Bacterial meningitis: epidemiology, herd protection, clinical characteristics, and risk assessment
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CHAPTER 1
Introduction
Meningitis is an infection of the meninges and the subarachnoid space that can also involve the brain parenchyma (meningo-encephalitis). Bacterial meningitis is a devastating disease that is associated with substantial mortality and morbidity. An estimated 303,500 deaths, and 21 million disability adjusted life years were attributed to bacterial meningitis in 2013 worldwide.

The clinical characteristics of bacterial meningitis have been described by Hippocrates in the 5th century B.C. Gaspard Vieusseux was the first to give a detailed description of the clinical syndrome during an epidemic of meningococcal meningitis in Geneva in 1805. Adult patients with community-acquired bacterial meningitis usually complain of headache, nausea, vomiting and photophobia. Almost all patients will present with at least two of the signs and symptoms: headache, fever, neck stiffness, and altered mental status.

The prognosis of meningitis before the twentieth century was dismal; more than three quarters of patients with meningococcal meningitis and nearly all with pneumococcal or Haemophilus influenzae meningitis died. The introduction of intravenous and intrathecal administration of specific antisera in the 1920s greatly improved outcome. After the introduction of sulphonamides in the 1930s, over three quarters of patients survived H. influenzae and meningococcal meningitis. The use of penicillin therapy for pneumococcal meningitis began in the mid-1940s, reducing the case fatality rate from nearly 100% to less than 50%. At the turn of the century the case fatality rate in the Netherlands had declined to 7% for meningococcal meningitis and 30% for pneumococcal meningitis patients.

The most common causative pathogens of bacterial meningitis worldwide are Streptococcus pneumoniae, Neisseria meningitidis, and H. influenzae type b, respectively causing 26%, 22% and 21% of global cases in 2013. These bacteria are transmitted from person to person through droplets of respiratory or throat secretions. Humans are the main reservoir for pneumococci, and N. meningitidis, and H. influenzae are exclusively human pathogens. Transmission usually results in a period of asymptomatic colonization of the nasopharynx, before they are cleared by the host, or supplanted by other pathogens. Asymptomatic carriage is much more common than invasive disease. The mechanism whereby colonization in the host progresses to disease is not fully understood, but is thought to depend on the interaction of environmental, host susceptibility and bacterial virulence factors.

The main virulence factor of the most common causative bacteria of meningitis is the polysaccharide capsule. Whereas many carried isolates are unencapsulated, isolates that cause disease almost invariably express the polysaccharide capsule. Differences between capsules are used to classify meningococci into 13 serogroups, H. influenzae into six serotypes and pneumococci into more than ninety serotypes. Most meningococcal disease is caused by six serogroups (A, B, C, W, X, Y), and serotype b causes the majority of H. influenzae disease. Meningococci are further classified based on serological and genetic differences of outer membrane proteins (e.g. porA, porB).
Another typing scheme, Multi Locus Sequence Typing (MLST), identifies differences in seven genes required for the maintenance of basic cellular function. Based on allelic variants at these seven loci, isolates are classified into sequence types that can subsequently be grouped into clonal complexes. Isolates in these clonal complexes can share important clinical characteristics, such as the propensity to cause invasive disease.

Large scale immunization programs against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b are among the most effective public health interventions of the last 50 years. The observation that anti-capsular bactericidal antibodies protect against disease led to the use of purified capsular polysaccharides in vaccine formulations. Because polysaccharides are T-cell-independent antigens that cannot be presented to T cells in conjunction with MHC class II molecules, plain polysaccharide vaccines do not stimulate the development of memory B cells. Consequently, the vaccine works poorly or not at all in young children, and no memory response is generated in adults. Conjugation of the bacterial polysaccharide to a carrier protein induces a T-cell-dependent immune response. Conjugate vaccines are, in general, immunogenic from early infancy and induce a longer lasting immune response.

Conjugate vaccines against *H. influenzae* type b were introduced in the late 1980s. A conjugate vaccine against serogroup C meningococci was introduced in 1999, followed by vaccines against serogroups A, W and Y. Because the serogroup B polysaccharide is identical to a polysialic acid of human glycoproteins and poorly immunogenic, there is no vaccine against the serogroup B polysaccharide capsule. Pneumococcal conjugate vaccines against a limited number of the most common serotypes became available in the year 2000.

Although initially developed for individual protection against disease, conjugate vaccines proved effective against nasopharyngeal carriage as well. Reduced carriage leads to reduced transmission, thereby protecting the unvaccinated population. The impact of herd protection elicited by conjugate vaccines was largely unexpected. Randomized controlled trials were too small to elicit herd protection, or had not been performed at all.

The long-term effectiveness of conjugate vaccines is uncertain. Because vaccines are available against a limited subset of meningococcal serogroups and pneumococcal serotypes only, non-vaccine types could replace vaccine types. Long-term surveillance data offers invaluable information for the post licensure evaluation of vaccine impact, and the planning of future vaccine development and implementation. It can be used to evaluate herd protection and serogroup or serotype replacement.

In the Netherlands, Charlotte Ruys, professor of Bacteriology, Epidemiology and Immunity at the Laboratory of Hygiene of the University of Amsterdam, started to systematically collect *N. meningitis* isolates from patients with meningitis in 1959. This was the basis for the establishment of the Netherlands Reference Laboratory for Bacterial Meningitis in 1975 by the Department of Medical Microbiology of the University of Amsterdam and the National Institute for Public Health
and the Environment (RIVM). Nationwide, an estimated 85% of isolates cultured from blood or cerebrospinal fluid from patients with (suspected) meningitis are sent to this reference laboratory.\textsuperscript{15,16} The Netherlands Reference Laboratory has one of the largest and oldest collections of meningococcal, pneumococcal, and Haemophilus isolates from patients with (suspected) meningitis in the world.

In chapter two we describe the epidemiology, clinical characteristics and outcome of adult community-acquired bacterial meningitis after the introduction of adjunctive dexamethasone therapy and nationwide implementation of paediatric conjugate vaccines. 1,412 episodes of community-acquired bacterial meningitis identified between January 2006 and July 2013 through the National Reference Laboratory for Bacterial Meningitis or individual physicians, were prospectively evaluated.

In chapter three we present national surveillance data from the Netherlands Reference Laboratory of Bacterial Meningitis (NRLBM) for invasive meningococcal disease from Jan 1, 1960, to Jan 1, 2013. The variability and distribution of serogroups, serosubtypes and porA sequencing data over time are described. This is valuable information for future vaccine implementation strategies and serogroup B vaccine development and post licensure evaluation of vaccine impact. There was a 99% decline in serogroup C meningococcal disease after the introduction of serogroup C conjugate vaccine. In chapter four we show how 36% of the reduction in serogroup C cases occurred in unvaccinated age groups, and was most profound for meningococcal sequence types that have a high propensity to express the serogroup C polysaccharide capsule during colonization. This illustrates the importance of herd protection for serogroup C conjugate vaccine efficacy.

In 2013 the European Centre for Disease Prevention and Control called for enhanced surveillance and retrospective investigation of serogroup C cases in young men, in response to the clusters of invasive meningococcal disease among men who have sex with men (MSM) that were reported in several cities in North America and Europe. In chapter five we show that there was no evidence of serogroup C clusters in young men in the Netherlands. The National Institute of Public Health and the Environment (RIVM) convened a meeting to discuss the reported clusters of IMD among MSM. Because no case of serogroup C IMD had been reported in the Dutch MSM community and because of the high vaccine coverage of young males in the Netherlands, the RIVM made the recommendation to the Ministry of Health, Welfare and Sport (VWS) to take no specific action at this time.

Group B streptococcus is the most common cause of neonatal infections. In chapter six we studied the clinical and molecular epidemiology of invasive group B streptococcus infection in children younger than 3 months in the Netherlands over 25 years. We found that the introduction of prevention guidelines for invasive group B streptococcus disease in 1999, consisting of intravenous antibiotic prophylaxis during labour in case of premature labour, prolonged rupture
of membranes, or fever during delivery, did not reduce the incidence of disease in neonates. These guidelines should be reassessed and alternative approaches to prevent infant invasive group B streptococcus disease should be sought.

Clinical deterioration can occur rapidly in bacterial meningitis and is often difficult to predict. Identifying patients at high risk of an adverse clinical outcome is important for counselling patients and their families, as well as deciding upon optimal patient management. We developed a risk score in chapter seven that identifies adults with cerebrospinal fluid (CSF) pleocytosis and a negative CSF Gram stain at low risk of an urgent treatable cause. In chapter eight we performed an external validation study of risk scores that predict adverse clinical outcome in bacterial meningitis. Risk scores were identified through a systematic review of the literature.

This thesis concludes with a general discussion (Chapter 9) in which the implications of the presented studies are discussed and suggestions for future research are proposed.
References