Predicting the long-term outcome of bacterial meningitis in childhood

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Chapter 1

General introduction
INTRODUCTION

Bacterial meningitis (BM) is a severe infection of the central nervous system with potential devastating consequences in both adults and children. In the Netherlands, data about incidence and pathogens of BM is collected and analyzed by the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM). The NRLBM receives approximately 90% of the isolates of Dutch meningitis patients and publishes this data in their annual report. Until the start of the vaccination program against *Haemophilus influenzae* type b (Hib) in 1993 there were about 800 pediatric cases of BM yearly in the Netherlands. After the introduction of the vaccine, Hib meningitis has almost completely disappeared (Figure 1).

A further strong decrease of the incidence of BM was achieved with the introduction of vaccination against *Neisseria meningitidis* type C in 2002 and a seven-valent vaccine against *Streptococcus pneumoniae* in 2006 that was replaced by a ten-valent vaccine in 2011. Further, a spontaneous decrease of *N. meningitidis* serogroup B infections played a key role in the total decrease in incidence of BM in Western countries. Figure 2 illustrates the reduction in meningitis caused by the three predominantly causative pathogens in the first ten years of this century. As a result, the incidence of 800 children in the age of 0-19 years old suffering from BM in 1993 was reduced to 550 in 2000 and 127 in 2010.

Although it has become a relatively rare disease in developed countries, BM is still very common in developing countries. For instance, BM caused by *N. meningitidis* is still epidemic in Africa with an estimate of 88,199 suspected cases and including 5352 deaths in 14 African countries during the 2009 epidemic. A recently published systematic review of the literature including data from 21 African countries reports mortality up to 35% and neuropsychological sequelae up to 47% after a follow-up period of 5 years.

![Figure 1](image.png)

*Figure 1*: The distribution of H. influenzae type b and non-type b meningitis cases in the Netherlands, 1990-2010 (Bacterial meningitis in the Netherlands: annual report 2010, NRLBM, with permission)
When it comes to sequelae, the research focus has shifted the last two decades from mortality and severe morbidity (sensorineural hearing loss, epilepsy, motor handicaps, hydrocephalus and mental retardation) to more subtle outcomes like neuropsychological, academic and behavioral problems. However, these problems appeared to be highly underestimated, both in incidence and impact on quality of life.

In the nineteen nineties two research groups, one in the UK and one in Australia, performed long-term follow-up studies of large cohorts of survivors from childhood BM. Besides major complications they investigated behavioral and learning problems at different ages 5-11. In the Netherlands it was the research group of Koomen and Van Furth et al. that was the first to look at general health problems, academic or behavioral problems and their impact on quality of life after childhood BM. This work was initiated by the Dutch Meningitis Foundation (“Nederlandse Meningitis Stichting, NMS)), that was approached by a rapidly growing number of parents that were worried about school performance and behavior of their children.

Further, Koomen et al. explored the incidence of post-BM hearing loss and developed two clinical prediction models: one to identify children at risk of developing hearing loss and one for the prediction of academic or behavioral limitations after BM. This work was published and bundled in a PhD thesis which was successfully defended by I. Koomen in 2003 12-16.

After completion of this work the next step that had to be taken was external validation and implementation of the two clinical prediction models. The performance of a prediction model is known to be less strong in a population different from the one it was developed for. Therefore predictive abilities must be tested in a new cohort. It has been shown that

Figure 2: Meningococcal, Haemophilus and pneumococcal meningitis in the Netherlands, 2001-2010 (Bacterial meningitis in the Netherlands: annual report 2010, NRLBM 1, with permission)
an increasingly amount of clinical prediction models are developed and published, but the vast majority is never externally validated. But before implementation in clinical practice is possible, this kind of validation is essential. It was this requirement that provided the starting point of the further research presented in this thesis. In 2005 the files of the NRLBM were searched for children born between January 1986 and December 1994 who survived BM between January 1990 and December 1995. A cohort of 361 school-age BM survivors was compiled for the creation of validation cohorts for the two prediction models. This work was strongly supported by the collaboration with the EMGO institute of the VU University Medical Center. Further, this cohort and the cohort studied by Koomen et al. were used for secondary research questions on behavior, structural damage to the brain after BM and for model updating studies. Along the way, intensive collaboration with the Laboratory for Immunogenetics of the VU University Medical Center arose. This gave an excellent opportunity to blend the interest in and the knowledge of pediatric infectious diseases, clinical prediction modeling and genetic variation. Besides numerous other studies, this led to a study of the influence of genetic variation on the prediction model for hearing loss after BM as part of this thesis. We hope that the work presented in this thesis provides a good basis for the implementation of prediction models and for further research on the long-term effects of childhood BM.

AIMS AND OUTLINE OF THIS THESIS

This thesis focuses on a broad range of long-term sequelae after childhood BM in general and on the prediction of these sequelae in particular. As a general overview for what is known about childhood BM and prognosis research, Chapter 2 presents a systematic review of prognostic studies summarizing and appreciating the evidence of prognostic factors regarding mortality and long-term sequelae in developed and developing countries. After this overview the next chapters focus on the prediction of hearing loss and academic or behavioral problems after childhood BM. In Chapter 3 a previously developed clinical prediction model for hearing loss is validated externally in a new, independent, cohort of childhood BM survivors. Chapter 4 describes the addition of host genetic variants to this prediction rule to find out if further improvement of prediction can be achieved. Chapter 5 proceeds with the external validation of the other previously developed clinical prediction model designed for the prediction of academic or behavioral limitations that children can develop after meningitis. The part of this thesis regarding prediction will be completed by Chapter 6, in which the effect of pneumococcal vaccination on the generalizability of the two prediction rules is explored by simulation of this vaccination in the development cohorts. In Chapter 7 the emotional and behavioral sequelae of childhood BM are further investigated. In the first part of this chapter we compare the diagnostic capabilities of the Strength and
Difficulties Questionnaire (SDQ) with the “gold standard", the Child Behavior Checklist (CBCL). Then, it describes the increased incidence of behavioral problems in BM survivors in multiple domains of behavioral functioning using the SDQ.

In Chapter 8 the hypothesis that BM can lead to structural differences in the brain is tested, with cerebral Magnetic Resonance Imaging (MRI) scans. With regard to academic or behavioral problems there is a special focus on possible decrease in volume of the hippocampus, but possible differences in other regions of the brain are investigated as well.

Chapter 9 concludes this thesis with a general discussion and future perspectives.
REFERENCES


