PhD thesis

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# Preamble

Placeholder

# Introduction

Table 1 List of abbreviations

|  |  |
| --- | --- |
| Term | Abbreviation |
| 10-valent pneumococcal conjugate vaccine | PCV10 |
| 11-valent pneumococcal conjugate vaccine | PCV11 |
| 13-valent pneumococcal conjugate vaccine | PCV13 |
| 23-valent pneumococcal polysaccharide vaccine | PPV-23 |
| 7-valent pneumococcal conjugate vaccine | PCV7 |
| Acute otitis media | AOM |
| Anatomical-Therapeutic-Chemical | ATC |
| Community-acquired pneumonia | CAP |
| Confidence intervals | CI |
| Cost-benefit analysis | CBA |
| Cost-effectiveness acceptability curve | CEAC |
| Cost-effectiveness analysis | CEA |
| Cost-utility analysis | CUA |
| 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 |
| International Society for Pharmacoeconomics and Outcome Research | ISPOR |
| 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 |
| Organisation for Economic Co-operation and Development | OECD |
| Pneumococcal conjugate vaccine | PCV |
| Principal component analysis | PCA |
| Probabilistic sensitivity analysis | PSA |
| Quality-adjusted life-years | QALY |
| 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); D. A. 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 (Robert 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 (Janet R 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 (Janet R 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); Janet R. Casey and Pichichero [2004](#ref-Casey2004); Janet R 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 (N. 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 (Vilhjalmur A 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 (Vilhjalmur A. 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 (O. S. 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% (M. H. 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 (S. a 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 (Robert 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 (Robert 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); M. 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 (Robert 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 (Robert 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 (R 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 (Robert 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 (Robert 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 (S. Black et al. [2000](#ref-Black2000); S. B. Black et al. [2002](#ref-Black2002c); Eskola et al. [2001](#ref-Eskola2001); Fireman et al. [2003](#ref-Fireman2003); K. L. 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 (S. 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 (S. 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 (R. Dagan et al. [2001](#ref-Dagan2001); Eskola et al. [2001](#ref-Eskola2001)). R. 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 S. 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 S. 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 (T 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); T 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 (A. A. I. 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 (T 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 (K. L. 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. The specific pneumococcal conjugate vaccine under study is presented. The enrollment period may be considered the start of the study. R. Dagan et al. ([2001](#ref-Dagan2001)) did not present sufficient information to know the exact enrollment period. Vaccine efficacy is presented along with 95% confidence intervals.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Vaccine | Enrollment period | Country | No. of children | Efficacy against otitis media episodes |
| (S. Black et al. [2000](#ref-Black2000); Fireman et al. [2003](#ref-Fireman2003)) | PCV7 (CRM197) | Oct 1995-Aug 1998 | United States | 37868 | 7.8% (5.4% to 10.2%) |
| (R. Dagan et al. [2001](#ref-Dagan2001)) | PCV9 (CRM197) | Unclear | Isreal | 264 | 17% (-2% to 33%) |
| (Eskola et al. [2001](#ref-Eskola2001)) | PCV7 (CRM197) | Dec 1995-Apr 1997 | Finland | 1662 | 6% (-4% to 16%) |
| (T Kilpi et al. [2003](#ref-Kilpi2003)) | PCV7 (MOMPC) | Dec 1995-Apr 1997 | Finland | 1666 | -1% (-12% to 10% |
| (Prymula et al. [2006](#ref-Prymula2006)) | PCV9 (HiD) | Oct 2000-Sep 2002 | Czech Republic & Slovakia | 4968 | 33.6% (20.8% to 44.3% |
| (O’Brien et al. [2008](#ref-OBrien2008)) | PCV7 (CRM197 | Apr 1997-Aug 2000 | United States | 856 | -0.4% (-19.4% to 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

(T.M. 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

A. A. Palmu et al. ([2013](#ref-Palmu2013))

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

Healthcare operates under resource constraints. In this setting of scarcity, the decision to fund one project invariably results in another project remaining unfunded. Economic analyses are one of many tools that may aid decision-makers in allocating resources optimally. Interventions are contrasted with two or more alternatives, and costs and benefits are systematically compared. Economic analyses require data on the efficacy of the interventions being compared, the burden of disease and subgroups of the population which are affected (Gray et al. [2011](#ref-Gray2011)).

All methods of economic analyses measure the monetary costs associated with the interventions being evaluated, but differ in how they measure the resultant benefits. Cost-benefit analysis translates the effect of an intervention into a monetary value, and calculates the total cost associated with the intervention once any potential savings have been accounted. In cost-effectiveness analysis, the effect of the intervention is measured in units of the condition being intervened upon, e.g. deaths prevented, life-years gained. The results of such an analysis are commonly presented as an incremental cost-effectiveness ratio, which represents the cost associated with one unit change in the effect measure. Cost-effectiveness analyses are preferred over cost-benefit analyses in the healthcare context, as placing a monetary value on a health-effect is both controversial and impractical. One drawback however, is difficulty in comparing cost-effectiveness ratios between studies that use different measurements of effect. Cost-utility analyses remedy this by standardizing a combined effect that measures the quality and quantity of life gained. This combined effect is most often measured in units of quality-adjusted life-years (QALY) (Gray et al. [2011](#ref-Gray2011)).

Quality-adjusted life-years are constructed by dividing each persons life into units of time. A unit of time lived in perfect health is assigned a value of one, while death is assigned a value of zero. Each disease is assigned a utility, which represents the health-related quality of life an individual is expected to have while suffering from the disease. Three methods are generally used to obtain utility values for a given health state. These are the rating scale method, time trade-off and standard gamble. Each method is intended to capture the preferences of the population in which the economic analysis is meant to inform, and they are not meant to be generalized to other populations except with extreme caution (Petrou and Kupek [2009](#ref-Petrou2009)). Even then, some external criteria must be used for the results to be interpretable. Decision-makers must specify the threshold incremental cost-effectiveness ratio, below which an intervention is deemed cost-effective.

Measuring costs associated with an intervention is deceptively simple. The costs associated with an intervention depend on from what perspective the intervention is evaluated (Byford and Raftery [1998](#ref-Byford1998)). When examined from the societal perspective, an expensive medication may be cost-saving, if it allows individuals who would have otherwise required disability benefits to participate in the workforce . The same medication may be considered prohibitively costly when examined from the healthcare sector perspective. The choice of perspective should reflect the purpose of the analysis and the intended audience. For the health-economic analysis of vaccines, the general consensus is to choose the societal perspective but also include an analysis from the perspective of the healthcare sector (G. D. Sanders et al. [2016](#ref-Sanders2016)).

Interventions are compared at a single point in time but accrue costs and benefits over a variably long time period. The time horizon is the term used for the time period over which an intervention is evaluated. In general, the time horizon should be chosen to reflect the duration of the effect of the intervention. In the context of cost-effectiveness analyses of vaccines, the consensus is to use a lifetime horizon, unless there are compelling reasons otherwise (Mauskopf et al. [2018](#ref-Mauskopf2018); Wilkinson et al. [2016](#ref-Wilkinson2016)). To accurately compare interventions with differential distributions in the timing of costs and benefits, it has become standard practice to discount future cost and benefit. The rationale is grounded in both the psychology of human behavior and economic principles (Severens and Milne [2004](#ref-Severens2004)). Society tends to value current costs and benefits higher than those that occur in the future. The exact discount rate, whether it should be constant and whether costs and benefits should be discounted at the same rate are debated (Claxton et al. [2011](#ref-Claxton2011)). However, the general consensus is to use a constant 3% discount rate for both costs and benefits (Mauskopf et al. [2018](#ref-Mauskopf2018); G. D. Sanders et al. [2016](#ref-Sanders2016); Wilkinson et al. [2016](#ref-Wilkinson2016)).

Economic analyses are built upon a set of assumptions that may influence the outcome. In the case of pneumococcal conjugate vaccines, the assumptions include the incidence of disease in the target population, the proportion caused by *Streptococcus pneumoniae*, the serotype distribution, the degree of vaccine uptake, the vaccine efficacy in vaccinated and unvaccinated members of the population, costs and utilities associated with disease states, cost of the vaccine, perspective, time horizon and discounting (M. Wasserman et al. [2018](#ref-Wasserman2018)). These assumptions are combined together in mathematical model which describes the result, given the input parameters. Decision analysis models are static scenario based models in which individuals are independently assumed to progress through a decision tree. The tree has one branch for each intervention being evaluated, and each branch contains an identical set of nodes that represent the health outcomes being considered. However, the nodes on each branch are associated with a different set of costs, consequences and probabilities of occurring, The model is run and the number of individuals in each node are tallied along with the associated cost and consequence to produce the final result. This generally means that the model cannot incorporate different probabilities depending on age or time from the start of the intervention (Gray et al. [2011](#ref-Gray2011)). For example, a decision analysis model would assume that the difference in invasive pneumococcal disease with and without the vaccine were constant, regardless of how many years had passed since the vaccine introduction. Markov models expand upon this framework, by removing the tree structure and allowing individuals to transition between nodes (which are termed health states in Markov models) in any direction. The transitions between health states occur in Markov cycles. At the end of each cycle, the costs and consequences associated with the current health state are recorded, before the next cycle begins. Thus an individual accumulates cost and benefit over time and may transition in and out of health states – an improvement over the static once-only decision analysis models. The transition probabilities may be either constant or time-dependent. However, the Markovian assumption requires that all individuals within a given health state should be homogeneous, regardless of their previous health states or the length of time that they have been in their current state. Thus the transition between health states may depend on the time that has elapsed from the start of the model but cannot depend on what has happened in a prior cycle (Gray et al. [2011](#ref-Gray2011)). A Markov model would assume that an individual who has previously been hospitalized twice for pneumonia, has the same probability of being hospitalized again as someone who has never been hospitalized. Transmission dynamic models expand upon the Markov process by using a set of differential equations to remove the need for the Markovian assumption (Pitman et al. [2012](#ref-Pitman2012)).

Because of the subjective nature of many of the modeling assumptions, a sensitivity analysis that explores the cost-effectiveness outcome over a plausible range of each of the assumptions is necessary. Consensus statements from the World Health Organization and the International Society for Pharmacoeconomics and Outcome Research (ISPOR) require at minimum, a one-way sensitivity analysis of each of the assumptions (Mauskopf et al. [2018](#ref-Mauskopf2018); D. G. Walker, Hutubessy, and Beutels [2010](#ref-Walker2010)). One-way sensitivity analysis imply that each parameter is individually varied across its probability distribution, while other parameters are held constant. The results are often presented as a tornado plot. Scenario analyses show the result of specific combinations of parameter values, which are often based on common situations that Both consensus statements strongly recommend the inclusion of a probabilistic sensitivity analysis, in which the analysis is repeatedly run and the assumptions simultaneously varied across their respective probability distributions (Gray et al. [2011](#ref-Gray2011)). The resulting spread of cost-effectiveness estimates reflects the uncertainty of the analysis. This can be paired with threshold analysis, which shows the proportion of the resulting spread that is above a stated cost-effectiveness threshold, or a generalization of a threshold analysis called the cost-effectiveness acceptability curve (CEAC) (Gray et al. [2011](#ref-Gray2011)).

A large number of cost-effectiveness analyses of pneumococcal conjugate vaccines have been published (Saokaew et al. [2016](#ref-Saokaew2016); Vooren et al. [2014](#ref-VandeVooren2014a); Wu et al. [2015](#ref-Wu2015)). They display great variation in their results, underlying assumptions and modeling choices. In this thesis, cost-effectiveness analyses of pneumococcal conjugate vaccines in high-income countries will be reviewed. The studies included in this review are summarized in Table 3. This review focuses on studies published in 2009 and later, after the introduction of the higher-valent pneumococcal conjugate vaccines. Other published reviews have examined cost-effectiveness studies prior to 2006 (Beutels, Thiry, and Van Damme [2007](#ref-Beutels2007)) and studies in low- and middle income countries (Saokaew et al. [2016](#ref-Saokaew2016)). All of the included studies found pneumococcal conjugate vaccines to be cost-effective compared to no vaccine, but varied as to whether PCV7, PCV10 or PCV13 dominated as compared to the others. The aim of this review is to explore the studies’ design and underlying assumptions, rather than the results.

Table 3 A summary of the economic analyses of pneumococcal conjugate vaccines in high-income countries from 2009-2018. All analyses are either a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA). Costs and benefit are either considered from the societal or health sector perspective, depending on whether indirect costs such as productivity loss are included in the analyses, The time horizon of the studies er presented in years. A lifetime horizon is based on the life-expectancy of the population, and is most commonly assumed to be 100 years. Discount rates are presented separately for costs and benefits. When the time horizon is one year or less, discount rates are not applicable and are presented with a hyphen (-). Earnshaw et al. ([2012](#ref-Earnshaw2012b)) did not publish sufficent information to know what discount rate was used. The table is partially adapted from Wu et al. ([2015](#ref-Wu2015)).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Country | Study type | Perspective | Time horizon (years) | Discount rate of costs (%) | Discount rate of benefits (%) |
| (M. A. O’Brien et al. [2009](#ref-OBrien2009a)) | United States | CUA | Societal | Lifetime | 3 | 3 |
| (Chuck et al. [2010](#ref-Chuck2010)) | Canada | CUA | Health sector | 1 | - | - |
| (Mark H Rozenbaum et al. [2010](#ref-Rozenbaum2010)) | Netherlands | CEA, CUA | Health sector, societal | 5 | 4 | 1.5 |
| (Rubin et al. [2010](#ref-Rubin2010)) | United States | CUA | Socital | 10 | 3 | 3 |
| (Talbird et al. [2010](#ref-Talbird2010)) | Canada, Germany, Mexico, Norway | CEA, CUA | Societal | 1 | - | - |
| (Robberstad et al. [2011](#ref-Robberstad2011)) | Norway | CEA, CUA | Societal | Lifetime | 4 | 4 |
| (A. T. Newall et al. [2011](#ref-Newall2011)) | Australia | CUA | Health sector | 100 | 5 | 5 |
| (Díez-Domingo et al. [2011](#ref-Diez-Domingo2011)) | Spain | CEA, CUA | Health sector | Lifetime | 3 | 3 |
| (Knerer, Ismaila, and Pearce [2012](#ref-Knerer2012)) | Canada, United Kingdom | CEA, CUA | Health sector, societal | Lifetime | 3, 3.5 | 3, 3.5 |
| (Earnshaw et al. [2012](#ref-Earnshaw2012b)) | Canada | CUA | Health sector | Lifetime | Not specified | Not specified |
| (By et al. [2012](#ref-By2012)) | Sweden | CUA | Societal | Lifetime | 3 | 3 |
| (D. R. Strutton et al. [2012](#ref-Strutton2012)) | Germany, Greece, Netherlands | CEA, CUA | Health sector | 1 | - | - |
| (Blank and Szucs [2012](#ref-Blank2012)) | Switzerland | CEA, CUA | Health sector | 10 | 3 | 3 |
| (Hoek et al. [2012](#ref-VanHoek2012)) | England | CUA | Health sector | 30 | 3.5 | 3.5 |
| (R. M. Klok et al. [2013](#ref-Klok2013)) | Denmark, Sweden | CEA, CUA | Health sector | 1 | 3 | 3 |
| (Zhou et al. [2014](#ref-Zhou2014)) | United States | CUA | Health sector, societal | Lifetime | 3 | 3 |
| (Delgleize et al. [2016](#ref-Delgleize2016)) | United Kingdom | CUA | Health sector, societal | Lifetime | 3.5 | 3.5 |
| (A. Newall et al. [2016](#ref-Newall2016)) | Australia | CUA | Health sector | - | 5 | 5 |
| (Castiglia et al. [2017](#ref-Castiglia2017)) | Italy | CUA | Health sector | 18 | 3 | 3 |
| (Gouveia et al. [2017](#ref-Gouveia2017)) | Portugual | CEA | Societal | Lifetime | 5 | 5 |
| (Kuhlmann and Schulenburg [2017](#ref-Kuhlmann2017)) | Germany | CUA | Health sector, societal | 50 | 3 | 3 |

### Vaccine efficacy assumptions in economic analyses of pneumococcal conjugate vaccines

Because *Streptococcus pneumoniae* causes a wide range of clinical infections, economic analyses that study the cost-effectiveness of pneumococcal conjugate vaccines must make choices regarding which health outcomes to include in the analysis. Most, but not all, include acute otitis media, pneumonia and invasive pneumococcal disease. The way in which each study measures these health outcomes differs, and the studies assume divergent vaccine efficacies for outcomes. Each of the health outcomes considered may or may not be associated with further health care consumption and disease burden. Repeated acute otitis media may lead to a tympanostomy tube procedure, and invasive pneumococcal disease may cause death or long term disability. If and how disease sequlae are taken into account is variable between studies. Finally, the studies differ in whether they consider health outcomes in unvaccinated members of the population (Holubar et al. [2017](#ref-Holubar2017); Isaacman et al. [2008](#ref-Isaacman2008)).

Most of the cost-effectiveness analyses that were reviewed based their vaccine efficacy estimates for acute otitis media on the results of the Northern California Kaiser Permente trial (S. Black et al. [2000](#ref-Black2000); Fireman et al. [2003](#ref-Fireman2003)). Others, (Castiglia et al. [2017](#ref-Castiglia2017); Delgleize et al. [2016](#ref-Delgleize2016); R. M. Klok et al. [2013](#ref-Klok2013); Knerer, Ismaila, and Pearce [2012](#ref-Knerer2012); Robberstad et al. [2011](#ref-Robberstad2011); D. R. Strutton et al. [2012](#ref-Strutton2012); Talbird et al. [2010](#ref-Talbird2010)) based the efficacy of PCV7 and PCV13 on Eskola et al. ([2001](#ref-Eskola2001)), and justified a higher vaccine efficacy estimate for PHiD-CV10 based on Prymula et al. ([2006](#ref-Prymula2006)) or Tregnaghi et al. ([2014](#ref-Tregnaghi2014)), by also assuming efficacy against otitis media caused by non-typable *Haemophilus influenzae*. The validity of this assumption has been called into question (M. Wasserman et al. [2018](#ref-Wasserman2018)). Few studies did not base their efficacy estimates on data from randomized clinical trials. Gouveia et al. ([2017](#ref-Gouveia2017)) based their otitis media efficacy estimates on observational data from the United Kingdom, which used a crude interrupted time series analysis to ascertain impact (Lau et al. [2015](#ref-Lau2015)). Hoek et al. ([2012](#ref-VanHoek2012)) assumed the otitis media efficacy to be a linear ratio of their estimated efficacy for invasive pneumococcal disease, which they based on a complex transmission dynamic model. Chuck et al. ([2010](#ref-Chuck2010)) also based the efficacy for otitis media on invasive pneumococcal disease, but used the observed change in invasive disease before and after vaccine introduction without any adjustments for secular trends in the pre-vaccine period. Similarly, Zhou et al. ([2014](#ref-Zhou2014)) did not use any efficacy estimates, but instead directly compared published incidence rates of otitis media before and after vaccine introduction and assumed any difference was due to the vaccine.

The vaccine efficacy estimates for hospitalized and non-hospitalized pneumonia were generally based on S. B. Black and Shinefield ([2002](#ref-Black2002)). As with otitis media, Delgleize et al. ([2016](#ref-Delgleize2016)) and Castiglia et al. ([2017](#ref-Castiglia2017)) based their estimates on Tregnaghi et al. ([2014](#ref-Tregnaghi2014)). A. Newall et al. ([2016](#ref-Newall2016)) based the efficacy against outpatient pneumonia on S. B. Black and Shinefield ([2002](#ref-Black2002)), as did other studies. However, the efficacy estimates for inpatient pneumonia and invasive disease was estimated using a novel time-series methodology. They projected the rate of disease in the pre-vaccine period to the post-vaccine period using a Poisson regression, and corrected for changes in population demographics using an offset term. Because they only had access to three years of annual pre-vaccine incidence rates, they were unfortunately only able to correct for an intercept term and they acknowledge this in their discussion section (A. Newall et al. [2016](#ref-Newall2016)). Nevertheless, the methodology is interesting. In the case of pneumonia, a larger proportion of studies based their estimates on either unadjusted observational studies from other populations or did not provide sufficient information to ascertain what estimates was used. Chuck et al. ([2010](#ref-Chuck2010)) and Hoek et al. ([2012](#ref-VanHoek2012)) again assumed the efficacy for pneumonia to be a fixed ratio of their invasive pneumococcal disease efficacy estimate. Talbird et al. ([2010](#ref-Talbird2010)) and Gouveia et al. ([2017](#ref-Gouveia2017)) never explicitly state what their assumed vaccine efficacy is, and no rationale is provided. The estimate cannot be deduced from tables and references. Díez-Domingo et al. ([2011](#ref-Diez-Domingo2011)) assumed a 42% efficacy against hospitalized pneumonia cases but did not provide any rationale or reference for this assumption. Zhou et al. ([2014](#ref-Zhou2014)) directly compared published incidence rates for pneumonia in the pre- and post-vaccine periods, and assumed any difference to be a direct result of vaccination. Finally, M. A. O’Brien et al. ([2009](#ref-OBrien2009a)) did not consider pneumonia or invasive pneumococcal disease as health outcomes.

Invasive pneumococcal disease vaccine efficacy estimates were most often based on S. Black et al. ([2000](#ref-Black2000)), and Kuhlmann and Schulenburg ([2017](#ref-Kuhlmann2017)) based their estimate on A. A. Palmu et al. ([2013](#ref-Palmu2013)). A. Newall et al. ([2016](#ref-Newall2016)) used a novel regression methodology as previously described, and Chuck et al. ([2010](#ref-Chuck2010)) used simple unadjusted pre- and post-vaccine observational data. The remaining studies based their efficacy estimates on non-randomized studies observational studies in different populations. Hoek et al. ([2012](#ref-VanHoek2012)) utilized a complex transmission dynamic model on meticulously collected prospective surveillance data to estimate the effect of PCV13, but did not provide any reference or rationale for the efficacy parameters used in the model.  
Castiglia et al. ([2017](#ref-Castiglia2017)) assumed that the vaccine efficacy of PCV10 and PCV13 were the average of two observational studies (A. Palmu et al. [2015](#ref-Palmu2015); Waight et al. [2015](#ref-Waight2015)). By et al. ([2012](#ref-By2012)), Delgleize et al. ([2016](#ref-Delgleize2016)), Knerer, Ismaila, and Pearce ([2012](#ref-Knerer2012)), A. T. Newall et al. ([2011](#ref-Newall2011)) and Robberstad et al. ([2011](#ref-Robberstad2011)) based their efficacy estimate on a matched case-control study of PCV7, conducted in the United States in 2001-2002 (Whitney et al. [2006](#ref-Whitney2006)). Talbird et al. ([2010](#ref-Talbird2010)) failed to provide any reference or rationale for their efficacy estimates.

Critical appraisals of cost-effectiveness assumptions have shown that they can have large effects on the study’s outcomes (M. Wasserman et al. [2018](#ref-Wasserman2018)). The included cost-effectiveness and cost-utility analyses base their efficacy estimates on many different studies. An alarmingly large proportion of studies cite observational data from other time-periods and study populations that used a different formulation of pneumococcal conjugate vaccine. In most cases were randomized controlled trials are utilized, the most commonly referenced studies were conducted ten years prior in a completely vaccine naive population using PCV7. A. Newall et al. ([2016](#ref-Newall2016)) introduced a thoughtful time-series approach were local pre-vaccine trends in disease were statistically extrapolated to the post-vaccine period to simulate what would have occurred, had the vaccine not been introduced. This was ten subtracted from the observed rates of disease to estimate the true vaccine impact. However, as the authors concede in their discussion, they did not have access to adequate pre-vaccine data and were thus unable to conduct a robust statistical extrapolation (A. Newall et al. [2016](#ref-Newall2016)). The care with which these data are incorporated also varies between studies, with only some considering vaccine coverage, waning vaccine protection and adjusting for local serotype distribution and herd effect 4. Additionally, a large variation existed in how the pre-vaccine incidence of disease was defined, with some studies borrowing incidence estimates from other countries. A review of the epidemiological rationale used in each of the studies is beyond the scope of this thesis.

Table 4 A summary of modeling assumptions used in economic analyses of pneumococcal conjugate vaccines in high-income countries from 2009-2018. Several different modeling strategies were used, which are discussed in more detail in chapter 2.3.. Vaccine protection is known to wane over an unknown length of time. The assumed length of protection is presented with a hyphen (-) if the study assumed infinite protection or did not provide sufficient data to ascertain over which period the protection waned. Similarly, a hyphen indicates that assumed vaccine coverage was not specified. When herd effect was included in the model, it was often only included for invasive pneumococcal disease (IPD). Serotype replacement was often only incorporated for indirect effects (herd immunity, herd effect). When models are based on ecological data, they implicitly includ both herd effects and serotype replacement. Only Hoek et al. ([2012](#ref-VanHoek2012)) directly modelled the serotype replacement. Sensitivity analyses are can be either deterministic, such as 1-Way, 2-Way and scenario analyses, or stochastic, such as proabilistic sensitivity analyses (PSA) and cost-effectiveness acceptability curves (CEAC). Sensitivity analyses are discussed in more detail in chapter 2.3.. The table is partially adapted from Wu et al. ([2015](#ref-Wu2015)).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Model structure | Vaccine protection (years) | Vaccine uptake (%) | Herd effect | Serotype replacement | Sensitivity analyses |
| (M. A. O’Brien et al. [2009](#ref-OBrien2009a)) | Markov | - | - | No | No | 1-Way, 2-Way, threshold |
| (Chuck et al. [2010](#ref-Chuck2010)) | Steady-state population | - | 83.8 | Yes, IPD only | No | PSA |
| (Mark H Rozenbaum et al. [2010](#ref-Rozenbaum2010)) | Decision analysis | 5 | - | Yes, IPD only | Yes, herd effect only | 1-Way, PSA, threshold, CEAC, scenario |
| (Rubin et al. [2010](#ref-Rubin2010)) | Markov state transition | 5 | 90 | Yes | Yes, ecological data | - |
| (Talbird et al. [2010](#ref-Talbird2010)) | Steady-state population | - | 80-91 | Yes | Yes, herd effect only | 1-Way, threshold |
| (Robberstad et al. [2011](#ref-Robberstad2011)) | Markov cohort | 9 | 80-95 | Yes, IPD only | Yes, herd effect only | 1-Way, 2-Way, PSA, CEAC, scenario |
| (A. T. Newall et al. [2011](#ref-Newall2011)) | Markov state transition | 10 | 75-95 | Yes | Yes, increased incidence | 1-Way, PSA, CEAC, scenario |
| (Díez-Domingo et al. [2011](#ref-Diez-Domingo2011)) | Markov cohort | 6 | 95 | Yes | Yes, increased incidence | 1-Way, scenario |
| (Knerer, Ismaila, and Pearce [2012](#ref-Knerer2012)) | Markov cohort | 10 | 100 | Yes, IPD only | Yes, herd effect only | 1-Way, PSA |
| (Earnshaw et al. [2012](#ref-Earnshaw2012b)) | Markov cohort | - | - | Yes | No | 1-Way, threshold, scenario |
| (By et al. [2012](#ref-By2012)) | Markov cohort | 10 | 100 | Yes, IPD only | Yes, herd effect only | 1-Way, scenario |
| (D. R. Strutton et al. [2012](#ref-Strutton2012)) | Markov cohort | - | 80-95 | Yes | Yes, ecological data | 1-Way, scenario |
| (Blank and Szucs [2012](#ref-Blank2012)) | Decision analysis | 5 | 83 | No | No | 1-Way |
| (Hoek et al. [2012](#ref-VanHoek2012)) | Transmission dynamic | 10 | - | Yes | Yes, directly | PSA, threshold, CEAC, scenario |
| (R. M. Klok et al. [2013](#ref-Klok2013)) | Markov state transission | - | - | Yes | Yes, ecological data | 1-Way, scenario |
| (Zhou et al. [2014](#ref-Zhou2014)) | Decision analysis | - | - | No | No | 1-Way, scenario |
| (Delgleize et al. [2016](#ref-Delgleize2016)) | Markov cohort | 10 | 100 | Yes, IPD only | Yes, herd effect only | 1-Way, PSA, threshold, CEAC, scenario |
| (A. Newall et al. [2016](#ref-Newall2016)) | Markov state transition | 10 | - | Yes, IPD only | Yes, ecological data | PSA, threshold, CEAC, scenario |
| (Castiglia et al. [2017](#ref-Castiglia2017)) | Markov cohort | 10 | 87.46 | Yes, IPD only | Yes, herd effect only | 1-Way, PSA, threshold, scenario |
| (Gouveia et al. [2017](#ref-Gouveia2017)) | Markov cohort | 25 | 60.8 | Yes, IPD only | No | 1-Way, scenario |
| (Kuhlmann and Schulenburg [2017](#ref-Kuhlmann2017)) | Markov state transition | 8 | 90 | Yes | Yes | 1-Way, PSA, threshold, CEAC, scenario |

### Assumptions regarding costs and utilities in economic analyses of pneumococcal vaccines

Cost-utility analyses present their results as the cost of an intervention per additional quality-adjusted life-year gained. QALYs are a good universal measure of benefit, provided that the quality adjustments for the included health outcomes accurately reflect the true preferences of the population for which the cost-utility analysis is supposed to inform decision making. Otherwise, the resulting cost-utility ratio is at best externally valid in comparison to other studies which use the same utility weights, but has no intrinsic meaning in informing decision-makers. Similarly, the costs associated with each vaccine and health outcome must necessarily be derived from accurate estimates from the population under study. If costs are measured imprecisly or obtained from other countries or time-periods, it becomes difficult to imagine what relevance the economic analysis has to the decision that needs to be made.

To date, only three studies have been published that estimate utility values for pneumococcal diseases in high-income countries by interviewing children or parents of children who have experienced the disease. One study in the United States in 2001 used time trade-off and willingness-to-pay methods to estimate the utility values associated with simple and complex acute otitis media, moderate and severe pneumonia, meningitis and bacteremia (Prosser et al. [2004](#ref-Prosser2004)). Another study from the United Kingdom used the health utility index to estimate utility values for pneumococcal meningitis (Legood et al. [2009](#ref-Legood2009)). It is unclear from the publication over which time period the study was conducted. Finally, the utility values for adult pneumococcal pneumonia were estimated using the EuroQoL five dimensional questionnaire in France (Andrade et al. [2018](#ref-Andrade2018)). Additionally, J. E. Bennett et al. ([2000](#ref-Bennett2000)) estimated utility values for meningitis sequlae; deafness and moderate and severe brain damage by interviewing parents of toddlers presenting to urgent care for unrelated illnesses. Oostenbrink, A Moll, and Essink-Bot ([2002](#ref-Oostenbrink2002)) surveyed 28 pediatricians in the Netherlands using the health utility index and EuroQoL five dimensional questionnaires to ascertain utility weights for long term sequlae of bacterial meningitis.

With few exceptions, all of the reviewed cost-utility analyses used the same two references for utilities (J. E. Bennett et al. [2000](#ref-Bennett2000); Herdman et al. [2016](#ref-Herdman2016); Oostenbrink, A Moll, and Essink-Bot [2002](#ref-Oostenbrink2002)). Most (Kuhlmann and Schulenburg [2017](#ref-Kuhlmann2017); A. T. Newall et al. [2011](#ref-Newall2011); A. Newall et al. [2016](#ref-Newall2016); Mark H Rozenbaum et al. [2010](#ref-Rozenbaum2010); Rubin et al. [2010](#ref-Rubin2010); Talbird et al. [2010](#ref-Talbird2010)) did so indirectly, and instead cited a cost-utility analysis by Melegaro and Edmunds ([2004](#ref-Melegaro2004a)), which itself based it’s estimates on the two studies. This is important as Melegaro and Edmunds ([2004](#ref-Melegaro2004a)) incorrectly translated the utility values to QALYs (Herdman et al. [2016](#ref-Herdman2016)). Earnshaw et al. ([2012](#ref-Earnshaw2012b)), Knerer, Ismaila, and Pearce ([2012](#ref-Knerer2012)) and By et al. ([2012](#ref-By2012)) took the extra step of citing Morrow et al. ([2007](#ref-Morrow2007)), which itself cites Melegaro and Edmunds ([2004](#ref-Melegaro2004a)). M. A. O’Brien et al. ([2009](#ref-OBrien2009a)) base their utility values on Prosser et al. ([2004](#ref-Prosser2004)). R. M. Klok et al. ([2013](#ref-Klok2013)) uses utilities based on a Maddigan, Feeny, and Johnson ([2005](#ref-Maddigan2005)) which is a study of the quality of life of diabetic adults in Canada, and provides no rationale for the how this could be relevant to pneumococcal disease in Danish and Swedish children. D. R. Strutton et al. ([2012](#ref-Strutton2012)) claim to use country specific utilities for Germany, Greece and the Netherlands, but provide no reference for the utility values, which are the same for each country and identical to those in Maddigan, Feeny, and Johnson ([2005](#ref-Maddigan2005)). Chuck et al. ([2010](#ref-Chuck2010)) references the Canadian National advisory committee on immunization statement on recommended use of pneumococcal conjugate vaccine, which is not available online. Desipite the considerable uncertainty associated with utilities, they were often not examined with sensitivity analyses (Blank and Szucs [2012](#ref-Blank2012); Chuck et al. [2010](#ref-Chuck2010); Earnshaw et al. [2012](#ref-Earnshaw2012b); Gouveia et al. [2017](#ref-Gouveia2017); R. M. Klok et al. [2013](#ref-Klok2013); A. Newall et al. [2016](#ref-Newall2016); D. R. Strutton et al. [2012](#ref-Strutton2012); Talbird et al. [2010](#ref-Talbird2010)).

The costs that are included in the economic analyses are divided into direct and indirect costs. Direct costs include the cost of each vaccine dose, cost of hospitalized and outpatient health outcomes, and the cost of long-term sequelae. The reviewed studies invariably used the list price of pneumococcal conjugate vaccines currently available in the respective country during the time the cost-effectiveness analysis was undertaken. This would be considered a conservative estimate, as healthcare systems generally negotiate the purchase price of the vaccine considerably lower than the list price. Studies comparing two higher-valency pneumococcal conjugate vaccines most commonly used the list price of the available vaccine and assumed price parity, which negates the possibility of competition between the two vaccine manufacturers and seems like an unreasonable assumption. Ideally, such an assumption would be examined in sensitivity analyses. Some of the reviewed studies did not perform such an analysis for any of the cost components (Chuck et al. [2010](#ref-Chuck2010); Earnshaw et al. [2012](#ref-Earnshaw2012b); Gouveia et al. [2017](#ref-Gouveia2017); R. M. Klok et al. [2013](#ref-Klok2013); A. Newall et al. [2016](#ref-Newall2016); D. R. Strutton et al. [2012](#ref-Strutton2012); Talbird et al. [2010](#ref-Talbird2010)).

The most common method employed to estimate the direct costs associated with hospitalized health outcomes, was to use official statistics of costs associated with diagnostic related groupings and unit costs from national tariffs. Expert opinion was then used to decide which resources would be used on average for each health outcome, to construct a hypothetical reference case used to calculate the direct cost. Outpatient health outcomes were often solely based on the assumptions of expert opinion, except for the studies conducted in the Netherlands, Germany and the United Kingdom, were official statistics on outpatient unit costs are available. Rationale as to what was considered expert opinion was only stated in one case (Knerer, Ismaila, and Pearce [2012](#ref-Knerer2012)). Sometimes this resulted in suspect estimates, e.g. that each case of outpatient acute otitis media in Greece cost 3861 euros – 30-300 times higher than the estimate for the two other countries included in the study (D. R. Strutton et al. [2012](#ref-Strutton2012)). This is particularly unfortunate because costs were not included in the sensitivity analysis. Díez-Domingo et al. ([2011](#ref-Diez-Domingo2011)) and Hoek et al. ([2012](#ref-VanHoek2012)) obtained average costs and hospital length of stay for each health condition directly from medical records. The direct cost of long-term sequale was with few exceptions based on assumptions and expert opinion.

Indirect costs mainly compromises lost workdays, and were only included in few of the reviewed studies (By et al. [2012](#ref-By2012); Delgleize et al. [2016](#ref-Delgleize2016); Gouveia et al. [2017](#ref-Gouveia2017); Kuhlmann and Schulenburg [2017](#ref-Kuhlmann2017); Robberstad et al. [2011](#ref-Robberstad2011); Mark H Rozenbaum et al. [2010](#ref-Rozenbaum2010)). M. A. O’Brien et al. ([2009](#ref-OBrien2009a)) included parental time spent for outpatient visit, but not lost workdays. Generally, average wage and unemployment rates were extracted from official statistics and multiplied by the days of work lost to estimate the indirect cost. The days of work lost were assumed to be equal to the hospital length of stay for hospitalized cases for both adults and parents of admitted children. The days of work lost for outpatient cases were assumed to be half of that of hospitalized cases. In the case of outpatient acute otitis media, parents were assumed to lose from zero to three days depending on the study, and no rationale was provided in most studies.

# 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

Placeholder

## Data collection and sources

### Statistics Iceland

### Landspitali University Hospital patient registry

### The Primary Care Registry

### The National Vaccine Registry

### The National Drug Prescription Registry

### Reimbursement database of Icelandic Health Insurance

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

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

## Impact on outpatient antimicrobial prescriptions (Paper III)

## Impact on tympanostomy tube procedures (Paper IV)

## Impact on respiratory associated hospitalizations (Paper V)

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

### Data sources

### Statistical analysis

# Results

Placeholder

## Data collection and sources

### Statistics Iceland

### Landspitali University Hospital patient registry

### The Primary Care Registry

### The National Vaccine Registry

### The National Drug Prescription Registry

### Reimbursement database of Icelandic Health Insurance

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

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

## Impact on outpatient antimicrobial prescriptions (Paper III)

## Impact on tympanostomy tube procedures (Paper IV)

## Impact on respiratory associated hospitalizations (Paper V)

# Discussion

Placeholder

## Main findings

## Data collection and sources

## Epidemiology and impact of PHiD-CV10 on otitis media in Iceland (Papers I, II, III, V and VI)

### Epidemiology of acute otitis media in Iceland (Papers II and V)

### Impact on primary care visits for otitis media (Papers II and VI)

Paragraph comparing our results to the results of others

### Impact on pediatric emergency department visits for acute otitis media (Paper I)

Paragraph comparing our results to the results of others

### Impact on outpatient antimicrobial prescriptions for otitis media (Paper III)

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

### Impact on hospital admissions for otitis media (Paper V)

### Evidence of herd-effect of PHiD-CV10 on the incidence of otitis media in the unvaccinated population (Papers II and VI)

## Impact of PHiD-CV10 on tympanostomy tube placements (Paper IV)

## Impact of PHiD-CV10 on pneumonia in Iceland (Papers V and VI)

### Impact on pneumonia hospitalizations (Papers V and VI)

### Evidence of herd-effect of PHiD-CV10 on the incidence of pneumonia hospitalization in the unvaccinated population (Papers V and VI)

## Impact of PHiD-CV10 on invasive pneumococcal disease (Papers V and VI)

## Cost-effectiveness of introduction of PHiD-CV10 into the Icelandic pediatric vaccination program (Paper VI)

# Conclusions

* Study the herd-effect of PHiD-CV10 introduction.

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