PhD thesis

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# Preamble

I am currently writing my PhD thesis on the impact of pneumococcal vaccination in Iceland. I decided to host the thesis on github and distribute on social media. I am doing this for mostly selfish reasons. I believe I will be more motivated if my productiveness – or lack thereof, is held accountable to anyone who wishes to check. I would be grateful for any and all comments on any aspect of the thesis under construction.

# Introduction

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

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

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

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

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

## Clinical manifestations of *Streptococcus pneumoniae*

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

Pneumococcus has gone by many names since first isolated in 1881. Originally termed *Micrococcus pasteuri* by Sternberg (Sternberg [1882](#ref-Sternberg1881)) in 1920, 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, the relationship between pneumococcus and humans is complex. Most children are colonized by pneumococcus within the first months of life (Leino et al. [2001](#ref-Leino2001a)). The serotype distribution of the initial colonization in a child is influenced by the distribution of serotypes within the child’s family . Over the course of the their lifetime, a child will be colonized by many different serotypes. Their immune system will learn to recognize newly acquired serotypes and will either clear the colonization or maintain an equilibrium in which the serotype is kept within a certain limit of reproduction (Dowling, Sheehe, and Feldman [1971](#ref-Dowling1971); MELEGARO, GAY, and MEDLEY [2004](#ref-Melegaro2004)). In this manner, the contribution of pneumococcus to the human upper respiratory flora is in a state of constant flux. New serotypes enter while the old exit, and the relative density of serotypes shifts. In some cases, the equilibrium between pneumococcus and the host is destabilized, triggering a rapid growth of pneumococcus and resulting in clinical manifestations. It is thought that this is most likely to occur directly following the acquisition of new serotype into the nasopharyngeal flora.

All serotypes of pneumococcus have the potential to cause disease in humans. Some are, however, more virulent than others. The prevalence of asymptomatic carriage in the nasopharynx varies greatly by serotype, as does the propensity of a serotype to cause clinical infections. Quantifying the pathogenic potential of serotypes is challenging, as both their prevalence and propensity to cause disease must be considered. With few exceptions, the acquisition of a new serotype into the nasopharyngeal flora proceeds the onset of clinical disease caused by that serotype. The pathogenesis of pneumococcal pneumonia is thought to occur through micro-aspiration of upper respiratory secretions, provoking a subsequent rapid proliferation of pneumococcus in the lower respiratory tract. Invasive disease occurs when pneumococcus penetrates the host’s immunological defenses and proliferates in normally sterile tissue. This can occur as a primary event, or can be secondary to infections of the upper or lower respiratory tract. Generally, IPD is considered to encompass meningitis, bacteraemia and septic arthritis. While some may argue that the middle ear is normally sterile, AOM is not considered invasive disease.

### Acute otitis media

Otitis media is an inflammatory state of the middle ear. It is most often caused by viral or bacterial infection. The clinical presentation of otitis media is variable. Its onset ranges from abrupt to gradual, and its duration from short to protracted. Several categories have been defined to facilitate communication concerning this variability. They are not mutually exclusive, but rather represent a continuum of the disease process.

Otitis media can manifest itself in an acute inflammatory event. This is classical AOM with which most parents are familiar. Conversely, it can take the form of a a chronic low-grade process. The later condition includes otitis media with effusion and chronic suppurative otitis media. Otitis media with effusion is defined as the protracted collection of serous fluid in the middle ear. By convention, it is considered to be present if middle ear effusion has been documented to have lasted for three months or longer. It may follow AOM, or be detected without an obvious inciting event. Chronic suppurative otitis media may be thought of as a protracted case of AOM. The child remains sickly and the middle ear is filled with puss. The tympanic membrane often ruptures as a result.

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

It should be clear from the above that From this discussion of middle ear anatomy, it should be clear that any pathogen 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. It is therefore not surprising that the microbiology of otitis media is complex. It can be caused by many different pathogens, both viral and bacterial. Several pathogens can act in unison to produce clinical disease. The most common bacterial causes of otitis media are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. The relative contribution of these three pathogens is remarkably stable between countries and over time. This is most likely a consequence of how common they are in the nasopharyngeal flora of children. Pneumococcal otitis media is slightly more likely than other otopathogens to lead to recurrent otitis media and chronic suppurative otitis media, but is otherwise indistinguishable from otitis media caused by other otopathogens.

The healthcare burden caused by otitis media is disproportionate to its severity. Acute otitis media is the most common reason for physician visit among children, a fact which has been frequently documented in multiple countries. Likewise, it is responsible for the majority of antimicrobial prescriptions, and thus contributes significantly to antimicrobial resistance. Furthermore, tympanic tube procedures are the most common surgical procedure in the paediatric population.

Paragraph focusing on the situation in Iceland for all of the above

### Pneumonia

~ 4 – 5 pages - Define: CAP, nosocomial, PP, NBPP and IPP. - Pathogens, estimated % caused by pneumococcus - Proposed mechanism by which carriage -> pneumonia - Epidemiology, both serotype and age - Risk factors - Burden of disease caused by pneumonia, health care utilization - Ways of defining severity; CURB-65 etc. - GP visits, antibacterial consumption, Hospitalization rates - Days of work lost - Mortality, sequelae - Review of Icelandic literature and changing epidemiology - Pneumococcal pneumonia prevalence and serotype distribution - Rate of hospitalization, healthcare consumption - Rate of sequelae - Risk factors

### Invasive pneumococcal disease

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

## Pneumococcal conjugate vaccines

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

### A brief history of pneumococcal vaccination

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

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

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

### Key concepts in pneumococcal vaccine epidemiology

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

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

Acute otitis media is still most often caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* despite changes in otopathogens. Prevention of IPD in children and the associated morbidity and mortality was the driving force in the development of pneumococcal conjugate vaccines. However, the public most often associates them with AOM. Most children experience AOM and the dramatic decrease in incidence following pneumococcal conjugate vaccination is what families noticed. Despite this, AOM is a difficult outcome for trialist. AOM exists on a continuum. It does not have universally adhered to diagnostic criteria and its signs and symptoms greatly overlap with those of other common diseases. Because AOM is benign and most often self-limited, the probability that a child with AOM is even seen by a physician varies greatly with parental health seeking behavior. Even when AOM is accurately diagnosed it is not possible to ascertain the causative pathogen without invasive sampling, which is not warranted given the benign nature of the disease. This precludes measuring the serotype specific effect of vaccination for most studies - and more importantly, it precludes measuring the effect on pneumococcal AOM. Thus any estimation of an effect of pneumococcal vaccination will necessarily by diluted by the subjectiveness of AOM diagnosis and the continued lack of protection against other otopathogens. Despite these difficulties, AOM has been associated with pneumococcal vaccination in children from the beginning. It was used as an outcome measure in the earliest trials of the pneumococcal polysaccharide vaccines (Mäkelä et al. [1981](#ref-Makela1981); Sloyer, Ploussard, and Howie [1981](#ref-Sloyer1981)).

#### Randomized controlled trials

The first published randomized controlled trial of a pneumococcal conjugate vaccine reported, among other outcomes, the efficacy against AOM (S. Black et al. [2000](#ref-Black2000)). The study recruited 37,868 children between October 1995 and August 1998 and randomized them to the either PCV7CRM197 or the meningococcus C CRM197 conjugate vaccine. On the basis of a planned interim analysis in August of 1998 the study met predefined efficacy criteria and the Study Advisory Group recommended termination of the trial. Blinded follow-up was continued until April 20, 1999. However, for the AOM portion of the paper, the data had only been analysed until April 1998. A separate publication from the same trial was published in 2003, and examined the effect of PCV7CRM197 on AOM in more detail using the full data until study completion in April 1999 (Fireman et al. [2003](#ref-Fireman2003)). Median follow-up time was not reported in either publication, but 89% children were reported to have completed the primary series of vaccination in the Fireman et al paper. The data on AOM was obtained from routine electronic health records. The assessors were not specifically trained to evaluate AOM as these were simply routine visits. The outcome measure AOM was defined in at least eight different ways to account for the difficulties in measurement. Visits and episodes were defined separately. A visit was considered to be due to the same episode of AOM if the child presented within 21 days of a previous AOM associated visit. Frequent otitis media was then defined as either three episodes within a six month period, or four episodes within a twelve month period. It is unclear exactly which statistical procedures were used for which outcomes. Both the Andersen-Gill extension of the Cox proportional hazards model with robust variance estimation and the binomial test with Klopper-Pearson confidence intervals were used and efficacy was reported as . The study presented both per-protocol and intention-to-treat estimates. Only the per-protocol effects will be examined in this thesis though none of the intention to treat results diverged from them. The estimated vaccine efficacy against otitis media visits was 7.8% (95%CI 5.4%-10.2%). Slightly higher point estimates were found for otitis media episodes, frequent otitis media and ventilatory tube placements (S. Black et al. [2000](#ref-Black2000); Fireman et al. [2003](#ref-Fireman2003))

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

The later study published in 2001 compared two heptavalent pneumococcal vaccines to a hepatitis B vaccine control (Eskola et al. [2001](#ref-Eskola2001)). The two heptavalent pneumococcal vaccines differed in their use of carrier protein. One was the same vaccine as in the Black et al. study (PCV7CRM197), and the other was a conjugated to meningococcal outer membrane protein complex (PCV7MOMPC). The Eskola et al. paper reported comparison of the PCV7CRM197 to the hepatitis B vaccine. The analogous comparison of the PCV7MOMPC was reported in a separate publication (T Kilpi et al. [2003](#ref-Kilpi2003)). No head-to-head comparison of the two heptavalent vaccines was ever reported. The study methodology was identical between the two publications as they report different arms of the same study (Eskola et al. [2001](#ref-Eskola2001); T Kilpi et al. [2003](#ref-Kilpi2003)). The study was specifically designed to address the difficulties associated with estimating the effect of pneumococcal vaccination on AOM. A total of 2,497 children were enrolled between December 1995 and April 1997, of which 835 received the PCV7MOMPC vaccine and were therefore not reported in the Eskola et al. paper. Children were followed until their last visit at 24 months of age. Of the enrolled children, 95.1% completed full follow-up time and there was no evidence of differential dropout. The study defined beforehand the criteria for what constituted AOM and employed a trained study nurse and physician at each study site. Children were seen at enrollment at two months of age, and periodically assessed thereafter at four, six, seven, twelve, thirteen and 24 months of age. Parents were encouraged to present with their child to one of the study clinics for assessment of any symptoms suggesting respiratory infection or AOM. If AOM was diagnosed as defined by the study criteria, myringotomy and aspiration of middle-ear fluid were performed and samples sent for culture. In this way, the study was able to deduce the causative otopathogen. Episodes of AOM were classified as all-cause AOM; culture-confirmed and otopathogen specific AOM; and AOM due to serotypes included in the vaccine. The statistical analysis was again conducted using the Andersen-Gill extension of the Cox proportional hazards model with robust variance estimates and efficacy was reported as . The results were most consistent with a 6% efficacy against all-cause AOM with 95% confidence limits of -4% and 16%. In this case the negative lower confidence limit indicates the data could be consistent with the possibility of a 4% increase in all-cause AOM, given the specified model. The PCVCRM197 efficacy against culture-confirmed pneumococcal AOM was 35% (95%CI 21%-45%) and was 57% (95%CI 44%-67%) for the seven serotypes included in the vaccine. Similarly, the study demonstrated 57% (95%CI 27%-76%) efficacy against AOM caused by serotype 6A, which is considered a cross-reactive pneumococcal serotype. The study was also one of the first to demonstrate clinically relevant serotype replacement, showing a 33% (95%CI -1%-80%) increase in pneumococcal AOM caused by serotypes not included in the vaccine. Children who completed the Eskola et al. trial and were still living in the study area were invited for a follow-up interview when they were four to five years of age (A. A. I. Palmu et al. [2004](#ref-Palmu2004)). In the extended follow-up trial, the vaccine effectiveness against all tympanostomy tube placements was estimated to be 39% (95%CI 4%-61%). However, this was unblinded study following the unmasking of the original study and there was differential recruitment between the placebo and PCV7CRM197 arms. There was therefore a substantial risk of bias in the study.

The effect estimates for the PCV7MOMPCagainst culture-confirmed pneumococcal AOM was 25% (95%CI 11%-37%) and was 56% (95%CI 44%-66%) for the seven serotypes included in the vaccine (T Kilpi et al. [2003](#ref-Kilpi2003)). However, unlike PCVCRM197, it did not seem to confer protection against cross-reactive serotypes. Interestingly, virtually no effect was seen on all-cause AOM with this vaccine preparation. The effect estimate was -1% (95%CI -12%-10%). These surprising results were not presented in the main text and no explanation was given in the discussion chapter of the paper.

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

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

Study

Vaccine

Enrollment period

Country

No. of children

Efficacy against Otitis media episodes

Black, 2000 & Fireman, 2003

PCV7 (CRM197)

Oct 1995-Aug 1998

United States

37868

7.8% (5.4%-10.2%)

Dagan, 2001

PCV9 (CRM197)

Unclear

Isreal

264

17% (-2%-33%)

Eskola, 2001

PCV7 (CRM197)

Dec 1995-Apr 1997

Finland

1662

6% (-4%-16%)

Kilpi, 2003

PCV7 (MOMPC)

Dec 1995-Apr 1997

Finland

1666

-1% (-12%-10%

Prymula, 2006

PCV9 (HiD)

Oct 2000-Sep 2002

Czech Republic & Slovakia

4968

33.6% (20.8%-44.3%

O’Brien, 2008

PCV7 (CRM197

Apr 1997-Aug 2000

United States

856

-0.4% (-19.4%-15.6%

#### Observational studies

### Pneumonia

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

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

### Invasive pneumococcal disease

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

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

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

### Measurement of effectiveness and choice of health outcomes

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

#### Health outcomes considered

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

#### Effectiveness of PCV7

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

#### Effectiveness of PCV10

~2-3 pages - What effectiveness rationale is used, methods and rationale: critique - Carriage - AOM - Pneumonia - IPD

#### Effectiveness of PCV13

~ 2- 3 pages - What effectiveness rationale is used, methods and rationale: critique - Carriage - AOM - Pneumonia - IPD

### Estimating resources and cost

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

# Aims

# Materials and methods

We describe our methods in this chapter.

# Results

# Discussion

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