Bacterial meningitis: epidemiology, herd protection, clinical characteristics, and risk assessment
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Discussion
Introduction

The first objective of this thesis was to study the epidemiology of community-acquired bacterial meningitis, invasive meningococcal disease and neonatal group B streptococcal disease in the Netherlands. In chapter two we described 1412 episodes of community-acquired meningitis included in the nationwide prospective MeninGene cohort from 2006 to 2014. In chapter three laboratory surveillance data on invasive meningococcal disease from 1960 to 2012 is presented. In chapter four post-licensure evidence is shown of the impact of the nationwide vaccination campaign against serogroup C meningococcal disease. Serogroup C has largely disappeared after vaccine introduction, and at least a third of the effectiveness was due to herd protection. In chapter five we evaluated if there was evidence of increased serogroup C disease in men who have sex with men, after several outbreaks in the gay community had been described in Germany, Belgium, France, and North America. We found no evidence of clusters of serogroup C disease in Men who have sex with men in the Netherlands. In chapter six we described the incidence rates and genetic epidemiology of invasive disease due to Streptococcus agalactiae (group B streptococcus, GBS) in newborns from 1987 to 2011. We found that the introduction of guidelines for the prevention of perinatal group B streptococcal disease did not reduce neonatal meningitis or sepsis due to GBS.

The second objective was to describe the clinical features of adult community-acquired bacterial meningitis after the introduction of adjunctive dexamethasone therapy and routine paediatric conjugate vaccines against H. influenzae type b, S. pneumoniae and N. meningitidis serogroup C. This was done by an analysis of clinical features from 1412 episodes from the MeninGene cohort (chapter two). We found that outcome improved substantially after the widespread introduction of adjunctive dexamethasone treatment, both in pneumococcal and non-pneumococcal meningitis.

The third objective of this thesis was to identify predictors of severe illness, both in adults with bacterial meningitis as well as in patients presenting with cerebrospinal pleocytosis and a negative cerebrospinal fluid gram stain. 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.

In this chapter we will discuss our main findings in a more general perspective, discuss methodological strengths and limitations and provide recommendations for future research.
Epidemiology

The Dutch Meningitis Study cohort included patients from 1998 to 2002, and had a similar research design to the MeninGene cohort described in chapter two. The mean incidence rate of community acquired bacterial meningitis in this previous study was 2.6 per 100,000 adults per year. We found a lower incidence rate of 1.72 cases per 100,000 adults in 2007-08, that further declined to 0.94 per 100,000 adults in 2013-14 (figure 1). Rates of adult bacterial meningitis decreased most sharply among pneumococcal serotypes included in paediatric conjugate vaccine, and in meningococcal meningitis.

Cases in both cohorts were identified through the Netherlands Reference Laboratory for Bacterial Meningitis and by individual physicians. With any surveillance system, the possibility for bias exists if case reporting changes over time. However, comparison of our data to the mandatory notification data from National Institute for Public Health and the Environment (RIVM) was similar over time, as was the proportion of additional patients reported by treating physicians between the two cohorts.

Figure 1. Incidence rates of bacterial meningitis in the Netherlands

The first bars represent mean incidence during the Dutch Meningitis Study cohort.
The incidence rate of meningococcal meningitis was 95% lower in 2013-14 than during the Dutch Meningitis Study cohort of 1998-2002. The introduction of vaccination against *N. meningitidis* serogroup C in 2002 can only partly explain this reduction, because most disease was caused by serogroup B. After 15 years of hyper endemic incidence rates in the Netherlands, serogroup B incidence has been steadily declining since 1993 (chapter three). A systematic review of global serogroup B incidence rates found that most countries had low incidence rates during the last 15 years, and that serogroup B incidence tended to decrease in countries that collected data consistently. The reasons for this decline in serogroup B disease are unknown, but could include population immunity to strains currently circulating, and changes in the prevalence of behavioural risk factors. Our finding that several genetic meningococcal types increased and decreased simultaneously during the hyperendemic period suggests that changes in the risk factors for meningococcal carriage and diseases play an important role.

Meningococcal incidence rates and serogroup distribution are unpredictable and vary over time and by geographic region. Endemic meningococcal disease at an annual attack rates of around 1 to 3 per 100,000 of the population are found in many countries around the world. Endemic disease can be interrupted by hyperendemic periods, local outbreaks and large epidemics. In hyper-endemic periods the incidence rate increases simultaneously in the whole population for several years. In high-income countries, localised outbreaks occur in small communities like colleges or nursing homes, but the majority of cases are sporadic. The largest epidemics occur in the "meningitis belt", an area extending from Senegal in the west to Ethiopia in the east, and can exceed 1000 cases per 100,000 population. The mechanisms underlying these epidemic patterns are poorly understood. A recent systematic review of incidence and carriage data from the meningitis belt found that carriage prevalence did not substantially increase between endemic and hyperendemic periods. This suggests that either hosts become more susceptible to invasion, or meningococci express more virulence factors during carriage. In contrast, the occurrence of epidemics was associated with a substantial increase in meningococcal transmission and colonisation, and to a lesser extent with increased risk of meningitis given carriage.

**Vaccination and herd protection**

The implementation of conjugate polysaccharide vaccines against *S. pneumoniae, N. meningitidis, and H. influenzae* type b has been one of the most effective public health innovations of the last decades. Although these three bacteria still cause most cases of bacterial meningitis worldwide, incidence and case-fatality rates have decreased substantially. Worldwide, deaths due to pneumococcal, meningococcal and *H. influenzae* type b meningitis, decreased respectively by 29%, 25% and 45% between 1990 and 2013.

A conjugate vaccine against *H. influenzae* type b was introduced into the Dutch National Immunization Program in 1993, and a seven-valent pneumococcal conjugate vaccine has been offered
to children since 2006. In response to a sharp increase in serogroup C meningococcal disease in 1998, children aged 1-18 years were offered a single meningococcal serogroup C polysaccharide conjugate vaccination in 2002. Vaccine coverage during the mass vaccination campaign against serogroup C was 89% to 94% depending on age. Routine vaccination at 14 months was subsequently introduced.

In the Netherlands *H. influenzae* type b meningitis decreased from over 200 episodes per year before vaccine introduction to less than 20 episodes per year in recent years. We found a strong reduction in adult pneumococcal meningitis due to serotypes included in the seven-valent conjugate vaccine between 2006 and 2014 (figure 1), and only 10 episodes of serogroup C meningitis occurred in the MeninGene cohort.

The temporal relationship between the introduction of these paediatric conjugate vaccines and the strong decline in adult cases due to bacteria covered by these vaccines is suggestive of a causal relationship. However, the majority of adults are not directly protected by these vaccines. The first children vaccinated against *H. influenzae* type b were 22 years old at the end of the observation period of the current cohort, and only adults below the age of 30 years in 2014 had been eligible for routine vaccination against serogroup C. Routine pneumococcal vaccination for adults is not advised by the Health Council of the Netherlands, with the exception of high-risk groups (e.g., those with hyposplenism or asplenia, sickle cell disease, and cerebrospinal fluid leak-age). Based on sales records from Dutch pharmacies pneumococcal vaccine coverage among adults over 65 years old in the Netherlands is low.

The impact of conjugate vaccines on adult bacterial meningitis is therefore likely due to herd protection, whereby reduced nasopharyngeal carriage and transmission in the vaccinated part of the population protects the unvaccinated, by limiting their exposure to the bacteria covered by the vaccine. This is illustrated by our finding in chapter four. We found that genetic meningococcal types that are known to frequently express a capsule during nasopharyngeal carriage were more affected by the introduction of the serogroup C conjugate vaccine, than sequence types that express the capsule infrequently. This finding provides further evidence that reduced carriage is an important factor of vaccine impact. Thirty-six percent of the overall reduction in serogroup C cases occurred in the unvaccinated population. Because many cases will have been prevented by reduced carriage and transmission in the vaccinated population as well, the true impact of herd protection will have been even higher.

The long-term effectiveness of conjugate polysaccharide vaccines against *S. pneumoniae, N. meningitidis*, and *H. influenzae* type b is by no means guaranteed. Currently available vaccines do not include all capsule types and these bacteria are capable of capsular switching. Capsular switching occurs through horizontal gene transfer and makes it possible for a genetic lineage to change its capsular phenotype. The selective pressure that is introduced by mass vaccination, using vaccines that do not offer protection against all capsule types, could lead to an increase in
strains not covered by the vaccines, replacing the strains that were covered by the vaccines. The possibility of capsular switching has been clearly established.\textsuperscript{5,15,16} The evidence of serotype or serogroup replacement after mass immunization is less clear.\textsuperscript{16-18}

A temporary increase in \textit{H. influenzae} meningitis due to serotype a has been reported in Brazil,\textsuperscript{19,20} and Portugal experienced a transitory increase in unencapsulated disease.\textsuperscript{21} Canadian surveillance data on \textit{H. influenzae} disease from 1989 and 2007 identified some replacement by serotype f and non-typeable strains in children under 5 years old.\textsuperscript{22} However, an analysis of three separate surveillance systems in the United States between 1987 and 1995 showed no increase in the incidence of non-type-b disease following vaccine introduction.\textsuperscript{23} The European Union Invasive Bacterial Infections Surveillance Network collects surveillance data from 29 European countries and did not find evidence of serotype replacement between 1999 and 2004.\textsuperscript{23} In the Netherlands, there was a transitory rise in \textit{H. influenzae} type b disease between 1999 and 2004.\textsuperscript{8} The number of non-typeable isolates cultured from blood has increased over the last twenty years, and serotype f seems to be on the rise as well.\textsuperscript{12} The incidence rate of \textit{H. influenzae} type b meningitis has remained low after vaccine introduction in 1993, causing 3\% of episodes in both the Dutch Meningitis Study and MeninGene cohorts.\textsuperscript{1}

Conjugate vaccines against serogroup C meningococcal disease were introduced in the United Kingdom in 1999. No evidence of serogroup replacement has been reported.\textsuperscript{17} An affordable conjugate vaccine against serogroup A has been developed to combat meningococcal disease in the meningitis belt. It has recently been introduced in several sub-Saharan countries, and has proven highly effective against serogroup A carriage and disease.\textsuperscript{24} A major serogroup C outbreak in Nigeria, the first in the African meningitis belt since 1979, started in 2013 and was still showing rapid expansion at the time of writing.\textsuperscript{25}

There is strong evidence in pneumococcal nasopharyngeal carriage that non-vaccine types have increased among carriers in vaccinated populations.\textsuperscript{18} Studies on serotype replacement in invasive pneumococcal disease are more heterogeneous, with some studies reporting complete replacement resulting in no net indirect benefit, whereas others report relatively little replacement.\textsuperscript{18} The large magnitude of serotype replacement in carriage compared to disease might indicate lower invasiveness of non-vaccine serotypes.\textsuperscript{18}

In pneumococcal meningitis, a surveillance study in the United States covering approximately 17.4 million persons during 1998-2007, found evidence of serotype replacement. The increase of non-vaccine types was age dependent, increasing 90\% in children under five, 61\% at any age, and 18\% in patients over 65 years old.\textsuperscript{26} We found no evidence of serotype replacement in adult pneumococcal meningitis in the Netherlands between 2006 and 2014. Dutch surveillance data did show serotype replacement in invasive pneumococcal disease, but not in meningitis.\textsuperscript{9,13}

Nationwide post-licensure observational studies are suitable to identify the population-wide effect of mass vaccination.\textsuperscript{18} However, these observational studies are more prone to biases in-
roduced by changes in clinical practice and case ascertainment. These biases tend to be less for a well-defined disease like meningitis, compared to other pneumococcal disease. This might partly explain the larger estimates of serotype replacement in all invasive pneumococcal disease compared to meningitis only.

**Future directions**

The large impact of conjugate vaccines on carriage and the strong reduction of cases in the unvaccinated population were largely unexpected, and mostly identified by post-licensure surveillance studies. Randomized controlled trials had not been performed, or the number of study participants was unlikely to confer herd protection. Continuous, long-term, and high quality surveillance studies will be essential for the evaluation and planning of future public health interventions.

Capsular polysaccharide vaccines against serogroup B are not available. However, two serogroup B vaccines (4CMenB, Trumenba), have recently been licenced. Both use outer-membrane proteins as their antigens. Licensure was based on safety and immunogenicity. Efficacy data are not available because of the difficulty in conducting a clinical trial for a low incidence infection. The 4CMenB vaccine has been used in several outbreaks in Canada and the United States, and The Joint Committee on Vaccination and Immunization, which advises U.K. health departments on immunization issues, has recommended an infant 4CMenB schedule, with doses to be given at 2, 4, and 12 months of age. Because of the historically low incidence rate of serogroup B disease in the Netherlands, vaccine introduction at this time does not seem likely. Due to the unpredictable nature of meningococcal epidemiology, this could change in the near future. Post-licensure evaluation studies in the North America and the UK will first have to establish the impact of these vaccines on carriage and disease. The results of these studies are eagerly awaited.

Surveillance data are essential for the early detection of the re-emergence of vaccine type strains, or the replacement by non-vaccine type strains. Age groups with the highest burden of disease are usually targeted for vaccination. However, these groups also tend to have the poorest vaccination response. It has for instance become clear in recent years that antibody levels against serogroup C decline rapidly in the majority of children vaccinated before the age of five years. The immune response of children who were over five years old during the catch-up campaign in 2002 persist much longer. However, as these children become adults, protection against carriage and disease in the adolescent population will diminish. Because meningococcal carriage has the highest prevalence in teenagers and young adults, lasting herd protection is unlikely. The current single serogroup C vaccine at 14 months of age in insufficient, and a booster vaccination at the age of 12-15 years has recently been suggested.

Although speculative, the magnitude of herd protection elicited by conjugate vaccines could possibly open the door to protection of infants, the elderly, and the immunocompromised by only vaccinating the part of the population with both high carriage rates and a good vaccination response.
For instance, maternal vaccination against GBS has been suggested as the most promising strategy to reduce perinatal GBS disease.\textsuperscript{31,32} GBS is the leading cause of neonatal sepsis and meningitis in high-income countries.\textsuperscript{33} GBS frequently colonizes the human genital and gastrointestinal tracts, and usually results in asymptomatic carriage. In resource-rich countries 20–30\% of pregnant women are colonized with GBS, approximately 50\% of their babies become colonized and 1\% will develop invasive disease.\textsuperscript{33,34} Early onset disease, occurring in the first week of life, occurs after aspiration of amniotic fluid infected with bacteria that have ascended from the colonized genital tract of the mother.\textsuperscript{33,34} Late-onset disease (day 8 to 90 after birth) can be acquired from the mother or from environmental sources. Currently, many high-income countries have implemented prevention strategies for perinatal GBS disease that include intrapartum antibiotic prophylaxis for all pregnant woman identified to be colonized with GBS or intrapartum antibiotic prophylaxis for woman with specific risk factors.\textsuperscript{35} Although these guidelines were based on studies of poor methodological quality, surveillance studies from several countries found reduced incidence of early onset disease after guideline implementation.\textsuperscript{31,36} Intrapartum antibiotic prophylaxis has no impact on late onset GBS infection.\textsuperscript{33} Despite the introduction of perinatal GBS prevention guidelines in the Netherlands in 1999, the incidence of invasive group B streptococcus infection has steadily increased (\textit{chapter six}). Maternal vaccination could result in direct protection of the newborn by the placental transfer of GBS antibodies, or could provide protection against maternal GBS colonization and reduce transmission. Phase I and phase II clinical trials of maternal GBS vaccines have shown promising results.\textsuperscript{37} GBS vaccines are expected to become available in coming years. To evaluate the possible benefit of maternal GBS vaccination in the Netherlands, a prospective cohort study should be set up to determine the current burden of GBS disease, and a nationwide cross-sectional carriage study of GBS isolates from pregnant woman could be used to evaluate possible coverage of GBS vaccines.

**Clinical features**

Although the epidemiology of community bacterial meningitis has changed after the introduction of paediatric conjugate vaccines, over 95\% of patients still present with at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. Median age in adult bacterial meningitis increased from 52 years in the Dutch Meningitis Study cohort (1998-2002),\textsuperscript{1} to 61 years in the present cohort. As patients became older, the proportion of patients with comorbidity increased.

Cranial imaging on admission was performed in 86\% of episodes in the MeninGene cohort, compared to 71\% in the 1998-2002 cohort. Abnormalities were recorded in 47\% of episodes from the current cohort, and 34\% in the previous cohort. In adults with suspected meningitis, clinical features have been shown to identify those who are unlikely to have abnormal findings on cranial CT.\textsuperscript{38} Clinical features at base line that were associated with an abnormal finding on CT of the
head were an age of at least 60 years, immunocompromised state, a history of central nervous system disease, and a history of seizure within one week before presentation, as well as the following neurologic abnormalities: an abnormal level of consciousness, an inability to answer two consecutive questions correctly or to follow two consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language (e.g., aphasia). Absence of all of these factors occurred in 41% of patients who underwent cranial imaging and had a negative predictive value of 97%.

An important reason to perform imaging before lumbar puncture is to identify patients with brain shift, who are at increased risk of acute herniation after lumbar puncture. Dutch guidelines recommend cranial imaging before lumbar puncture in all patients suspected of bacterial meningitis with aphasia, hemiparesis, monoparesis, seizures, papilledema, score on the Glasgow Coma Scale below 10, active cancer or HIV at admission. We found that imaging before lumbar puncture was performed in 88% of episodes with a guideline indication, as well as 83% of episodes without a documented guideline indication. Overall, imaging before lumbar puncture increased from 67% in 1998-2002 to 86% in the present cohort.

Dutch guidelines recommend empiric treatment with a combination of amoxicillin and a third generation cephalosporin in adults with (suspected) community acquired bacterial meningitis. Adjunctive dexamethasone therapy should be added before or together with antibiotic treatment. If lumbar puncture is postponed because of cranial imaging, treatment should be initiated before the patient is sent to radiology, but after blood cultures are drawn. We found that a combination of amoxicillin with a third generation cephalosporin was started in only a third of episodes. In episodes where cranial imaging preceded lumbar puncture, antibiotics therapy was delayed in almost two thirds of patients. The use of adjunctive dexamethasone, increased from 17% in the previous cohort to 89% of episodes in current study.

Overall outcome did not improve between the two cohorts, but this is due to the relative increase of the more severe pneumococcal compared to meningococcal meningitis. For the subgroup of pneumococcal meningitis, the proportions of patients with an unfavourable outcome or death have decreased substantially; unfavourable outcome from 50% to 41% and death from 30% to 18%. In meningococcal meningitis, the case fatality rate decreased from 7% to 3%.

Adjunctive dexamethasone treatment was independently associated with a favourable outcome and increased survival. The use of observational data precludes strong conclusions in the evaluation of treatment effects, but our current finding in combination with a randomized study in the same population, suggests that implementation of dexamethasone therapy has improved the prognosis of bacterial meningitis in the Netherlands. A recent Cochrane review found that adjunctive corticosteroid use in bacterial meningitis was associated with a non-significant decrease in mortality (RR 0.90, 95% CI 0.80 to 1.01). Use of adjunctive corticosteroids was
not associated with a decrease in long-term neurological sequelae (RR 0.90, 95% CI 0.74 to 1.10). Subgroup analysis on *S. pneumoniae* showed a favourable effect of corticosteroids on mortality (RR 0.84, 95% CI 0.72 to 0.98). A non-significant reduction in mortality was found in *N. meningitidis* (RR 0.71, 95% CI 0.35 to 1.46).

**Future directions**

Efforts should be made to improve guideline adherence. Both the impact of these interventions on patient management, as well as the possible effect on patient outcome should be studied. Previously identified characteristics of patients who are unlikely to have abnormal findings on cranial CT should be validated in external cohorts. Our study found a previous history of meningitis in 7% of episodes. Causes of recurrent meningitis are cerebrospinal fluid leakage and immunodeficiency, which should carefully be evaluated in patients with recurrent meningitis. Given the high rate of recurrence, vaccination against common causative pathogens of bacterial meningitis could be considered in patient with a first episode of bacterial meningitis.

**Risk stratification**

When a patient presents with symptoms and signs that are suggestive of meningitis, the differential diagnosis is broad and includes both life threatening and self-limiting diseases. Being able to quickly and accurately identify patients with a self-limiting illness could reduce the number of admissions, diagnostic tests and empiric antibiotic treatment. In chapter seven we have developed a risk score that could possibly help physicians to identify adults with CSF pleocytosis and a negative CSF Gram stain at low risk of an urgent treatable cause. The negative predictive value of the low risk category was excellent in the derivation and validation cohorts.

Clinical deterioration can occur rapidly in bacterial meningitis, and poor outcome is common. An accurate prognosis, early on in the course of the disease, could help physicians to better counsel patients and their families, as well as decide upon optimal patient management. Accurate prognostic stratification can also be a valuable tool in evaluating and correcting for case mix in clinical research and for targeting intervention strategies.

Several risk scores have previously been developed that predict outcome in bacterial meningitis. Adequate performance of these scores in new patients is not guaranteed. Poor generalizability of risk scores is common, and can be partly explained by overfitting, and differences in characteristics between the target population and the development cohort. Overfitting can occur when risk scores are not only based on associations between predictors and outcome in the population, but also on idiosyncrasies and random variations in the development sample.

In chapter eight we evaluated the performance of nine risk scores that predict outcome in bacterial meningitis in 2108 episodes of bacterial meningitis from the Netherlands. Risk scores
were identified by a systematic review of the literature. Seven risk scores had not been previously evaluated in a new study. We found that these risk scores were able to identify some patients at high risk of an adverse outcome, although many patients with a poor prognosis were missed. Inspection of the calibration curves showed adequate agreement between predicted and observed outcomes for four scores.

To be useful in clinical practice the calculated risks should be accurate, but also differ enough from baseline risk to justify specific treatment or counselling options. For instance, the baseline risk of an unfavourable outcome in bacterial meningitis is 38%, a prediction of 25% might be accurate, but would not be helpful for the treating physician. The baseline case fatality rate in meningococcal meningitis is 6%. Not being classified as high-risk reduced the probability of death to between one and five percent. A high-risk classification was rare, and almost always corresponded to an observed probability of death around 25 to 50%.

Compared to the original study, performance of all scores was reduced in our validation cohort. There were clear differences between the development cohorts of the risk scores and our validation cohort. Six risk scores were developed for invasive meningococcal disease, both meningitis, sepsis and meningitis or sepsis only. Meningococcal sepsis has a worse overall outcome than meningococcal meningitis, which is likely reflected in the higher cases fatality rates in five of the six developmental cohorts compared to our validation cohort. The high rate of adjunctive dexamethasone treatment in our validation might explain the overestimation of the risk score for death in pneumococcal meningitis.

None of the risk scores could be recommended for routine use at this time. However, these scores could be of use in the design and interpretation of scientific studies. For instance, a trial that wanted to evaluate the effect on outcome of an experimental treatment that is expensive or burdensome, could reduce the number of patients that would have to undergo the novel treatment by excluding patients with a very high or very low risk of a clinical adverse outcome. Also, these scores could be used as a measure of severity of illness and be used to correct for case mix between studies or study sites.

**Future directions**

The risk score that predicts an urgent treatable cause in patients with cerebrospinal fluid pleocytosis and a negative Gram stain could possibly be useful in clinical practice. Over a third of patients in the American validation cohort were categorized as low risk of any urgent treatable cause, and could be considered for outpatient management. However, future studies should first establish if these results are generalizable to new patient populations, whether physicians using the score are better at recognizing patients at low risk of an urgent treatable cause than physicians that do not use the score, and if implementation of the score leads to a safe reduction of healthcare expenditure or improved patient outcome.
An important limitation of our external validation study on outcome in bacterial meningitis was that the quality of reporting of the studies on prediction of outcome in bacterial meningitis did not conform to current standards. Most identified studies, gave little information on calibration of the model and multivariable regression analyses were either not performed, or regression coefficients were not fully reported. In 2015 The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative published a set of recommendations for the reporting of studies developing, validating, or updating of a prediction model, whether for diagnostic or prognostic purposes.\textsuperscript{43} Adherence to this guideline would aid the interpretation and subsequent validation of future risk scores.

One strategy to reduce overfitting of prediction models, and thereby possibly improve the generalizability of the model, is to select potential predictors on the basis of previous literature instead of analysis of the development cohort.\textsuperscript{42} We are currently updating a previously reported risk score for outcome in the cohort described in chapter two, using our systematic review as an overview of possible additional predictor variables.

To facilitate the use of risk scores in clinical practice, the number of predictors is generally kept to a minimum. Generally, only predictors with a strong and independent association with outcome in the derivation cohort are included in the score. However, a strong association identified in a single dataset tends to be weaker, or not even replicable in another dataset.\textsuperscript{44} Furthermore, reproducible associations may change over time as clinical practice changes. The widespread introduction of electronic medical records could pave the way for risk scores that include a multitude of predictors with small individual associations, which are automatically updated to changes in disease epidemiology.

In conclusion, although bacterial meningitis is still a formidable disease with high mortality and morbidity, progress has been made. The improvement in outcome that is associated with adjunctive dexamethasone treatment is the largest step forward in decades. Conjugate paediatric vaccines have greatly reduced the incidence of meningococcal, pneumococcal and \textit{H. influenzae} type b meningitis worldwide. These vaccines have been unexpectedly effective against colonization, thereby making it possible to protect infants, immunocompromised patients, and the elderly by vaccinating healthy carriers. High quality and long-term surveillance studies have been essential for vaccine development, implementation and evaluation.
References


