PhD thesis

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Contents

Chapter 1

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.

Chapter 2

Introduction

Streptococcus pneumoniae is a commensal bacterium found in the nasopharynx of humans where it plays an integral role in the normal upper respiratory flora. It is also a common pathogen and is 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 that is usually found in pairs. In fact, pneumococcus is *the* Gram-positive coccus, being first bacteria that Christian Gram noted which retained the dark aniline-gentian violet stain that now bears his name (Gram, 1884). Pneumococcus was first isolated in 1881 by two microbiologist, George M. Sternberg in the United States and Louis Pasteur in France (Pasteur, 1881; Sternberg, 1882; Watson et al., 1993). In both cases the sample from which the bacterium was isolated originated from healthy carriers, rather than ill patients. The causal association between this newly discovered bacterium and pneumonia was firmly established only five years later (Weichselbaum, 1886), and in the following decade, all clinical presentations of pneumococcal infection had been described (Austrian, 1981). Pneumococcus has gone by many names since its first isolation in 1881. Originally it was named *Micrococcus pasteuri* by Sternberg (Sternberg, 1882) but, by 1920 a scientific consensus was reached in which it was agreed that the official name should be *Diplococcus pneumoniae* (Winslow et al., 1920). It was not until 1974 that pneumococcus received its current name, *Streptococcus pneumoniae* (Deibel and Seeley, 1974).

Pneumococcus is encapsulated by a polysaccharide coating that protects it from environmental factors. The polysaccharide capsule acts as an "invisibility cloak" to the human immune system, which is rendered unable to detect pneumococcus except through certain patterns in the oligosaccharides contained within the capsule (Tuomanen et al., 1995). Based on these patterns, pneumococcus has been classified into over 97 different serotypes to date. Additionally, as the capsule contains only polysaccharides and not proteins, the immune response is T-cell independent and therefore poorly immunogenic, even after identification by the immune system (Geno et al., 2015). These characteristics are the fundamental challenges faced by scientists engineering new pneumococcal vaccines. The significance of serotypes on the development of vaccines should not be understated. The failure of the original attempt of Wright and colleagues in 1911 to prevent pneumococcal pneumonia with vaccination was indeed due to lack of knowledge about serotype-specific immunogenicity (Wright et al., 1914).

All serotypes of pneumococcus have the potential to cause disease in humans. However, some are more virulent than others. The prevalence of asymptomatic carriage in the nasopharynx varies greatly by serotype as does the propensity of serotypes to cause clinical infections. Quantifying the pathogenic potential of serotypes is difficult as both their prevalence and propensity to cause disease need to be considered. With few exceptions, acquisition of a new serotype into the nasopharyngeal flora proceeds the onset of clinical disease caused by that serotype. Pneumococcal epidemiology is dominated by this effect - children act as a reservoir of asymptomatic pneumococcal carriage from which other children and adults acquire serotypes that may lead to symptomatic disease. Because of this, vaccinations that decrease the pneumococcal carriage in children have the potential of reducing the incidence of disease both in other unvaccinated children and in adults. This phenomenon is called a herd-effect, and is integral to the development of vaccination strategies to combat pneumococcal disease.

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 in acute otitis media (AOM) – an infection of the middle ear. AOM is the most common reason for physician visit and for antimicrobial prescription in the paediatric population. However, the disease course is benign and rarely results in permanent disability. The pathogenesis of AOM is complex and can both be caused by viral and bacterial pathogens. Bacterial AOM is most often caused by pneumococcus and *Haemophilus influenzae*. Acute sinusitis is another common, though benign, manifestation of pneumococcal disease. Pneumococcus is also a common cause of pneumonia – the disease from which it gets its name. Pneumonia often requires hospitalization and intravenous antimicrobial treatment, and, though uncommonly, can lead to permanent disability and death. Finally, if pneumococcus gains access to normally sterile tissue, it may cause invasive infections. This 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%.

Pneumococcus became an early target for vaccine development because of the broad range of disease caused by pneumococcus. The vaccine benefit can be quantified in two different ways. On one hand it can prevent uncommon but serious manifestations of disease and has the potential to prevent death and serious disability. On the other hand, it also prevents common infections that cumulatively present a large healthcare burden due to frequent physician visits, antimicrobial prescriptions as well as work hours lost by parents and caregivers. The earliest attempts to use vaccination to lessen the morbidity and mortality associated with pneumococcus date back to 1911 when Wright used whole cell innoculi to vaccinated miners in South Africa (Wright et al., 1914). In the following decades, multiple animal studies showed that injection of the pneumococcal polysaccharide coating in animals protected against subsequent pneumococcal infections. On the basis of these findings, the first polysaccharide vaccine was shown to be effective (Macleod et al., 1945). This lay the foundation for modern polysaccharide pneumococcal vaccines. However, it soon became apparent that the polysaccharide vaccines were not adequately immunogenic in young children, the ill or the elderly. In response, pneumococcal conjugate vaccines were developed. The first such vaccine to be mass produced was the heptavalent Prevenar developed by Pfizer Pharmaceuticals.

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. Iceland, as other Nordic countries, has a rich legacy of national health-related registers. With a wealth of medical documentation, a unique whole-population ecological study examining the impact of systematic pneumococcal vaccination was enabled.

2.1 Clinical manifestations of *Streptococcus pneumoniae*

The relationship between pneumococcus and humans is complex. Most children are colonized by pneumococcus within the first months of life. The serotype distribution of the initial colonization is influenced by the distribution of serotypes within the family. Over the course of the child's lifetime, they will be colonized by many different serotypes. The child's immune system will learn to recognize the currently colonizing serotypes and will either clear the colonization or maintain a equilibrium in which the serotype is kept within a certain limit of reproduction. Consequently, the contribution of pneumococcus to the human upper respiratory flora is in a state of constant flux. New serotypes enter while old exit, and the relative density of serotypes changes. In some cases the equilibrium between pneumococcus and the host is destabilized resulting in rapid growth of pneumococcus which results in clinical manifestations. It is thought that this is most likely to occur immidietly following the acquisition of new serotype into the nasopharyngeal flora. This

most commonly occurs in the upper respiratory tract where pneumococcus is generally located and results in the common clinical manifestations of pneumococcal infections, i.e. AOM, acute sinusitis and conjunctivitis. The pathogenesis of pneumococcal pneumonia is thought to occur through micro-aspiration of upper respiratory secretions with subsequent rapid proliferation of pneumococcus in the lower respiratory tract. Invasive disease occurs when pneumococcus penetrates the host immunological defenses and proliferates in normally sterile tissue. This can be secondary to infections of the upper or lower respiratory tract, or can occur as a primary event. 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.

It has been known from the first pneumococcal vaccine trials that vaccination has different efficacy against the different manifestations of pneumococcal disease. The largest effects are consistently seen in the prevention of IPD and pneumococcal lobar pneumonia. The effects on carriage and AOM are often lesser in magnitude. This may be a true biological gradient or a consequence of the accuracy with which disease is measured. The more serious the illness is the more testing is performed resulting in a more accurate diagnosis. Much of the AOM attributed to pneumococcus may be caused by other pathogens, while by definition IPD is always caused by pneumococcus. Furthermore, it wasn't until the advent of pneumococcal conjugate vaccines that vaccines started to become efficacious in children and it is precisely in children that AOM occurs. The largest trials of modern pneumococcal vaccines have fit the above narrative. The 23-valent pneumococcal polysaccharide vaccine was trialed in 12,000 adults and showed an efficacy of 75% in preventing IPD and a 50% efficacy against radiologically confirmed pneumonia. The heptavalent pneumococcal conjugate vaccine was trialed in children and produced a 97% efficacy in preventing IPD.

2.1.1 Carriage

~ 3-4 pages - Define carriage; age-specific prevalence, serotype distribution - Explain that most are born carriage free - Evidence for co-carriage of different serotypes - Age at which most children acquire carriage - Risk factor: daycare, siblings, smoking etc. - Children are the main vectors of pneumococcus - Rate of clearance dependent on age - With increasing age -> increasing immunity, decreasing prevalence - Senescence and carriage in the elderly - Evidence for carriage being the predecessor infections - Evidence of asymptomatic carriage -> main spread of disease - Variable propensity of serotypes to cause disease, attack-rates - Review the Icelandic literature and changing epidemiology - Carriage prevalence - Serotype distribution - Risk factors

2.1.2 Acute otitis media

~ 3 - 4 pages - Define different types of otitis media; acute otitis media - Pathogens, estimated % caused by pneumococcus - Proposed mechanism by which carriage -> AOM - Epidemiology, both serotype and age - Risk factors - Burden of disease caused by AOM; health care utilization, cost - Incidence and prevalence - GP visits, antibacterial consumption, hospitalization (?) - Days of work-lost by parents - Sequelae; multiple infections, effusion, tympanostomies - Evidence of benefit of delaying 1st presentation - Review of Icelandic literature and changing epidemiology - AOM prevalence and serotype distribution - Risk factors - Associated healthcare consumption, cost - Rate of sequelae

2.1.3 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

2.1.4 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

2.2 Pneumococcal conjugate vaccines

The history of pneumococcal vaccination begins in 1911 when Wright and colleagues attempted to use whole killed bacteria to vaccinate South African miners against pneumococcal pneumonia (Wright et al., 1914). It should however be noted that in his original description of pneumococcus in 1881, George Sternberg observed that rabbits who were injected with his saliva mixed with alcohol and quinine did not ubiquitously die and were later resistant to re-injection with saliva (Austrian, 1999, Sternberg (1882)). Sternberg had inadvertently immunized the laboratory animals against subsequent infection by injecting killed pneumococci, proving the concept 30 years before it was first attempted. The 1911 trial by Wright failed to show efficacy due to lack of knowledge of the significance of serotypes and serotype specific immunogenicity. Several trials using whole killed bacteria were published in the following two decades (Cecil, 1918; Lister, 1916; Lister and Ordman, 1936; Maynard, 1913) The researchers benefited from the knowledge of serotypes which had been discovered in 1910 and used multivalent vaccines. They were however victims of underdeveloped epidemiological methodology for vaccine field trials. Due to inconsistencies in study design, the efficacy of whole bacteria pneumococcal vaccines remained fiercely debated though there seemed to be a suggestion of benefit (Austrian, 1999). Vaccines based on whole killed bacteria were soon replaced with polysaccharide vaccines, following discoveries in the 1920s and 1930 of the immunogenicity of the polysaccharide capsule (Dochez and Avery, 1917; Finland, 1931; Francis and Tillett, 1930; Heidelberger and Avery, 1923; Schiemann and Casper, 1927). The first such trial tested a bivalent polysaccharide vaccine on 29,000 adult males in the American Civilian Conservation Corps in iterations in the 1930s (Ekwurzel et al., 1938). It suffered from the same methodological problems as did the previous trials of the whole killed bacteria and its results were debated. A second large trial was conducted in the late 1930s using a tetravalent vaccine (Macleod et al., 1945). This trial built upon the experience of the previous trials and was able to show convincing efficacy against pneumococcal pneumonia. The results of this trial led 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. Alas, these early vaccines fell victim to unfortunate timing. Because in 1944, Tillet and colleagues showed that bacteraemic pneumococcal pneumonia could be cured by parenteral administration of benzylpenicillin (Tillett et al., 1944). Following this discovery, the medical community was stricken with a kind of nonchalance. 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 their use (Austrian, 1999) Interest in pneumococcal vaccination re-emerged in the 1950s when it was noted that the mortality benefit of penicillin was not ubiquitous. The elderly and those who had underlying disease did not experience a decrease in their case fatality ratio (Austrian and Gold, 1964). 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, Smit (1977)) 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). Early in the development of pneumococcal vaccinations there was an interested in vaccinating children. Two trials were conducted in the early 1980s which attempted to use polysaccharide vaccines in young children. Neither showed benefit (Mäkelä et al., 1981; Sloyer et al., 1981). This is perhaps unsurprising in light of previous trials. The first polysaccharide trial that was conducted in children in 1937 failed to detect any immunological response (Davies, 1937). Laboratory studies in the 1930s and 1940s revealed that the reason for this lack of efficacy was due to the thymus independent immunse response to purely sacharide antigens. These same studies showed that this could be remedied by adding a protein adjuvant, thus inducing a T-cell response. The strategy of protein conjugation saw its first success in

the development of the *Haemophilus influenzae* type b vaccine. Subsequently, several different pneumococcal conjugate vaccines entered phase II and phase III clinical trials in the late 1990s (Austrian, 1999). The first of which to receive licensure was the seven valent pneumococcal conjugate vaccine which was licensed in 2000 in the United States. It included purified polysaccharides for seven serotypes of pneumococcus (4, 9V, 14, 19F, 23F, 18C and 6B) conjugated to CRM197 ($PCV7_{CRM197}$), a nontoxic variant of the diptheria toxin. It was shown to be efficacious for IPD, pneumococcal pneumonia and AOM in several randomized trials (Black et al., 2000, 2002; Eskola et al., 2001; Fireman et al., 2003; O'Brien et al., 2003, 2008). Higher valancy conjugated vaccines were developed and recieved licensure in the new millennium 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.

2.3 Impact of pneumococcal conjugate vaccines

~ 3 pages - Present evidence of magnitude of effect on VT carriage **The three Dagan studies mentioned in (Eskola et al., 2001), also (Prymula et al., 2006; O'Brien et al., 2007)** - Serotype distribution vs. carriage prevalence - Serotype replacement - Herd-effect, i.e. effect on carriage of adults and non-vaccinated

From their inception, dozens of randomized controlled trials evaluating the efficacy of different pneumococcal conjugate vaccines have been performed.

2.3.1 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.

2.3.1.1 Randomised controlled trials

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; Sloyer et al., 1981). The first published randomized controlled trial of a pneumococcal conjugate vaccine reported, among other outcomes, the efficacy against AOM (Black et al., 2000). The study recruited 37,868 children between October 1995 and August 1998 and randomized them to the either $PCV7_{CRM197}$ 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 continued until April 20, 1999. However, for the AOM portion of the paper, the data had only been analysed until April 1998 A seperate publication from the same trial was published in 2003, and examined the effect of $PCV7_{CRM197}$ on AOM in more detail using the full data until study completion in April 1999 (Fireman et al., 2003). 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 $(1 - \mathit{ratio\ measure}) * 100\%$. 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 (Black et al., 2000; Fireman et al., 2003)

The following year the results of another randomized controlled trial were reported (Eskola et al., 2001). This study compared two heptavalent pnuemococcal vaccines to a hepatitis B vaccine control. The two heptavalent pneumococcal vaccines differed in their use of carrier protein. One was the same vaccine as in the Black et al. study ($\text{PCV7}_{\text{CRM197}}$), and the other was a conjugated to meningococcal outer membrane protein complex ($\text{PCV7}_{\text{MOMPC}}$). This publication only reported the comparison of the $\text{PCV7}_{\text{CRM197}}$ to the hepatitis B vaccine. The analogous comparison of the $\text{PCV7}_{\text{MOMPC}}$ was reported in a seperate publication (Kilpi et al., 2003). 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; Kilpi et al., 2003). 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 $\text{PCV7}_{\text{MOMPC}}$ 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 $(1 - \mathit{hazard\ ratio}) * 100\%$. 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 $\text{PCV}_{\text{CRM197}}$ 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 (Palmu et al., 2004). 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 $\text{PCV7}_{\text{CRM197}}$ arms. There was therefore a substantial risk of bias in the study.

The effect estimates for the $\text{PCV7}_{\text{MOMPC}}$ 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). However, unlike PCV_{CRM197}, it did not seem to confer protection against cross-reactive serotypes. Interestingly, virtually no effect was seen on all-cause AOM with this vaccine preperation. The effect estimate was -1% (95%CI -12%-10%). These suprising results were not presented in the main text and no explanation was given in the discussion chapter of the paper.

The randomized controlled trial of $PCV7_{CRM197}$ among the Navajo and White Mountain Apache infants has previously been described in the 2.3

Study	Vaccine	Enrollment period	Country	No. of children	I
Black, 2000 & Fireman, 2003	PCV7 (CRM197)	Oct 1995-Aug 1998	United States	37868	7
Eskola, 2001	PCV7 (CRM197)	Dec 1995-Apr 1997	Finland	1662	6
Kilpi, 2003	PCV7 (MOMPC)	Dec 1995-Apr 1997	Finland	1666	-
Prymula, 2006	PCV9 (HiD)	Oct 2000-Sep 2002	Czech Republic & Slovakia	4968	3
O'Brien, 2008	PCV7 (CRM197	Apr 1997-Aug 2000	United States	856	-

2.3.2 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

2.3.3 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

2.4 Cost-effectiveness 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

2.4.1 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

2.4.1.1 Health outcomes considered

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

2.4.1.2 Effectiveness of PCV7

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

2.4.1.3 Effectiveness of PCV10

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

2.4.1.4 Effectiveness of PCV13

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

2.4.2 Estimating resources and cost

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

Chapter 3

Aims

Chapter 4

Materials and methods

We describe our methods in this chapter.

Chapter 5

Results

Chapter 6

Discussion

Bibliography

Austrian, R. (1981). Pneumococcus: the first one hundred years. *Reviews of infectious diseases*, 3(2):183–9.

Austrian, R. (1999). A brief history of pneumococcal vaccines. *Drugs & aging*, 15 Suppl 1:1–10.

Austrian, R., Douglas, R. M., Schiffman, G., Coetzee, A. M., Koornhof, H. J., Hayden-Smith, S., and Reid, R. D. (1976). Prevention of pneumococcal pneumonia by vaccination. *Transactions of the Association of American Physicians*, 89:184–94.

Austrian, R. and Gold, J. (1964). Pneumococcal Bacteremia With Especial Reference To Bacteremic Pneumococcal Pneumonia. *Annals of internal medicine*, 60:759–776.

Black, S., Shinefield, H., Fireman, B., Lewis, E., Ray, P., Hansen, J. R., Elvin, L., Ensor, K. M., Hackell, J., Siber, G., Malinoski, F., Madore, D., Chang, I., Kohberger, R., Watson, W., Austrian, R., and Edwards, K. (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.

Black, S. B., Shinefield, H. R., Ling, S., Hansen, J., Fireman, B., Spring, D., Noyes, J., Lewis, E., Ray, P., Lee, J., and Hackell, J. (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):810–815.

Cecil, R. L. (1918). RESULTS OF PROPHYLACTIC INOCULATION AGAINST PNEUMOCOCCUS IN 12,519 MEN. *Journal of Experimental Medicine*, 28(1):19–41.

Davies, J. A. V. (1937). The Response of Infants to Inoculation with Type I Pneumococcus Carbohydrate. *The Journal of Immunology*.

Deibel, R. and Seeley, H. (1974). Family II: Streptococcuceae. In Buchanan, R. E. and Gibbons, N. E., editors, *Bergey's Manual of Determinative Bacteriology*, pages 490–517. The William and Wilkins Co, Baltimore, 8 edition.

Dochez, A. L. and Avery, O. T. (1917). The elaboration of specific soluble substance by pneumococcus during growth. *The Journal of experimental medicine*.

Ekwurzel, G. M., Simmons, J. S., Dublin, L. I., and Felton, L. D. (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):1877–1893.

Eskola, J., Kilpi, T., Palmu, A., Jokinen, J., Haapakoski, J., Herva, E., Takala, A., Käyhty, H., Karma, P., Kohberger, R., Siber, G., Mäkelä, P. H., Eerola, M., Others, Kayhty, H., and Makela, P. H. (2001). Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*, 344(6):403–409.

Finland, M. (1931). SPECIFIC CUTANEOUS REACTIONS AND CIRCULATING ANTIBODIES IN THE COURSE OF LOBAR PNEUMONIA: I. CASES RECEIVING NO SERUM THERAPY. *Journal of Experimental Medicine*, 54(5):637–652.

Fireman, B., Black, S. B., Shinefield, H. R., Lee, J., Lewis, E., and Ray, P. (2003). Impact of the pneumococcal conjugate vaccine on otitis media. Technical Report 1.

Francis, T. and Tillett, W. S. (1930). Cutaneous reactions in pneumonia. The development of antibodies following the intradermal injection of type-specific polysaccharide. *The Journal of experimental medicine*.

Geno, K. A., Gilbert, G. L., Song, J. Y., Skovsted, I. C., Klugman, K. P., Jones, C., Konradsen, H. B., and Nahm, M. H. (2015). Pneumococcal Capsules and Their Types: Past, Present, and Future. *Clinical Microbiology Reviews*, 28(3):871–899.

Gram, C. (1884). Ueber die isolierte Fabung der Schizomyceten in Schnitt und Trockenpraparaten. *Fortschritte der Medicin*, 2:185–189.

Heidelberger, M. and Avery, O. T. (1923). THE SOLUBLE SPECIFIC SUBSTANCE OF PNEUMOCOCCUS. *The Journal of experimental medicine*.

Kilpi, T., Ahman, H., Jokinen, J., Lankinen, K. S., Palmu, A., Savolainen, H., Gronholm, M., Leinonen, M., Hovi, T., Eskola, J., Kayhty, H., Bohidar, N., Sadoff, J. C., and Makela, P. H. (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):1155–1164.

Lister, F. S. (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*, 8:231–287.

Lister, F. S. and Ordman, D. (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.

Macleod, C. M., Hodges, R. G., Heidelberger, M., and Bernhard, W. G. (1945). PREVENTION OF PNEUMOCOCCAL PNEUMONIA BY IMMUNIZATION WITH SPECIFIC CAPSULAR POLYSACCHARIDES. *The Journal of experimental medicine*, 82(6):445–65.

Mäkelä, P. H., Leinonen, M., Pukander, J., and Karma, P. (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.

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.

O'Brien, K. L., David, A. B., Chandran, A., Moulton, L. H., Reid, R., Weatherholtz, R., and Santosham, M. (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.

O'Brien, K. L., Millar, E. V., Zell, E. R., Bronsdon, M., Weatherholtz, R., Reid, R., Becenti, J., Kvamme, S., Whitney, C. G., and Santosham, M. (2007). Effect of Pneumococcal Conjugate Vaccine on Nasopharyngeal Colonization among Immunized and Unimmunized Children in a Community-Randomized Trial. *The Journal of Infectious Diseases*, 196(8):1211–1220.

O'Brien, K. L., Moulton, L. H., Reid, R., Weatherholtz, R., Oski, J., Brown, L., Kumar, G., Parkinson, A., Hu, D., Hackell, J., Chang, I., Kohberger, R., Siber, G., and Santosham, M. (2003). Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. *Lancet*, 362(9381):355–61.

Palmu, A. A. I., Verho, J., Jokinen, J., Karma, P., and Kilpi, T. M. (2004). The seven-valent pneumococcal conjugate vaccine reduces tympanostomy tube placement in children. *The Pediatric infectious disease journal*, 23(8):732–738.

Pasteur, L. (1881). Note sur la maladie nouvelle provoquee par la salive d'un enfant mort de la rage. Technical Report 10, I'Academie de Medicine, Paris.

Prymula, R., Peeters, P., Chrobok, V., Kriz, P., Novakova, E., Kaliskova, E., Kohl, I., Lommel, P., Poolman, J., Prieels, J. P., and Schuerman, L. (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):740–748.

Schiemann, O. and Casper, W. (1927). Sind die spezifisch pracipitablen Substanzen der 3 Pneumokokkentypen Haptene? *Zeitschrift fur Hygiene und Infektionskrankheiten*.

Sloyer, J. L., Ploussard, J. H., and Howie, V. M. (1981). Efficacy of pneumococcal polysaccharide vaccine in preventing acute otitis media in infants in Huntsville, Alabama. *Reviews of infectious diseases*, 3 Suppl:S119–23.

Smit, P. (1977). Protective Efficacy of Pneumococcal Polysaccharide Vaccines. *JAMA: The Journal of the American Medical Association*, 238(24):2613.

Sternberg, G. M. (1882). A fatal form of septicemia in the rabbit produced by subcutaneous injection of human saliva. Technical report, National Board of Health, Washington.

Tillett, W. S., Cambier, M. J., and McCormack, J. E. (1944). The Treatment of Lobar Pneumonia and Pneumococcal Empyema with Penicillin. *Bulletin of the New York Academy of Medicine*, 20(3):142–78.

Tuomanen, E. I., Austrian, R., and Masure, H. R. (1995). Pathogenesis of Pneumococcal Infection. *New England Journal of Medicine*, 332(19):1280–1284.

Watson, D. A., Musher, D. M., Jacobson, J. W., and Verhoef, J. (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.

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

Winslow, C.-E. E., Broadhurst, J., Buchanan, R. E., Krumwiede, C., Rogers, L. A., and Smith, G. H. (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.

Wright, A., Parry Morgan, W., Colebrook, L., and Dodgson, R. (1914). Observations ON PROPHYLACTIC INOCULATION AGAINST PNEUMOCOCCUS INFECTIONS. AND ON THE RESULTS WHICH HAVE BEEN ACHIEVED BY IT. *The Lancet*, 183(4715):87–95.