:[10.1002/14651858.CD012017.pub2](https://doi.org/10.1002/14651858.CD012017.pub2).

Watson, David A, Daniel M Musher, James W Jacobson, and Jan Verhoef. 1993. “A Brief History of the Pneumococcus in Biomedical Research: A Panoply of Scientific Discovery Description of the Organism and Demonstration of Its Virulence.” *Clinical Infectious Diseases* 17: 913–24. doi:[10.1093/clinids/17.5.913](https://doi.org/10.1093/clinids/17.5.913).

Weichselbaum, A. 1886. “Ueber die Aetiologie der acuten Lungen-und Rippenfellentzundungen.” *Medizinische Jahrbücher.*, 483–554.

Winslow, C.-E. E, Jean Broadhurst, R. E. Buchanan, C Krumwiede, L. A. Rogers, and G. H Smith. 1920. “The Families and Genera of the Bacteria: Final Report of the Committee of the Society of American Bacteriologists on Characterization and Classification of Bacterial Types.” *Journal of Bacteriology* 5 (3): 191–229. doi:[10.1086/278854](https://doi.org/10.1086/278854).

World Health Organization Pneumonia Vaccine Trial Investigators’ Group. 2001. “Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children.” Geneva: World Health Organization. <http://www.who.int/iris/handle/10665/66956>.

Wright, AlmrothE., W. Parry Morgan, L Colebrook, and R.W. Dodgson. 1914. “Observations ON PROPHYLACTIC INOCULATION AGAINST PNEUMOCOCCUS INFECTIONS. AND ON THE RESULTS WHICH HAVE BEEN ACHIEVED BY IT.” *The Lancet* 183 (4715): 87–95. doi:[10.1016/S0140-6736(01)56449-1](https://doi.org/10.1016/S0140-6736(01)56449-1).

Yagupsky, P, N Porat, D Fraser, F Prajgrod, M Merires, L McGee, K P Klugman, and R Dagan. 1998. “Acquisition, Carriage, and Transmission of Pneumococci with Decreased Antibiotic Susceptibility in Young Children Attending a Day Care Facility in Southern Israel.” *Journal of Infectious Diseases* 177 (4): 1003–12. doi:[10.1086/515239](https://doi.org/10.1086/515239).

Youngster, Ilan, Jerry Avorn, Valeria Belleudi, Anna Cantarutti, Javier Díez-Domingo, Ursula Kirchmayer, Byung-Joo Park, et al. 2017. “Antibiotic Use in Children – A Cross-National Analysis of 6 Countries.” *The Journal of Pediatrics* 182 (March). Elsevier Inc.: 239–244.e1. doi:[10.1016/j.jpeds.2016.11.027](https://doi.org/10.1016/j.jpeds.2016.11.027).