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, in that it was the first bacteria that Christian Gram noted to retain 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 Loius 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 from its first isolation in 1881. Originally named *Micrococcus pasteuri* by Sternberg (Sternberg, 1882), a scientific consensus was reached in 1920 whereupon it was agreed that the official name should be *Diplococcus pneumoniae* (Winslow et al., 1920). It was not until 1974 when 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 in regard 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 as of the writing of this thesis. Additionally, as the capsule only contains 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 are the fundamental problems faced by scientists when engineering new pneumococcal vaccines. The significance of serotypes on the development of vaccines should not be understated. Lack of knowledge about serotype-specific immunogenicity was the main reason for the failure of the original attempts at preventing pneumococcal pneumonia by Wright in South Africa (Wright et al., 1914). Because of this, the feasibility of pneumococcal vaccination wasn't definitively demonstrated until 1945 (Macleod et al., 1945).

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 prevalence of serotypes causing clinical infections. Quantifying the pathogenic potential of serotypes can be difficult as both need to be considered. With few exemptions, acquisition of a new serotype into the nasopharyngeal flora proceeds clinical disease caused by that serotype. Pneumococcal epidemiology is dominated by this effect, wherein children act as a reservoir of asymptomatic pneumococcal carriage from which other children and adults acquire serotypes that may lead to symptomatic disease. Vaccinations that decrease the pneumococcal carriage in children do therefore have the potential to reduce the incidence of disease in both other unvaccinated children and 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 sites. 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 antimicrobial prescription in the pediatric 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 influnzae. Acute sinusitis is another common but benign manifestation of pneumococcal disease. Pneumococcus is also a common cause of pneumonia – from which it gets its name. Pneumonia often requires hospitalization and intravenous antimicrobial treatment and can uncommonly lead to permanent disability and death. Finally, if pneumococcus gains access to normally sterile sites 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 this 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 prevents common infections that cumulatively present a large healthcare burden due to frequent physician visits, antimicrobial prescriptions and days of work lost by parents and caregivers. The earliest attempts to use vaccination to lessen the morbidity and mortality associated with pneumococcus date back to 1914 when Wright used whole cell innoculi to vaccinated miners in South Africa (Wright et al., 1914). In 1934, armed with the knowledge of different pneumococcal serotypes and serotype specific immunogenicity, Lister and Ordman demonstrated the effectiveness of polyvalent whole-cell vaccines against pneumococcal pneumonia. In the following decades, repeated 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 demonstrated to be effective (Macleod et al., 1945). This lay the foundation for modern polysaccharide pneumococcal vaccines. Unfortuneatly, it soon became apparent that the polysaccharide vaccines were not addequetly immunogenic in young children, the ill and the elderly. This lead to the development of pneumococcal conjugate vaccines. The first such vaccine to be mass produced was the heptavalent Prevenar developed by Pfizer pharmacouticals.

Iceland is an independent island nation located in the mid-Atlantic. It has a homogenous populuation of roughly 330,000 individuals. The first systamatic 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 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 systamatic vaccination effort had been undertaken in Iceland. Like the other Nordic countries, Iceland has a rich history of national health related registers. This allowed for a unique whole population ecological study to examine the impact of systamatic pneumococcal vaccination.

2.1 Clinical manifestations of *Streptococcus pneumoniae*

~ 2 pages - Build transmission dynamics, carriage and disease mentioned in introduction - Short overview of mechanism by which individuals become colonized - Asymptomatic carriage the predecessor of infections - Non-invasive vs. invasive infections - Explain relevance of differentiating the two - list manifestations in each category building on introduction - Explain that vaccines have variable impact on different manifestations - Use examples from the two large RCTs

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 serotype and will either clear the colonization or maintain a equilibrium in which the serotype is kept within a certain limit of repro-

duction. 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. This most commonly occurs in the upper respiratory tract where pneumococcus is generally located. This 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.

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 - Describe mathematical method to estimate adult carriage from observed carriage in children.

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

~ 1 -2 pages - PPSV23 original studies, downsides, immunogenicity - Development of protein conjugate vaccines, reasons - PCV7 - Higher valency PCVs

2.3 Impact of pneumococcal conjugate vaccines

~ 3 pages - Present evidence of magnitude of effect on VT carriage - Serotype distribution vs. carriage prevalence - Serotype replacement - Herd-effect, i.e. effect on carriage of adults and non-vaccinated

2.3.1 Acute otitis media

~ 1-2 pages <- much fewer studies - Present evidence of magnitude of effect on all-cause AOM - VT vs. NVT serotypes - Serotype replacement (?)
- Herd-effect in non-vaccinated

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

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