PhD thesis

Elías Sæbjörn Eyþórsson

2019-01-12

Table of Contents

# automatically create a bib database for R packages

Placeholder

# Introduction

*Streptococcus pneumoniae* is a commensal bacterium found in the nasopharynx of humans (Hussain et al. [2005](#ref-Hussain2005)). It is also a common pathogen, and one of the most common bacterial causes of lower respiratory disease in humans (K. L. O’Brien et al. [2009](#ref-OBrien2009); Troeger et al. [2018](#ref-Troeger2018)). 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 the Danish scientist Christian Gram that retained the dark aniline-gentian violet stain that now bears his name (Gram [1884](#ref-Gram1884)). Pneumococcus was first isolated in 1881 by two microbiologist, George M. Sternberg in the United States and Louis Pasteur in France (Pasteur [1881](#ref-Pasteur1881); Sternberg [1882](#ref-Sternberg1881); Watson et al. [1993](#ref-Watson1993)). The causal association between this newly discovered bacterium and pneumonia was firmly established only five years later (Weichselbaum [1886](#ref-Weichselbaum1886)), and in the following decade, all clinical presentations of pneumococcal infections had been described (Austrian [1981](#ref-Austrian1981)).

The infectious manifestations of pneumococcal disease are, broadly speaking, local infections of the respiratory tract and infections of previously sterile tissue. They range from common to uncommon, and from benign to serious. The most common infectious manifestation of pneumococcus is acute otitis media (AOM) – an infection of the middle ear (Coker et al. [2010](#ref-Coker2010); Ngo et al. [2016](#ref-Ngo2016)). The disease course is benign and rarely results in permanent disability (Vergison et al. [2010](#ref-Vergison2010)). On the other hand, AOM is the most common reason for physician visit and for antimicrobial prescription in the paediatric population (Grijalva, Nuorti, and Griffin [2009](#ref-Grijalva2009); Todberg et al. [2014](#ref-Todberg2014)). Antimicrobial consumption is causally related to antimicrobial resistance, a major threat to public health (Arason et al. [1996](#ref-Arason1996); Austin, Kristinsson, and Anderson [1999](#ref-Austin1999)).  
Recurrent or persistent otitis media is sometimes treated with the surgical placement of tympanic tubes, rendering it the most common surgical procedure requiring general anesthesia in children (Cullen, Hall, and Golosinskiy [2009](#ref-Cullen2009)). Thus, while AOM is a benign disease, it is associated with a large healthcare burden (Arguedas et al. [2010](#ref-Arguedas2010); Monasta et al. [2012](#ref-Monasta2012)).

A potentially more serious manifestation of pneumococcal 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 (Troeger et al. [2017](#ref-Troeger2017)). 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 (Feikin et al. [2000](#ref-Feikin2000); Ricketson et al. [2013](#ref-Ricketson2013); Tsigrelis et al. [2008](#ref-Tsigrelis2008)). The case-fatality ratio (CFR) from pneumococcal meningitis in Icelandic children and adults is estimated at 13% and 8% respectively (Snaebjarnardóttir et al. [2013](#ref-Snaebjarnardottir2013); Þórðardóttir et al. [2014](#ref-Pordardottir2014)). Pneumococcal infections are responsible for a large healthcare burden that spans the range from outpatient to inpatient treatment (Backhaus et al. [2016](#ref-Backhaus2016); Pulido and Sorvillo [2010](#ref-Pulido2010)).

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 defined 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 (Habib, Porter, and Satzke [2014](#ref-Habib2014a)). As the capsule contains only polysaccharides and not proteins, the immune response is T-cell independent and therefore poorly immunogenic, especially in children, 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 (Beutels et al. [2006](#ref-Beutels2006)). Because young children do not have 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, often without 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); Quirk et al. [2018](#ref-Quirk2018)). 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 (Halloran, Longini, and Struchiner [2010](#ref-Halloran2010); Tsaban and Ben-Shimol [2017](#ref-Tsaban2017)). Serotype replacement can also occur, where previously rare serotypes appear and fill the ecological niche vacated by the vaccine serotypes (Weinberger, Malley, and Lipsitch [2011](#ref-Weinberger2011a); Quirk et al. [2018](#ref-Quirk2018)).

Health systems operate under constraints on budgets and resources. Demonstrating vaccine benefit for individuals is essential, but not the only factor to consider when making health policy decisions. Cost and resource allocation are also of great importance. The diseases prevented by an intervention have associated expenses which must be accounted for when the expenditures for the intervention are evaluated. This is especially complicated in the case of vaccines, because benefits are not seen immediately but rather over time and occur in both vaccinated and unvaccinated members of the population (Isaacman et al. [2008](#ref-Isaacman2008); Kim and Goldie [2008](#ref-Kim2008)). 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 (Gray et al. [2011](#ref-Gray2011)). To adequately perform such 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 relatively homogeneous population of roughly 350,000 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 12 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 can be linked between the 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; otitis media, pneumonia and invasive pneumococcal disease, including the pathophysiology, natural disease course, and healthcare 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)). Over the course of their lifetime, a child will be colonized by many different serotypes (Hussain et al. [2005](#ref-Hussain2005); Le Polain de Waroux et al. [2014](#ref-LePolaindeWaroux2014)). 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 (Devine et al. [2015](#ref-Devine2015)). New serotypes enter and are carried for a variable period of time, and the relative density of serotypes changes (Rodrigues et al. [2016](#ref-Rodrigues2016); Thors et al. [2018](#ref-Thors2018)).

In some cases, the equilibrium between pneumococcus and the host is destabilized resulting in clinical manifestations (Bergenfelz and Hakansson [2017](#ref-Bergenfelz2017)). It is thought that this is most likely to occur directly following the acquisition of new serotype into the nasopharyngeal flora, though it may occur at any time (Casey, Adlowitz, and Pichichero [2009](#ref-Casey2010)). Because pneumococcus is carried in the nasopharynx, this disequilibrium results in infections of adjacent tissue; the sinuses, middle ear and conjunctiva (Syrjänen et al. [2005](#ref-Syrjanen2005)). 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 (Cilloniz et al. [2016](#ref-Cilloniz2016)).

Invasive disease occurs when pneumococcus penetrates the host’s immunological defenses and proliferates in normally sterile tissue (Song, Nahm, and Moseley [2013](#ref-Song2013)). 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 bacteremic pneumonia, empyemia, septicemia and meningitis (Song, Nahm, and Moseley [2013](#ref-Song2013)). 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 that is most often caused by a viral or bacterial infection (Bergenfelz and Hakansson [2017](#ref-Bergenfelz2017); Heikkinen and Chonmaitree [2003](#ref-Heikkinen2003a)). The clinical presentation of otitis media is variable. Its onset ranges from abrupt to gradual, and its duration from short to protracted (Thornton et al. [2011](#ref-Thornton2011)). 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 an acute inflammatory event. This is the classical acute otitis media 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 12 month period (Pichichero et al. [2008](#ref-Pichichero2008); Venekamp et al. [2018](#ref-Venekamp2018)). 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 (Chen et al. [2013](#ref-Chen2013); Rosenfeld et al. [2016](#ref-Rosenfeld2016))

#### 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. Though most studies focus on bacterial pathogens, the most common cause of AOM is Eustachian tube dysfunction caused by viral infection (Heikkinen and Chonmaitree [2003](#ref-Heikkinen2003a)). Even when bacteria are cultured from middle ear fluid of children experiencing AOM, the causative agent may still be a virus, and the bacteria an innocent bystander that was trapped in the middle ear following acute closure of the Eustachian tube (Chonmaitree et al. [2016](#ref-Chonmaitree2016)). In upwards of 90% of otitis media cases with a positive bacterial culture, the bacteria aspirated from the middle ear fluid will also be found in the nasopharynx (Casey, Adlowitz, and Pichichero [2009](#ref-Casey2010)). The most common bacterial causes of otitis media are non-typable *Haemophilus influenzae* (NTHi), *Streptococcus pneumoniae* and *Moraxella catarrhalis* (Bluestone, Stephenson, and Martin [1992](#ref-Bluestone1992); Casey and Pichichero [2004](#ref-Casey2004); Casey, Adlowitz, and Pichichero [2009](#ref-Casey2010); Ngo et al. [2016](#ref-Ngo2016); Pumarola et al. [2013](#ref-Pumarola2013)). The relative contribution of these three pathogens is remarkably stable between countries and over time (Ngo et al. [2016](#ref-Ngo2016)). 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% of acute otitis media 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 predominantly due to NTHi (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)).

#### Healthcare burden of otitis media

The healthcare burden caused by otitis media is disproportionate to the severity of the disease (Ahmed, Shapiro, and Bhattacharyya [2014](#ref-Ahmed2014)). Acute otitis media is the most common reason for physician visit among children, a fact which has been frequently documented in multiple countries (Arguedas et al. [2010](#ref-Arguedas2010); Marchisio et al. [2012](#ref-Marchisio2012); Monasta et al. [2012](#ref-Monasta2012)). 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 (Blank et al. [2014](#ref-Blank2014)). A Dutch study which surveyed parents of children younger than one year of age repeatedly for 12 consecutive months found that the incidence of parentally reported acute otitis media episodes was 624 per 1,000 person-years, and that only half resulted in physician visits (Fortanier et al. [2015](#ref-Fortanier2015)). By a child’s third birthday, 60% to 80% will have experienced at least one episode of AOM (Kaur, Morris, and Pichichero [2017](#ref-Kaur2017); Teele, Klein, and Rosner [1989](#ref-Teele1989)). The incidence of outpatient AOM in children is reviewed in Table 1.

Table 1 A review of observed incidence rates of acute otitis media in high-income countries prior to the introduction of paediatric pneumococcal conjugate vaccination. Countries are displayed in alphabetical order. The studies report incidence for different age-groups. The incidence is provided per 100 person-years. When applicable, the cumulative incidence of children who had experienced at least one episode of otitis media by a certain age are displayed. Only two studies were designed to capture this measure of incidence. Missing information is indicated with a hyphen (-)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Country | Observation year | Age (years) | Incidence (per 100 person-years) | Cumulative incidence |
| De Wals et al. ([2009](#ref-DeWals2009)) | Canada | 2000 | 0-5 | 59 | - |
| Todberg et al. ([2014](#ref-Todberg2014)) | Denmark | 2010 | 0-7 | - | 60% by seven |
| Usonis et al. ([2016](#ref-Usonis2016)) | Estonia | 2013 | 0-5 | 14 | - |
| Adam and Fehnle ([2008](#ref-Adam2008)) | Germany | 2007 | 0-2 | 29 | - |
| Liese et al. ([2014](#ref-Liese2014)) | Germany | 2010 | 0-5 | 26 | - |
| Esposito et al. ([2007](#ref-Esposito2007)) | Italy | 2002 | 0-2.5 | 47 | - |
| Marchisio et al. ([2012](#ref-Marchisio2012)) | Italy | 2004 | 0-6 | 16 | - |
| Liese et al. ([2014](#ref-Liese2014)) | Italy | 2010 | 0-5 | 20 | - |
| Usonis et al. ([2016](#ref-Usonis2016)) | Lithuania | 2013 | 0-5 | 18 | - |
| Gribben et al. ([2012](#ref-Gribben2012)) | New Zealand | 2009 | 0-4 | 27 | 74% by five |
| Usonis et al. ([2016](#ref-Usonis2016)) | Poland | 2013 | 0-5 | 12 | - |
| Usonis et al. ([2016](#ref-Usonis2016)) | Romania | 2013 | 0-5 | 14 | - |
| Usonis et al. ([2016](#ref-Usonis2016)) | Slovenia | 2013 | 0-5 | 34 | - |
| Liese et al. ([2014](#ref-Liese2014)) | Spain | 2010 | 0-5 | 33 | - |
| Gisselsson-Solen ([2017](#ref-Gisselsson-Solen2017)) | Sweden | 2009 | 0-4 | 47 | - |
| Liese et al. ([2014](#ref-Liese2014)) | Sweden | 2010 | 0-5 | 26 | - |
| Lau et al. ([2015](#ref-Lau2015)) | United Kingdom | 2005 | 0-10 | 13 | - |
| Liese et al. ([2014](#ref-Liese2014)) | United Kingdom | 2010 | 0-5 | 23 | - |
| Grijalva, Nuorti, and Griffin ([2009](#ref-Grijalva2009)) | United States | 1996 | 0-5 | 95 | - |
| Grijalva et al. ([2006](#ref-Grijalva2006)) | United States | 1999 | 0-2 | 142 | - |
| Zhou et al. ([2008](#ref-Zhou2008)) | United States | 1999 | 0-2 | 207 | - |
| Poehling ([2004](#ref-Poehling2004)) | United States | 2000 | 0-2 | 178-225 | - |

Likewise, otitis media is also responsible for the majority of antimicrobial prescriptions, and thus contributes significantly to antimicrobial resistance (Austin, Kristinsson, and Anderson [1999](#ref-Austin1999); Grijalva, Nuorti, and Griffin [2009](#ref-Grijalva2009)). Though often benign and self-limiting, AOM can progress to recurrent or chronic infection and require more invasive treatment (Cullen, Hall, and Golosinskiy [2009](#ref-Cullen2009); Vlastarakos et al. [2007](#ref-Vlastarakos2007)). Mastoiditis is a rare but serious complication of AOM that invariably requires hospital admission and administration of intravenous antimicrobials (Finnbogadóttir et al. [2009](#ref-Finnbogadottir2009); Groth et al. [2011](#ref-Groth2011)).

#### 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 requiring general anesthesia in the paediatric population (Black [1984](#ref-Black1984); Cullen, Hall, and Golosinskiy [2009](#ref-Cullen2009)). Despite their popularity, there is little evidence for the use of tympanostomy tubes for their two most common indications; recurrent otitis media and hearing loss associated with otitis media with effusion (Browning et al. [2010](#ref-Browning2010); Paradise et al. [2001](#ref-Paradise2001); Paradise et al. [2007](#ref-Paradise2007); Venekamp et al. [2018](#ref-Venekamp2018)). 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 (Table 2).

Table 2 A review of observed incidence rates of tympanostomy tube placements in high-income countries prior to the introduction of paediatric pneumococcal conjugate vaccination. Countries are displayed in alphabetical order. The studies report incidence for different age-groups. The incidence is provided per 100 person-years. When applicable, the cumulative incidence of children who had undergone at least one procedure by a certain age are displayed. Missing information is indicated with a hyphen (-)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Country | Observation year | Age (years) | Incidence (per 100 person-years) | Cumulative incidence |
| Spilsbury et al. ([2006](#ref-Spilsbury2006)) | Australia | 2005 | 0-14 | 6 | 8% by 15 |
| Falster et al. ([2013](#ref-Falster2013)) | Australia | 2007 | 0-8 | 6 | 4% by eight |
| Coyte et al. ([2001](#ref-Coyte2001)) | Canada | 1999 | 0-14 | 8 | - |
| Desai, Kellner, and Drummond ([2002](#ref-Desai2002)) | Canada | 2000 | 0-15 | 11 | 7% by three |
| Howitz et al. ([2017](#ref-Howitz2017)) | Denmark | 2007 | 0-15 | 38 | - |
| Djurhuus et al. ([2014](#ref-Djurhuus2014)) | Denmark | 2007 | 0-15 | 32 | 29% by five |
| Groth, Thomsen, and Ovesen ([2015](#ref-Groth2015)) | Denmark | 2007 | 0-2 | 76 | 1% by 10 |
| Pedersen et al. ([2016](#ref-Pedersen2016)) | Denmark | 2007 | 0-3 | 101 | 24% by three |
| Haapkylä et al. ([2008](#ref-Haapkyla2008)) | Finland | 2005 | 0-7 | 15 | - |
| Sarasoja et al. ([2013](#ref-Sarasoja2013)) | Finland | 2008 | 2-13 | - | 15% by 13 |
| Palmu et al. ([2017](#ref-Palmu2017)) | Finland | 2009 | 0-5 | 5 | - |
| A. Palmu et al. ([2015](#ref-Palmu2015)) | Finland | 2010 | 0-2 | 8 | 13% by two |
| Arason et al. ([2002](#ref-Arason2002)) | Iceland | 1998 | 0-5 | - | 30% by six |
| Arason et al. ([2005](#ref-Arason2005)) | Iceland | 2003 | 0-5 | - | 34% by six |
| Kvaerner, Nafstad, and Jaakkola ([2002](#ref-Kvaerner2002)) | Norway | 1996 | 0-4 | - | 9% by five |
| Haapkylä et al. ([2008](#ref-Haapkyla2008)) | Norway | 2005 | 0-7 | 12 | - |
| Florentzson and Finizia ([2012](#ref-Florentzson2012)) | Sweden | 2006 | 0-10 | - | - |
| Gisselsson-Solen ([2017](#ref-Gisselsson-Solen2017)) | Sweden | 2007 | 0-4 | 8 | - |
| Black ([1984](#ref-Black1984)) | United Kingdom | 1982 | 0-9 | 9 | - |
| Bright et al. ([1993](#ref-Bright1993)) | United States | 1988 | 0-17 | - | 13% by 18 |
| Kogan et al. ([2000](#ref-Kogan2000)) | United States | 1991 | 0-3 | - | 7% by three |
| Cullen, Hall, and Golosinskiy ([2009](#ref-Cullen2009)) | United States | 2006 | 0-14 | 11 | - |

The variation can possibly be explained by different thresholds for performing the procedure. By carefully examining the medical records of all children who underwent tympanic tube procedures in five hospitals in New York, Keyhani et al. were able to show that 92% of the procedures would not have been recommended according to the guidelines in force at the time of surgery (Keyhani et al. [2008](#ref-Keyhani2008)).

#### Acute otitis media in Iceland

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

### Pneumonia

Pneumonia is defined as the infectious infiltration of the lung parenchyma. It 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. 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 (Mackenzie [2016](#ref-Mackenzie2016)).

#### 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 in children are *Streptococcus pneumoniae* and *Haemophilus influnzae* (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 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 determine the causative pathogen in this age group (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 have consistently demonstrated the importance of viruses in paediatric pneumonia (Berg et al. [2016](#ref-Berg2016); Jain et al. [2015](#ref-Jain2015); Rudan et al. [2013](#ref-Rudan2013a)). Results have either indicated that viruses are the primary etiological factor, or that viruses weaken the respiratory defenses and allow bacterial disease to develop (Feikin et al. [2017](#ref-Feikin2017)). The considerable heterogeneity in the proportion of pneumonias found to be caused by various pathogens, underscores the importance of study population, time-period and, most importantly, the methods used in determining the causative pathogen (Feikin et al. [2017](#ref-Feikin2017)). A large multicenter study, The Pneumonia Etiology Research for Child Health (PERCH), is underway to clarify the etiology of paediatric pneumonia (Levine et al. [2012](#ref-Levine2012)). Its results have not yet been published.

One of the first prospective studies of paediatric pneumonia was undertaken in Chapel Hill, North Carolina, from 1963 to 1971. The study investigated all lower respiratory infections in children, and found most to be caused by respiratory syncytial virus (RSV), 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. ([1984](#ref-PAISLEY1984)) found pneumococcus to be a contributor in 19% of paediatric pneumonias from 1978-1979. 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)). The other 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 is complicated by the lack of direct sampling from the lungs. In studies that used strict radiological inclusion criteria and lung aspiration to determine the etiology, pneumococcus was found to cause from 20% to 40% of pneumonias (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 studies 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 (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%. Another meta-analysis estimated pneumococcus to be the etiology of 24.8% of community acquired pneumonia (Said et al. [2013](#ref-Said2013)). In a prospective population based study in Iceland, 373 consecutive patients admitted to Landspitali University Hospital for pneumonia were recruited and systematically tested for etiology (Bjarnason et al. [2015](#ref-Bjarnason2015)). Pneumococcus was found to be the causative agent in 28% of community acquired pneumonias, and 41% of healthcare-associated pneumonias.

#### 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 to 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 (Troeger et al. [2018](#ref-Troeger2018)). Large variations exist in the incidence, morbidity and mortality of pneumonia between countries (Troeger et al. [2018](#ref-Troeger2018)). Pneumonia disproportionately affects developing countries, which experience over half of the pneumonia associated mortality (Troeger et al. [2018](#ref-Troeger2018)). Yet pneumonia is still a large healthcare burden in developed countries, and accounts for 3%-18% of all childhood hospital admissions (Madhi et al. [2012](#ref-Madhi2013)). In developed countries, the incidence of pneumonia in children under five years of age is 34-40 cases per 1,000 person-years (Madhi et al. [2012](#ref-Madhi2013)).

The burden of pneumonia is not isolated to mortality. Studies have shown a large impact on health-related quality of life that lasts for months after hospitalization for pneumonia (Andrade et al. [2018](#ref-Andrade2018); Mangen et al. [2017](#ref-Mangen2017)), and in detailed cost analyses, hospitalized cases of pneumonia are associated with large direct and indirect monetary expenditure (Birnbaum et al. [2002](#ref-Birnbaum2002); Keitel et al. [2014](#ref-Keitel2014)).

### Invasive pneumococcal disease

Invasive pneumococcal disease represents the most serious infectious presentation of *Streptococcus pneumoniae*. It occurs when pneumococcus gains access to normally sterile tissue. IPD is an umbrella term that compromises empyema, septic arthritis, bacteremia and meningitis.

The case-fatality ratio (CFR) of hospitalized pneumococcal bacteremia was reported to be 24.8% between 1952 and 1962 (Austrian [1964](#ref-Austrian1964)). Most patients died within five days of hospital admission despite antimicrobial treatment. Though the CFR has improved in the modern era, most patients who die, still do so within five days of hospitalization (Drijkoningen and Rohde [2014](#ref-Drijkoningen2014); Harboe et al. [2010](#ref-Harboe2010); Mufson and Stanek [1999](#ref-Mufson1999); Ladhani et al. [2013](#ref-Ladhani2013); Ricketson et al. [2013](#ref-Ricketson2013); Tsigrelis et al. [2008](#ref-Tsigrelis2008)). The improvement in case-fatality is best demonstrated by a Swedish study which reported the incidence, case-fatality and mortality of hospitalized IPD from 1964 to 2008 (Backhaus et al. [2016](#ref-Backhaus2016)). The overall CFR was 20% from 1964-1980, 15% from 1981-1995 and 9% from 1996-2008 (Backhaus et al. [2016](#ref-Backhaus2016)). A report from an enhanced surveillance database of IPD in 26 European countries, documented CFR of 2.4% in children under five years of age, 9.1% in individuals 5-64 years of age, and 18.6% in adults 65 years of age and older (Torné et al. [2014](#ref-Torne2014)). Pneumococcal serotypes have a variable propensity to cause death (Harboe et al. [2009](#ref-Harboe2009); Hoek, Andrews, et al. [2012](#ref-VanHoek2012a); Weinberger et al. [2010](#ref-Weinberger2010)), and interactions between IPD CFR and seasonal influenza epidemics have been reported (Weinberger et al. [2013](#ref-Weinberger2013)). However, a review of this is beyond the scope of this thesis.

Of the different manifestations of invasive disease, meningitis is associated with the highest CFR. The CFR of paediatric pneumococcal meningitis in Europe and the United States is estimated to be 38% and 8.4% respectively (K. L. O’Brien et al. [2009](#ref-OBrien2009); Hsu et al. [2009](#ref-Hsu2009)) From 1995-2005, the CFR of adult pneumococcal meningitis in Iceland was 8% (Þórðardóttir et al. [2014](#ref-Pordardottir2014)), and a CFR of 13% was documented for pediatric meningitis between 1975-2010 (Snaebjarnardóttir et al. [2013](#ref-Snaebjarnardottir2013)). Of those who survive, morbidity is common. In a single-center case series of pneumococcal meningitis, only 48% of patients were discharged from hospital with good neurological outcome (Kastenbauer and Pfister [2003](#ref-Kastenbauer2003)). Another such study demonstrated long-term neurological sequelae in 30% of survivors (Weisfelt et al. [2006](#ref-Weisfelt2006)). The proportion of surviving children experiencing morbidity is even higher, with 49% having one or more long-term sequelae (Chandran et al. [2011](#ref-Chandran2011)). The effect of these conditions on health-related quality of life is devastating (Oostenbrink, A Moll, and Essink-Bot [2002](#ref-Oostenbrink2002)).

## Pneumococcal vaccines

In this chapter the history of pneumococcal vaccination is reviewed to better understand the current vaccine climate. Special attention is paid to the scientific discourse that led to conjugating pneumococcal polysaccharides to a protein carrier. The scientific literature on the impact of pneumococcal conjugate vaccines on acute otitis media, pneumonia and invasive pneumococcal disease is reviewed and discussed.

### A brief history of pneumococcal vaccination

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

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

Early in the development of pneumococcal vaccines, there was an interested in vaccinating children. Two trials were conducted in the early 1980s which tested the use of polysaccharide vaccines on 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 a response could be induced by adding a protein adjuvant (Austrian [1999](#ref-Austrian1999a)). Several different pneumococcal conjugate vaccines entered phase II and phase III clinical trials in the late 1990s (Austrian [1999](#ref-Austrian1999a)). The first of these to receive licensure was the seven valent pneumococcal conjugate vaccine, licensed in 2000 in the United States (Austrian [1999](#ref-Austrian1999a)). It included the purified polysaccharides of seven serotypes of pneumococcus (4, 9V, 14, 19F, 23F, 18C and 6B) conjugated to CRM197 (PCV7CRM197), a nontoxic variant of the diphtheria toxin. It was shown to be efficacious for IPD, pneumococcal pneumonia and AOM in several randomized trials (Black et al. [2000](#ref-Black2000); Black et al. [2002](#ref-Black2002c); Eskola et al. [2001](#ref-Eskola2001); Fireman et al. [2003](#ref-Fireman2003); O’Brien et al. [2003](#ref-OBrien2003); O’Brien et al. [2008](#ref-OBrien2008)). In the 2000s, higher valency conjugated vaccines were developed and received licensure, based on the randomized trials conducted for the heptavalent conjugated vaccine. They have been shown to be effective in several cluster randomized trials and observational studies.

### 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 (Ngo et al. [2016](#ref-Ngo2016)). It was used as an outcome measure in the earliest trials of pneumococcal polysaccharide vaccines (Mäkelä et al. [1981](#ref-Makela1981); Sloyer, Ploussard, and Howie [1981](#ref-Sloyer1981)). In the following sub-chapters, evidence regarding the efficacy and impact of PCV on otitis media will be reviewed. Randomized controlled trials will be reviewed in greater depth, as they represent the highest quality of evidence of true efficacy. Observational studies will be reviewed more generally.

#### Randomized controlled trials evaluating the efficacy of pneumococcal conjugate vaccines for otitis media

Eight randomized controlled trials have examined the efficacy of pneumococcal conjugate vaccines on acute otitis media (Black et al. [2000](#ref-Black2000); Dagan et al. [2001](#ref-Dagan2001); Eskola et al. [2001](#ref-Eskola2001); Fireman et al. [2003](#ref-Fireman2003); Kilpi et al. [2003](#ref-Kilpi2003); O’Brien et al. [2008](#ref-OBrien2008); A. Palmu et al. [2015](#ref-Palmu2015); Prymula et al. [2006](#ref-Prymula2006); Tregnaghi et al. [2014](#ref-Tregnaghi2014); Vesikari et al. [2016](#ref-Vesikari2016)). Six trials reported the efficacy for vaccine-type pneumococcal AOM and pneumococcal AOM regardless of serotype revealing large and statistically significant effects. Six trials demonstrated a moderate efficacy against all-cause AOM, but only three reached statistical significance. The studies are summarized in Table 3.

The first published randomized controlled trial of a pneumococcal conjugate vaccine reported, among other outcomes, the efficacy against AOM (Black et al. [2000](#ref-Black2000)). The study recruited 37,868 children and randomized them to the either PCV7CRM197 or the meningococcus C CRM197 conjugate vaccine. A separate publication from the same trial examined the effect of PCV7CRM197 on AOM in more detail using the full data (Fireman et al. [2003](#ref-Fireman2003)). The estimated vaccine efficacy against otitis media visits was 7.8% (95%CI 5.4% to 10.2%). Slightly higher point estimates were found for otitis media episodes, frequent otitis media and ventilatory tube placements (Black et al. [2000](#ref-Black2000); Fireman et al. [2003](#ref-Fireman2003))

The following year the results of two more randomized controlled trials were published (Dagan et al. [2001](#ref-Dagan2001); Eskola et al. [2001](#ref-Eskola2001)). Dagan et al. ([2001](#ref-Dagan2001)) enrolled 264 children ages 12-35 months of age attending eight daycare centers in Beer-Sheva, Isreal. The study’s primary endpoint was vaccine-type nasopharyngeal carriage and the secondary endpoint was parent-reported respiratory infections. The study reported an efficacy of 17% (95%CI -2% to 33%) for otitis media episodes and 20% (95%CI 14% to 26%) for antimicrobial treated otitis media, as measured by days spent on antimicrobials.

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

A total of 2,497 children were enrolled, of which 835 received the PCV7MOMPC vaccine and were therefore not reported in the Eskola et al. ([2001](#ref-Eskola2001)) paper. If AOM was diagnosed as defined by the study criteria, myringotomy and aspiration of middle-ear fluid were performed and samples sent for culture. The results were most consistent with a 6% efficacy against all-cause AOM with 95% confidence limits of -4% and 16%. 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.

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

Table 3 Randomized controlled trials evaluating the efficacy of pneumococcal conjugate vaccines for acute otitis media (AOM) and tympanostomy procedures. Dagan et al. ([2001](#ref-Dagan2001)) did not present sufficient information to ascertain the exact enrollment period. Vaccine efficacy is presented along with 95% confidence intervals. Information that was not reported in a particular trial is indicated with a hyphen (-). Some studies did not present intention to treat estimates. In those cases, per-protocol efficacy estimates are presented and indicated with an asterix (\*)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | No. of children | Vaccine-type AOM | Pneumococcal AOM | All-cause AOM | Recurrent AOM | Tympanostomy tube placement |
| Black et al. ([2000](#ref-Black2000)); Fireman et al. ([2003](#ref-Fireman2003)) | 37,868 | 65% (not specified) | - | 7.8% (5.4% to 10.2%) | 9% (3% to 15% | 20% (2% to 35% |
| Dagan et al. ([2001](#ref-Dagan2001)) | 264 | - | - | 17% (-2% to 33%) | - | - |
| Eskola et al. ([2001](#ref-Eskola2001)) | 1,662 | 54% (41% to 64%) | 34% (21% to 45%) | 6% (-4% to 16%) | 16% (-6% to 35%) | 4% (-19% to 23%) |
| Kilpi et al. ([2003](#ref-Kilpi2003)) | 1,666 | 56% (44% to 66%)\* | 25% (11% to 37%) | -1% (-12% to 10%) | - | - |
| Prymula et al. ([2006](#ref-Prymula2006)) | 4,968 | 53% (35% to 66%) | 52% (37% to 63%) | 33.6% (20.8% to 44.3%)\* | 56% (-2% to 81%) | 60% (-27% to %88) |
| O’Brien et al. ([2008](#ref-OBrien2008)) | 856 | 64% (-34% to 90%)\* | - | -0.4% (-19.4% to 15.6%) | 5% (-52% to 41%) | 28% (-225% to 84%) |
| Tregnaghi et al. ([2014](#ref-Tregnaghi2014)) | 23,821 | 69.9% (29.8% to 87.1% | 55.7% (21.5% to 75%) | 19% (4.4% to 31.4%) | - | - |
| A. Palmu et al. ([2015](#ref-Palmu2015)); Vesikari et al. ([2016](#ref-Vesikari2016)) | 6,178 | - | - | 6.4% (-5.5% to 17.2% | - | 13% (-2% to 26%) |

In 2006, Prymula et al. ([2006](#ref-Prymula2006)) reported a randomized study of an 11-valent pneumococcal conjugate vaccine in 4,968 children recruited from paediatric centers in the Czech Republic and Slovakia (Prymula et al. [2006](#ref-Prymula2006)). The 11-valent vaccine was conjugated to *Haemophilus influenzae* protein D, and of the study aims was to estimate the efficacy against AOM caused by non-typable *Haemophilus influenzae*. In the intention to treat analysis, the vaccine efficacy for the first occurrence of AOM caused by pneumococcus was 52.6% (95%CI 36.1% to 65.5%) and was 32.7% (95%CI 0.77% to 54.3%) for the first occurrence of AOM caused by NTHi. Only per-protocol efficacy was presented for all-cause AOM, which was estimated to be 33.6% (20.8% to 44.3%).

In 2003, the first paper from a cluster randomized controlled trial of PCV7CRM197 among the Navajo and White Mountain Apache infants was published (O’Brien et al. [2003](#ref-OBrien2003)), and 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. 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%).

Tregnaghi et al. ([2014](#ref-Tregnaghi2014)) reported a randomized controlled trial of PHiD-CV10 conducted in Argentina, Panama and Colombia with an enrollment period from 2007-2011. The primary outcome was bacterial community acquired pneumonia in the per-protocol cohort, and the first secondary outcome was clinically diagnosed AOM. All clinically suspected cases of AOM were subsequently referred to otolaryngologists associated with the study, who confirmed the diagnosis and performed tympanocentesis if middle ear fluid was present. The study reported a 19% (95%CI 4.4% to 31.4%) vaccine efficacy for clinically diagnosed AOM in the intention to treat analysis. The estimated efficacy for pneumococcal AOM was 55.7% (95%CI 21.5% to 75%) and the estimated efficacy for vaccine-type AOM was 69.9% (95%CI 29.8% to 87.1%). Unlike Prymula et al. ([2006](#ref-Prymula2006)), the study did not find a statistically significant efficacy against AOM caused by NTHi, though the point estimate was similar 21.5% (95%CI -43.4% to 57.0%) (Tregnaghi et al. [2014](#ref-Tregnaghi2014)).

Finally, the results of a cluster-randomized controlled trial on AOM and tympanostomy tube placements conducted in Finland in 2009 were reported in two publications (A. Palmu et al. [2015](#ref-Palmu2015); Vesikari et al. [2016](#ref-Vesikari2016)). The details of the trial are outlined in Chapter 2.2.4. Tympanic tube placements were evaluated in the main trial, while the efficacy against AOM was evaluated in a smaller trial, nested within the main trial. Vaccine efficacy for tympanic tube placements was 13% (955CI -2% to 26%) (A. Palmu et al. [2015](#ref-Palmu2015)). The efficacy of parent-reported, physician diagnosed AOM was assessed with active surveillance through means of text messaging, and was estimated as 6.4% (95%CI -5.5% to 17.2%) (Vesikari et al. [2016](#ref-Vesikari2016)).

#### Observational studies evaluating the impact of pneumococcal conjugate vaccines for otitis media.

The observational studies discussed in this chapter were obtained from two systematic reviews of the impact of pneumococcal conjugate vaccines on otitis media (Taylor et al. [2012](#ref-Taylor2012a); Vojtek, Nordgren, and Hoet [2017](#ref-Vojtek2017)). The discussion will focus on if and how the studies accounted for secular trends in the incidence of AOM prior to the introduction of PCV, and whether population based data were used.

Eight of the nine studies included acknowledged an observed decreasing trend of AOM prior to vaccine introduction (Grijalva et al. [2006](#ref-Grijalva2006); Grijalva, Nuorti, and Griffin [2009](#ref-Grijalva2009); Poehling [2004](#ref-Poehling2004); Poehling et al. [2007](#ref-Poehling2007); Lau et al. [2015](#ref-Lau2015); Magnus et al. [2012](#ref-Magnus2012); Marom et al. [2014](#ref-Marom2014); Singleton et al. [2009](#ref-Singleton2009)). Only three studies attempted to correct for the observed secular trend. Grijalva et al. ([2006](#ref-Grijalva2006)) employed a crude difference-in-differences approach, in which the relative risk ratio between young vaccine eligible children and older vaccine non-eligible children in the pre- and post-vaccine periods were compared. This approach assumes that secular trends in AOM are identical in children under the age of three, and between three and six years of age and that no other changes than vaccination occurred that could upset this balance. This resulted in an estimated impact of 0.80 (95%CI 0.66 to 0.96).

Lau et al. ([2015](#ref-Lau2015)) and Marom et al. ([2014](#ref-Marom2014)) used a variation of linear interrupted time-series analysis. Interrupted time-series analysis is a segmented regression, which fits a linear trend in a defined pre-intervention period, and compares this to a linear trend in a defined post-intervention period (Penfold and Zhang [2013](#ref-Penfold2013); Wagner et al. [2002](#ref-Wagner2002)). The major threats to the validity of such analyses are few pre- and post-intervention observations, the existence of other possible changes that correlate with the intervention and inappropriate use of linear trends (Jandoc et al. [2015](#ref-Jandoc2015)). Lau et al. ([2015](#ref-Lau2015)) demonstrated a roughly 20% sequential decrease in the incidence of otitis media among children younger than 10 years of age following the introduction of PCV7 and PCV13. There do not seem to be obvious threats to the validity of this study. In Marom et al. ([2014](#ref-Marom2014)), a version of segmented linear regression was performed on 11 annual incidence estimates of otitis media to estimate the added benefit of PCV13 over PCV7. A linear trend was constructed from eight of these estimates, which was then projected without any uncertainty over the last two years of the study period. Any difference between the observed incidence of otitis media and the projected line is assumed to be due to the effect of PCV13. Projected trends are subject to uncertainty and should not be used as a baseline truth. Furthermore, the number of observations used in the regression was extremely few, rendering segmented regression inappropriate (Jandoc et al. [2015](#ref-Jandoc2015)).

Ben-Shimol et al. ([2014](#ref-Ben-Shimol2014)) did not specifically discuss whether a trend was occurring in the pre-vaccine period. They report a detailed prospective population based study of pathogen specific otitis media, which included a four year period prior to vaccine introduction. Visual inspection of the included figures seems to reveal an abrupt decrease in pneumococcal AOM one year prior to the introduction of PCV7. This is said to be due to the private market availability of the vaccine one year before general introduction into the pediatric vaccination program. However, only 18% of children younger than one year of age had received two or more vaccine doses when the decrease was visually underway. It is also not clear from the publication whether the rate of tympanocentesis among children presenting with AOM decreased disproportionately following vaccine introduction. This could independently explain the observed decrease in pneumococcal AOM, but would not confound the substantial decrease in vaccine-type pneumococcal AOM. Of the included studies, only Ben-Shimol et al. ([2014](#ref-Ben-Shimol2014)) used population based data.

### The impact of pneumococcal conjugate vaccines on pneumonia

Four randomized controlled trials have evaluated the efficacy of pneumococcal conjugate vaccines for pneumonia (Black et al. [2002](#ref-Black2002c); Cutts et al. [2005](#ref-Cutts2005); Kilpi et al. [2018](#ref-Kilpi2018); Tregnaghi et al. [2014](#ref-Tregnaghi2014)). In 2005, the World Health Organization published a consensus statement defining WHO criteria for pneumonia (Cherian et al. [2004](#ref-Cherian2004)). Black et al. ([2002](#ref-Black2002c)), Tregnaghi et al. ([2014](#ref-Tregnaghi2014)) and Kilpi et al. ([2018](#ref-Kilpi2018)) are publications from randomized controlled trials that are extensively reviewed in Chapters 2.2.2.1 and 2.2.4. Black et al. ([2002](#ref-Black2002c)) reported the intention to treat efficacy estimate of the secondary end-point of clinically diagnosed pneumonia to be 6% (95%CI -1.5% to 11%). Following the development of the WHO-criteria (Cherian et al. [2004](#ref-Cherian2004)), the data was re-analyzed and the efficacy against WHO-criteria radiographically confirmed pneumonia was 25.5% (95%CI 6.5% to 40.7%) (Hansen et al. [2006](#ref-Hansen2006)). Tregnaghi et al. ([2014](#ref-Tregnaghi2014)) reported the intention to treat analysis efficacy estimate of the primary outcome of bacterial community acquired pneumonia as 18.2% (95% 5.5% to 29.1%), and secondary end-points included clinically suspected pneumonia, 7.3% (95%CI 2.1% to 12.3%). Finally, Kilpi et al. ([2018](#ref-Kilpi2018)) reported efficacy estimates for hospital-diagnosed pneumonia to be 27% (95%CI 14% to 38%) and radiographically confirmed pneumonia as 28% (95%CI 5% to 46%).

Cutts et al. ([2005](#ref-Cutts2005)) reported the results of a randomized controlled trial of 17,437 children recruited in the Gambia from 2000 to 2003, who received either a nine-valent pneumococcal vaccine conjugated to CRM197, or the diphtheria-pertussis-tetanus vaccine. At the time of publication, the WHO consensus statement on radiographically confirmed pneumonia had not yet been published. However, the study did employ WHO trained radiologists. The efficacy for clinically and radiographically diagnosed pneumonia was 7% (95%CI 1% to 12%) and 37% (95%CI 25% to 48%) respectively. The results of the randomized controlled trials are summarized in Table 4.

Table 4 Randomized controlled trials evaluating the efficacy of pneumococcal conjugate vaccines for pneumonia. The specific pneumococcal conjugate vaccine used in the study is presented. The seven and nine-valent pneumococcal conjugate vaccine (PCV7, PCV9) were conjugate to CRM197. The 10-valent vaccine was conjugated to Haemophilus influenzae protein D (PHiD-CV10). Vaccine efficacy is presented along with 95% confidence intervals. Radiographically confirmed pneumonia is based on WHO-criteria (Cherian et al. [2004](#ref-Cherian2004)). Cutts et al. ([2005](#ref-Cutts2005)) did not report intention to treat estimates and did not report WHO-criteria radiographically confirmed pneumonia. The per-protocol radiographically confirmed pneumonia estimates using the study’s criteria are presented. These are indicated with an asterix (\*). Kilpi et al. ([2018](#ref-Kilpi2018)) only reported hospital-diagnosed pneumonia, not clinically suspected pneumonia (\*\*)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Vaccine | Country | No. of children | Clinically suspected pneumonia | Radiographically confirmed pneumonia |
| Black et al. ([2002](#ref-Black2002c)); Hansen et al. ([2006](#ref-Hansen2006)) | PCV7 (CRM197) | United States | 37,868 | 6 (-1.5 to 11) | 25.5% (6.5% to 40.7%) |
| Cutts et al. ([2005](#ref-Cutts2005)) | PCV9 (CRM197) | The Gambia | 17,437 | 7% (1% to 12%)\* | 37% (25% to 48%)\* |
| Tregnaghi et al. ([2014](#ref-Tregnaghi2014)) | PHiD-CV10 | Argentina, Panama and Colombia | 23,821 | 7.3% (2.1% to 12.3%) | 18.2% (5.5% to 29.1%) |
| Kilpi et al. ([2018](#ref-Kilpi2018)) | PHiD-CV10 | Finland | 6,178 | 27% (14% to 38%)\*\* | 28% (5% to 46%) |

A multitude of observational studies evaluating the effect of the introduction of pneumococcal conjugate vaccines on pneumonia have been published. They use different case definitions and design, and reviewing each study individually is beyond the scope of this thesis. A systematic review of pneumonia impact studies identified 60 publications and found robust evidence, with 60% of studies finding significant reductions in clinically diagnosed pneumonia and 55% showing reductions in radiographically confirmed pneumonia (Loo et al. [2014](#ref-Loo2014a)). Most of the included studies did not use controls or correct for pre-vaccine time-trends, however no attempt was made to summarize the studies with regards to methodological factors. In another systematic review and meta-analysis of the impact of PCV10 and PCV13 on pneumonia, the quality of the studies was analysed and a random-effect model was used to summarize the results (Alicino et al. [2017](#ref-Alicino2017)). This review included 12 studies, of which only six corrected for secular trends and five used some form of control – most often total hospital admissions. The meta-analysis concluded that in children aged 24 months and younger, the introduction of the higher valency conjugate vaccines resulted in a 17% (95%CI 11% to 22%) reduction in clinical pneumonia and a 31% (95%CI 26% to 35%) in radiographically confirmed pneumonia (Alicino et al. [2017](#ref-Alicino2017)).

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

Invasive pneumococcal disease represents an optimal outcome for trialists to evaluate with randomized controlled trials. It is diagnosed when *Streptococcus pnemoniae* is cultured from normally sterile bodily fluids – there is little risk of subjectivity bias in the outcome. Five randomized controlled trials evaluated the efficacy of PCV for IPD, of which four have been extensively reviewed in Chapters 2.2.2.1 and 2.2.3 (Black et al. [2000](#ref-Black2000); Cutts et al. [2005](#ref-Cutts2005); O’Brien et al. [2003](#ref-OBrien2003); Palmu et al. [2013](#ref-Palmu2013); Tregnaghi et al. [2014](#ref-Tregnaghi2014)). Black et al. ([2000](#ref-Black2000)) reported the efficacy of PCV7 for vaccine-type IPD to be 93.9% (95%CI 79.6% to 98.5%). One fully vaccinated child was diagnosed with IPD caused by 19F. The vaccine-efficacy against IPD regardless of serotype was 89.1% (73.7% to 95.85%). Cutts et al. ([2005](#ref-Cutts2005)) only reported the per-protocol estimates of vaccine efficacy, which were 77% (95%CI 51% to 90%) and 50% (95%CI 21% to 69%) for vaccine-type and all-cause IPD respectively. The only randomized controlled trial to report statistically non-significant results of PCV on all-cause IPD was O’Brien et al. ([2003](#ref-OBrien2003)), with 46.3% (95%CI -16.5% to 75.3%) in the intention to treat analysis. The efficacy against vaccine-type IPD was 86.4% (95%CI 40.3% to 96.9%). Tregnaghi et al. ([2014](#ref-Tregnaghi2014)) did not include IPD as the primary or first secondary outcome measure. They reported a 100% (95%CI 77.3% to 100%) efficacy for vaccine-type IPD and a 66.7% (95%CI 21.8% to 85.9%) efficacy for all-cause IPD.

Palmu et al. ([2013](#ref-Palmu2013)) reports a cluster-randomized controlled trial in Finland, in which 47,366 children were randomized to either PHiD-CV10 or Hepatitis A vaccine from February 2009. The primary outcome was vaccine-type IPD among children who received at least one dose of PHiD-CV10 before seven months of age, in the three primary dose + one booster dose schedule. The efficacy for vaccine-type IPD among children who were randomized to the 3+1 schedule and received at least one dose before seven months of age, was 100% (95%CI 83% to 100%). The efficacy for children randomized to the 2+1 schedule was 92% (95%CI 58% to 100%). The intention to treat estimate of the vaccine efficacy for the combined 2+1 and 3+1 group was not reported – the per-protocol estimate was 100% (95%CI 91% to 100%) Finally, the efficacy for IPD regardless of serotype in the combined 2+1 and 3+1 schedules was 93% (95%CI 75% to 99%). The results of the randomized controlled trials are summarized in Table 5.

Table 5 Randomized controlled trials evaluating the efficacy of pneumococcal conjugate vaccines for invasive pneumococcal disease (IPD). The specific pneumococcal conjugate vaccine used in the study is presented. The seven and nine-valent pneumococcal conjugate vaccine (PCV7, PCV9) were conjugate to CRM197. The 10-valent vaccine was conjugated to Haemophilus influenzae protein D (PHiD-CV10). Vaccine efficacy for vaccine-type IPD, and IPD regardless of serotype are presented along with 95% confidence intervals. Some studies did not present intention to treat estimates. In those cases, per-protocol efficacy estimates are presented and indicated with an asterix (\*)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Vaccine | Country | No. of children | Vaccine-type IPD | IPD regardless of serotype |
| Black et al. ([2000](#ref-Black2000)) | PCV7 (CRM197) | United States | 37,868 | 93.9% (79.6% to 98.5%) | 89.1% (73.7% to 95.85%) |
| Cutts et al. ([2005](#ref-Cutts2005)) | PCV9 (CRM197) | The Gambia | 17,437 | 77% (51% to 90%)\* | 50% (21% to 69%)\* |
| O’Brien et al. ([2003](#ref-OBrien2003)) | PCV7 (CRM197) | United States | 856 | 86.4% (40.3% to 96.9%) | 46.3% (-16.5% to 75.3%) |
| Tregnaghi et al. ([2014](#ref-Tregnaghi2014)) | PHiD-CV10 | Argentina, Panama and Colombia | 23,821 | 100% (77.3% to 100%) | 66.7% (21.8% to 85.9%) |
| Palmu et al. ([2013](#ref-Palmu2013)) | PHiD-CV10 | Finland | 47,366 | 100% (91% to 100%)\* | 93% (77% to 99%) |

Too many observational studies of the impact of pneumococcal conjugate vaccines on invasive pneumococcal disease have been published for them to be individually reviewed in this thesis (Myint et al. [2013](#ref-Myint2013)). A systematic review and meta-analysis of all published studies in high-income countries from 1994-2010 identified 242 publications and summarized the results with a Bayesian random-effect model (Shiri et al. [2017](#ref-Shiri2017)). The model was used to predict the time in years from the introduction of a PCV into a country’s pediatric vaccination program, until a 50% and 90% reduction in vaccine-type IPD had occurred in the whole country’s population. The average time until a 50% reduction in vaccine-type IPD was observed was 2.3 years (95% credible intervals 1.9 to 2.7), and the average time to 90% reduction was 8.9 years (95% credible intervals 7.8 to 10.3) (Shiri et al. [2017](#ref-Shiri2017)).

## 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 inevitably results in another project remaining unfunded. Economic analyses are one of many tools to aid decision-makers in allocating resources optimally. Interventions are compared with two or more alternatives, and costs and benefits are systematically scrutinized. Economic analyses require data on the efficacy of the interventions being evaluated, the burden of disease, and the subgroups of the population which are affected (Gray et al. [2011](#ref-Gray2011)).

All methods of economic analysis measure the monetary costs associated with the relevant interventions, 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 applied. In cost-effectiveness analysis, the effect of the intervention is measured in units of the condition being intervened upon, e.g. number of deaths prevented, years of life 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 the difficulty of comparing cost-effectiveness ratios between studies that use different measurements of effect. Cost-utility analyses remedy this by standardizing a combined effect that measures both 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 determined 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 termed the rating scale method, the time trade-off and the standard gamble. Each method is intended to capture the preferences of the population to which the economic analysis pertains, and they are not meant to be generalized to other populations except with extreme caution (Petrou and Kupek [2009](#ref-Petrou2009)).

Measuring costs associated with an intervention is deceptively simple. They depend on from which 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 perspectives should reflect the purpose of the analysis and the intended audience. In 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 (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. Time horizon is the term used for the period of time over which an intervention is evaluated. In general, the time horizon should be chosen to reflect the duration of the intervention’s effect. 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 in 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 a constant rate, and whether costs and benefits should be discounted at the same rate, are all 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); 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 (Wasserman et al. [2018](#ref-Wasserman2018)). These assumptions are combined together in a mathematical model which generates an outcome, given the input parameters. Decision analysis models are static scenario-based models in which individuals are assumed to progress independently 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 defined by 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 costs and consequences, producing a final result. Generally, this model requires the assumption that probabilities are fixed, and do not vary depending on age or elapsed time (Gray et al. [2011](#ref-Gray2011)). For example, a decision analysis model would assume that the difference in the probability of contracting pneumonia with and without the vaccine was constant, regardless of the years elapsed since vaccine introduction.

Markov models expand upon this framework by removing the tree structure and allowing individuals to transition in any direction between nodes, which are termed “health states” in Markov models. In these models, the transitions between health states occur in 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 costs and benefits over time and may transition in and out of health states – an improvement over the static decision analysis models. The transition probabilities may either be constant or time-dependent. However, the Markovian assumption dictates that all individuals within a given health state are 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 annul the Markovian assumption (Pitman et al. [2012](#ref-Pitman2012)).

Because of the subjective nature of many of the modeling assumptions, a sensitivity analysis is necessary to explore the cost-effectiveness outcomes over a range of plausible input parameters. 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); Walker, Hutubessy, and Beutels [2010](#ref-Walker2010)). One-way sensitivity analysis implies that each parameter is individually varied across its probability distribution, while other parameters are held at a constant value. 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 decision-makers may find useful. Both consensus statements strongly recommend the inclusion of a probabilistic sensitivity analysis (PSA), in which the analysis is repeatedly run and all parameters are 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 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 6. 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 was the dominant strategy. The aim of this review is to explore the studies’ design and underlying assumptions, rather than the results.

Table 6 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 benefits are considered either 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 is 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 determine 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 | - | - |
| 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 |
| 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 |
| 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, Choi, et al. ([2012](#ref-VanHoek2012)) | England | CUA | Health sector | 30 | 3.5 | 3.5 |
| 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 |
| 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 of the cost-effectiveness of pneumococcal conjugate vaccines must choose which health outcomes to include in the analysis. Most, but not all, include acute otitis media, pneumonia and invasive pneumococcal disease. The studies include variable definitions of what constitutes each health outcome, assume differing baseline probabilities of the outcome occurring, and assume divergent vaccine efficacies for the included outcomes. Each of the health outcomes considered may or may not be associated with further healthcare consumption and disease burden. Repeated AOM may lead to a tympanostomy tube procedure, and IPD 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 reviewed cost-effectiveness analyses based their vaccine efficacy estimates for AOM on the results of the Northern California Kaiser Permente trial (Black et al. [2000](#ref-Black2000); Fireman et al. [2003](#ref-Fireman2003)). A large proportion of the remaining studies (Castiglia et al. [2017](#ref-Castiglia2017); Delgleize et al. [2016](#ref-Delgleize2016); Klok et al. [2013](#ref-Klok2013); Knerer, Ismaila, and Pearce [2012](#ref-Knerer2012); Robberstad et al. [2011](#ref-Robberstad2011); Strutton et al. [2012](#ref-Strutton2012); Talbird et al. [2010](#ref-Talbird2010)) based their efficacy of PCV7 and PCV13 on Eskola et al. ([2001](#ref-Eskola2001)). These studies often 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 for AOM caused by non-typable *Haemophilus influenzae*. The validity of this assumption has been called into question (Wasserman et al. [2018](#ref-Wasserman2018)). Few studies did not base their efficacy estimates for AOM on data from randomized clinical trials. Gouveia et al. ([2017](#ref-Gouveia2017)), for example, based their AOM 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, Choi, et al. ([2012](#ref-VanHoek2012)) assumed AOM efficacy to be a linear ratio of their estimated efficacy for IPD, based on a complex transmission dynamic model. Chuck et al. ([2010](#ref-Chuck2010)) also based the efficacy for AOM on IPD, 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 AOM before and after vaccine introduction, and assumed any observed difference was due to the vaccine.

The vaccine efficacy estimates for hospitalized and non-hospitalized pneumonia were generally based on Black and Shinefield ([2002](#ref-Black2002)). As was the case for AOM, Delgleize et al. ([2016](#ref-Delgleize2016)) and Castiglia et al. ([2017](#ref-Castiglia2017)) based their pneumonia efficacy estimates on Tregnaghi et al. ([2014](#ref-Tregnaghi2014)). In the case of pneumonia, a larger proportion of studies based their estimates on either unadjusted observational studies or did not provide sufficient information to ascertain what estimates were used. Chuck et al. ([2010](#ref-Chuck2010)) and Hoek, Choi, et al. ([2012](#ref-VanHoek2012)) again assumed the efficacy for pneumonia to be a fixed ratio of their IPD efficacy estimate. Talbird et al. ([2010](#ref-Talbird2010)) and Gouveia et al. ([2017](#ref-Gouveia2017)) never explicitly stated their assumed vaccine efficacy, and no rationale was provided. 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. Newall et al. ([2016](#ref-Newall2016)) based the efficacy against outpatient pneumonia on Black and Shinefield ([2002](#ref-Black2002)), as did most other studies. However, the efficacy estimates for inpatient pneumonia and IPD were determined 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 model, and corrected for changes in population demographics using an offset term. With access to only three years of annual pre-vaccine incidence rates, they were unfortunately only able to correct for an intercept term, and acknowledge this in their discussion section (Newall et al. [2016](#ref-Newall2016)). Nevertheless, the methodology is interesting. Finally, M. A. O’Brien et al. ([2009](#ref-OBrien2009a)) did not consider pneumonia or invasive pneumococcal disease as health outcomes.

Vaccine efficacy estimates for IPD were most often based on Black et al. ([2000](#ref-Black2000)). One other randomized controlled trial (Palmu et al. [2013](#ref-Palmu2013)) was used by Kuhlmann and Schulenburg ([2017](#ref-Kuhlmann2017)). The remaining studies based their efficacy estimates on non-randomized or observational studies. 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. Hoek, Choi, 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. a Palmu et al. [2015](#ref-Palmu2015a); 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)), 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 they can profoundly affect a study’s outcome (Wasserman et al. [2018](#ref-Wasserman2018)). The cost-effectiveness and cost-utility analyses included in this discussion based their efficacy estimates on many different studies. An alarmingly large proportion cited observational data from other time-periods and study populations, which often used a different formulation of pneumococcal conjugate vaccine. In most cases where randomized controlled trials were utilized, the most commonly referenced studies were conducted 10 years prior, in a completely vaccine naive population using PCV7. Newall et al. ([2016](#ref-Newall2016)) introduced a thoughtful time-series approach where local pre-vaccine trends in disease were statistically extrapolated to the post-vaccine period, simulating what would have occurred had the vaccine not been introduced. This was then 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 (Newall et al. [2016](#ref-Newall2016)).

The care with which the referenced efficacy data were incorporated also varied between studies. Only some considered vaccine coverage and waning vaccine protection, and few adjusted for local serotype distribution and herd effect (Table 7). Additionally, there was great variability in how the included studies defined the pre-vaccine incidence of disease, 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 7 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. If a study assumed infinite protection, or did not provide sufficient data to ascertain the waning period, then the length of protection is presented wih a hyphen (-). Similarly, a hyphen indicates that vaccine uptake 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 effect). When models are based on ecological data, they implicitly include both herd effects and serotype replacement. Only Hoek, Choi, et al. ([2012](#ref-VanHoek2012)) directly modeled the serotype replacement. Sensitivity analyses can be either deterministic, such as 1-Way, 2-Way and scenario analyses, or stochastic, such as probabilistic 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 |
| 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 |
| 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 |
| 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, Choi, et al. ([2012](#ref-VanHoek2012)) | Transmission dynamic | 10 | - | Yes | Yes, directly | PSA, threshold, CEAC, scenario |
| 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 |
| 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 results as the cost of an intervention per additional quality-adjusted life-years 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 informing decision making. Without this correlation, 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 validity to inform decision-makers. Similarly, the costs associated with each vaccine and health outcome must necessarily be derived from accurate estimates of the population under study. If costs are measured imprecisely or obtained from other countries or time-periods, it is difficult to imagine what relevance the economic analysis has to the decisions at hand.

To date, only three studies have been published that estimate utility values for pneumococcal diseases 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)). In a French study (Andrade et al. [2018](#ref-Andrade2018)), the utility values for adult pneumococcal pneumonia were estimated using the EuroQoL five dimensional questionnaire. Two additional studies examined utility values in populations that had not experienced pneumococcal disease. Bennett et al. ([2000](#ref-Bennett2000)) estimated utility values for meningitis sequelae; deafness and moderate and severe brain damage by interviewing parents of mildly sick 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 sequelae of bacterial meningitis.

With few exceptions, all of the reviewed cost-utility analyses used the same two references for utilities (Bennett et al. [2000](#ref-Bennett2000); Herdman et al. [2016](#ref-Herdman2016); Oostenbrink, A Moll, and Essink-Bot [2002](#ref-Oostenbrink2002)). Most of the studies did so indirectly (Kuhlmann and Schulenburg [2017](#ref-Kuhlmann2017); Newall et al. [2011](#ref-Newall2011); Newall et al. [2016](#ref-Newall2016); Rozenbaum et al. [2010](#ref-Rozenbaum2010); Rubin et al. [2010](#ref-Rubin2010); Talbird et al. [2010](#ref-Talbird2010)), and instead cited a cost-utility analysis by Melegaro and Edmunds ([2004](#ref-Melegaro2004a)), which itself based its estimates on the two studies. 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)). This is significant, as the method Melegaro and Edmunds ([2004](#ref-Melegaro2004a)) used to aggregate and translate utility values to QALYs is controversial (Herdman et al. [2016](#ref-Herdman2016)). M. A. O’Brien et al. ([2009](#ref-OBrien2009a)) based their utility values on Prosser et al. ([2004](#ref-Prosser2004)). Klok et al. ([2013](#ref-Klok2013)) used 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 provided no rationale for its relevance to pneumococcal disease in Danish and Swedish children. Strutton et al. ([2012](#ref-Strutton2012)) claimed to use country specific utilities for Germany, Greece and the Netherlands, but provided 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 the recommended use of pneumococcal conjugate vaccine, which is not available online. Despite 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); Klok et al. [2013](#ref-Klok2013); Newall et al. [2016](#ref-Newall2016); Strutton et al. [2012](#ref-Strutton2012); Talbird et al. [2010](#ref-Talbird2010)).

Costs included in economic analyses are divided into direct and indirect costs. Direct costs include the cost of each vaccine dose, the 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 which were available in their respective countries at the time the cost-effectiveness analysis was undertaken. These valuations must be considered conservative estimates, as healthcare systems generally negotiate the purchase price of vaccines at a considerably lower prices than listed. Studies comparing two higher-valency pneumococcal conjugate vaccines most commonly used the list price of the available vaccine and assumed price parity. By negating the possibility of competition between the two vaccine manufacturers, the studies make an unreasonable assumption. At the very least, such assumptions call for a sensitivity analysis, which some of the reviewed studies failed to perform for any of the cost components (Chuck et al. [2010](#ref-Chuck2010); Earnshaw et al. [2012](#ref-Earnshaw2012b); Gouveia et al. [2017](#ref-Gouveia2017); Klok et al. [2013](#ref-Klok2013); Newall et al. [2016](#ref-Newall2016); Strutton et al. [2012](#ref-Strutton2012); Talbird et al. [2010](#ref-Talbird2010)).

The included studies most commonly estimated direct costs associated with hospitalized health outcomes, by utilizing official statistics of resources associated with diagnostic related groupings, and unit costs derived from national tariffs. Expert opinion was then sought to decide which resources on average, would be used for each health outcome. With this input, a hypothetical reference case was constructed and used to calculate the direct cost. Outpatient health outcomes were often solely based on the assumptions of expert opinion, with the exception of studies conducted in the Netherlands, Germany and the United Kingdom, where official statistics on outpatient unit costs are available. The basis of what was considered expert opinion was stated in only one case (Knerer, Ismaila, and Pearce [2012](#ref-Knerer2012)). This practice sometimes resulted in suspect estimates, for example, that in Greece, each case of outpatient AOM cost 3,861 euros which was 30-300 times higher than for the two other countries included in the study (Strutton et al. [2012](#ref-Strutton2012)). This is particularly unfortunate as costs were not included in the sensitivity analysis in that study. Díez-Domingo et al. ([2011](#ref-Diez-Domingo2011)) and Hoek, Choi, 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 sequelae 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); 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 length of hospital stay in 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 AOM, parents were assumed to lose from zero to three days depending on the study, with no rationale 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-effectiveness 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 acute 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 acute 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)

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

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

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

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

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

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

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

### Evidence of herd-effect of PHiD-CV10 on 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.

Adam, D, and K Fehnle. 2008. “Safety and effectiveness against respiratory tract infections for pneumococcal conjugate vaccine co-administered with routine vaccine combinations.” *Vaccine* 26 (47): 5944–51. doi:[10.1016/j.vaccine.2008.08.058](https://doi.org/10.1016/j.vaccine.2008.08.058).

Ahmed, Sameer, Nina L Shapiro, and Neil Bhattacharyya. 2014. “Incremental health care utilization and costs for acute otitis media in children.” *The Laryngoscope* 124 (1): 301–5. doi:[10.1002/lary.24190](https://doi.org/10.1002/lary.24190).

Alicino, Cristiano, Chiara Paganino, Andrea Orsi, Matteo Astengo, Cecilia Trucchi, Giancarlo Icardi, and Filippo Ansaldi. 2017. “The impact of 10-valent and 13-valent pneumococcal conjugate vaccines on hospitalization for pneumonia in children: A systematic review and meta-analysis.” *Vaccine* 35 (43). The Authors: 5776–85. doi:[10.1016/j.vaccine.2017.09.005](https://doi.org/10.1016/j.vaccine.2017.09.005).

Andrade, Luiz Flavio, Grèce Saba, Jean-Damien Ricard, Jonathan Messika, Jacques Gaillat, Pierre Bonnin, Christian Chidiac, et al. 2018. “Health related quality of life in patients with community-acquired pneumococcal pneumonia in France.” *Health and Quality of Life Outcomes* 16 (1). Health; Quality of Life Outcomes: 28. doi:[10.1186/s12955-018-0854-6](https://doi.org/10.1186/s12955-018-0854-6).

Arason, V A, K G Kristinsson, J A Sigurdsson, G Stefánsdóttir, S Mölstad, and S Gudmundsson. 1996. “Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study.” *BMJ (Clinical Research Ed.)* 313 (7054): 387–91. doi:[10.1136/bmj.313.7054.387](https://doi.org/10.1136/bmj.313.7054.387).

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

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

Arguedas, A., K. Kvaerner, J. Liese, A.G.M. Schilder, and S.I. Pelton. 2010. “Otitis media across nine countries: Disease burden and management.” *International Journal of Pediatric Otorhinolaryngology* 74 (12). Elsevier Ireland Ltd: 1419–24. doi:[10.1016/j.ijporl.2010.09.022](https://doi.org/10.1016/j.ijporl.2010.09.022).

Austin, D J, K G Kristinsson, and R M Anderson. 1999. “The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance.” *Proceedings of the National Academy of Sciences of the United States of America* 96 (3): 1152–6. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=15366{\&}tool=pmcentrez{\&}rendertype=abstract>.

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

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

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

———. 1999. “A brief history of pneumococcal vaccines.” *Drugs & Aging* 15 Suppl 1: 1–10. doi:[10.2165/00002512-199915001-00001](https://doi.org/10.2165/00002512-199915001-00001).

Backhaus, Erik, Stefan Berg, Rune Andersson, Gunilla Ockborn, Petter Malmström, Mats Dahl, Salmir Nasic, and Birger Trollfors. 2016. “Epidemiology of invasive pneumococcal infections: manifestations, incidence and case fatality rate correlated to age, gender and risk factors.” *BMC Infectious Diseases* 16 (1): 367. doi:[10.1186/s12879-016-1648-2](https://doi.org/10.1186/s12879-016-1648-2).

Ben-Shimol, Shalom, Noga Givon-Lavi, Eugene Leibovitz, Simon Raiz, David Greenberg, and Ron Dagan. 2014. “Near-Elimination of Otitis Media Caused by 13-Valent Pneumococcal Conjugate Vaccine (PCV) Serotypes in Southern Israel Shortly After Sequential Introduction of 7-Valent/13-Valent PCV.” *Clinical Infectious Diseases* 59 (12): 1724–32. doi:[10.1093/cid/ciu683](https://doi.org/10.1093/cid/ciu683).

Bennett, Jonathan E., Walton Sumner, Stephen M. Downs, and David M. Jaffe. 2000. “Parents’ Utilities for Outcomes of Occult Bacteremia.” *Archives of Pediatrics & Adolescent Medicine* 154 (1). American Medical Association: 43–48. doi:[10-1001/pubs.Pediatr Adolesc Med.-ISSN-1072-4710-154-1-poa9043](https://doi.org/10-1001/pubs.Pediatr Adolesc Med.-ISSN-1072-4710-154-1-poa9043).

Berg, Are Stuwitz, Christopher Stephen Inchley, Audun Aase, Hans Olav Fjaerli, Reidun Bull, Ingeborg Aaberge, Truls Michael Leegaard, and Britt Nakstad. 2016. “Etiology of Pneumonia in a Pediatric Population with High Pneumococcal Vaccine Coverage: A Prospective Study.” *The Pediatric Infectious Disease Journal* 35 (3): e69–75. doi:[10.1097/INF.0000000000001009](https://doi.org/10.1097/INF.0000000000001009).

Bergenfelz, Caroline, and Anders P Hakansson. 2017. “Streptococcus pneumoniae Otitis Media Pathogenesis and How It Informs Our Understanding of Vaccine Strategies.” *Current Otorhinolaryngology Reports* 5 (2): 115–24. doi:[10.1007/s40136-017-0152-6](https://doi.org/10.1007/s40136-017-0152-6).

Beutels, P., Z. Shkedy, M. Aerts, and P. Van Damme. 2006. “Social mixing patterns for transmission models of close contact infections: exploring self-evaluation and diary-based data collection through a web-based interface.” *Epidemiology and Infection* 134 (06): 1158. doi:[10.1017/S0950268806006418](https://doi.org/10.1017/S0950268806006418).

Beutels, Philippe, Nancy Thiry, and Pierre Van Damme. 2007. “Convincing or confusing? Economic evaluations of childhood pneumococcal conjugate vaccination–a review (2002-2006).” *Vaccine* 25 (8): 1355–67. doi:[10.1016/j.vaccine.2006.10.034](https://doi.org/10.1016/j.vaccine.2006.10.034).

Birnbaum, Howard G, Melissa Morley, Paul E Greenberg, M Cifaldi, and G L Colice. 2002. “Economic burden of pneumonia in an employed population.” *Archives of Internal Medicine* 161 (2): 2725–31. doi:[10.1001/archinte.161.22.2725](https://doi.org/10.1001/archinte.161.22.2725).

Bjarnason, Agnar, Hilmir Asgeirsson, Olafur Baldursson, Karl G Kristinsson, and Magnus Gottfredsson. 2015. “Mortality in healthcare-associated pneumonia in a low resistance setting: a prospective observational study.” *Infectious Diseases (London, England)* 47 (3): 130–36. doi:[10.3109/00365548.2014.980842](https://doi.org/10.3109/00365548.2014.980842).

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

Black, Nick. 1984. “Surgery for glue ear—A modern epidemic.” *The Lancet* 323 (8381): 835–37. doi:[10.1016/S0140-6736(84)92280-3](https://doi.org/10.1016/S0140-6736(84)92280-3).

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

Black, Steven B, and H Shinefield. 2002. “Safety and efficacy of the seven-valent pneumococcal conjugate vaccine: evidence from Northern California.” *Eur J Pediatr* 161 Suppl: S127–31. doi:[10.1007/s00431-002-1064-z](https://doi.org/10.1007/s00431-002-1064-z).

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

Blank, Patricia R., and Thomas D. Szucs. 2012. “Cost-effectiveness of 13-valent pneumococcal conjugate vaccine in Switzerland.” *Vaccine* 30 (28): 4267–75. doi:[10.1016/j.vaccine.2012.04.028](https://doi.org/10.1016/j.vaccine.2012.04.028).

Blank, Sarah J, David J Grindler, Kristine A Schulz, David L Witsell, and Judith E C Lieu. 2014. “Caregiver Quality of Life Is Related to Severity of Otitis Media in Children.” *Otolaryngology-Head and Neck Surgery* 151 (2). NIH Public Access: 348–53. doi:[10.1177/0194599814531912](https://doi.org/10.1177/0194599814531912).

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

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

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

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

By, Åsa, Patrik Sobocki, Arne Forsgren, and Sven-Arne Silfverdal. 2012. “Comparing Health Outcomes and Costs of General Vaccination with Pneumococcal Conjugate Vaccines in Sweden: A Markov Model.” *Clinical Therapeutics* 34 (1): 177–89. doi:[10.1016/j.clinthera.2011.12.007](https://doi.org/10.1016/j.clinthera.2011.12.007).

Byford, S, and J Raftery. 1998. “Economics notes: Perspectives in economic evaluation.” *BMJ* 316 (7143): 1529–30. doi:[10.1136/bmj.316.7143.1529](https://doi.org/10.1136/bmj.316.7143.1529).

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

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

Castiglia, Paolo, Lorenzo Pradelli, Stefano Castagna, Veronica Freguglia, Giorgio Palù, and Susanna Esposito. 2017. “Overall effectiveness of pneumococcal conjugate vaccines: An economic analysis of PHiD-CV and PCV-13 in the immunization of infants in Italy.” *Human Vaccines & Immunotherapeutics* 13 (10). Taylor & Francis: 2307–15. doi:[10.1080/21645515.2017.1343773](https://doi.org/10.1080/21645515.2017.1343773).

Cecil, R. L. 1918. “Results of prophylactic inoculation against pneumococcus in 12,519 men.” *Journal of Experimental Medicine* 28 (1): 19–41. doi:[10.1084/jem.28.1.19](https://doi.org/10.1084/jem.28.1.19).

Chandran, Aruna, Hadley Herbert, Derek Misurski, and Mathuram Santosham. 2011. “Long-term sequelae of childhood bacterial meningitis: an underappreciated problem.” *The Pediatric Infectious Disease Journal* 30 (1): 3–6. doi:[10.1097/INF.0b013e3181ef25f7](https://doi.org/10.1097/INF.0b013e3181ef25f7).

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

Cherian, T, EK Mulholland, JB Carlin, and H Ostensen. 2004. “Standardized Interpretation of Paediatric Chest Radiographs for the Diagnosis of Pneumonia in Epidemiological Studies Variability in the Interpretation of Chest Radiographs ! Standardized Method for Identifying Radiological Pneumonia Would Facilitate Read.” *Bulletin of the World Health Organisation* 83 (5): 353–59.

Chonmaitree, Tasnee, Rocio Trujillo, Kristofer Jennings, Pedro Alvarez-Fernandez, Janak A Patel, Michael J Loeffelholz, Johanna Nokso-Koivisto, et al. 2016. “Acute Otitis Media and Other Complications of Viral Respiratory Infection.” *PEDIATRICS* 137 (4): e20153555–e20153555. doi:[10.1542/peds.2015-3555](https://doi.org/10.1542/peds.2015-3555).

Chuck, Anderson W., Philip Jacobs, Gregory Tyrell, and James D. Kellner. 2010. “Pharmacoeconomic evaluation of 10- and 13-valent pneumococcal conjugate vaccines.” *Vaccine* 28: 5485–90. doi:[10.1016/j.vaccine.2010.05.058](https://doi.org/10.1016/j.vaccine.2010.05.058).

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

Claesson, Bo A, Birger Trollfors, Inger Brolin, Marta Granström, J Henrichsen, Ulf Jodal, Per Juto, et al. 1989. “Etiology of community-acquired pneumonia in children based on antibody responses to bacterial and viral antigens.” *The Pediatric Infectious Disease Journal* 8 (12): 856–61. doi:[10.1097/00006454-198912000-00006](https://doi.org/10.1097/00006454-198912000-00006).

Claxton, Karl, Mike Paulden, Hugh Gravelle, Werner Brouwer, and Anthony J. Culyer. 2011. “Discounting and decision making in the economic evaluation of health-care technologies.” *Health Economics* 20 (1): 2–15. doi:[10.1002/hec.1612](https://doi.org/10.1002/hec.1612).

Coker, Tumaini R, Linda S Chan, Sydne J Newberry, Mary Ann Limbos, Marika J Suttorp, Paul G Shekelle, and Glenn S Takata. 2010. “Diagnosis, Microbial Epidemiology, and Antibiotic Treatment of Acute Otitis Media in Children.” *JAMA* 304 (19): 2161. doi:[10.1001/jama.2010.1651](https://doi.org/10.1001/jama.2010.1651).

Coyte, P C, Ruth Croxford, C V Asche, T To, W Feldman, and J Friedberg. 2001. “Physician and population determinants of rates of middle-ear surgery in Ontario.” *JAMA* 286 (17): 2128–35. doi:[10.1001/jama.286.17.2128](https://doi.org/10.1001/jama.286.17.2128).

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

Cutts, Felicity T, S M Zaman, Godwin C Enwere, S Jaffar, O S Levine, J B Okoko, C Oluwalana, et al. 2005. “Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial.” *Lancet* 365 (9465): 1139–46. doi:[10.1016/s0140-6736(05)71876-6](https://doi.org/10.1016/s0140-6736(05)71876-6).

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

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

De Wals, Philippe, Steven Black, Ray Borrow, and David Pearce. 2009. “Modeling the impact of a new vaccine on pneumococcal and nontypable Haemophilus influenzae diseases: A new simulation model.” *Clinical Therapeutics* 31 (10). Excerpta Medica Inc: 2152–69. doi:[10.1016/j.clinthera.2009.10.014](https://doi.org/10.1016/j.clinthera.2009.10.014).

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

Delgleize, Emmanuelle, Oscar Leeuwenkamp, Eleni Theodorou, and Nicolas Van de Velde. 2016. “Cost-effectiveness analysis of routine pneumococcal vaccination in the UK: a comparison of the PHiD-CV vaccine and the PCV-13 vaccine using a Markov model.” *BMJ Open* 6 (11): e010776. doi:[10.1136/bmjopen-2015-010776](https://doi.org/10.1136/bmjopen-2015-010776).

Desai, Shalini N, James D Kellner, and Derek Drummond. 2002. “Population-based, age-specific myringotomy with tympanostomy tube insertion rates in Calgary, Canada.” *The Pediatric Infectious Disease Journal* 21 (4): 348–50. <http://www.ncbi.nlm.nih.gov/pubmed/12075770>.

Devine, V. T., J. M. Jefferies, S. C. Clarke, and S. N. Faust. 2015. “Nasopharyngeal Bacterial Carriage in the Conjugate Vaccine Era with a Focus on Pneumococci.” *Journal of Immunology Research* 2015: 1–8. doi:[10.1155/2015/394368](https://doi.org/10.1155/2015/394368).

Díez-Domingo, Javier, Manuel Ridao-López, M Victoria Gutiérrez-Gimeno, Joan Puig-Barberá, Jose a Lluch-Rodrigo, and Eliseo Pastor-Villalba. 2011. “Pharmacoeconomic assessment of implementing a universal PCV-13 vaccination programme in the Valencian public health system (Spain).” *Vaccine* 29 (52). Elsevier Ltd: 9640–8. doi:[10.1016/j.vaccine.2011.10.038](https://doi.org/10.1016/j.vaccine.2011.10.038).

Djurhuus, Bjarki Ditlev Ditlev, Axel Skytthe, Kaare Christensen, and Christian Emil Emil Faber. 2014. “Increasing rate of middle ear ventilation tube insertion in children in Denmark.” *International Journal of Pediatric Otorhinolaryngology* 78 (9): 1541–4. doi:[10.1016/j.ijporl.2014.06.034](https://doi.org/10.1016/j.ijporl.2014.06.034).

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

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

Drijkoningen, J J C, and G G U Rohde. 2014. “Pneumococcal infection in adults: burden of disease.” *Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases* 20 Suppl 5 (May): 45–51. doi:[10.1111/1469-0691.12461](https://doi.org/10.1111/1469-0691.12461).

Earnshaw, Stephanie R, Cheryl L McDade, Giovanni Zanotti, Raymond A Farkouh, and David Strutton. 2012. “Cost-effectiveness of 2 + 1 dosing of 13-valent and 10-valent pneumococcal conjugate vaccines in Canada.” *BMC Infectious Diseases* 12 (1): 101. doi:[10.1186/1471-2334-12-101](https://doi.org/10.1186/1471-2334-12-101).

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

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

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

Esposito, Susanna, Alessandro Lizioli, Annalisa Lastrico, Enrica Begliatti, Alessandro Rognoni, Claudia Tagliabue, Laura Cesati, Vittorio Carreri, and Nicola Principi. 2007. “Impact on respiratory tract infections of heptavalent pneumococcal conjugate vaccine administered at 3, 5 and 11 months of age.” *Respiratory Research* 8 (January): 12. doi:[10.1186/1465-9921-8-12](https://doi.org/10.1186/1465-9921-8-12).

Falster, Kathleen, Deborah Randall, Emily Banks, Sandra Eades, Hasantha Gunasekera, Jennifer Reath, and Louisa Jorm. 2013. “Inequalities in ventilation tube insertion procedures between Aboriginal and non-Aboriginal children in New South Wales, Australia: a data linkage study.” *BMJ Open* 3 (11): e003807. doi:[10.1136/bmjopen-2013-003807](https://doi.org/10.1136/bmjopen-2013-003807).

Feikin, Daniel R, Anne Schuchat, Margarette Kolczak, Nancy L Barrett, Lee H Harrison, Lewis Lefkowitz, Allison McGeer, et al. 2000. “Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997.” *American Journal of Public Health* 90 (2): 223–29. doi:[10.1097/00006454-200011000-00030](https://doi.org/10.1097/00006454-200011000-00030).

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

Finland, M. 1931. “Specific cutaneous reactions and circulating antibodies in the course of lobar pneumonia.” *Journal of Experimental Medicine* 54 (5): 637–52. doi:[10.1084/jem.54.5.637](https://doi.org/10.1084/jem.54.5.637).

Finnbogadóttir, Anna Freyja, Hannes Petersen, Þröstur Laxdal, Fridrik Gudbrandsson, Þórólfur Gudnason, and Ásgeir Haraldsson. 2009. “An increasing incidence of mastoiditis in children in Iceland.” *Scandinavian Journal of Infectious Diseases* 41 (2): 95–98. doi:[10.1080/00365540802593461](https://doi.org/10.1080/00365540802593461).

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

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

Fortanier, Alexandre C, Roderick P Venekamp, Marieke L A de Hoog, Cuno S P M Uiterwaal, Anne C van der Gugten, Cornelis K van der Ent, Arno W Hoes, and Anne G M Schilder. 2015. “Parent-Reported Symptoms of Acute Otitis Media during the First Year of Life: What Is beneath the Surface?” Edited by Herminia de Lencastre. *PLOS ONE* 10 (4). Public Library of Science: e0121572. doi:[10.1371/journal.pone.0121572](https://doi.org/10.1371/journal.pone.0121572).

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

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

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

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

Gisselsson-Solen, Marie. 2017. “Trends in Otitis Media Incidence After Conjugate Pneumococcal Vaccination; A National Observational Study.” *The Pediatric Infectious Disease Journal* 36 (11): 1. doi:[10.1097/INF.0000000000001654](https://doi.org/10.1097/INF.0000000000001654).

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

Gouveia, Miguel, Francesca Fiorentino, Gonçalo Jesus, João Costa, and Margarida Borges. 2017. “Cost-effectiveness of the 13-valent Pneumococcal Conjugate Vaccine in Children in Portugal.” *The Pediatric Infectious Disease Journal* 36 (8): 782–87. doi:[10.1097/INF.0000000000001587](https://doi.org/10.1097/INF.0000000000001587).

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

Gray, Alastair M, Philip M Clarke, Jane L Wolstenholme, and Sarah Wordsworth. 2011. *Applied Methods of Cost-effectiveness Analysis in Health Care*. New York: Oxford University Press.

Gribben, Barry, Lesley J Salkeld, Simon Hoare, and Hannah F Jones. 2012. “The incidence of acute otitis media in New Zealand children under five years of age in the primary care setting.” *Journal of Primary Health Care* 4 (3): 205–12. <http://www.ncbi.nlm.nih.gov/pubmed/22946068>.

Grijalva, C. G., K. A. Poehling, J. P. Nuorti, Y. Zhu, S. W. Martin, K. M. Edwards, and M. R. Griffin. 2006. “National Impact of Universal Childhood Immunization With Pneumococcal Conjugate Vaccine on Outpatient Medical Care Visits in the United States.” *PEDIATRICS* 118 (3): 865–73. doi:[10.1542/peds.2006-0492](https://doi.org/10.1542/peds.2006-0492).

Grijalva, Carlos G, J Pekka Nuorti, and Marie R Griffin. 2009. “Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings.” *JAMA : The Journal of the American Medical Association* 302 (7): 758–66. doi:[10.1001/jama.2009.1163](https://doi.org/10.1001/jama.2009.1163).

Groth, Anita, Frida Enoksson, Ann Hermansson, Malou Hultcrantz, Joacim Stalfors, and Karin Stenfeldt. 2011. “Acute mastoiditis in children in Sweden 1993-2007-No increase after new guidelines.” *International Journal of Pediatric Otorhinolaryngology* 75 (12): 1496–1501. doi:[10.1016/j.ijporl.2011.08.015](https://doi.org/10.1016/j.ijporl.2011.08.015).

Groth, Christina, Reimar W Thomsen, and Therese Ovesen. 2015. “Association of pneumococcal conjugate vaccination with rates of ventilation tube insertion in Denmark: population-based register study.” *BMJ Open* 5 (6). BMJ Group: e007151. doi:[10.1136/bmjopen-2014-007151](https://doi.org/10.1136/bmjopen-2014-007151).

Haapkylä, Johanna, Gunnhild Karevold, Kari Jorunn Kværner, and Anne Pitkäranta. 2008. “Trends in otitis media surgery: A decrease in adenoidectomy.” *International Journal of Pediatric Otorhinolaryngology* 72 (8): 1207–13. doi:[10.1016/j.ijporl.2008.04.012](https://doi.org/10.1016/j.ijporl.2008.04.012).

Habib, Maha, Barbara D. Porter, and Catherine Satzke. 2014. “Capsular Serotyping of Streptococcus pneumoniae Using the Quellung Reaction.” *Journal of Visualized Experiments*, no. 84 (February). doi:[10.3791/51208](https://doi.org/10.3791/51208).

Halloran, M. Elizabeth, Ira M. Longini, and Claudio J. Struchiner. 2010. *Design and Analysis of Vaccine Studies*. Statistics for Biology and Health. New York, NY: Springer New York. doi:[10.1007/978-0-387-68636-3](https://doi.org/10.1007/978-0-387-68636-3).

Hansen, John, Steven Black, Henry Shinefield, Thomas Cherian, Jane Benson, Bruce Fireman, Edwin Lewis, Paula Ray, and Janelle Lee. 2006. “Effectiveness of Heptavalent Pneumococcal Conjugate Vaccine in Children Younger Than 5 Years of Age for Prevention of Pneumonia.” *The Pediatric Infectious Disease Journal* 25 (9): 779–81. doi:[10.1097/01.inf.0000232706.35674.2f](https://doi.org/10.1097/01.inf.0000232706.35674.2f).

Harboe, Zitta B, Reimar W Thomsen, Anders Riis, Palle Valentiner-Branth, Jens Jørgen Christensen, Lotte Lambertsen, Karen A Krogfelt, Helle B Konradsen, and Thomas Benfield. 2009. “Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study.” *PLoS Medicine* 6 (5). Public Library of Science: e1000081. doi:[10.1371/journal.pmed.1000081](https://doi.org/10.1371/journal.pmed.1000081).

Harboe, Zitta B, Palle Valentiner-Branth, Thomas Benfield, Jens Jørgen Christensen, Peter H Andersen, Michael Howitz, Karen A Krogfelt, Lotte Lambertsen, and Helle B Konradsen. 2010. “Early effectiveness of heptavalent conjugate pneumococcal vaccination on invasive pneumococcal disease after the introduction in the Danish Childhood Immunization Programme.” *Vaccine* 28 (14): 2642–7. doi:[10.1016/j.vaccine.2010.01.017](https://doi.org/10.1016/j.vaccine.2010.01.017).

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

Heikkinen, T, and T Chonmaitree. 2003. “Importance of respiratory viruses in acute otitis media.” *Clin Microbiol Rev* 16 (2): 230–41.

Herdman, Michael, Amanda Cole, Christopher K Hoyle, Victoria Coles, Stuart Carroll, and Nancy Devlin. 2016. “Sources and Characteristics of Utility Weights for Economic Evaluation of Pediatric Vaccines: A Systematic Review.” *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 19 (2): 255–66. doi:[10.1016/j.jval.2015.11.003](https://doi.org/10.1016/j.jval.2015.11.003).

Hoek, Albert Jan van, Nick Andrews, Pauline a. Waight, Robert George, and Elizabeth Miller. 2012. “Effect of serotype on focus and mortality of invasive pneumococcal disease: Coverage of different vaccines and insight into non-vaccine serotypes.” *PLoS ONE* 7 (7). doi:[10.1371/journal.pone.0039150](https://doi.org/10.1371/journal.pone.0039150).

Hoek, Albert Jan van, Yoon Hong Choi, Caroline Trotter, Elizabeth Miller, and Mark Jit. 2012. “The cost-effectiveness of a 13-valent pneumococcal conjugate vaccination for infants in England.” *Vaccine* 30 (50). Elsevier Ltd: 7205–13. doi:[10.1016/j.vaccine.2012.10.017](https://doi.org/10.1016/j.vaccine.2012.10.017).

Holubar, Marisa, Maria Christina Stavroulakis, Yvonne Maldonado, John P A Ioannidis, and Despina Contopoulos-Ioannidis. 2017. “Impact of vaccine herd-protection effects in cost-effectiveness analyses of childhood vaccinations. A quantitative comparative analysis.” *PLoS ONE* 12 (3): 1–22. doi:[10.1371/journal.pone.0172414](https://doi.org/10.1371/journal.pone.0172414).

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

Howitz, Michael Frantz, Zitta Barrella Harboe, Helene Ingels, Palle Valentiner-Branth, Kåre Mølbak, and Bjarki Ditlev Djurhuus. 2017. “A nationwide study on the impact of pneumococcal conjugate vaccination on antibiotic use and ventilation tube insertion in Denmark 2000-2014.” *Vaccine* 35 (43). Elsevier Ltd: 5858–63. doi:[10.1016/j.vaccine.2017.09.006](https://doi.org/10.1016/j.vaccine.2017.09.006).

Hsu, Heather E, Kathleen A Shutt, Matthew R Moore, Bernard W Beall, Nancy M Bennett, Allen S Craig, Monica M Farley, et al. 2009. “Effect of pneumococcal conjugate vaccine on pneumococcal meningitis.” *The New England Journal of Medicine* 360 (3): 244–56. doi:[10.1056/NEJMoa0800836](https://doi.org/10.1056/NEJMoa0800836).

Hussain, M., A. Melegaro, R. G. Pebody, R. George, W.J. Edmunds, R. Talakudr, S. A. Martin, A. Efstratiou, and E. Miller. 2005. “A longitudinal household study of Streptococcus pneumoniae nasopharyngeal carriage in a UK setting.” *Epidemiology and Infection* 133 (05): 891. doi:[10.1017/S0950268805004012](https://doi.org/10.1017/S0950268805004012).

Isaacman, Daniel J, David R Strutton, Edward a Kalpas, Nathalie Horowicz-Mehler, Lee S Stern, Roman Casciano, and Vincent Ciuryla. 2008. “The impact of indirect (herd) protection on the cost-effectiveness of pneumococcal conjugate vaccine.” *Clinical Therapeutics* 30 (2): 341–57. doi:[10.1016/j.clinthera.2008.02.003](https://doi.org/10.1016/j.clinthera.2008.02.003).

Jain, Seema, Derek J. Williams, Sandra R. Arnold, Krow Ampofo, Anna M. Bramley, Carrie Reed, Chris Stockmann, et al. 2015. “Community-Acquired Pneumonia Requiring Hospitalization among U.S. Children.” *New England Journal of Medicine* 372 (9): 835–45. doi:[10.1056/NEJMoa1405870](https://doi.org/10.1056/NEJMoa1405870).

Jandoc, Racquel, Andrea M. Burden, Muhammad Mamdani, Linda E. Lévesque, and Suzanne M. Cadarette. 2015. “Interrupted time series analysis in drug utilization research is increasing: Systematic review and recommendations.” In *Journal of Clinical Epidemiology*, 68:950–56. 8. doi:[10.1016/j.jclinepi.2014.12.018](https://doi.org/10.1016/j.jclinepi.2014.12.018).

Kastenbauer, S., and H.-W. Pfister. 2003. “Pneumococcal meningitis in adults: Spectrum of complications and prognostic factors in a series of 87 cases.” *Brain* 126 (5): 1015–25. doi:[10.1093/brain/awg113](https://doi.org/10.1093/brain/awg113).

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

Keitel, K, G Alcoba, L Lacroix, S Manzano, a Galetto-Lacour, and a Gervaix. 2014. “Observed costs and health care use of children in a prospective cohort study on community-acquired pneumonia in Geneva, Switzerland.” *Swiss Medical Weekly* 144 (April): w13925. doi:[10.4414/smw.2014.13925](https://doi.org/10.4414/smw.2014.13925).

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

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

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

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

Kim, Sun-young, and Sue J Goldie. 2008. “Cost-effectiveness analyses of vaccination programmes : a focused review of modelling approaches.” *PharmacoEconomics* 26 (3): 191–215. doi:[2634 [pii]](https://doi.org/2634 [pii]).

Klok, Rogier M, Rose-Marie Lindkvist, Mats Ekelund, Raymond a Farkouh, and David R Strutton. 2013. “Cost-Effectiveness of a 10- Versus 13-Valent Pneumococcal Conjugate Vaccine in Denmark and Sweden.” *Clinical Therapeutics* 35 (2). Elsevier Inc.: 119–34. doi:[10.1016/j.clinthera.2012.12.006](https://doi.org/10.1016/j.clinthera.2012.12.006).

Knerer, Gerhart, Afisi Ismaila, and David Pearce. 2012. “Health and economic impact of PHiD-CV in Canada and the UK: a Markov modelling exercise.” *Journal of Medical Economics* 15 (1): 61–76. doi:[10.3111/13696998.2011.622323](https://doi.org/10.3111/13696998.2011.622323).

Kogan, M D, M D Overpeck, H J Hoffman, and M L Casselbrant. 2000. “Factors associated with tympanostomy tube insertion among preschool-aged children in the United States.” *American Journal of Public Health* 90 (2): 245–50. <http://search.ebscohost.com/login.aspx?direct=true{\%}7B{\&}{\%}7Ddb=rzh{\%}7B{\&}{\%}7DAN=107110611{\%}7B{\&}{\%}7Dsite=ehost-live{\%}7B{\&}{\%}7Dscope=site http://www.ncbi.nlm.nih.gov/pubmed/10667186 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1446140 http://search.ebscoh>.

Kuhlmann, Alexander, and J-Matthias Graf von der Schulenburg. 2017. “Modeling the cost-effectiveness of infant vaccination with pneumococcal conjugate vaccines in Germany.” *The European Journal of Health Economics* 18 (3). Springer Berlin Heidelberg: 273–92. doi:[10.1007/s10198-016-0770-9](https://doi.org/10.1007/s10198-016-0770-9).

Kvaerner, Kari J, Per Nafstad, and Jouni J K Jaakkola. 2002. “Otolaryngological surgery and upper respiratory tract infections in children: an epidemiological study.” *The Annals of Otology, Rhinology, and Laryngology* 111 (11): 1034–9. doi:[10.1177/000348940211101115](https://doi.org/10.1177/000348940211101115).

Ladhani, Shamez N., Mary P E Slack, Nick Andrews, Pauline a. Waight, Ray Borrow, and Elizabeth Miller. 2013. “Invasive pneumococcal disease after routine pneumococcal conjugate vaccination in children, England and Wales.” *Emerging Infectious Diseases* 19 (1): 61–68. doi:[10.3201/eid1901.120741](https://doi.org/10.3201/eid1901.120741).

Lau, Wallis C Y, Macey Murray, Aisha El-Turki, Sonia Saxena, Shamez Ladhani, Paul Long, Mike Sharland, Ian C K Wong, and Yingfen Hsia. 2015. “Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom.” *Vaccine* 33 (39): 5072–9. doi:[10.1016/j.vaccine.2015.08.022](https://doi.org/10.1016/j.vaccine.2015.08.022).

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

Legood, Rosa, Pietro G Coen, Kyle Knox, Russell M Viner, Haitham El Bashir, Deborah Christie, Bharat C Patel, and Robert Booy. 2009. “Health related quality of life in survivors of pneumococcal meningitis.” *Acta Paediatrica* 98 (3): 543–47. doi:[10.1111/j.1651-2227.2008.01136.x](https://doi.org/10.1111/j.1651-2227.2008.01136.x).

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

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

Liese, J. G., S. A. Silfverdal, C. Giaquinto, A. Carmona, J. H. Larcombe, J. Garcia-Sicilia, A. Fuat, et al. 2014. “Incidence and clinical presentation of acute otitis media in children aged <6 years in European medical practices.” *Epidemiology and Infection* 142 (8). Cambridge University Press: 1778–88. doi:[10.1017/S0950268813002744](https://doi.org/10.1017/S0950268813002744).

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

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

Loo, Jennifer D., Laura Conklin, Katherine E. Fleming-Dutra, Maria Deloria Knoll, Daniel E. Park, Jennifer Kirk, David Goldblatt, et al. 2014. “Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on prevention of pneumonia.” *The Pediatric Infectious Disease Journal* 33 Suppl 2 (1): S140–51. doi:[10.1097/INF.0000000000000082](https://doi.org/10.1097/INF.0000000000000082).

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

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

Maddigan, Sheri L., David H. Feeny, and Jeffrey A. Johnson. 2005. “Health-related quality of life deficits associated with diabetes and comorbidities in a Canadian National Population Health Survey.” *Quality of Life Research* 14 (5): 1311–20. doi:[10.1007/s11136-004-6640-4](https://doi.org/10.1007/s11136-004-6640-4).

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

Magnus, Maria C, Didrik F Vestrheim, Wenche Nystad, Siri Eldevik Håberg, Hein Stigum, Stephanie J London, Marianne R A R Bergsaker, Dominique A Caugant, Ingeborg S Aaberge, and Per Nafstad. 2012. “Decline in early childhood respiratory tract infections in the Norwegian mother and child cohort study after introduction of pneumococcal conjugate vaccination.” *The Pediatric Infectious Disease Journal* 31 (9): 951–5. doi:[10.1097/INF.0b013e31825d2f76](https://doi.org/10.1097/INF.0b013e31825d2f76).

Mangen, Marie-Josée J, Susanne M. Huijts, Marc J M Bonten, and G. Ardine de Wit. 2017. “The impact of community-acquired pneumonia on the health-related quality-of-life in elderly.” *BMC Infectious Diseases* 17 (1). BMC Infectious Diseases: 208. doi:[10.1186/s12879-017-2302-3](https://doi.org/10.1186/s12879-017-2302-3).

Marchisio, Paola, Luigi Cantarutti, Miriam Sturkenboom, Silvia Girotto, Gino Picelli, Daniele Dona, Antonio Scamarcia, Marco Villa, Carlo Giaquinto, and Pedianet. 2012. “Burden of acute otitis media in primary care pediatrics in Italy: a secondary data analysis from the Pedianet database.” *BMC Pediatrics* 12 (1). BMC Pediatrics: 185. doi:[10.1186/1471-2431-12-185](https://doi.org/10.1186/1471-2431-12-185).

Marom, Tal, Alai Tan, Gregg S. Wilkinson, Karen S. Pierson, Jean L. Freeman, and Tasnee Chonmaitree. 2014. “Trends in otitis media-related health care use in the United States, 2001-2011.” *JAMA Pediatrics* 168 (1). American Medical Association: 68–75. doi:[10.1001/jamapediatrics.2013.3924](https://doi.org/10.1001/jamapediatrics.2013.3924).

Mauskopf, Josephine, Baudouin Standaert, Mark P. Connolly, Anthony J. Culyer, Louis P. Garrison, Raymond Hutubessy, Mark Jit, Richard Pitman, Paul Revill, and Johan L. Severens. 2018. “Economic Analysis of Vaccination Programs: An ISPOR Good Practices for Outcomes Research Task Force Report.” *Value in Health* 21 (10). Elsevier Inc.: 1133–49. doi:[10.1016/j.jval.2018.08.005](https://doi.org/10.1016/j.jval.2018.08.005).

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

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

Melegaro, A, and W.J. Edmunds. 2004. “Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales.” *Vaccine* 22 (31-32): 4203–14. doi:[10.1016/j.vaccine.2004.05.003](https://doi.org/10.1016/j.vaccine.2004.05.003).

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

Monasta, Lorenzo, Luca Ronfani, Federico Marchetti, Marcella Montico, Liza Vecchi Brumatti, Alessandro Bavcar, Domenico Grasso, et al. 2012. “Burden of disease caused by otitis media: Systematic review and global estimates.” *PLoS ONE* 7 (4): e36226. doi:[10.1371/journal.pone.0036226](https://doi.org/10.1371/journal.pone.0036226).

Morrow, Adrienne, Philippe De Wals, Geneviève Petit, Maryse Guay, and Lonny James Erickson. 2007. “The Burden of Pneumococcal Disease in the Canadian Population Before Routine Use of the Seven-Valent Pneumococcal Conjugate Vaccine.” *Canadian Journal of Infectious Diseases and Medical Microbiology* 18 (2): 121–27. doi:[10.1155/2007/713576](https://doi.org/10.1155/2007/713576).

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

Mufson, M A, and R J Stanek. 1999. “Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997.” *The American Journal of Medicine* 107 (1A): 34S–43S. <http://www.ncbi.nlm.nih.gov/pubmed/10451007>.

Myint, Tin Tin Htar, Harish Madhava, Paul Balmer, Dina Christopoulou, Sepideh Attal, Damianos Menegas, Ralf Sprenger, and Eric Bonnet. 2013. “The impact of 7-valent pneumococcal conjugate vaccine on invasive pneumococcal disease: a literature review.” *Advances in Therapy* 30 (2): 127–51. doi:[10.1007/s12325-013-0007-6](https://doi.org/10.1007/s12325-013-0007-6).

Newall, A.T., J.F. Reyes, P. McIntyre, R. Menzies, P. Beutels, and J.G. Wood. 2016. “Retrospective economic evaluation of childhood 7-valent pneumococcal conjugate vaccination in Australia: Uncertain herd impact on pneumonia critical.” *Vaccine* 34 (3). Elsevier Ltd: 320–27. doi:[10.1016/j.vaccine.2015.11.053](https://doi.org/10.1016/j.vaccine.2015.11.053).

Newall, Anthony T., Prudence Creighton, David J. Philp, James G. Wood, and C. Raina MacIntyre. 2011. “The potential cost-effectiveness of infant pneumococcal vaccines in Australia.” *Vaccine* 29: 8077–85. doi:[10.1016/j.vaccine.2011.08.050](https://doi.org/10.1016/j.vaccine.2011.08.050).

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

Oostenbrink, Rianne, Henriëtte A Moll, and Marie-Louise Essink-Bot. 2002. “The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis.” *Journal of Clinical Epidemiology* 55 (8): 791–99. doi:[10.1016/S0895-4356(02)00448-1](https://doi.org/10.1016/S0895-4356(02)00448-1).

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

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

O’Brien, Katherine L., Lara J. Wolfson, James P. Watt, Emily Henkle, Maria Deloria-Knoll, Natalie McCall, Ellen Lee, et al. 2009. “Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates.” *The Lancet* 374 (9693). Elsevier Ltd: 893–902. doi:[10.1016/S0140-6736(09)61204-6](https://doi.org/10.1016/S0140-6736(09)61204-6).

O’Brien, Megan A, Lisa A Prosser, Jack L Paradise, G Thomas Ray, Martin Kulldorff, Marcia Kurs-Lasky, Virginia L Hinrichsen, Jyotsna Mehta, D Kathleen Colborn, and Tracy A Lieu. 2009. “New vaccines against otitis media: projected benefits and cost-effectiveness.” *Pediatrics* 123 (6): 1452–63. doi:[10.1542/peds.2008-1482](https://doi.org/10.1542/peds.2008-1482).

Paisley, John W., Brian A. Lauer, Kenneth Mcintosh, Mary P. Glode, Julius Schachter, and Acarol Rumack. 1984. “Pathogens associated with acute lower respiratory tract infection in young children.” *The Pediatric Infectious Disease Journal* 3 (1): 14–19. doi:[10.1097/00006454-198401000-00005](https://doi.org/10.1097/00006454-198401000-00005).

Palmu, Arto A, Jukka Jokinen, Dorota Borys, Heta Nieminen, Esa Ruokokoski, Lotta Siira, Taneli Puumalainen, et al. 2013. “Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial.” *Lancet* 381 (9862): 214–22. doi:[10.1016/s0140-6736(12)61854-6](https://doi.org/10.1016/s0140-6736(12)61854-6).

Palmu, Arto a, Terhi M Kilpi, Hanna Rinta-Kokko, Hanna Nohynek, Maija Toropainen, J Pekka Nuorti, and Jukka Jokinen. 2015. “Pneumococcal Conjugate Vaccine and Clinically Suspected Invasive Pneumococcal Disease.” *Pediatrics* 136 (1): e22 LP–e27. doi:[10.1542/peds.2015-0458](https://doi.org/10.1542/peds.2015-0458).

Palmu, Arto A, Hanna Rinta-Kokko, Hanna Nohynek, J Pekka Nuorti, and Jukka Jokinen. 2017. “Impact of National Ten-Valent Pneumococcal Conjugate Vaccine Programme on Reducing Antimicrobial Use and Tympanostomy Tube Placements in Finland.” *The Pediatric Infectious Disease Journal* 37 (1): 1. doi:[10.1097/INF.0000000000001810](https://doi.org/10.1097/INF.0000000000001810).

Palmu, Arto, Jukka Jokinen, Heta Nieminen, Hanna Rinta-Kokko, Esa Ruokokoski, Taneli Puumalainen, Magali Traskine, et al. 2015. “Effectiveness of the 10-Valent Pneumococcal Conjugate Vaccine Against Tympanostomy Tube Placements in a Cluster-Randomized Trial.” *The Pediatric Infectious Disease Journal* 34 (11): 1230–5. doi:[http://dx.doi.org/10.1097/INF.0000000000000857](https://doi.org/http://dx.doi.org/10.1097/INF.0000000000000857).

Paradise, Jack L., Heidi M. Feldman, Thomas F. Campbell, Christine A. Dollaghan, D. Kathleen Colborn, Beverly S. Bernard, Howard E. Rockette, et al. 2001. “Effect of Early or Delayed Insertion of Tympanostomy Tubes for Persistent Otitis Media on Developmental Outcomes at the Age of Three Years.” *New England Journal of Medicine* 344 (16): 1179–87. doi:[10.1056/NEJM200104193441601](https://doi.org/10.1056/NEJM200104193441601).

Paradise, Jack L., Heidi M. Feldman, Thomas F. Campbell, Christine A. Dollaghan, Howard E. Rockette, Dayna L. Pitcairn, Clyde G. Smith, et al. 2007. “Tympanostomy Tubes and Developmental Outcomes at 9 to 11 Years of Age.” *New England Journal of Medicine* 356 (3): 248–61. doi:[10.1056/NEJMoa062980](https://doi.org/10.1056/NEJMoa062980).

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

Pedersen, Tine Marie, Anna-Rosa Cecilie Mora-Jensen, Johannes Waage, Hans Bisgaard, and Jakob Stokholm. 2016. “Incidence and Determinants of Ventilation Tubes in Denmark.” *PloS One* 11 (11): e0165657. doi:[10.1371/journal.pone.0165657](https://doi.org/10.1371/journal.pone.0165657).

Penfold, Robert B, and Fang Zhang. 2013. “Use of interrupted time series analysis in evaluating health care quality improvements.” *Academic Pediatrics* 13 (6 Suppl): S38–44. doi:[10.1016/j.acap.2013.08.002](https://doi.org/10.1016/j.acap.2013.08.002).

Petrou, Stavros, and Emil Kupek. 2009. “Estimating preference-based health utilities index mark 3 utility scores for childhood conditions in England and Scotland.” *Medical Decision Making : An International Journal of the Society for Medical Decision Making* 29 (3): 291–303. doi:[10.1177/0272989X08327398](https://doi.org/10.1177/0272989X08327398).

Pichichero, Michael E., Janet R. Casey, Alejandro Hoberman, and Richard Schwartz. 2008. “Pathogens causing recurrent and difficult-to-treat acute otitis media, 2003-2006.” *Clinical Pediatrics* 47 (9): 901–6. doi:[10.1177/0009922808319966](https://doi.org/10.1177/0009922808319966).

Pitman, Richard, David Fisman, Gregory S. Zaric, Maarten Postma, Mirjam Kretzschmar, John Edmunds, and Marc Brisson. 2012. “Dynamic Transmission Modeling.” *Medical Decision Making* 32 (5): 712–21. doi:[10.1177/0272989X12454578](https://doi.org/10.1177/0272989X12454578).

Poehling, K. A. 2004. “Population-Based Impact of Pneumococcal Conjugate Vaccine in Young Children.” *PEDIATRICS* 114 (3): 755–61. doi:[10.1542/peds.2003-0592-F](https://doi.org/10.1542/peds.2003-0592-F).

Poehling, Katherine A, Peter G Szilagyi, Carlos G Grijalva, Stacey W Martin, Bonnie LaFleur, Ed Mitchel, Richard D Barth, J Pekka Nuorti, and Marie R Griffin. 2007. “Reduction of Frequent Otitis Media and Pressure-Equalizing Tube Insertions in Children After Introduction of Pneumococcal Conjugate Vaccine.” *PEDIATRICS* 119 (4): 707–15. doi:[10.1542/peds.2006-2138](https://doi.org/10.1542/peds.2006-2138).

Prosser, Lisa A, G Thomas Ray, M. O’Brien, Ken Kleinman, Jeanne Santoli, and Tracy A Lieu. 2004. “Preferences and Willingness to Pay for Health States Prevented by Pneumococcal Conjugate Vaccine.” *PEDIATRICS* 113 (2): 283–90. doi:[10.1542/peds.113.2.283](https://doi.org/10.1542/peds.113.2.283).

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

Pulido, Marifi, and Frank Sorvillo. 2010. “Declining invasive pneumococcal disease mortality in the United States, 1990-2005.” *Vaccine* 28 (4): 889–92. doi:[10.1016/j.vaccine.2009.10.121](https://doi.org/10.1016/j.vaccine.2009.10.121).

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

Quirk, Sigríður J, Gunnsteinn Haraldsson, Helga Erlendsdóttir, Martha Á Hjálmarsdóttir, Andries J van Tonder, Birgir Hrafnkelsson, Samuel Sigurdsson, et al. 2018. “Effect of Vaccination on Pneumococci Isolated from the Nasopharynx of Healthy Children and the Middle Ear of Children with Otitis Media in Iceland.” Edited by Daniel J. Diekema. *Journal of Clinical Microbiology* 56 (12): 1–14. doi:[10.1128/JCM.01046-18](https://doi.org/10.1128/JCM.01046-18).

Ricketson, Leah J, Alberto Nettel-Aguirre, Otto G Vanderkooi, Kevin B Laupland, and James D Kellner. 2013. “Factors Influencing Early and Late Mortality in Adults with Invasive Pneumococcal Disease in Calgary, Canada: A Prospective Surveillance Study.” *PloS One* 8 (10): e71924. doi:[10.1371/journal.pone.0071924](https://doi.org/10.1371/journal.pone.0071924).

Robberstad, Bjarne, Carl R. Frostad, Per E. Akselsen, Kari J. Kværner, and Aud K H Berstad. 2011. “Economic evaluation of second generation pneumococcal conjugate vaccines in Norway.” *Vaccine* 29: 8564–74. doi:[10.1016/j.vaccine.2011.09.025](https://doi.org/10.1016/j.vaccine.2011.09.025).

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

Rodrigues, Fernanda, Leon Danon, Begonia Morales-Aza, Paulina Sikora, Valtyr Thors, Muriel Ferreira, Katherine Gould, Jason Hinds, and Adam Finn. 2016. “Pneumococcal Serotypes Colonise the Nasopharynx in Children at Different Densities.” Edited by Jose Melo-Cristino. *PLOS ONE* 11 (9): e0163435. doi:[10.1371/journal.pone.0163435](https://doi.org/10.1371/journal.pone.0163435).

Rosenfeld, Richard M., Jennifer J. Shin, Seth R. Schwartz, Robyn Coggins, Lisa Gagnon, Jesse M. Hackell, David Hoelting, et al. 2016. “Clinical Practice Guideline: Otitis Media with Effusion (Update).” *Otolaryngology–head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery* 154 (1 Suppl): S1–S41. doi:[10.1177/0194599815623467](https://doi.org/10.1177/0194599815623467).

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

Rozenbaum, Mark H, Elisabeth a M Sanders, Albert Jan van Hoek, Angelique G S C Jansen, Arie van der Ende, Germie van den Dobbelsteen, Gerwin D Rodenburg, Eelko Hak, and Maarten J Postma. 2010. “Cost effectiveness of pneumococcal vaccination among Dutch infants: economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines.” *BMJ* 340 (jun02 1): c2509–c2509. doi:[10.1136/bmj.c2509](https://doi.org/10.1136/bmj.c2509).

Rubin, Jaime L., Lisa J. McGarry, David R. Strutton, Keith P. Klugman, Stephen I. Pelton, Kristen E. Gilmore, and Milton C. Weinstein. 2010. “Public health and economic impact of the 13-valent pneumococcal conjugate vaccine (PCV13) in the United States.” *Vaccine* 28 (48). Elsevier Ltd: 7634–43. doi:[10.1016/j.vaccine.2010.09.049](https://doi.org/10.1016/j.vaccine.2010.09.049).

Rudan, Igor, Katherine L O’Brien, Harish Nair, Li Liu, Evropi Theodoratou, Shamim Qazi, Ivana Lukšić, Christa L Fischer Walker, Robert E Black, and Harry Campbell. 2013. “Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries.” *Journal of Global Health* 3 (1): 010401. doi:[10.7189/jogh.03.010401](https://doi.org/10.7189/jogh.03.010401).

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

Said, Maria a., Hope L. Johnson, Bareng a S Nonyane, Maria Deloria-Knoll, and Katherine L. O′Brien. 2013. “Estimating the Burden of Pneumococcal Pneumonia among Adults: A Systematic Review and Meta-Analysis of Diagnostic Techniques.” Edited by Philip C. Hill. *PLoS ONE* 8 (4): e60273. doi:[10.1371/journal.pone.0060273](https://doi.org/10.1371/journal.pone.0060273).

Sanders, Gillian D., Peter J. Neumann, Anirban Basu, Dan W. Brock, David Feeny, Murray Krahn, Karen M. Kuntz, et al. 2016. “Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses.” *JAMA* 316 (10): 1093. doi:[10.1001/jama.2016.12195](https://doi.org/10.1001/jama.2016.12195).

Saokaew, Surasak, Ajaree Rayanakorn, David Bin-Chia Wu, and Nathorn Chaiyakunapruk. 2016. “Cost Effectiveness of Pneumococcal Vaccination in Children in Low- and Middle-Income Countries: A Systematic Review.” *PharmacoEconomics* 34 (12). Springer International Publishing: 1211–25. doi:[10.1007/s40273-016-0439-3](https://doi.org/10.1007/s40273-016-0439-3).

Sarasoja, Ilona, Jukka Jokinen, Mika Lahdenkari, Terhi Kilpi, and Arto A. Palmu. 2013. “Long-term effect of pneumococcal conjugate vaccines on tympanostomy tube placements.” *The Pediatric Infectious Disease Journal* 32 (5): 517–20. doi:[10.1097/INF.0b013e31827c9bcc](https://doi.org/10.1097/INF.0b013e31827c9bcc).

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

Severens, Johan L., and Richard J. Milne. 2004. “Discounting health outcomes in economic evaluation: the ongoing debate.” *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 7 (4): 397–401. doi:[10.1111/j.1524-4733.2004.74002.x](https://doi.org/10.1111/j.1524-4733.2004.74002.x).

Shiri, Tinevimbo, Samik Datta, Jason Madan, Alexander Tsertsvadze, Pamela Royle, Matt J. Keeling, Noel D. McCarthy, and Stavros Petrou. 2017. “Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis.” *The Lancet Global Health* 5 (1). The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY license: e51–e59. doi:[10.1016/S2214-109X(16)30306-0](https://doi.org/10.1016/S2214-109X(16)30306-0).

Singleton, Rosalyn J., Robert C. Holman, Randall Plant, Krista L. Yorita, Steve Holve, Edna L. Paisano, and James E. Cheek. 2009. “Trends in otitis media and myringtomy with tube placement among American Indian/Alaska native children and the US general population of children.” *The Pediatric Infectious Disease Journal* 28 (2): 102–7. doi:[http://dx.doi.org/10.1097/INF.0b013e318188d079](https://doi.org/http://dx.doi.org/10.1097/INF.0b013e318188d079).

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

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

Snaebjarnardóttir, Kolfinna, Helga Erlendsdóttir, Ingi Karl Reynisson, Karl Kristinsson, Sandra Halldórsdóttir, Hjördís Hardardóttir, Thórólfur Gudnason, Magnús Gottfredsson, and Ásgeir Haraldsson. 2013. “Bacterial meningitis in children in Iceland, 1975-2010: a nationwide epidemiological study.” *Scandinavian Journal of Infectious Diseases* 45 (11): 819–24. doi:[10.3109/00365548.2013.817680](https://doi.org/10.3109/00365548.2013.817680).

Song, Joon Young, Moon H. Nahm, and M. Allen Moseley. 2013. “Clinical Implications of Pneumococcal Serotypes: Invasive Disease Potential, Clinical Presentations, and Antibiotic Resistance.” *Journal of Korean Medical Science* 28 (1): 4. doi:[10.3346/jkms.2013.28.1.4](https://doi.org/10.3346/jkms.2013.28.1.4).

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

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

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

Strutton, David R, Raymond a Farkouh, Stephanie R Earnshaw, Sharon Hwang, Ulrike Theidel, Stathis Kontodimas, Rogier Klok, and Sotiria Papanicolaou. 2012. “Cost-effectiveness of 13-valent pneumococcal conjugate vaccine: Germany, Greece, and The Netherlands.” *Journal of Infection* 64 (1). Elsevier Ltd: 54–67. doi:[10.1016/j.jinf.2011.10.015](https://doi.org/10.1016/j.jinf.2011.10.015).

Syrjänen, Ritva K, Kari Auranen, Tuija M Leino, Terhi M Kilpi, and P Helena Mäkelä. 2005. “Pneumococcal acute otitis media in relation to pneumococcal nasopharyngeal carriage.” *The Pediatric Infectious Disease Journal* 24 (9): 801–6. doi:[10.1097/01.inf.0000178072.83531.4f](https://doi.org/10.1097/01.inf.0000178072.83531.4f).

Talbird, Sandra E, Thomas N Taylor, Stefanie Knoll, Carl Richard Frostad, and Sebastián García Martí. 2010. “Outcomes and costs associated with PHiD-CV, a new protein D conjugate pneumococcal vaccine, in four countries.” *Vaccine* 28 Suppl 6 (November). Elsevier Ltd: G23–9. doi:[10.1016/j.vaccine.2010.06.016](https://doi.org/10.1016/j.vaccine.2010.06.016).

Taylor, Sylvia, Paola Marchisio, Anne Vergison, Julie Harriague, William P. Hausdorff, and Mark Haggard. 2012. “Impact of pneumococcal conjugate vaccination on otitis media: A systematic review.” *Clinical Infectious Diseases* 54 (12): 1765–73. doi:[10.1093/cid/cis292](https://doi.org/10.1093/cid/cis292).

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

Thornton, Ruth B, Paul J Rigby, Selma P Wiertsema, Pierre Filion, Jennifer Langlands, Harvey L Coates, Shyan Vijayasekaran, Anthony D Keil, and Peter C Richmond. 2011. “Multi-species bacterial biofilm and intracellular infection in otitis media.” *BMC Pediatrics* 11 (1): 94. doi:[10.1186/1471-2431-11-94](https://doi.org/10.1186/1471-2431-11-94).

Thors, Valtyr, Hannah Christensen, Begonia Morales-Aza, Elizabeth Oliver, Paulina Sikora, Ian Vipond, Peter Muir, and Adam Finn. 2018. “High Density Bacterial Nasal Carriage in Children is Transient and Associated With Respiratory Viral Infections – Implications for Transmission Dynamics.” *The Pediatric Infectious Disease Journal*, November, 1. doi:[10.1097/INF.0000000000002256](https://doi.org/10.1097/INF.0000000000002256).

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

Todberg, Tanja, Anders Koch, Mikael Andersson, Sjurdur F. SF F Olsen, Jørgen Lous, Preben Homøe, W Nystad, et al. 2014. “Incidence of otitis media in a contemporary danish national birth cohort.” Edited by C M Schooling. *PloS One* 9 (12). Public Library of Science: e111732. doi:[10.1371/journal.pone.0111732](https://doi.org/10.1371/journal.pone.0111732).

Torné, Adoración Navarro, Joana Gomes Dias, Chantal Quinten, Frantiska Hruba, Marta Cecilia Busana, Pier Luigi Lopalco, Andrew J Amato Gauci, and Lucia Pastore-Celentano. 2014. “European enhanced surveillance of invasive pneumococcal disease in 2010: Data from 26 European countries in the post-heptavalent conjugate vaccine era.” *Vaccine* 32 (29): 3644–50. doi:[10.1016/j.vaccine.2014.04.066](https://doi.org/10.1016/j.vaccine.2014.04.066).

Tregnaghi, Miguel W. Marcelo, Xavier Sáez-Llorens, Pio López, Hector Abate, Enrique Smith, Adriana Pósleman, Arlene Calvo, et al. 2014. “Efficacy of pneumococcal nontypable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in young Latin American children: A double-blind randomized controlled trial.” Edited by Elizabeth Miller. *PLoS Medicine* 11 (6). Public Library of Science: e1001657. doi:[10.1371/journal.pmed.1001657](https://doi.org/10.1371/journal.pmed.1001657).

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

Troeger, Christopher, Mohammad Forouzanfar, Puja C Rao, Ibrahim Khalil, Alexandria Brown, Scott Swartz, Nancy Fullman, et al. 2017. “Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015.” *The Lancet Infectious Diseases* 17 (11). Elsevier: 1133–61. doi:[10.1016/S1473-3099(17)30396-1](https://doi.org/10.1016/S1473-3099(17)30396-1).

Tsaban, Gal, and Shalom Ben-Shimol. 2017. “Indirect (herd) protection, following pneumococcal conjugated vaccines introduction: A systematic review of the literature.” *Vaccine* 35 (22): 2882–91. doi:[10.1016/j.vaccine.2017.04.032](https://doi.org/10.1016/j.vaccine.2017.04.032).

Tsigrelis, Constantine, Imad M. Tleyjeh, Brian D. Lahr, Lisa M. Nyre, Abinash Virk, and Larry M. Baddour. 2008. “Decreases in Case‐Fatality and Mortality Rates for Invasive Pneumococcal Disease in Olmsted County, Minnesota, during 1995–2007: A Population‐Based Study.” *Clinical Infectious Diseases* 47 (11): 1367–71. doi:[10.1086/592970](https://doi.org/10.1086/592970).

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

Usonis, Vytautas, Teresa Jackowska, Sigita Petraitiene, Alicja Sapala, Andrea Neculau, Izabella Stryjewska, Raghavendra Devadiga, Monica Tafalla, and Katsiaryna Holl. 2016. “Incidence of acute otitis media in children below 6 years of age seen in medical practices in five East European countries.” *BMC Pediatrics* 16 (1). BioMed Central: 108. doi:[10.1186/s12887-016-0638-2](https://doi.org/10.1186/s12887-016-0638-2).

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

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

Vergison, Anne, Ron Dagan, Adriano Arguedas, Jan Bonhoeffer, Robert Cohen, Ingeborg DHooge, Alejandro Hoberman, et al. 2010. “Otitis media and its consequences: beyond the earache.” *The Lancet Infectious Diseases* 10 (3): 195–203. doi:[10.1016/S1473-3099(10)70012-8](https://doi.org/10.1016/S1473-3099(10)70012-8).

Vesikari, Timo, Aino Forsten, Ilkka Seppa, Tarja Kaijalainen, Taneli Puumalainen, Anu Soininen, Magali Traskine, et al. 2016. “Effectiveness of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D-conjugated vaccine (PHiD-CV) against carriage and acute otitis media-a double-blind randomized clinical trial in Finland.” *Journal of the Pediatric Infectious Diseases Society* 5 (3). doi:[10.1093/jpids/piw010](https://doi.org/10.1093/jpids/piw010).

Vlastarakos, Petros V., Thomas P. Nikolopoulos, Stavros Korres, Evangelia Tavoulari, Antonios Tzagaroulakis, and Eleftherios Ferekidis. 2007. “Grommets in otitis media with effusion: the most frequent operation in children. But is it associated with significant complications?” *European Journal of Pediatrics* 166 (5): 385–91. doi:[10.1007/s00431-006-0367-x](https://doi.org/10.1007/s00431-006-0367-x).

Vojtek, Ivo, Marcus Nordgren, and Bernard Hoet. 2017. “Impact of pneumococcal conjugate vaccines on otitis media: A review of measurement and interpretation challenges.” *International Journal of Pediatric Otorhinolaryngology* 100 (September). Elsevier Ltd: 174–82. doi:[10.1016/j.ijporl.2017.07.009](https://doi.org/10.1016/j.ijporl.2017.07.009).

Vooren, K van de, S Duranti, A Curto, and L Garattini. 2014. “Cost effectiveness of the new pneumococcal vaccines: a systematic review of European studies.” *Pharmacoeconomics* 32: 29–45. doi:[10.1007/s40273-013-0113-y](https://doi.org/10.1007/s40273-013-0113-y).

Wagner, A K, S B Soumerai, F Zhang, and D Ross-Degnan. 2002. “Segmented regression analysis of interrupted time series studies in medication use research.” *Journal of Clinical Pharmacy and Therapeutics* 27 (4): 299–309. <http://www.ncbi.nlm.nih.gov/pubmed/12174032>.

Waight, Pauline A., Nicholas J. Andrews, Shamez N. Ladhani, Carmen L. Sheppard, Mary P.E. E Slack, and Elizabeth Miller. 2015. “Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: An observational cohort study.” *The Lancet Infectious Diseases* 15 (5): 535–43. doi:[10.1016/S1473-3099(15)70044-7](https://doi.org/10.1016/S1473-3099(15)70044-7).

Walker, Damian G, Raymond Hutubessy, and Philippe Beutels. 2010. “WHO Guide for standardisation of economic evaluations of immunization programmes.” *Vaccine* 28 (11). Elsevier Ltd: 2356–9. doi:[10.1016/j.vaccine.2009.06.035](https://doi.org/10.1016/j.vaccine.2009.06.035).

Wasserman, Matt, Heather L. Sings, Dylan Jones, Sarah Pugh, Margaret Moffatt, and Raymond Farkouh. 2018. “Review of vaccine effectiveness assumptions used in economic evaluations of infant pneumococcal conjugate vaccine.” *Expert Review of Vaccines* 17 (1). Taylor & Francis: 71–78. doi:[10.1080/14760584.2018.1409116](https://doi.org/10.1080/14760584.2018.1409116).

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

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

Weinberger, Daniel M, Zitta B Harboe, Cécile Viboud, Tyra G Krause, Mark Miller, Kåre Mølbak, and Helle B Konradsen. 2013. “Pneumococcal disease seasonality: incidence, severity, and the role of influenza activity.” *The European Respiratory Journal*, September, 1–19. doi:[10.1183/09031936.00056813](https://doi.org/10.1183/09031936.00056813).

Weinberger, Daniel M, Richard Malley, and Marc Lipsitch. 2011. “Serotype replacement in disease after pneumococcal vaccination.” *Lancet* 378 (9807): 1962–73. doi:[10.1016/S0140-6736(10)62225-8](https://doi.org/10.1016/S0140-6736(10)62225-8).

Weinberger, Daniel M., Zitta B. Harboe, Elisabeth A. M. Sanders, Moses Ndiritu, Keith P. Klugman, Simon Rückinger, Ron Dagan, et al. 2010. “Association of Serotype with Risk of Death Due to Pneumococcal Pneumonia: A Meta‐Analysis.” *Clinical Infectious Diseases* 51 (6): 692–99. doi:[10.1086/655828](https://doi.org/10.1086/655828).

Weisfelt, Martijn, Diederik van de Beek, Lodewijk Spanjaard, Johannes B Reitsma, and Jan de Gans. 2006. “Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series.” *The Lancet. Neurology* 5 (2): 123–9. doi:[10.1016/S1474-4422(05)70288-X](https://doi.org/10.1016/S1474-4422(05)70288-X).

Whitney, C G, T Pilishvili, Monica M Farley, W Schaffner, Allen S Craig, R Lynfield, A C Nyquist, et al. 2006. “Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study.” *Lancet* 368: 1495–1502. doi:[S0140-6736(06)69637-2 [pii]\r10.1016/S0140-6736(06)69637-2](https://doi.org/S0140-6736(06)69637-2 [pii]\r10.1016/S0140-6736(06)69637-2).

Wilkinson, Thomas, Mark J. Sculpher, Karl Claxton, Paul Revill, Andrew Briggs, John A. Cairns, Yot Teerawattananon, et al. 2016. “The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought.” *Value in Health* 19 (8). Elsevier: 921–28. doi:[10.1016/j.jval.2016.04.015](https://doi.org/10.1016/j.jval.2016.04.015).

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

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

Wright, AlmrothE., W. Parry Morgan, L Colebrook, and R.W. Dodgson. 1914. “Observations on prophylactic inoculation against pneumococcus infections and on the results which have been achieved by it.” *The Lancet* 183 (4715): 87–95. doi:[10.1016/S0140-6736(01)56449-1](https://doi.org/10.1016/S0140-6736(01)56449-1).

Wu, David Bin-Chia, Nathorn Chaiyakunapruk, Huey-Yi Chong, and Philippe Beutels. 2015. “Choosing between 7-, 10- and 13-valent pneumococcal conjugate vaccines in childhood: A review of economic evaluations (2006–2014).” *Vaccine* 33 (14). Elsevier Ltd: 1633–58. doi:[10.1016/j.vaccine.2015.01.081](https://doi.org/10.1016/j.vaccine.2015.01.081).

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

Zhou, F., Abigail Shefer, J. Wenger, M. Messonnier, L. Y. Wang, A. Lopez, M. Moore, T. V. Murphy, M. Cortese, and L. Rodewald. 2014. “Economic Evaluation of the Routine Childhood Immunization Program in the United States, 2009.” *PEDIATRICS* 133 (4): 577–85. doi:[10.1542/peds.2013-0698](https://doi.org/10.1542/peds.2013-0698).

Zhou, Fangjun, Abigail Shefer, Yuan Kong, and J Pekka Nuorti. 2008. “Trends in acute otitis media-related health care utilization by privately insured young children in the United States, 1997-2004.” *Pediatrics* 121 (2): 253–60. doi:[10.1542/peds.2007-0619](https://doi.org/10.1542/peds.2007-0619).

Þórðardóttir, Ásgerður, Helga Erlendsdóttir, Bryndís Sigurðardóttir, Hjördís Harðardóttir, Ingi Karl Reynisson, Magnús Gottfreðsson, and Sigurður Guðmundsson. 2014. “Bacterial meningitis in adults in Iceland, 1995–2010.” *Scandinavian Journal of Infectious Diseases* 46 (5): 354–60. doi:[10.3109/00365548.2014.880184](https://doi.org/10.3109/00365548.2014.880184).