



UMEÅ UNIVERSITY

# Bacterial meningitis in children

## Clinical aspects and preventive effects of vaccinations

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*To all of you that made this possible*

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# Abstract

Bacterial meningitis, one of the most severe infections a child can contract, can be caused by several different strains of bacteria. Most commonly, *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis*. These colonize the upper respiratory tract, then either cause localized infections acting as primary foci or directly spread to the brain. As preventive measure, general infant Hib and pneumococcal vaccinations were introduced in Sweden in 1993 and in 2009, respectively. Although evaluated extensively elsewhere, their long-term effects in Arctic regions are less studied. For the individual child with bacterial meningitis, treatment involves many challenges starting with correctly identifying the condition, guiding treatment, and finally identifying both short-term and long-term disabilities.

In this thesis, the overall aim was to study clinical aspects of bacterial meningitis and preventive effects of vaccinations in an Arctic region. We used two datasets in the Västerbotten Region to investigate incidence rates during the time-periods adjacent to vaccine introductions. This allowed us to study the preventive effects of general infant vaccinations on bacterial meningitis in one of the Swedish Arctic regions. More precisely, we investigated changes in incidence of bacterial meningitis and sepsis during the period of 1986-2015 and of respiratory tract infections during the period of 2005-2014, in the Västerbotten Region, Sweden. We also reviewed medical records of children being treated for bacterial meningitis in the Västerbotten Region to study clinical presentation, short-term outcome, and to develop a new predictive score for identifying adverse outcome and need of invasive procedures. Additionally, by reviewing medical records and child health records from discharge and onwards we assessed long-term disabilities and evaluated clinical guidelines' follow-up recommendations.

Following introduction of general infant Hib vaccination, incidence of all-cause bacterial meningitis and *Haemophilus meningitis* in children aged one month to four years declined by 82.3% and 95.3%, respectively. Likewise, all-cause bacterial meningitis and pneumococcal meningitis declined by 48.0% and 67.5%, respectively, following pneumococcal vaccination. In addition, incidence of sepsis caused by *H. influenzae* and by *S. pneumoniae* also decreased in the same age group. Finally, respiratory tract infections in children under five years of age decreased following pneumococcal vaccination; by 41.5% for all-cause acute otitis media, by 80.7% for sinusitis and by 28.6% for pneumonia.

At admission to the hospital, difference in clinical presentation mostly depended on age. Younger children were more ill at admission but also presented with more diffuse symptoms. When evaluating clinical decision rules for detecting bacterial meningitis, none reached 100% sensitivity. The predictive score developed by us could identify all children in need of invasive procedures to manage the intracerebral pressure and were graded as excellent in the ROC analysis at this task. However, neither this score nor any other could adequately predict complications or death. Finally, permanent disabilities affected more than half of surviving children with psychiatric disease being diagnosed in 30%, and another 5% had ongoing investigations for symptoms of psychiatric disease. Notably, psychiatric disabilities were detected late, in average 14 years after having had bacterial meningitis.

From these findings, we concluded that vaccinations are excellent at protecting children against bacterial meningitis, also in the Arctic region, with the added bonus of providing protection against sepsis and less severe infections such as pneumonia and acute otitis media. Further, treating children with bacterial meningitis involves several challenges starting with correctly identifying this severe disease. For this task, no clinical decision rule is perfect. When making difficult treatment decisions such as deciding on invasive procedures to manage the intracerebral pressure, the predictive score developed and tested by us, the MeningiSSS, can be very helpful. Finally, permanent disabilities may be more common than previously thought. With more than one third of survivors being affected by psychiatric disabilities, specific long-term follow-up strategies are needed to reduce suffering caused by undetected psychiatric disabilities.

# Abbreviations

ADHD	Attention deficit hyperactivity disorder
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the curve
CI	Confidence interval of 95%
CRP	C-reactive protein
DSM	Diagnostic and Statistical Manual of Mental Disorders
Hib	<i>Haemophilus influenzae</i> type b
ICD	International Classification of Diseases and Related Health Problems
MeningiSSS	Meningitis Swedish Survival Score
ROC	Receiver operating curve characteristics
SIRS	Systemic inflammatory response syndrome
WBC	White blood cell

# List of publications

This thesis is based on the following five papers referred to by the corresponding numerals. The papers are listed in order of their main subject instead of year of publication. Here, papers I and II focus on preventive effects of vaccinations and papers III to V focus on clinical aspects of bacterial meningitis.

- I. Johansson Kostenniemi U, Norman D, Sellin M, Silfverdal SA. Sustained reductions of invasive infectious disease following general infant *Haemophilus influenzae* type b and pneumococcal vaccination in a Swedish Arctic region. *Acta Paediatrica* 2019; 108: 1871-8.
- II. Johansson Kostenniemi U, Palm J, Silfverdal SA. Reductions in otitis and other respiratory tract infections following childhood pneumococcal vaccination. *Acta Paediatrica* 2019; 107: 1601-9.
- III. Johansson Kostenniemi U, Norman D, Borgström M, Silfverdal SA. The clinical presentation of acute bacterial meningitis varies with age, sex and duration of illness. *Acta Paediatrica* 2015; 104: 1117-24.
- IV. Johansson Kostenniemi U, Karlsson L, Silfverdal SA, Mehle C. MeningiSSS: A New Predictive Score to Support Decision on Invasive Procedures to Monitor or Manage the Intracerebral Pressure in Children with Bacterial Meningitis. *Neurocritical Care* 2020; 32: 586-95.
- V. Johansson Kostenniemi U, Bazan A, Karlsson L, Silfverdal SA. Psychiatric disabilities and other long-term consequences of childhood bacterial meningitis. *The Pediatric Infectious Disease Journal* [Internet]. Forthcoming 2020; doi: 10.1097/INF.0000000000002908 [Epub ahead of print].

Thanks to the kindness of our publishers, reprints of these papers have been added at the back of this dissertation paper.

# Aims

In this thesis, the overall aim was to study bacterial meningitis, one of the most severe infections a child can contract. With better understanding of clinical aspects and preventive effects of vaccinations, we can hopefully reduce future suffering caused by bacterial meningitis.

The specific aims of the individual papers are listed below:

- I. In this study, we aimed to evaluate the long-term effects of general infant vaccinations against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* on bacterial meningitis and other severe infections in one of the Swedish Arctic regions.
- II. In this study, we aimed to assess what impact general infant vaccinations against *Streptococcus pneumoniae* have had on respiratory tract infections, especially those that later can develop into bacterial meningitis, in one of the Swedish Arctic regions.
- III. In this study, we examined the clinical presentation of bacterial meningitis in children and evaluated clinical decision rules for identifying bacterial meningitis, with the aim of enabling better identification of bacterial meningitis.
- IV. In this study, we developed and tested a new predictive score for children with bacterial meningitis intended for identifying children at high risk of needing invasive procedures, thereby providing support in difficult treatment decisions and enabling actions to be taken earlier.
- V. In this study, we aimed to assess the occurrence of psychiatric disabilities and other long-term consequences of bacterial meningitis in childhood, as well as evaluate current guidelines' strategies for detecting these potentially devastating disabilities.

# Sammanfattning på svenska

Länge har infektionssjukdomar varit en vanlig orsak till sjukdom och död, såväl bland barn som i befolkningen generellt. Medan infektionssjukdomar har minskat i Sverige är detta fortfarande en av de vanligaste dödsorsakerna i stora delar av världen. Denna avhandling undersöker hur en av de allvarligaste infektionssjukdomarna ett barn kan drabbas av, bakterieorsakad hjärnhinneinflammation, bättre kan förebyggas och behandlas. I ett längre perspektiv hoppas vi att denna avhandling kan bidra till att minska konsekvenserna av denna allvarliga infektionssjukdom.

## Introduktion till ämnet

Bakterieorsakad hjärnhinneinflammation är en av de allvarligaste infektionssjukdomarna ett barn kan drabbas av. Infektionen angriper hjärnan med hög dödlighet och hög risk för bestående handikapp.

### *Vad är hjärnhinneinflammation?*

Bakterieorsakad hjärnhinneinflammation är en infektion orsakad av bakterier lokaliserad i det vätskefyllda rum som finns mellan de skyddande hinnorna som omger hjärnan.

Hjärnan är väl skyddad mot infektioner. Detta beror på att den befinner sig i ett omslutet rum i skallbenet, samt att ett speciellt filter kallat blod-hjärnbarriären omger hjärnans blodkärl vilket minskar spridning av bakterier från blodet. Dessa skydd kan ibland svikta, antingen genom att en lokal infektion såsom öroninflammation bryter sig igenom skallbenet eller genom att en generellt spridd infektion såsom sepsis tar sig över blod-hjärnbarriären. I båda fallen är hjärnan då mycket sårbar eftersom den har ett mycket begränsat lokalt verkande immunförsvar.

Skador i hjärnan uppstår när hjärnans celler dör av bakteriernas angrepp eller den inflammation som angreppet orsakar. Inflammationen kan även orsaka ökat tryck i hjärnan med minskat blodflöde, syrebrist och ytterligare nervcellsöd som följd. Vid omfattande skador kan det medföra både bestående funktionsbortfall och död. Om barnet även har en samtidigt förekommande sepsis kan den leda till stor skada genom att orsaka svikt i flera viktiga organsystem.

### ***Vilka har ökad risk att drabbas av hjärnhinneinflammation?***

Störst risk att drabbas av hjärnhinneinflammation har små barn, äldre samt personer med nedsatt immunförsvar. Även personer med vissa typer av skador på skallbenet eller nyligen genomgångna operationer i närområdet har ökad risk.

### ***Hur kan hjärnhinneinflammation förebyggas?***

För att skydda befolkningen mot allvarliga infektionssjukdomar, inklusive hjärnhinneinflammation, är det viktigt att arbeta med insatser som förbättrar den allmänna folkhälsan. Detta kan exempelvis innefatta att förespråka amning och uppmuntra till sunda levnadsvanor. Till personer som på grund av särskilda tillstånd har kraftigt ökad risk kan man ibland ge förebyggande behandling, exempelvis immunstärkande läkemedel till personer med nedsatt immunförsvar eller antibiotika till personer med vissa typer av skador på skallbenet. I den allmänna befolkning är vaccinationer en insats som tack vare få biverkningar och relativt låg kostnad används i stor utsträckning för att skydda personer med ökad risk, exempelvis barn, mot allvarliga infektionssjukdomar.

Vaccinationer har med stor framgång använts för att bekämpa allvarliga infektionssjukdomar i mer än 200 år. Genom att introducera immunförsvaret för ett smittoämne i kontrollerad form kan immunförsvaret öva upp sin förmåga och senare i skarpt läge snabbare och mer kraftfullt bekämpa en infektion orsakad av detta smittoämne.

Från vaccination mot smittkoppor som infördes i Sverige på 1800-talet har det nationella vaccinationsprogrammet byggts ut till att idag omfatta vaccination mot 11 infektionssjukdomar. Av dessa är det två som framförallt ska ge skydd mot allvarliga bakterieorsakade infektioner hos barn; vaccination mot *Haemophilus* och mot pneumokocker.

Historiskt sätt har det länge varit just *Haemophilus* och pneumokocker, tillsammans med meningokocker, som har varit de vanligaste smittoämnena att orsaka hjärnhinneinflammation. Genom vaccination mot *Haemophilus* och pneumokocker har man i olika delar av världen lyckats minska förekomsten av hjärnhinneinflammation orsakat av dessa två smittoämnen med 70 – 90 %. Dock har få studier undersökt hur väl dessa förebygger infektioner i arktiska områden, där förekomsten av infektionssjukdomar många gånger kan vara mycket hög och effekten av olika vaccinationer tidigare varit lägre.

### ***Hur behandlas hjärnhinneinflammation?***

Att behandla barn med hjärnhinneinflammation medför ett flertal utmaningar där den första utmaningen uppstår redan vid den allra första sjukvårdskontakten. Att särskilja denna både ovanliga och allvarliga infektionssjukdom från vanliga virusorsakade infektionssjukdomar är svårt. Tyvärr kan ett misslyckande här leda till mycket allvarliga konsekvenser. Vissa kliniska beslutsstöd finns, men dessa är inte väl utvärderade.

Grunden i behandlingen av barn med hjärnhinneinflammation består av en adekvat antibiotikabehandling tillsammans med vissa medicinska tilläggsbehandlingar samt understödjande åtgärder som ibland innebär intensivvård. För detta finns bra riktlinjer på både nationell och internationell nivå. Tyvärr saknas bra verktyg för att identifiera barn i behov av särskilda insatser; specialingrepp som minskar risken för hjärnskador orsakat av ökat tryck i hjärnan genom att antingen operera in tryckmätare eller ett drän, alternativt att i extremfall operera bort delar av skallbenet. Dessa specialingrepp behövs endast i vissa svåra fall. Det problematiska är att dessa ingrepp enbart kan utföras på ett fåtal sjukhus och innebär risker i sig. Det är därför önskvärt att tidigt veta vilka barn som kommer vara i behov av dessa specialingrepp, så att man tidigt kan planera för detta.

### ***Medför hjärnhinneinflammation några långtidskonsekvenser?***

Risken att dö om man som barn drabbas av hjärnhinneinflammation är i höginkomstländer 6-8 %, medan dödligheten i låg- och medelinkomstländer är betydligt högre. Bland överlevande drabbas cirka var tredje barn av bestående handikapp, vanligen hörselnedsättningar.

På senaste år har rapporter om andra mindre synliga typer av handikapp framkommit. Indikationer finns att överlevande barn även kan vara drabbade av psykisk sjukdom, neuropsykiatriska funktionsnedsättningar och begåvningshandikapp, med stort lidande som följd. Då det idag saknas djupgående kunskap om denna typ av handikapp finns det en risk att de förblir dolda över lång tid. Dagens nationella och internationella riktlinjer rekommenderar specifika uppföljande tester av hörsel och neurologisk funktion, men inte rutinmässiga undersökningar riktad mot att upptäcka mindre synliga handikapp. Frågan är hur vanliga dessa handikapp är, och om de upptäcks eller förblir dolda över längre tid med onödigt lidande som följd?

## **Studiernas upplägg**

Denna avhandling består av fem delarbeten. De första två fokuserar på att undersöka vilken förebyggande effekt mot hjärnhinneinflammation som kan uppnås genom allmän barnvaccination mot *Haemophilus* och pneumokocker, medan de resterande tre delarbetena undersöker kliniska aspekter av hjärnhinneinflammation hos barn.

I de två första delarbetena har vi använt olika dataset för att undersöka hur vanligt förekommande allvarliga infektionssjukdomar är i Region Västerbotten, en av Sveriges två arktiska regioner, samt utvärdera vilken inverkan införandet av vaccinationer mot *Haemophilus* och pneumokocker haft i regionen. I det första delarbetet byggde vi upp ett dataset över barn som vårdats för allvarliga infektionssjukdomar i Region Västerbotten under åren 1986-2015 och i det andra delarbetet använde vi en regionsgemensam databas där vi tagit ut data för lunginflammation och andra luftvägsinfektioner för åren 2005-2014.

I de tre senare delarbetena har vi fortsatt arbetet med att utöka vårt dataset genom att gå igenom patientjournaler från insjuknande och den inläggande tiden på sjukhus för de barn som vårdats för hjärnhinneinflammation i Region Västerbotten. Därtill har vi även gått igenom patientjournaler efter utskrivning från sjukhus upp till vuxen ålder för att se om dessa barn fått bestående handikapp som upptäckts först senare i livet.

## **Resultat**

### ***Delarbete 1***

Förekomsten av allvarliga infektionssjukdomar hos barn i åldern en månad till fyra år har minskat i Region Västerbotten under den senaste trettioårsperioden. Efter att vaccination mot *Haemophilus* införts i region Västerbotten föll förekomsten av hjärnhinneinflammation med 82,3% hos barn den åldersgruppen. När även vaccination mot pneumokocker infördes 2009 sjönk förekomsten av hjärnhinneinflammation ytterligare, nu med 48,0%. Under tidsperioden minskade även sepsis orsakat av *Haemophilus* och av pneumokocker, medan sepsis av andra orsaker ökade.

### ***Delarbete 2***

Att införa vaccination mot pneumokocker i det nationella vaccinationsprogrammet har även haft andra positiva sidoeffekter. I detta delarbete såg vi en nedgång av öroninflammation på 41,5%, bihåleinflammation på 80,7% och lunginflammation på 28,6% för barn under fem års ålder i Region Västerbotten, jämfört med åren innan införandet.

### ***Delarbete 3***

När vi undersökte klinisk bild vid insjuknande i hjärnhinneinflammation såg vi ett flertal viktiga skillnader, framförallt mellan barn i olika åldrar. Yngre barn, i åldern en månad till fyra år, var vid inkomst till sjukhus mer påverkade, hade oftare kramper samt lägre medvetandegrad. Samtidigt hade yngre barn oftare ospecifika symptom som exempelvis matleda och mindre ofta symptom kopplade till hjärnan som exempelvis huvudvärk. Ett antal kliniska beslutsstöd testades, dessa kunde ge visst stöd men inget klarade att med säkerhet identifiera samtliga barn med hjärnhinneinflammation.

### ***Delarbete 4***

En viktig del under den ineliggande sjukhustiden är att kunna förutsäga vilka barn som kommer få komplikationer och vilka barn som är i behov av särskilda insatser. I detta delarbete utformade vi ett verktyg för riskvärdering baserat på kliniska fynd vid inkomst till sjukhus. Detta verktyg kunde med hög säkerhet identifiera samtliga barn i behov av specialingrepp för att reglera trycket i hjärnan för att minska risken för hjärnskador. Detta verktyg jämfördes med befintliga verktyg och överträffade dem.

### ***Delarbete 5***

Av samtliga patienter drabbades 56% av någon typ av permanent handikapp, vanligast psykisk sjukdom som förekom i 30-35%. Även hörselnedsättning och neurologiska skador var vanligt förekommande i efterförloppet. Medan de senare oftast upptäcktes under första året efter insjuknandet tog det betydligt längre tid innan psykisk sjukdom upptäcktes, i medel 14 år efter insjuknandet.

### **Slutsats**

Att förebygga allvarliga infektionssjukdomar genom vaccination är en välfungerande strategi, även i arktiska områden. Införandet av allmän barnvaccination mot *Haemophilus* och pneumokocker har minskat förekomsten av hjärnhinneinflammation hos barn i Region Västerbotten. Positiva effekter har även setts för sepsis och luftvägsinfektioner vilket är viktigt då dessa infektionssjukdomar har potential att senare spridas vidare och orsaka hjärnhinneinflammation.

Behandling av barn med hjärnhinneinflammation är svårt, men verktyg kan underlätta upptäckt och hjälpa till att styra behandlingen. För överlevande barn är bestående handikapp vanligare än man tidigare trott, speciellt psykisk sjukdom. Eftersom dessa inte upptäcks för än långt senare behövs nya strategier så att dessa handikapp inte missas med stort lidande för det enskilda barnet som följd.



# Introduction

Bacterial meningitis is considered one of the most severe infections a child can contract. The infection affecting the brain, has a high risk of death and permanent disabilities of varying degrees (1-2).

## What is bacterial meningitis?

Bacterial meningitis is a rare condition, occurring when a bacterial infection, located within the subarachnoid space, cause inflammation of the meninges (3). For this to occur, the bacteria must first breach the protective barriers to reach the subarachnoid space using one of two possible routes: a direct spread or a haematogenous spread (4). When bacteria enter the subarachnoid space, they elicit an immune response resulting in inflammation as part of the immune system attempting to combat the infection. This, in addition to the direct damage caused by the bacteria, risks to cause further damage to the central nervous system (1-4). Combined with the often concurrent sepsis, this results in a high risk of neurological disability and death (1-2).

*How common is bacterial meningitis and what bacteria can cause meningitis?*

Historically, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* have been the most common causative pathogens for bacterial meningitis (5-6). Besides these three, the list of possible pathogens also includes *Listeria monocytogenes*, *Escherichia coli*, *Staphylococcus aureus*, group B streptococci, among several others (7-8). In recent decades, several countries have introduced general infant vaccinations against *H. influenzae* type b (Hib), *S. pneumoniae* of varying serotypes and *N. meningitidis* of varying serogroups. This has resulted in a reduced occurrence of bacterial meningitis and a shift in the distribution of causative pathogens, mainly due to a marked decline of bacterial meningitis caused by pathogens being vaccinated against (7-8). Consequently, childhood bacterial meningitis is uncommon today in many high-income countries. Most European countries and the United States often report incidences well under 10 cases per 100,000 children and year in children under five years of age (9-10). At the same time, low-income countries have much higher incidences, reaching 52 cases per 100,000 children and year in the same age group in Africa (11) and 77 cases per 100,000 children and year in South Asia (12).

*How is the brain protected against bacterial infections such as bacterial meningitis?*

The brain is well protected against invasion of infectious agents thanks to several layers shielding it from the outside world. This important barrier consists of the outer skin layers, the skull and its periosteum and the thick durable fibrous outer meninges called dura mater (13). Combined, these layers form a strong mechanical barrier that effectively limits the entry of infectious agents to the brain (13). However, the physical barrier has some weaker areas that are prone to invasion, including the inner ear, the sinuses and the nasal cavity (14-15). Here, the layers separating the brain from the outside world are less impenetrable. This is mostly due to the lack of skin coverage, thinner bone structures or proximity to cranial nerve endings such as the olfactory bulb (13-15).

In addition to the physical barrier, the different structural build of small cerebral capillaries compared with capillaries in other parts of the body provides further protection against invasion of infectious agents (13, 16-17). When arterial blood vessels branch out into smaller vessels and finally into the smallest capillaries, the layers of smooth muscle and elastic fibres found in arteries reduces in size and finally disappears (16). In the normal capillaries, the only layer separating the blood from the surrounding tissue is a thin endothelium consisting of a single layer of cells. This provides the opportunity for fluids and smaller particles such as nutrients and electrolytes to easily cross the capillary wall into the tissue and allows for efficient gas exchange. However, this also means that bacteria can cross the capillary wall with relative ease (16). When capillaries later converge into small venous blood vessels and larger veins, they begin to be covered by layers of fibrous fibres. These provide tensile strength and hinders exchange of substances in between the blood and surrounding tissue (16). While larger cerebral blood vessels are similar in build to blood vessels found in other parts of the body, the small capillary blood vessels are not (17). In contrast to other capillaries, the cells in the cerebral capillaries are bound together more firmly by tight junctions between the endothelial cells. In addition, pericytes, astrocytes and the basement membrane also surrounding the cerebral capillaries add to the impermeability (17). Combined, these differences result in the cerebral capillaries being more difficult to cross for bacteria compared with the normal capillary walls (13, 16-17). These special types of capillaries constitute the blood brain barrier, also sometimes called the blood cerebrospinal fluid barrier when located in areas where the capillary is in direct contact with cerebrospinal fluid such as the choroid plexus or capillaries within the subarachnoid space (18).

The physical barrier and the blood brain barrier are very important since the immune function is not as strong in the central nervous system as elsewhere (19-23). Within the brain parenchyma itself, the microglia and perivascular macrophages are the only active immune cells present. These cells are involved in immunosurveillance and phagocytosis as well as maintaining the neuronal environment and repairing injury (19-20). The meningeal space including the subarachnoid space contain a number of immune cells such as dendritic cells and macrophages responsible for antigen presentation and activation of other immune cells, granulocytes that aid in the response to pathogen invasion, and T-cells and B-cells forming adaptive immunity (20-21). In addition to providing a protection against invading pathogens, immune cells in the meningeal space also preserve the neuronal environment (21). In normal settings, the blood brain barrier stops antibodies and immune cells circulating in the blood from entering the subarachnoid space (22). If bacteria enter the subarachnoid space, the immune response elicited by the immune cells residing in the subarachnoid space and the subsequent inflammation causes both a local recruitment of additional immune cells and impairs the integrity of the blood brain barrier (22). The latter enables recruitment of circulating monocytes and neutrophils from the blood resulting in a substantially increased number of immune cells and a more competent immune response (23).

Combined, the strong physical barriers, the blood brain barrier and the immune system are highly effective resulting in a very low occurrence of infections in the central nervous system (1-2).

*How can bacteria spread to the brain despite these strong barriers?*

Despite the strong barriers described earlier bacterial infections in the central nervous system do occur.

To breach the physical barrier, bacteria must cross all layers separating the brain from the outside world (13). Since the skin provides excellent protection, transmission of bacteria through surfaces covered by skin is rare and mostly seen in cases of penetration trauma (24). When an outside force such as falling debris penetrates the skull, the integrity of the normal physical barrier is violated and bacteria can be directly implanted into the central nervous system together with hair and pieces of foreign objects (24). Similarly, neurosurgical procedures can also result in implantation of bacteria in the central nervous system (25). This risk is further increased if any foreign material is left in the brain or if a portal to the outside world is created such as placement of an external ventricular drainage (26).

Mostly, entry to the central nervous system via direct transmission occur at one of the weaker areas of the physical barrier. Here, the middle and inner ear, sinuses and nasal cavity are most vulnerable (13-15). As these areas are all part of the upper respiratory tract, they are all colonized by similar strains of bacteria constituting the normal bacterial flora. These bacteria are often also responsible for causing infections here and the list includes *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis*, among several others (27).

It is well established that infections involving the middle ear such as acute otitis media can be a primary focus in cases of bacterial meningitis (28-30). In this area, the enclosed space together with the relatively thin temporal bone and proximity to the central nervous system increase the risk (31). Besides local hematogenous spread, bacteria can reach the arachnoid space if there are any anatomical abnormalities or if the infection spreads through the thin temporal bone. The latter can occur either directly or via the round or oval window into the inner ear and then through the bone (32-35).

Sinusitis has many similarities with infections in the middle and inner ear (36), and has also been linked to increased risk of bacterial meningitis (37-39). Infections in the frontal sinuses can penetrate the thin wall in the frontal bone or spread retrogradely through venous plexus, thereby reaching the central nervous system causing the infection to extend to this location (39).

Finally, the heavily colonized nasal cavity can be a primary focus of bacterial meningitis. In the nasal cavity, bacteria can spread to the central nervous system retrogradely via the exposed olfactory nerve (13). In addition, defects in the roof of the nasal cavity due to congenital abnormalities or trauma can cause cerebrospinal fluid leakage, greatly increasing the risk of bacterial meningitis (40-43).

The integrity of the blood brain barrier mainly remains intact, despite being exposed to bacteria at a daily basis due to transient bacteraemia following daily activities (44-46). However, there are several methods that bacteria can use to cross the barrier (47). Some bacteria, such as *S. pneumoniae*, can infect the endothelial cells causing damage resulting in disruption of the integrity of the blood brain barrier, thereby allowing the bacteria to gaining access to the subarachnoid space (47-49). *S. pneumoniae*, and several other bacteria, can also use transcytosis; essentially allowing themselves to be engulfed by an endothelial cell via pinocytosis or endocytosis, transported through the cell and finally released on the other side of the endothelium (47-49).

Another strategy to gain entry, mostly adopted by *L. monocytogenes*, is to infect leukocytes that migrate through the blood brain barrier. This essentially transforms the leukocyte into a Trojan horse carrying the bacteria across the blood brain barrier (47-48, 50). Finally, several pathogens such as *H. influenzae*, *S. pneumoniae* and *N. meningitidis* can cross the blood brain barrier paracellularly, meaning they pass in between endothelial cells. Normally, endothelial cells are bound together firmly by tight junctions. However, by releasing proteases and toxins, bacteria can either degrade the tight junctions directly or damage the endothelial cells causing cellular chain reactions resulting in degrading of tight junctions. In both cases, endothelial cells lose their otherwise firm linkage to each other and bacteria can pass through the blood brain barrier in the newly formed gaps in between endothelial cells (47-49, 51).

*Why does damage to the cerebral nervous system occur in bacterial meningitis?*

In bacterial meningitis, death and permanent disabilities can either be attributed to the intracerebral injury and subsequent inflammation caused locally by the infection, or be attributed to systemic effects of the often-concurrent sepsis (52).

When bacteria enter the subarachnoid space, this triggers an immune response as described earlier. In this process, proinflammatory cytokines released by immune cells together with bacterial toxins increase the intensity of the inflammation (53). Notably, bacteria differ in their inherent propensity to trigger inflammation. Certain strains of bacteria, such as *S. pneumoniae*, often elicit a more intense immune response (53). In the case of *S. pneumoniae*, this can be explained by the teichoic and lipoteichoic acids found in the bacterial membrane being strong inducers of inflammation (53-54). In addition, when bacteria lyse due to antibiotic treatment or the immune response, more bacterial toxins are released causing a further increase in inflammation (53).

Inflammation is necessary for the immune system to combat infections. However, inflammation can also have negative effects. Given the enclosed space of the ridged skull and the delicate nerve cells having very limited ability of regeneration, the negative effects of inflammation are especially important to consider (55-57). Inflammation in the subarachnoid space will have four effects; increase the permeability of the blood brain barrier, elicit invasion of leukocytes, stimulate microglial cells, and cause direct neuronal injury (53, 55-57).

Increasing the permeability of the blood brain barrier will disrupt the otherwise well-regulated environment within the subarachnoid space (53). An influx of different protein, smaller particles and fluids will occur resulting in a vasogenic oedema (58).

Leukocyte invasion is essential for the immune response. However, leukocytes release substances such as free reactive oxygen species. These substances, also being released by microglia and endothelial cells, can cause neuronal injury by damaging cellular membranes, proteins, and DNA-structures. Free reactive oxygen species can also lead to energy depletion and cause vasculitis resulting in reduced blood flow, subsequent ischemia, and further cell death (53). Furthermore, as leukocytes enter the subarachnoid space, the turbidity of the cerebrospinal fluid increases. This causes an increased outflow resistance and reduced cerebrospinal fluid uptake resulting in an interstitial oedema (58).

Microglial stimulation is an important step in initiating inflammation in the central nervous system (53). In recent years, microglial cells have also been linked to neural regeneration (55-57). However, stimulation of microglial cells can also cause neuronal injury as these cells can release neurotoxic substances damaging nerve cells (59).

Neuronal injury, either due to inflammation, toxins released by bacteria, or due to ischemia, will result in nerve cells losing their cellular integrity. As nerve cells die, leakage of intracellular substances causes a cytotoxic oedema leading to further neuronal injury (53). In affected areas, this can trigger vasculitis with restricted blood flow and subsequent ischemia leading to additional cell death. If nerve cell death is extensive or located within certain sensitive areas, this will result in temporary or permanent disabilities of varying degree (60).

As described, inflammation causes several types of oedema; vasogenic oedema due to increased permeability of the blood brain barrier, interstitial oedema due to leukocyte invasion, and cytotoxic oedema due to neuronal injury (53, 58). Combined, they increase the intracerebral pressure and can lead to devastating consequences (53, 58). An increased intracerebral pressure will impair cerebral blood flow resulting in further ischemia and cytotoxic oedema thereby creating a positive feedback loop (60-61). Besides extensive neuronal injury, this can also cause herniation of the brain resulting in either severe neurological disabilities or death (52, 60-62).

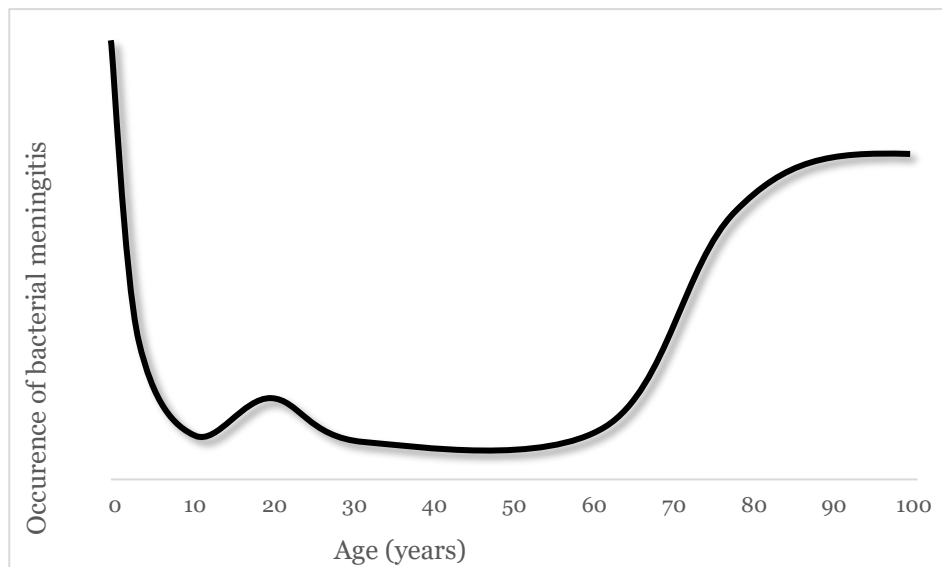
In addition to intracerebral injury caused by the infection and subsequent inflammation in the subarachnoid space, intracerebral injury can also be a result of the often-concurrent sepsis (52). In sepsis, the systemic inflammatory reaction causes organ dysfunction, most commonly affecting the circulatory system resulting in hypotension (63). A reduced mean arterial blood pressure leads to reduced cerebral perfusion pressure, with impair cerebral blood flow as consequence. This results in cerebral ischemia and further neuronal injury (64). Finally, organ dysfunction may progress into multiple organ failure with several negative implications including neuronal injury, permanent disabilities, and death (63-64).

### **What factors increase the risk of bacterial meningitis?**

There are two main factors increasing the risk of bacterial meningitis: either an impaired immune system, or some type of structural weakness in the physical barriers protecting the brain (65).

Several groups have increased risk of contracting bacterial meningitis due to impaired function of their immune system. These include children having a not yet fully developed immune system during their first years of life, as well as the elderly due to a declining function as part of normal aging (Figure 1) (65).

**Figure 1. Age as a risk factor for bacterial meningitis.**



This figure illustrates the association between bacterial meningitis and age in the form of the typical age-distribution of cases of bacterial meningitis, compiled from previous studies (65-68).

In addition, patients with certain genetic predispositions, primary immune deficiencies, or secondary immune deficiencies due to disease or medications also have an increased risk (66).

Since the physical barrier is of such importance, any breach in this barrier will drastically increase the risk of bacterial meningitis (13-15, 65-66). An especially high risk is seen in patients experiencing cerebrospinal fluid leakage due to congenital malformations or injuries (40-43). This group of patients may also have multiple episodes of bacterial meningitis before the cause of their cerebrospinal fluid leakage is discovered and can be surgically repaired (69).

### *Why are bacterial meningitis more common in younger children?*

As previously described, younger children are at higher risk of severe infections due to a not yet fully developed immune system.

During pregnancy, as the rest of the foetus' organs develops at different rates, so does the organs and cells that constitute the immune system. Here, development of hematopoietic stem cells from mesodermal cells and their migration to the liver, both occurring early in the first trimester, are the first steps towards developing an immune system (70). The liver is first to start developing. Thereafter follows the bone marrow and thymus gland in gestational week five and the spleen, lymph nodes and Peyer's Patches from gestational week 12 and onwards (70).

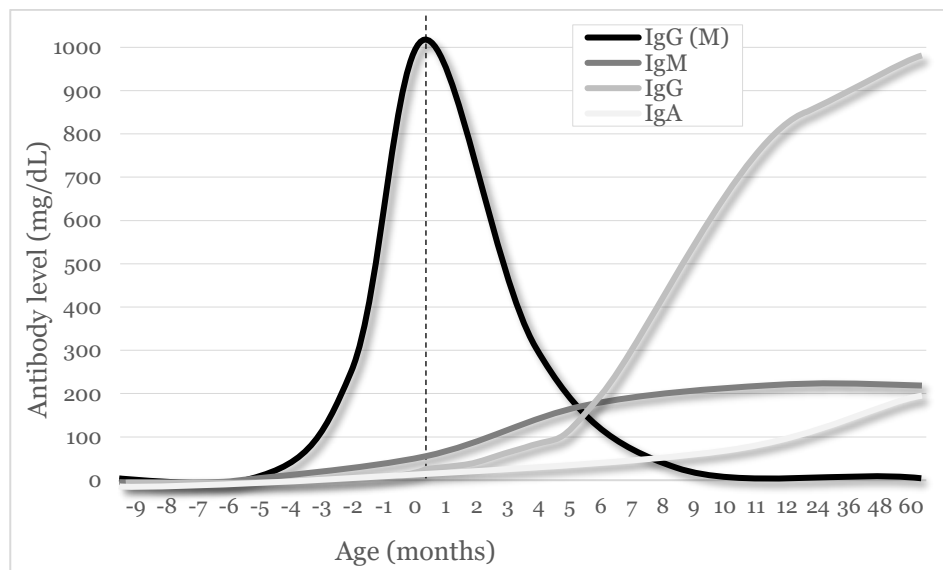
The cells constituting the innate immune system increase in number and functionality during pregnancy. At birth, neutrophils are fully matured and present in numbers equal to adults. Monocytes and natural killer cells on the other hand mature during the first three to five years of life, and do not gain their full function until the teenage years (70).

Lymphocytes start to appear around gestational week 15. These T-cells and B-cells constituting the adaptive immune system are relatively high in number already at birth, and increase rapidly during the first weeks of life to later decline to adult levels (70-71). The T-cells are functionally immature at birth and more prone towards downregulating cytotoxicity. As they mature during the first year of life, so does the ability to respond using cell mediated immunity (70-71).

At birth, the absolute majority of B-cells are naïve and immature as there is little in utero antigenic stimulation. Shortly after birth, there is high antibody production due to exposure to the outside world. Mainly, these are IgM type antibodies as production of IgG and IgA type antibodies does not reach adult levels as fast (70). One important note is that infants are not good at developing antibodies against polysaccharide antigens, possibly due to a less developed marginal zone of the spleen, lower complement function, or that B-cells in infants have fewer complement receptors. This means that infants are less adept at defending themselves against capsulated bacteria and respond less to polysaccharide vaccines (70, 72).

Although the infant’s own immune system is still immature at birth, the new-born will be provided additional protection elicited from maternal antibodies transferred via the placenta during pregnancy (Figure 2). These helps reduce the risk of infectious diseases until the function of the child’s own immune system improves. However, the result is still that the child has a considerably lower level of most types of antibodies until it reaches about five to ten years of age (71-74).

**Figure 2. Antibody levels in the foetus and child.**



This figure illustrates the antibody level in the foetus during pregnancy, after delivery and during the first five years of live. The black line represents the maternal antibodies transferred to the foetus via the placenta (M) whereas the remaining lines represents the antibodies produced by the foetus or child itself. The vertical dotted line indicate birth. This illustration is compiled from previous studies (70-74).

In addition to the maternal antibodies transferred via the placenta, further protection can be achieved if the child breastfeeds. Breast milk contains high levels of secretory antibodies of IgA type, and to a lesser extent also IgM and IgG type antibodies. Breast milk also contains cytokines and immune cells together with oligosaccharides and antibacterial peptides such as lactoferrin and lysozyme (70-71, 74). Combined, these help improve the mucosal immunity and provide additional protection against infectious agents (74-75). This link has been noted in several studies on gastrointestinal infections and respiratory tract infections, as well as for invasive infections such as bacterial meningitis (76-81).

The protective effects of breastfeeding is one of the reasons the World Health Organization recommends exclusive breastfeeding of infants for their first six months of life, and a combination of breastfeeding and supplements thereafter (82-83).

### **How can bacterial meningitis be prevented?**

Prevention of infectious diseases at a community level, as well as at an individual level, can be accomplished using several methods. Principally, the risk of contracting bacterial meningitis can be reduced either by reducing the occurrence of causative pathogens, hindering transmission, or by strengthening the individual's defence against infectious diseases.

Reducing the occurrence of bacteria able to cause meningitis within the community is a difficult task to accomplish. Mostly, these bacteria either constitute the normal human bacterial flora or are able to colonize without causing infection (1-2). The three most common causative pathogens of bacterial meningitis, *S. pneumoniae*, *H. influenzae* and *N. meningitidis*, all colonize the epithelium of the upper respiratory tract (27). Whilst eradication using antibiotics can be performed during local outbreaks of meningococcal meningitis within restricted groups, this is not an option at a community level. Nor is it an option for *S. pneumoniae* or *H. influenzae* (84-85). At a community level, the only viable option for reducing occurrence is vaccination. It has been shown that meningococcal vaccination reduces nasopharyngeal carriage by 18-100% and that pneumococcal vaccination cause a rapid serotype replacement in the nasopharyngeal carriage in vaccinated children and their unvaccinated siblings (86-87).

Hindering transmission is generally an important preventive measure in reducing occurrence of contagious infectious diseases. Strategies often include specific hygiene protocols, social distancing and isolation, among others (88-90). This can be an option in specific settings such as mass gatherings with high risk of outbreaks of meningococcal meningitis. However, these strategies are not generally utilized otherwise due to the widespread colonization by these pathogens within the community (1-2, 27, 91).

Finally, the last option is to strengthen the individual's defence against infectious diseases. Unfortunately, the physical barriers can only be strengthened by repairing rarely occurring defects causing cerebrospinal fluid leakage (40-43, 69) and the blood-brain barrier cannot be improved at all (13, 16-17). Therefore, strengthening the immune response is the only feasible strategy. At an individual level, this can be achieved by initiating immunoglobulin treatments in children with certain primary immune deficiencies, or by optimizing pre-existing illnesses in children with secondary immune deficiencies (92-96). At a community level, addressing important health determinants such as increasing breastfeeding rates and reducing smoking-rates among parents is important. However, the most powerful means of reducing the risk of severe infections such as bacterial meningitis at a community level is by implementing infant vaccinations (97).

#### *How does vaccines work?*

The basic principle of vaccines is to introduce a foreign substance to the immune system, allowing the immune system to respond to it thereby creating an immunological memory. This will enable the immune system to respond faster and more forcefully when being exposed to the same foreign substance in the future.

Vaccines are usually administered via intradermal, subcutaneous, or intramuscular injection. However, vaccines can also be administered using non-invasive methods such as oral, intranasal, or transcutaneous routes (98). The most important component of any vaccine is the antigen, since this is what the immune system will react to and develop an immune response against (99). The antigen can constitute an entire pathogen, either inactivated or weakened such as in live, attenuated vaccines. Further, antigens can consist of smaller subunits of a pathogen such as surface proteins, capsular polysaccharides, or bacterial toxins (99). These subunits can be either in free form or conjugated to something more immunogenic such as a bacterial toxin, to enhance the immune response (100).

As previously described, the immature immune system in younger children are not as able at eliciting an immune response against polysaccharide antigen. Therefore, many polysaccharide antigens are conjugated to more immunogenic substances. This includes the antigen the Hib vaccine and in many of the pneumococcal vaccines (99-101). Finally, vaccines utilizing other types of antigens exist in developmental stages, such as DNA-vaccines or recombinant vector vaccines (102-103). Besides the antigen, the vaccine will often contain several other components; adjuvants to enhance the immunogenicity of the vaccine resulting in a stronger immune response, stabilisers and preservatives to better preserve the vaccine and small amounts of residual substances from the manufacturing process (104).

When the immune system is exposed to an antigen, either naturally during an infection or artificially when introduced as part of a vaccine, an immune response will be initiated. This starts with the antigen being detected by the immune system, typically the immune cells of the innate immune system. Smaller subsections of the antigen are recognized as being foreign substances and the antigen is then engulfed by antigen presenting cells, such as monocytes or macrophages (99). Then, the antigen is processed within the antigen presenting cells and presented on the cell surface. Depending on what type of pathogen the antigen originates from, the antigen presenting cell will use different proteins thereby stimulating the adaptive immune system to respond by inducing either an antibody-mediated immunity or cell-mediated immunity (105-110).

Antigens originating from extracellular pathogens, such as most bacteria and parasites, are presented using proteins that will stimulate CD-4 positive T-helper cells (105). This will start a chain reaction resulting in the activation and clonal expansion of antigen-specific B-cells. These antigen-specific B-cells will either differentiate into antibody-producing plasma cells or memory B-cells (106). During the primary immune response, the plasma cell population will start producing a large number of IgM type antibodies and later convert into producing more effective IgG type antibodies (106-107). In case of a secondary exposure to the same antigen, the secondary immune response will mainly be driven by memory B-cells differentiating into plasma cells capable of rapidly producing large quantities of highly effective IgG type antibodies (108-109).

Antigens originating from intracellular pathogens, mainly viruses, are presented using proteins that instead stimulate CD-8 positive cells such as T-cytotoxic cells, involved in the cell-mediated immunity (110). When activated, the T-cytotoxic cell will also undergo clonal expansion and differentiate either into effector cells involved in the immune response against the ongoing infection or into memory T-cells resulting in a long-lasting cell-mediated immunity (110).

In both cases, differentiation into memory cells will result in an immunological memory. This enables the secondary immune response to be both faster and more forceful, which is the main goal of any vaccination (99). Depending on the immunogenicity of the antigen and several other factors such as host, environmental and behavioural factors, the duration of the immunological memory will differ when comparing different vaccines (111-112). Hence, a single dosage of one vaccine may result in a life-long immunity whilst another requires multiple priming dosages and need to be boosted in regular intervals for the immunological memory and protective effect to remain (113).

When included in immunisation programs such as a national general infant vaccination programme, additional factors need to be considered. The optimal dosage schedule for the individual vaccine needs to be adopted to fit together with already existing schedules to avoid additional occasions the child needs to receive vaccinations (114). Whereas some vaccines potentiate each other, others cannot be administered at the same time or withing specific time intervals of each other (115-116). Furthermore, some areas might have certain population demographics, occurrence of risk factors or health determinants, burden of disease or economic prerequisites requiring further consideration. Combined, all these factors influence the outline of the final dosage schedule being utilised (114-116). This is exemplified by the many different dosage schedules used for pneumococcal vaccinations around the world (117).

### *How can we measure the protective effects of vaccinations?*

Protective effects of vaccinations can be discussed at an immunological, individual, or community level. Therefore, it is important to have a common terminology. First, effects of vaccinations seen at the immunological level are logically termed immunogenicity. Second, the level of protection achieved in the individual vaccine recipient is termed vaccine efficacy. Finally, the effects obtained at a community level when a vaccination is introduced is termed vaccine effectiveness (118-124).

Typically, a safety and immunogenicity trial involving a limited number of study participants are the first ones conducted in the early phases of any vaccine development (118). Here, antibody response is measured including the number of patients that produce antibodies following one or several vaccine dosages, what levels are being reached and how long the antibody level lasts (118). This method has its limitation. Often, the protective effect elicited by cell-mediated immunity is not measured (119). Furthermore, the specific antibody level obtained is a surrogate marker and cannot always be directly translated into a specific level of protection against infection (120).

To prove that a vaccine able to elicit an immune response also leads to protection against infection, other types of studies are needed. One way of achieving this is by conducting a randomized control trial. Here, occurrence of a specific infectious disease in a smaller group of patients receiving the active vaccine can be compared with the occurrence in a group receiving placebo (121). These results obtained in a highly controlled environment are often termed vaccine efficacy and will provide information on what protective effects can be obtained under optimal circumstances. Although this can be very informative, it does not fully predict the effects a full-scale introduction of a vaccination will have within a region (122).

Lastly, before-after comparisons or comparisons between different regions having implemented different vaccinations are often used to evaluate the overall effects of vaccinations as an intervention when used in a real-world setting post-licensure (123). The advantage of this is that it provides information on the overall effects at a population level, including negative effects of real-world limitations and any positive effects due to herd immunity (123). At the same time, there are several challenges limiting the interpretations of such studies. Contrary to the controlled environment in a randomized controlled trial, these studies cannot control for other health interventions, changes in health determinants or other occurrences within the study area. Furthermore, differences in between regions may be too large to fully compensate for. Hence, results of these types of studies are subject to influence of multiple factors, some of whom may be unknown (123-124).

It is important to consider these advantages and disadvantages of the different study methods when viewing studies on protective effects of vaccinations. All different methods provide valuable information, and none is superior to the other. Rather, these methods all complement each other in trying to assess the protective effects of vaccinations.

*What vaccinations are offered to children in Sweden and how effective are they in reducing the risk of severe infections such as bacterial meningitis?*

Since vaccination against smallpox were introduced in Sweden in the 19<sup>th</sup> century, the national vaccination programme has been extended during the years. Today, all children in Sweden are offered vaccinations against 11 pathogens as part of the publicly funded national vaccination programme for children: Rota virus, Polio virus, Measles virus, Mumps virus, Rubella virus, Human Papillomavirus, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, *H. influenzae* type b and *S. pneumoniae*. In addition, vaccination against Hepatitis B virus are offered in all Swedish regions and vaccination against *Mycobacterium tuberculosis* are offered to specific risk groups (125-126). Of these vaccinations being offered, two are aimed specifically at reducing the risk of severe bacterial infections such as bacterial meningitis: the Hib vaccination and the pneumococcal vaccination (126).

General infant Hib vaccination started in 1992 in the Västerbotten Region and was introduced nationally in 1993 (126). Since the start, a subunit antigen polysaccharide-protein conjugate type vaccine has been used, either alone or as a combination vaccine together with antigens from other pathogens (127). When introduced, a three-dose schedule was adopted, with dosages given at three, five and 12 months of age without catch-up vaccination for older children (125-127).

When pneumococcal vaccination was introduced in the national vaccination programme in Sweden in 2009, a seven-valent subunit antigen polysaccharide-protein conjugate type vaccine was recommended, using the same dosage schedule as for the Hib vaccination (125-127). In the Västerbotten Region, the seven-valent Prevenar (Wyeth Pharmaceuticals Inc., Collegeville, PA, USA) was used when pneumococcal vaccination started in the region in 2009. This was later replaced in February 2010 by Prevenar 13 (Pfizer Inc., New York, NY, USA), a thirteen-valent vaccine. Finally, in March 2011 this was replaced by Synflorix (GlaxoSmithKline Biologicals S.A., Rixensart, Belgium), a ten-valent vaccine also containing protein D of non-typeable *H. influenzae*.

At a national level, both vaccinations have been successful (128-132). Before Hib vaccination was introduced, incidence of bacterial meningitis caused by *H. influenzae* was 26-28 cases per 100,000 children and year in children aged 0 to four years in Sweden. Within a few years after the vaccination was introduced in the Swedish national vaccination programme, incidence of meningitis caused by *H. influenzae* fell by 90-95% (128-130). Similarly, the increasing incidence of pneumococcal meningitis in Sweden during the late 1990s and early 2000s, reaching 5.8 cases per 100,000 children and year in children aged 0 to four years, was reversed after pneumococcal vaccination was introduced in the Swedish national vaccination programme. In only a few years, incidence of pneumococcal meningitis had been reduced by 57% in vaccination-eligible children (131-132). Although having been proven effective on a national level, neither general infant Hib nor pneumococcal vaccinations have been evaluated in all Swedish regions. Notably, no previous investigations have been conducted in the Swedish Arctic regions. This is a concern since some of the highest incidences of severe infections are found in the Arctic regions around the world.

The Arctic is not defined using one unanimous definition, rather it is defined by various criteria depending on several factors. By most definitions, the Arctic consists of the northernmost parts of Canada, Denmark (Greenland), Finland, Norway, Iceland, Russia, Sweden, and the United States. These are also the countries represented in the Arctic Council (133).

In the strictest definition, only the areas above the Arctic Circle at latitude 66 are considered as the Arctic. However, by this definition the Arctic would not include Iceland and only limited areas of the remaining Arctic countries. Further definitions based on temperature, flora, indigenous people, economic or cultural ties each draws the line slightly different (134-135). Whereas the Västerbotten Region shares many similarities with other Arctic regions such as the indigenous population and historical and cultural ties (135-136), it differs in other aspects such as having higher population density and longer life expectancy (137). Today, the Västerbotten Region together with the Norrbotten Region is defined by the Arctic Council as constituting the Swedish Arctic regions (138).

Invasive infections caused by *H. influenzae* and *S. pneumoniae* was previously common in many Arctic regions (139-147). Before introduction of Hib vaccination, incidence of bacterial meningitis caused by *H. influenzae* in children aged 0 to four years was 474 cases per 100,000 children and year in southwest Alaska (139). For invasive Hib disease, incidence was 131 cases per 100,000 children and year for the entire Alaska. After introduction, incidence of invasive Hib disease was reduced by 94% to 7.1 cases per 100,000 children and year (140).

For all-cause bacterial meningitis, incidence in Greenland prior to introduction of pneumococcal vaccination was 184 cases per 100,000 children and year in children under two years of age and 106 in children aged 0 to four years, substantially higher than in the remaining population in Denmark (141). During the period of introduction in the North American Arctic region consisting of Greenland together with Alaska and the northernmost parts of Canada, incidence of all-cause bacterial meningitis in children under two years of age was 35 cases per 100,000 children and year (142).

Incidence of invasive pneumococcal disease in children in the Arctic region was also high before pneumococcal vaccinations were introduced. In children under two years of age, incidence ranged from 186 cases per 100,000 children and year in Yukon, Northwest Territories and Nunavut regions of Canada to 174 in Alaska, 90 in Iceland, 77 in Greenland, 50 in Norway, 52 in Finland and 21 in the northernmost part of Sweden (143). Shortly after introduction of general infant vaccinations using seven-valent pneumococcal vaccines, incidence in this age group fell by 41% in the Canadian Arctic regions and by 54% in Alaska (143). In children aged 0 to four years, incidence of invasive pneumococcal disease was 248 cases per 100,000 children and year in the Nunavik region in the northernmost part of Canada and 97 cases per 100,000 children and year in Alaska prior to introduction of pneumococcal vaccinations (144-145). Following introduction, incidence of invasive pneumococcal disease initially decreased considerably. However, incidence started rising again within a few years due to serotype replacement, offsetting the initial decline and resulting in a total decrease of invasive pneumococcal disease by only 14% in Nunavik and 35% in Alaska (144-145). At the same time, incidence of invasive pneumococcal disease in the entire Quebec province where Nunavik is situated was reduced by 83% and in the United States mainland by 75% (146-147).

Although indigenous children in the Arctic region have the highest rates of invasive infections, incidence in non-indigenous children living in the Arctic regions are still higher than in other parts of the respective countries (139-147).

The higher occurrences of severe infections in some Arctic regions, as well as less substantial improvements following introduction of general infant vaccinations, raises an important question; are general infant vaccinations effective at preventing severe infections in children, such as bacterial meningitis, in the Swedish Arctic regions?

## **How is bacterial meningitis in children diagnosed and treated?**

For the individual child with bacterial meningitis, treatment involves many challenges starting with correctly identifying the condition, guiding treatment, and finally identifying both short-term and long-term disabilities.

*How do you determine if a child complaining of fever has a mild viral infection or a severe bacterial infection such as bacterial meningitis?*

Symptoms of infectious diseases often include fever, shivering, nausea, fatigue, dizziness, mental exhaustion, and headache among others (148). These symptoms can represent a mild viral infection but can also be the first signs of a severe bacterial infection (148-149). For bacterial meningitis, the triad often described in medical literature include fever, neck stiffness, and altered mental status. In addition, seizures and severe headache are also common symptoms in cases of bacterial meningitis (1-2). Although easily recognisable in theory, this can prove a challenge since the clinical presentation of bacterial meningitis sometimes differ considerably from how it is commonly description (150). When evaluating children, the task of separating mild viral infections from severe bacterial infections can be especially difficult. In addition to a different physiology resulting in varying clinical presentation in different ages, smaller children might not be able to convey their symptoms (148-151).

Laboratory analyses measuring inflammation such as C-reactive protein (CRP), procalcitonin or total white blood cell (WBC) count in blood might provide more information but is not enough to confirm nor rule out bacterial meningitis (152-154). To do so, only a lumbar puncture for acquiring cerebrospinal fluid for analysis will suffice (155-156). However, this procedure is painful and frightening for the child, difficult to perform, and involves risk of complications (157-158).

Numerous clinical decision rules for recognition severe infections exist. For bacterial meningitis, these are often based on the classical triad described earlier, together with additional criteria including a multitude of other symptoms, clinical findings, and laboratory findings. Whilst some clinical decision rules only use symptoms, clinical findings and easily accessible laboratory findings, others rely on the results of cerebrospinal fluid analyses making them more accurate but less easily applicable in clinical practice (156, 159-162).

For any clinical decision rule aimed at recognising bacterial meningitis, the most important objective is not to miss cases of bacterial meningitis. This would lead to devastating consequences due to the infection rapidly progressing, resulting in severe neurological disabilities or even death (53-52). At the same time, the clinical decision rule cannot grade all patients as high risk since this would lead to high costs and increase the risk of complications due to unnecessary procedures or treatments (157-158, 163-165).

A major problem is that few clinical decision rules have undergone external validation. This creates uncertainty regarding their abilities. Given the vast consequences of mistaking bacterial meningitis for a less severe infection, the question is; how reliable are clinical decision rules at the task of identifying bacterial meningitis in children?

*What steps are involved in the treatment of bacterial meningitis?*

When a child is suspected of having bacterial meningitis, a lumbar puncture is performed, and intravenous broad-spectrum antibiotic treatment is initiated immediately thereafter (1-2). In addition, intravenous corticosteroids are often given to reduce inflammation in the subarachnoid space, possibly reducing the risk of neurological disabilities (1-2, 166). Finally, intravenous antiviral medication is sometimes initially given if a viral encephalitis cannot be ruled out (167). This initial treatment is regulated by standard protocols and clinical guidelines. Whilst the recommended initial antibiotic regime differs depending on national antimicrobial resistance patterns, clinical guidelines are otherwise fairly similar world-wide (167-172).

As it is common for the child to also have a concurrent sepsis, a combination of intravenous fluid resuscitation and vasoactive drugs might be required to treat hypotension and reduce the risk of organ dysfunction due to sepsis (52-64, 173). Often, this involves admittance to an intensive care unit to closely monitor and support vital organ functions and maintain adequate mean arterial blood pressure (173). As intensive care units exist in most hospitals, the decision to admit the child to an intensive care unit when needed is often uncontroversial.

One of the major concerns for bacterial meningitis is the risk of intracerebral injury due to elevated intracerebral pressure. As the infection and inflammation in the subarachnoid space progresses, the increasing oedema will start to elevate the intracerebral pressure. If left untreated, this may result in neuronal injury, neurological disabilities and death (52-62). Before this occurs, several compensatory mechanisms will try to hinder a rise in intracerebral pressure. Thanks to compensatory mechanisms, the degree of oedema will not be linearly correlated to the increase in intracerebral pressure. Instead, there will be an exponential correlation. However, this also means that when the compensatory mechanisms reach their maximum capacity, any increase in oedema will cause a greater increase in the intracerebral pressure rapidly rising to harmful levels (174).

Measuring or estimating the intracerebral pressure can be accomplished using several methods. Most commonly, the opening pressure when conducting a lumbar puncture are used as an approximation of the intracerebral pressure (1-2). However, several sources of error have been reported indicating an uncertainty in this method (175-176), especially in children (177-178). Furthermore, performing a lumbar puncture will only provide a single point of measure contrary to other methods capable of continuous real-time monitoring (178).

Non-invasive methods of estimating the intracerebral pressure include different imaging techniques, measuring fluid dynamics, tympanometry, visual-evoked potentials, otoacoustic emissions assessment, optic nerve diameter, and intraocular pressure, among others. Unfortunately, none of these have been superior or equal to invasive methods. Therefore, invasive methods remain the gold standard (179-181).

Invasive methods directly measure the intracerebral pressure. This involves either placing an intracerebral pressure monitoring micro-transducer or placing an external ventricular drainage equipped with a pressure monitor, both able to provide continuous real-time data. Due to the complication risk, these neurosurgical procedures are reserved for severe cases where an elevated intracerebral pressure is suspected clinically. While the intracerebral pressure monitoring micro-transducer has a lower complication rate, it is not able to regulate the intracerebral pressure, contrary to an external ventricular drainage that can be used to lower the intracerebral pressure by draining cerebrospinal fluid from the ventricular system (182).

The advantage of real-time measurement of the intracerebral pressure is that this, combined with the mean arterial blood pressure obtained from an arterial catheter, allows the clinician to calculate the cerebral perfusion pressure as an estimate of cerebral blood flow (182). Besides not reaching an intracerebral pressure level that will cause neuronal injury, a delicate balance needs to be maintained so that the brain is supplied with enough oxygenated blood, but not so much as to elevate the intracerebral pressure further (182). Often, this can be accomplished by regulating the mean arterial blood pressure. However, if the intracerebral pressure rises beyond a certain point, the intracerebral pressure needs to be addressed directly (183).

The intracerebral pressure can be temporarily reduced using non-invasive procedures such as bed elevation, transient hyperventilation to reduce carbon dioxide, osmotic solutions involving mannitol or hypertonic saline, or sedation. To permanently reduce an elevated intracerebral pressure, placing an external ventricular drainage will often be the next step. If this fails in lowering the intracerebral pressure, a unilateral or bilateral hemicraniectomy can be performed in extreme cases (183-186).

The problem is that these invasive procedures, when needed, must be performed quickly otherwise the elevated intracerebral pressure may cause neuronal injury, permanent neurological disabilities, and death (174-186). Since far from all hospitals have the capacity to perform neurosurgical procedures, this will unfortunately often require transfer to another hospital. Any transfer between hospitals involve risk, especially in severely ill patients that may be in a condition where transfer is preferably avoided (187-188). The ability to identify children that later will need an invasive procedure to manage the intracerebral pressure would therefore be ideal. However, no predictive tool aimed at this have yet to reach clinical practice.

Is it possible to predict the need of invasive procedures to manage the intracerebral pressure, thereby enabling clinicians to make a referral decision early on, rather than when the child's condition is rapidly deteriorating?

## **Are there any long-term consequences of bacterial meningitis?**

Thanks to advances in modern medicine such as added knowledge of physiology and pathophysiology, discovery of new medications and antibiotics, and improvements in intensive care, outcome of many medical conditions have improved over the years.

As modern medicine improves, so does the chance of survival when suffering from severe infections. This also includes bacterial meningitis. Today, the survival rate in children are now as high as 92-94% in high-income countries (189). As survival rate increases, so does the interest in improving care for patients suffering from disabilities caused by their illness.

Disabilities following childhood bacterial meningitis commonly include hearing impairments seen in 4-30% of survivors (190-193), epilepsy in 2-15% (190-192, 194-195) and neurological disabilities in 3-14% ranging from isolated impairments to extensive disabilities affecting all aspects of the child's future live (190-192). In total, 20-50% of surviving children are expected to suffer one or more of these types of disabilities (190-195).

In recent years, there have been a rising number of reports of less noticeable disabilities following childhood bacterial meningitis. These include behavioural and learning difficulties, reduced quality of life due to lack of energy, increased anxiety, and social difficulties. In total, less noticeable disabilities have been suggested to affect 5-39% of surviving children (190-191, 196-199).

*Is it possible to predict which children will suffer disabilities?*

There is vast knowledge regarding risk factors for acquiring hearing impairment, epilepsy and neurological disabilities following childhood meningitis. The list of negative prognostic factors includes a long duration of fever or other symptoms before admission, impaired consciousness at admission, prolonged seizures during the hospital stay, circulatory failure, severely deranged cerebrospinal fluid parameters including low glucose level and high protein level together with male sex and a younger age (201). In addition, there are several predictive tools aimed at predicting adverse outcome (202-209). For less noticeable disabilities, less is known regarding risk factors. There are indications that factors increasing the risk of less noticeable disabilities are similar to those described above. However, less noticeable disabilities appear harder to predict and previous attempts at creating prediction models have been unsuccessful (210-212).

*What efforts are undertaken to identify children suffering from permanent disabilities following bacterial meningitis?*

Children having had bacterial meningitis will undergo several follow-up appointments, often regulated by standardized follow-up protocols in clinical guidelines (167-172). As these guidelines base their recommendations on previous studies on disabilities following bacterial meningitis (190-195), they often including a hearing test together with a neurological examination by a general paediatrician or paediatric neurologist (167-172). Currently, no major international guideline recommends routine follow-up appointments aimed specifically at detecting psychiatric disease or other types of less noticeable disabilities (167-172).

The emerging knowledge of less noticeable disabilities following childhood bacterial meningitis combined with prediction difficulties and current recommended follow-up protocols raises an important question; are psychiatric disabilities following childhood bacterial meningitis being missed today resulting in unnecessary suffering for the individual child?

# Materials and Methods

## Study setting

The Västerbotten Region is in the north of Sweden, at latitude 63, covering one eighth of the country's total land area. The Västerbotten Region, together with the Norrbotten Region, constitute the Swedish Arctic region (133-138). There are three cities in the otherwise mainly rural region, all with its own publicly run hospital; one University hospital located in the city of Umeå and two local hospitals located in the cities of Lycksele and Skellefteå. In addition, there were 39 primary healthcare centres operational when the studies were conducted; 32 of which were public and seven were in private regime.

The population in the Västerbotten Region is mainly Caucasian, with approximately 1-5% being indigenous people, Sámi, based on projections of historical ethnicity data (213-214). The mean annual population in the Västerbotten Region during the period of 1986-2015 was 256,536 inhabitants, of whom 55,688 were children under 18 years of age. Likewise, during the subperiod of 2005-2014, the mean annual population was 259,183, including 51,454 children under 18 years of age. At the same time as the total population increased during the study period, the number of children decreased slightly resulting in an overall aging population (215).

## Material and dataset

In this thesis, two different datasets were used; for papers I and III-V a dataset was compiled by us based on medical records, and for paper II we extracted data from an already existing database at the Västerbotten Region.

### *Dataset for papers I and III-V*

As part of these papers, we compiled a new dataset containing information on children aged one month to 17 years being treated for severe infections in the Västerbotten Region during the period of 1986-2015. To accomplish this, we conducted two data collections, first in 2014 focusing on the years 1986-2013 and later in 2016-2017 for the years 2014-2015. Both data collections were carried out in the same manner.

Cases were identified from two sources: first, patients with an international classification of diseases (ICD) diagnosis code of either sepsis (ICD-8/9: 038, ICD-10: A40 and A41) or bacterial meningitis (ICD-8/9: 036 and 320, ICD-10: A39 and G00) were identified from the Västerbotten Region's diagnosis registration. Second, all positive blood or cerebrospinal fluid cultures for *H. influenza*, *S. pneumonia* and *N. meningitidis* were identified using laboratory records at the Department of Laboratory Medicine at Umeå University Hospital, responsible for all laboratory cultures within the entire region.

To ensure that all cases in the dataset were correctly classified, all identified cases underwent a validation process based on pre-defined criteria. In this process, we reviewed medical records of all identified cases using a standardized protocol. During this process, we also collected data including patient information such as previous illnesses as well as symptoms, signs, and laboratory findings at admission to the hospital.

To be validated, cases had to fulfil at least two of the three criteria stated below. Cases that fulfilled both the criteria for sepsis and for bacterial meningitis were classified as meningitis.

- (i) ICD diagnosis; either of sepsis or of bacterial meningitis, or:
- (ii) Positive culture; either from blood for sepsis or from cerebrospinal fluid for bacterial meningitis, or:
- (iii) Clinical presentation; either consistent with sepsis according to the age-correlated systemic inflammatory response syndrome (SIRS) criteria (216) or consistent with bacterial meningitis using the Bacterial Meningitis Score (156) or the clinical decision rule stated by Oostenbrink et al (159).

### *Dataset for paper II*

In the second paper, we used the Västerbotten Region's patient register containing ICD diagnoses from all healthcare services in the region, including hospital clinics and public and private primary healthcare centres. From this database, patients with an ICD-10 diagnosis code of either a respiratory tract infection (H65-H68, H70, H72, J00-J06, and J10-J22) or gastroenteritis were identified (A08-A09), thereby creating a separate dataset.

## **Methods of individual papers**

In paper I, we performed a retrospective before-after study comparing incidence of severe infections in relation to introduction of general infant Hib and pneumococcal vaccinations in the Västerbotten Region. We included all cases of validated sepsis and bacterial meningitis where the child was residing in the Västerbotten Region. Together with population data from Statistics Sweden, we then calculated incidence of sepsis and bacterial meningitis as basis for our comparison.

In paper II, the study design was also that of a before-after study. Here, we extracted data the Västerbotten Region's patient register to compare incidence of respiratory tract infections in the Västerbotten Region before and after introduction of general infant pneumococcal vaccination. In addition, data on gastroenteritis was also obtained to identify any altered care-seeking patterns.

In paper III, we utilized the retrospectively collected data from the years 1986-2013. Here, information on symptoms, signs, and laboratory findings at admission to the hospital were used to study clinical presentation of bacterial meningitis in children and to test sensitivity of existing clinical decision rules for identifying severe infections in children.

In paper IV, we developed a new predictive score for bacterial meningitis in children called the Meningitis Swedish Survival Score (MeningiSSS). We based this score directly on individual risk factors identified in a major systematic review article of risk factors for adverse outcome in children with bacterial meningitis (201). From this, nine risk factors were included in the MeningiSSS and graded according to their relative risk increase (Table 1). Several cut-off levels were tested, and the best discrimination was noted for a cut-off level of six points or higher, which was later used when comparing the MeningiSSS with other predictive scores (Table 1).

**Table 1. Predictive score for adverse short-term outcome.**

Predictive scores	Criteria
<p><b>Aronin Scale (202)</b>  <i>This score indicates high risk of adverse short-term outcome if the child's total score is two points or higher.</i></p>	<ul style="list-style-type: none"> <li>✖ Seizures (1 point)</li> <li>✖ Altered mental status (1 point)</li> <li>✖ Systolic blood pressure <math>\leq</math> 90 mmHg or <math>&gt;</math> 40 mmHg decrease (1 point)</li> </ul>
<p><b>Herson-Todd Scale (203-204)</b>  <i>This score indicates high risk of adverse short-term outcome if the child's total score is 4.5 points or higher.</i></p>	<ul style="list-style-type: none"> <li>✖ Coma (3 points)</li> <li>✖ Body temperature <math>&lt;</math> 36.6 °C (2 points)</li> <li>✖ Seizure (2 points)</li> <li>✖ Systolic blood pressure <math>&lt;</math> 60 mmHg (1p)</li> <li>✖ Age under 12 months (1 point)</li> <li>✖ Haemoglobin <math>&lt;</math> 110 g/L (1 point)</li> <li>✖ Cerebrospinal fluid;               <ul style="list-style-type: none"> <li>- WBC count <math>&lt;</math> 1,000 cells/<math>\mu</math>L (1 point)</li> <li>- Glucose <math>&lt;</math> 1.1 mmol/L (0.5 points)</li> </ul> </li> <li>✖ Duration of symptoms longer than three days (0.5 points)</li> </ul>
<p><b>Meningitis Swedish Survival Score</b>  <i>This score indicates high risk of adverse short-term outcome if the child's total score is six points or higher.</i></p>	<ul style="list-style-type: none"> <li>✖ Altered consciousness (2 points)</li> <li>✖ Seizures (2 points)</li> <li>✖ Low blood WBC count<sup>1</sup> (2 points)</li> <li>✖ Circulatory distress, either circulatory shock<sup>1</sup> (2 points), or signs of peripheral circulatory failure (1 point)</li> <li>✖ Respiratory distress<sup>1</sup> (1 point)</li> <li>✖ Fever for more than seven days (1 point)</li> <li>✖ Cerebrospinal fluid with               <ul style="list-style-type: none"> <li>- WBC count <math>&lt;</math> 1,000 cells/<math>\mu</math>L (1 point)</li> <li>- Glucose <math>\leq</math> 0.6 mmol/L (1 point)</li> <li>- Protein <math>\geq</math> 2,500 mg/L (1 point)</li> </ul> </li> </ul>
<p><b>Niklasson Scale (202)</b>  <i>This score indicates high risk of adverse short-term outcome if the child's total score is three points or higher.</i></p>	<ul style="list-style-type: none"> <li>✖ Cerebrospinal fluid WBC count <math>&lt;</math> 100 cells/<math>\mu</math>L (1 point)</li> <li>✖ Systolic blood pressure <math>\leq</math> 100 mmHg (1 point)</li> <li>✖ Petechiae for less than 12 hours (1 point)</li> <li>✖ Body temperature <math>&gt;</math> 40 °C (1 point)</li> <li>✖ Blood WBC count <math>&lt;</math> <math>15 \times 10^9</math>/L (1 point)</li> <li>✖ Blood platelet count <math>&lt;</math> <math>100 \times 10^9</math>/L (1 point)</li> </ul>
<p><b>Simple Luanda Scale (204)</b>  <i>This score indicates high risk of adverse short-term outcome if the child's total score is seven points or higher, or death if the child's total score is eight points or higher.</i></p>	<ul style="list-style-type: none"> <li>✖ No electricity at home (2 points)</li> <li>✖ Symptoms for four to seven days (1 point), or more than eight days (2 points)</li> <li>✖ Seizures, focal (1 point) or general (2 points)</li> <li>✖ Altered consciousness (5 points) or coma (10 points)</li> <li>✖ Dyspnoea, moderate<sup>1</sup> (1 point) or severe<sup>2</sup> (2 points)</li> </ul>

In this table, the criteria for the predictive scores aimed at estimating risk of adverse short-term outcome for bacterial meningitis in children are presented.

<sup>1</sup> According to the age-correlated SIRS criteria (216).

<sup>2</sup> Severe dyspnoea was defined as need of ventilator.

Starting with the dataset used in papers I and III, we added information to the dataset by reviewing medical records for the entire hospital stay for all validated cases of bacterial meningitis using a standardized protocol. Now, we collected additional data on all treatments, invasive procedures, complications, or deaths occurring during the hospital stay. Furthermore, we used the Swedish population register to assess 30-day mortality. Finally, using these data we tested our predictive score's ability to predict death, any adverse outcome, complications, need of invasive procedures to manage the intracerebral pressure as well as need of intensive care, compared with four existing predictive scores and individual risk factors.

In paper V focusing on long-term disabilities, we included all children with bacterial meningitis that were alive at discharge and had their follow-up conducted in the Västerbotten Region.

For these children, we obtained and reviewed medical from the following clinics within the Västerbotten Region: paediatrics, child health, oto-rhino-laryngology, neurology, neurosurgery, child and adolescent habilitation, rehabilitation, psychiatry, and child and adolescent psychiatry. We then reviewed all medical records from discharge until present time using a standardized protocol. Here, we collected data on how the follow-up was conducted and any disabilities detected during the follow-up period as well as later in life. In addition to this, we obtained and reviewed child health records to extract data on developmental achievements.

Using these data, we studied how common long-term disabilities were and if they were discovered during the follow-up period or later in life. Finally, we tested if individual risk factors could predict long-term disabilities.

## Statistical methods

Several statistical methods were used in the papers; we used the Chi-square test for calculating and comparing percentages for categorical data between different groups and the Levene's test of equality combined with a t-test for calculating and comparing means for continuous numerical data. To assess statistical significance in these analyses, either a p-value or a confidence interval was used. Here, a p-value less than 0.05 or 95% confidence intervals not overlapping were deemed significant.

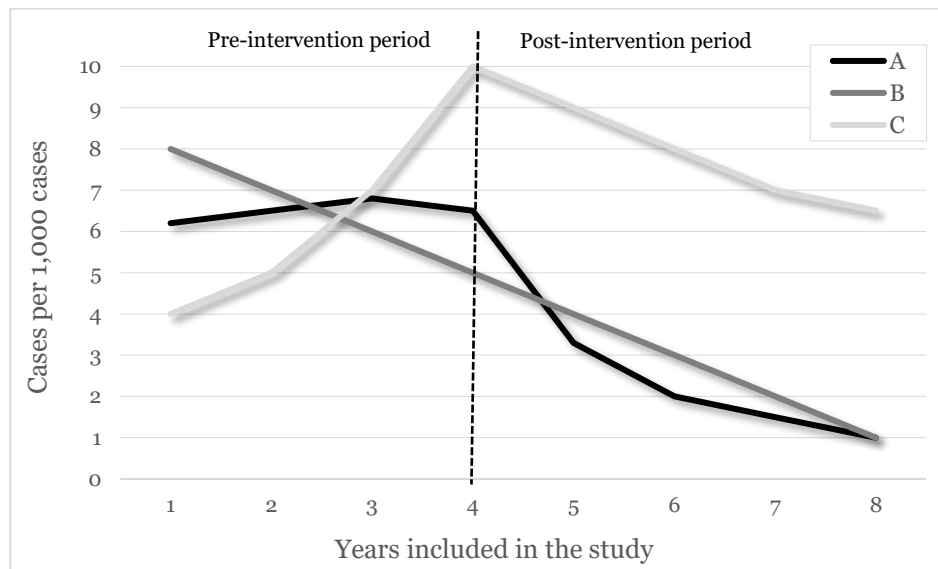
In papers I and II, being focused on epidemiological changes, these epidemiological changes were evaluated using two principal methods: A pooled incidence numbers before-after analysis and a time-series analysis.

First, we compared pooled incidence numbers for the pre-vaccination periods with the last included post-vaccination year or post-vaccination period by their 95% confidence intervals. Here, two 95% confidence intervals not overlapping each other were considered a significant change in incidence. This method has its limitations; while it reduces impact of year-to-year variation using a mean for the entire period, it is only able to give a correct assumption if the incidence before an intervention is varying around a stable level (Figure 3; example A). If incidence is declining already before the intervention due to other reasons, and the intervention has no real impact on incidence (Figure 3; example B), there would still be a significant difference when comparing the pre- and post-intervention period simply due to the already decreasing incidence before. In a third scenario, if incidence was increasing before the intervention and reduced afterwards (Figure 3; example C), it could appear as if the intervention had no effect at all using this statistical method.

In all three examples (Figure 3, example A-C), the pre-intervention period had an incidence of 6.5 cases per 1,000 persons and year and the post-intervention period an incidence of 2.0, 2.0 and 6.5 cases per 1,000 persons and year for example A, B and C respectively. Relying solely on this method, it would appear as if a reduction occurred in example A and B but not in example C. However, by instead looking at the figures, it is obvious that the intervention had a positive impact in examples A and C.

To address this issue, we conducted a time-series analyses using a linear regression model. This model identifies trends during a period by calculating the average slope of the curve for that period. Then, it compares this slope to the slope of another part of the same curve (217). Using this model, it is possible to identify underlying trends in the pre-intervention period, and to assess if a significant change in trends occurs from the pre-intervention to the post-intervention period (217). In the example (Figure 3, example A-C), the time-series analysis would indicate that a neutral trend was present in the pre-intervention period in example A, a negative trend in example B and a positive trend in example C. It would also identify that a change in trends had occurred in examples A and C. Finally, for example B, it would identify that the already negative trend in the pre-intervention period remained unchanged in the post-intervention period, meaning the intervention had no impact on incidence in the example.

**Figure 3. Example of ways to calculate incidence changes.**



This figure shows three examples of incidence in relation to different interventions, A, B and C. The coloured lines mark the incidence for each year in cases per 1,000 persons and year. The dotted line marks the intervention in year 4.

In the third paper, we wanted to consider the possible impact of confounders including sex, known predisposing conditions, duration of illness, and causative pathogen when analysing our results regarding clinical presentation for different age groups. We did so by using a one-way independent group analysis of covariance (ANCOVA) for multiple factors.

While the t-test will examine if an independent variable (e.g. patient's sex) is associated with a continuous variable (e.g. CRP), it cannot assess the effects of any confounders. The same is true when testing categorical variables using the chi-square test (218). There are many statistical methods to also test if an association is due to a confounding factor unevenly distributed within the different groups, (e.g. duration of illness), one being the one-way ANCOVA. Thus, while the t-test can assess if there is a significant association between patient's sex and CRP, the one-way ANCOVA can also assess if this association is due to another confounding factor such as duration of illness.

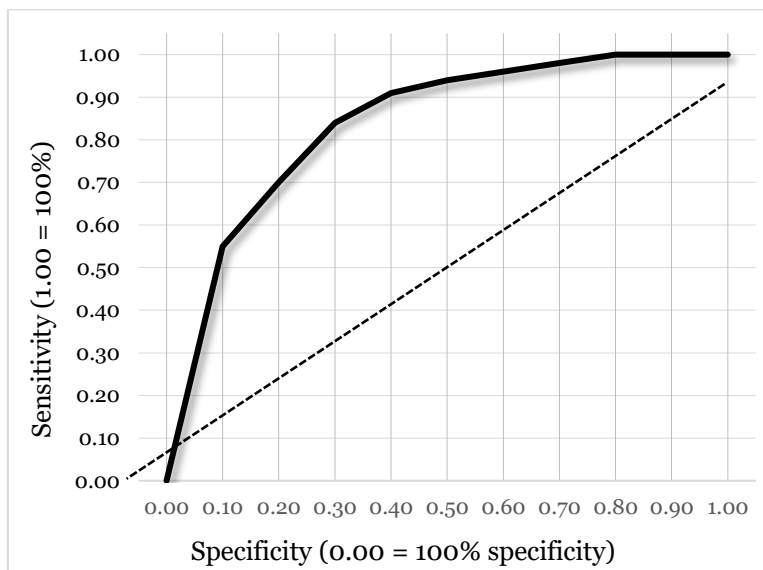
In doing so, the one-way ANCOVA, being based on an analysis of variance (ANOVA), will conduct a regression to test the variance between the independent and the dependent variable, split into between-groups and within-groups variance. Here, between-groups variance measures how the mean values of two groups vary from each other and within-group variance how much individual values vary within a group. The within-group variance is often called unexplained variance since it may be caused by an unknown confounder (219). The ANCOVA adds covariates to the analysis to tests if these can explain the unexplained within-group variance. Simplified, this will result in the association between the independent and dependent variable being tested without the covariates' impact (219).

When conducting an ANCOVA, the independent variable needs to be at least categorical. Since the ANOCVA uses means as comparison, both the dependent and covariate variables need to be continuous (220). This can be addressed by converting categorical variables into binary indicator variable (e.g. from a categorical variable being either male or female into a binary indicator variable where "1" is equal to female and "0" is equal to not female), allowing the regression which the ANCOVA is based on to handle the variables correctly (221-222). In paper III, we used this method when handling categorical variables. Although feasible, a more accurate approach would have been to instead conduct a multiple logistic regression model.

In paper IV, besides testing the different predictive scores at their cut-off levels using the chi-square test, we also performed a receiver operating curve (ROC) characteristics analysis to calculate area under the curve (AUC) for each predictive score. The ROC analysis was interpreted using previously validated AUC levels, classifying their respective predictive abilities ranging from excellent to fail (223). The way a ROC analysis works is that it tests each predictive score's sensitivity and specificity for a certain outcome at all values produced by the score (224). This is then plotted on a graph (Figure 4); the Y-axis in the graph marks the true positive rate, which is the same as a tests sensitivity, where the value 1.00 is equal to a sensitivity of 100%. The X-axis marks the false positive rate as an inverse measure of specificity, where the value 0.00 is equal to a specificity of 100% (224).

The best possible result of a ROC analysis is a curve that immediately goes from zero to the top-left corner and then straight across the graph as a horizontal line at 1.00. This curve would cover the entire graph resulting in an AUC value of 1.00. Such a result would mean that the predictive score separates the true positive and true negative perfectly without any overlap. This would be equal to a sensitivity and a specificity both at 100%. The worst result is an AUC value of 0.50. This value indicates that the predictive score has the predictive ability equivalent to flipping a coin (223-224).

**Figure 4. Example of a ROC analysis.**



*This figure shows an example of a ROC analysis. The dotted line marks a diagonal equivalent to an AUC of 0.5.*

## **Ethical considerations**

Conducting research is always an ethical balance between the good of the few and the good of the many. This is perhaps most apparent in early phases of pharmaceutical trials. Here, a small number of healthy study participants are administered previously untested medication, risking unknown side effects in the hopes of possibly finding new medications that can benefit others in the future.

Generally, the more the study participants are to gain, the higher risk or intrusion of their privacy are accepted. Therefore, a study with the possibility for helping the study participants directly often accepts more risk or intrusion of privacy than a study where study participants are not likely to be benefited directly from their involvement.

In the five papers constituting this thesis, we did not conduct any prospective research and therefore did not risk harming any study participants physically. Instead, the major ethical consideration of our papers lies in the intrusion of privacy these studies impair. As four of the five papers involves us accessing medical records of the study participants, this is an intrusion into their privacy. Especially delicate is the last paper since it investigates psychiatric disease and psychiatric disease often involve more stigma compared with other illnesses. To reduce the level of intrusion, only a limited number of researchers reviewed these medical records, and all information obtained were presented in such a manner that individual patients could not be identified in our publications.

Furthermore, the ethical approvals granted us access to the medical records without the consent of the study participants or their parents. This means that the study participants did not know that they were included in a study, nor that their medical records were being accessed. This merit some discussion since informed consent is one of the cornerstones of modern research. The reasoning behind our decision was that we were afraid that potential study participants could be harmed psychologically by us contacting them. When contacted, they would be reminded of this emotionally very difficult period in their lives. For many, having gone through a severe illness can cause a great amount of emotional stress. With time, these emotional scars heal. Most cases occurred more than a decade ago, and some study participants are not alive today. Reminding them or their living relatives of this period could be harmful and would therefore not be ethical. Considering this, we believe that the risk of tearing up old emotional scars outweigh the potential intrusion of privacy.

# Results

## Datasets and included cases

As described in the methods section, two different datasets were used in the five papers constituting this thesis.

In the dataset used in papers I and papers III-V, we collected cases at two occasions (Figure 5). Combined, a total of 1,143 cases were identified and reviewed, resulting in the complete dataset containing 104 validated cases of bacterial meningitis. All 104 validated cases fulfilled the ICD diagnosis criteria. Of these, 76 also had a positive cerebrospinal fluid culture whereas the remaining 28 were validated thanks to them fulfilled the clinical presentation criteria using the Bacterial Meningitis Score (156) (Table 2).

**Table 2. Cases of bacterial meningitis based on clinical presentation.**

<b>Cerebrospinal fluid findings available (No. = 24)</b>	<b>No.</b>
✗ Causative pathogen identified in cerebrospinal fluid using: <ul style="list-style-type: none"><li>- Polymerase chain reaction test</li><li>- Antigen test</li></ul>	5 6
✗ Visible bacteria in direct microscopy of cerebrospinal fluid	5
✗ Other findings consistent with bacterial meningitis <sup>1</sup>	8
<b>Cerebrospinal findings not available (No. = 4)</b>	<b>No.</b>
✗ Bulging fontanel <sup>2</sup>	2
✗ Neck stiffness <sup>2</sup>	1
✗ Other neurological findings consistent with bacterial meningitis <sup>2,3</sup>	1

In this table, the 28 validated cases of bacterial meningitis not having a positive cerebrospinal culture are presented in more detail.

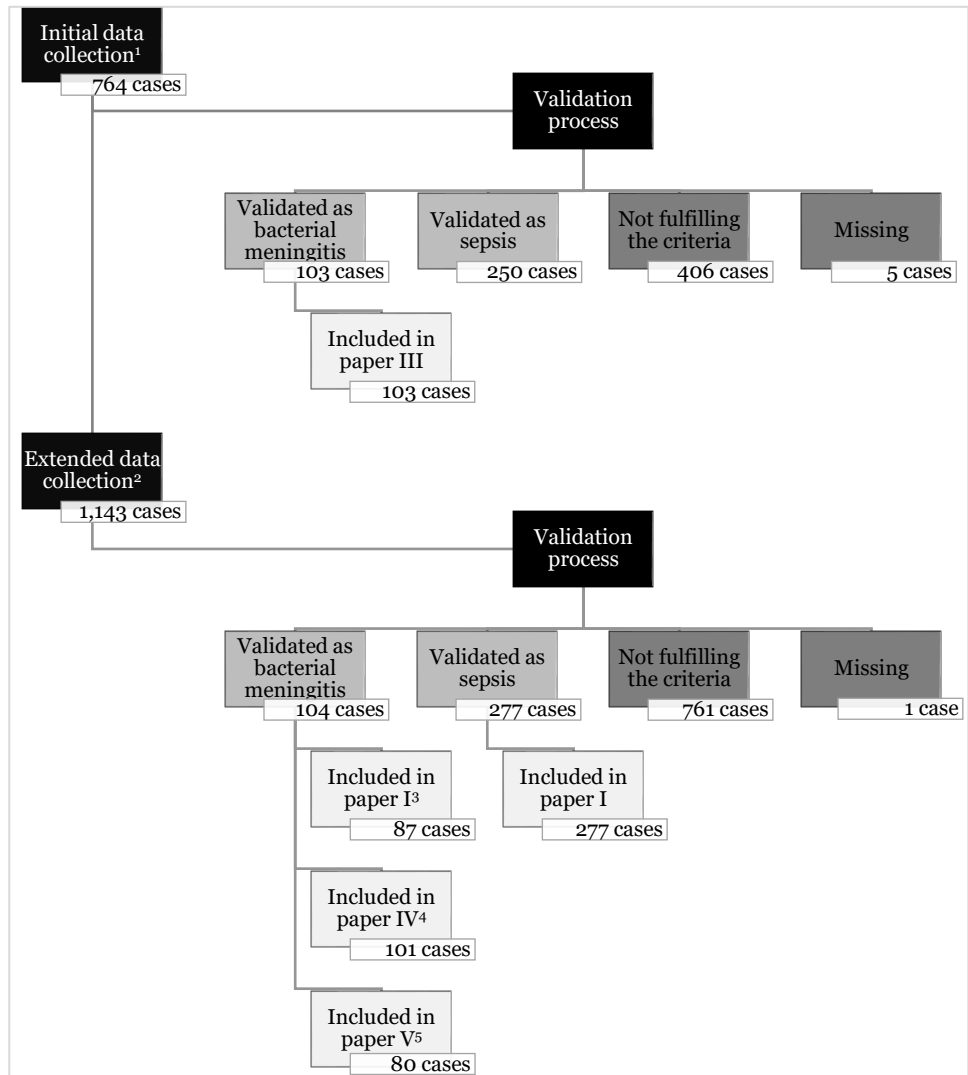
<sup>1</sup> These all had turbid appearance and biochemical analyses consistent with bacterial meningitis.

<sup>2</sup> These patients all fulfilled both the Bacterial Meningitis Score (119) and the clinical decision rule stated by Oostenbrink et al (122). They all had fever combined with elevated CRP and WBC count in blood ranging from 102-410 and 9.9-26.7, respectively.

<sup>3</sup> This included headache and abnormal neurological findings.

The dataset used for paper II included 374,234 individual cases having at least one correctly registered ICD diagnosis matching the inclusion criteria. This material included both children and adults. Also, the material included both bacterial and viral upper respiratory tract infections, as well as gastroenteritis used as comparison to identify and alterations in care-seeking patterns during the study period. Of all bacterial infections occurring in children under 18 years of age, 54,642 cases were upper respiratory tract infections, and 4,046 cases were lower respiratory tract infections.

**Figure 5. Case distribution for papers I and III-V.**



*In this figure, the distribution of cases for papers I and III-V are shown.*

<sup>1</sup> This only included data from the years 1986-2013.

<sup>2</sup> This included data from the years 1986-2015.

<sup>3</sup> Of the 104 validated cases, 17 cases were excluded due to the patient not residing in the Västerbotten Region. The remaining 87 cases were all included in this paper.

<sup>4</sup> Of the 104 validated cases, three cases were excluded due to the patient's medical records lacking information of the hospital stay and therefore not including the necessary information. The remaining 101 cases were all included in this paper.

<sup>5</sup> Of the 104 validated cases, four cases were excluded due to them being repeated episodes in the same child and seven cases were excluded due to the child dying during the hospital stay. In addition, 13 cases were excluded due to the child not residing in the Västerbotten Region. The remaining 80 cases were all included in this paper.

## Paper I

In this paper, we showed that incidence of bacterial meningitis declined in children aged one month to four years, whereas incidence in children aged five to 17 years remained stable at a low level during the entire 30-year study period. The most common causative pathogen was *H. influenzae* accounting for 47.1% of all cases, followed by *S. pneumoniae* and *N. meningitidis* at 29.9 and 8.7%, respectively. Other causative pathogens included *E. coli*, group A streptococci and group B streptococci.

Prior to introduction of general infant Hib vaccination in the Västerbotten Region, the mean annual incidence of all-cause bacterial meningitis was 37 (CI: 25-49) cases per 100,000 children and year during the period of 1986-1991. In the years thereafter, incidence significantly declined by 82.3% compared with the previous period, reaching a mean annual incidence of 6.6 (CI: 3.3-9.9) in the period of 1993-2008. This decline was predominantly due to a 95.3% significant decline in incidence of bacterial meningitis caused by *H. influenzae*. Following introduction of general infant pneumococcal vaccination in the Västerbotten Region, a further decline occurred for all-cause bacterial meningitis comparing with the previous period. This resulted in a mean annual incidence of 3.4 (CI: 0.0-7.3) cases per 100,000 children and year during the period of 2010-2015. This 48.0% reduction was mostly due to a 67.5% reduction noted for bacterial meningitis caused by *S. pneumoniae*.

In children aged five to 17 years, incidence of all-cause bacterial meningitis remained relatively stable during the entire study period. Initially, the mean annual incidence was 1.6 (CI: 0.0-3.2) cases per 100,000 children and year during the period of 1986-1991. A slight non-significant increase followed with the mean annual incidence reaching 1.8 (CI: 0.8-2.8) cases per 100,000 children and year during the period of 1993-2008 and finally 1.9 (CI: 0.0-3.7) cases per 100,000 children and year during the period of 2010-2015.

For sepsis, the year-to-year variation was greater compared with bacterial meningitis. Still, incidence of sepsis increased during the study period in both age groups; by a mean annual incidence increase of 0.7% ( $p = 0.44$ ) in children aged one month to four years and 13.4% ( $p < 0.01$ ) in children aged five to 17 years. This resulted in the last period of 2010-2015 having a mean annual incidence of sepsis of 33 (CI: 21-45) cases per 100,000 children and year in children aged one month to four years and of 18 (CI: 12-24) in children aged five to 17 years. Occurrence of sepsis caused by *H. influenzae* and by *S. pneumoniae* decreased during the study period. Hence, the net increase of sepsis was instead due to an increase of sepsis caused by several other pathogens, mostly occurring in children being treated for malignancies.

## **Paper II**

In the second paper, we noted that incidence of several bacterial respiratory tract infections decreases in the time-period following introduction of general infant pneumococcal vaccination in the Västerbotten Region. These declining incidences were mostly noted in the youngest children eligible for vaccination. However, reductions were also noted in other age groups.

For acute otitis media, significant reductions occurred both for all-cause acute otitis media and for acute otitis media having an ICD diagnosis specifying it as a bacterial infection. In the pre-vaccination period of 2005-2008, there was a trend of increasing incidence of all-cause acute otitis media in all age groups besides in elderly aged 65 years or older, and increasing incidence of acute otitis media having an ICD diagnosis specifying it as a bacterial infection in all age groups. This trend was reversed in both cases, starting in 2009 in children aged 0 to four years, in 2011 in children aged five to 17 years and in 2012-2013 in adults and elderly. In children, we noted that incidence of all-cause acute otitis media was significantly reduced when comparing the pre-vaccination period of 2005-2008 with the last included year post-vaccination of 2014. In children aged 0 to four years, incidence was reduced by 41.5% ( $p < 0.01$ ), declining from 275 (CI: 272-279) to 161 (CI: 155-167) cases per 1,000 children and year. Similarly, in children aged five years to 17 years, incidence was reduced by 20.9% ( $p < 0.01$ ), from 51 (CI: 50-52) to 40 (CI: 38-42) cases per 1,000 children and year. Reductions were observed in adults and elderly but were only statistically significant for all-cause acute otitis media in adults aged 40-64 years and elderly aged 65 years or more.

When looking specifically at acute otitis media having an ICD diagnosis specifying it as a bacterial infection, reductions in children aged 0 to four years and children aged five to 17 years were 48.1% ( $p < 0.01$ ) and 22.4% ( $p < 0.01$ ), respectively.

For sinusitis, incidences were stable in all age groups in the pre-vaccination period of 2005-2008. When comparing this period with the last included year post-vaccination, 2014, incidence declined from 1.1 (CI: 0.8-1.3) to 0.2 (CI: 0.0-0.4) cases per 1,000 children and year in children aged 0 to four years and from 3.4 (CI: 3.2-3.7) to 2.5 (CI: 2.0-3.0) in children aged five to 17 years. This was equivalent to a reduction of 80.7% ( $p < 0.01$ ) and 28.3% ( $p < 0.01$ ), respectively. Statistically significant reductions were also noted in adults aged 18-39 years and 40-64 years.

For pneumonia, a statistically significant decrease was noted only in children aged 0 to four years. Here, incidence decreased by 28.6% ( $p < 0.01$ ) when comparing the pre-vaccination period of 2005-2008 with the last included year post-vaccination, 2014, from 15 (CI: 14-16) to 10 (CI: 8.8-12) cases per 1,000 children and year. Incidence remained stable in children aged five to 17 years varying around five cases per 1,000 children and year whereas incidence increased in adults and elderly. The latter was explained by a pre-existing trend already occurring in the pre-vaccination period.

Finally, when investigating incidence of gastroenteritis, no sign of altered care-seeking patterns was observed.

### **Paper III**

In the third paper, we noted several statistically significant differences when clinical presentation of bacterial meningitis in children aged one month to four years were compared with children aged five to 17 years. Compared with the older children, children aged one month to four years more often had an altered mental status (71 vs. 46%,  $p = 0.02$ ) and had a tendency to present with seizures (15 vs. 4%,  $p = 0.12$ ) and a lower consciousness measured in the reaction level scale (2.1 vs 1.7,  $p = 0.09$ ). At the same time, younger children also tended to more often presented with anorexia (36 vs. 18%,  $p = 0.08$ ). Children aged one month to four years were also less likely presented with symptoms specific to the central nervous system such as headache (5 vs. 71%,  $p < 0.01$ ), photophobia (1 vs. 21%,  $p < 0.01$ ), vertigo (0 vs. 7%,  $p = 0.02$ ), increased pain sensitivity (3 vs. 25%,  $p < 0.01$ ) and neck stiffness (42 vs. 68%,  $p = 0.02$ ), compared with children aged five to 17 years.

We also tested the sensitivity of several clinical decision rules for identifying bacterial meningitis in children (Table 3). Only the two clinical decision rules that include results of a lumbar puncture, the Bacterial Meningitis Score (156) and the Meningitest (156) had a sensitivity of 100% in both age groups.

For the classical triad of bacterial meningitis, 35% of children aged one month to four years and 32% of children aged five to 17 years presented with all three signs, and 74% and 75% of children, respectively, had at least two of the three signs. In the clinical decision rules not including a lumbar puncture, the complicated clinical decision rule by Oostenbrink et. al (159) relying on a mathematical formula performed well, with a sensitivity of 90% in children aged one month to four years and 96% in children aged five to 17 years. The clinical decision rule by Weber et. al. (160) was found to have a sensitivity of 82% in both children aged one month to four years and in children aged five to 17 years.

**Table 3. Clinical decision rules for identifying bacterial meningitis.**

<b>Clinical decision rules</b>	<b>Criteria</b>
<p><b>Bacterial Meningitis Score (156)</b>  <i>Used to distinguish between bacterial meningitis and aseptic meningitis. Positive if the child fulfils at least one of the listed criteria.</i></p>	<ul style="list-style-type: none"> <li>✖ Seizures</li> <li>✖ Blood neutrophil count <math>\geq 10^9/L</math></li> <li>✖ Cerebrospinal fluid with either;               <ul style="list-style-type: none"> <li>- Positive gram stain, or</li> <li>- Protein <math>\geq 800</math> mg/L, or</li> <li>- Neutrophil count <math>\geq 1,000/\mu L</math></li> </ul> </li> </ul>
<p><b>Meningitest (156)</b>  <i>Used to distinguish between bacterial meningitis and aseptic meningitis. Positive if the child fulfils at least one of the listed criteria.</i></p>	<ul style="list-style-type: none"> <li>✖ Seizures</li> <li>✖ Purpura</li> <li>✖ Toxic appearance</li> <li>✖ Procalcitonin <math>\geq 0.5</math> ng/mL<sup>1</sup></li> <li>✖ Cerebrospinal fluid with either;               <ul style="list-style-type: none"> <li>- Positive gram stain, or</li> <li>- Protein <math>\geq 500</math> mg/L</li> </ul> </li> </ul>
<p><b>Classical triad (1-2)</b>  <i>Positive if the child fulfils all three listed criteria.</i></p>	<ul style="list-style-type: none"> <li>✖ Fever</li> <li>✖ Altered mental status</li> <li>✖ Neck stiffness</li> </ul>
<p><b>Oostenbrink et. al. (159)</b>  <i>The total score is calculated by adding the points of each criteria that the child fulfils and is positive if the child has a total score of 9.5 points or higher.</i></p>	<ul style="list-style-type: none"> <li>✖ Duration of symptoms in days (1 point per day)</li> <li>✖ Vomiting (2 points)</li> <li>✖ Meningeal irritation (7.5 points)</li> <li>✖ Cyanosis (6.5 points)</li> <li>✖ Petechiae (4 points)</li> <li>✖ Disturbed consciousness (8 points)</li> <li>✖ CRP (0.1 point per 10 mg/L)</li> </ul>
<p><b>Weber et. al. (160)</b>  <i>Positive if the child fulfils at least one of the listed criteria.</i></p>	<ul style="list-style-type: none"> <li>✖ Seizures</li> <li>✖ Lethargy or unconsciousness</li> <li>✖ Stiff neck</li> </ul>
<p><b>Berkley et. al. (161)</b>  <i>Positive if the child has fever and also fulfils at least one of the listed criteria.</i></p>	<ul style="list-style-type: none"> <li>✖ Bulging fontanel</li> <li>✖ Neck stiffness</li> <li>✖ Cyanosis</li> <li>✖ Seizures</li> <li>✖ Impaired consciousness</li> </ul>
<p><b>Traffic Light System Guideline (162)</b>  <i>If the child has a minor impairment<sup>2</sup> in at least one of the listed criteria, the child is graded into the category "Intermediate risk" whereas if the impairment is severe<sup>2</sup> it is graded into the category "High risk".</i></p>	<ul style="list-style-type: none"> <li>✖ Skin, lip or tung discoloration</li> <li>✖ Impaired activity</li> <li>✖ Impaired respiratory function</li> <li>✖ Impaired circulation or dehydration</li> <li>✖ Other warning symptoms<sup>3</sup></li> </ul>

In this table, the criteria for the clinical decision rules aimed at identifying bacterial meningitis in children are presented.

<sup>1</sup> We did not have any information on procalcitonin level in our study material. However, all cases were positive even without this criteria being considered.

<sup>2</sup> The Traffic Light System specifies what is considered as either a minor impairment or a severe impairment for each criteria.

<sup>3</sup> This category included high fever in children aged six months or less, fever for five days or more, rigors, swelling of a limb or joint, not using an extremity, non-blanching rash, and neurological symptoms.

The clinical decision rule by Berkley et. al. (161) had a sensitivity of 81% for children aged one month to four years and 79% for children aged five to 17 years. Finally, the 2013 edition of the Traffic Light System by the UK National Institute for Health and Care Excellence (NICE) (162) for predicting risk of severe infections in children under five years of age were evaluated. This grades children into either low, intermediate, or high risk of a severe infection. Here, 76 of the 77 eligible children were graded as having high risk, equivalent to a 99% sensitivity.

## **Paper IV**

In the fourth paper, we developed a predictive score called the Meningitis Swedish Survival Score (MeningiSSS) for children with bacterial meningitis aimed at identifying children at high risk of complications and need of invasive procedures. When comparing the MeningiSSS with four previously existing predictive scores (Table 1), the MeningiSSS was equal or better than these predictive scores in most analyses.

Most importantly, the MeningiSSS had the best result when testing the predictive scores ability to identify children later having to undergo invasive procedures to manage the intracerebral pressure. In the ROC analysis, the MeningiSSS (AUC = 0.90) was graded into the category “excellent”, the Simple Luanda Scale (AUC= 0.68) and the Niklasson Scale (AUC = 0.60) were both graded as “poor”, and the Aronin Scale (AUC = 0.59) and the Herson-Todd Scale (AUC = 0.58) were graded as “failed”. At their respective cut-off levels, the MeningiSSS had a sensitivity of 100% compare with the other predictive scales ranging from 0-56%.

In predicting need of intensive care during the hospital stay, the MeningiSSS was graded as “fair”. At this task, the MeningiSSS with an AUC of 0.79 and a sensitivity of 56% at its cut-off level performed better compared with the other predictive scores ranging from 0.75-0.65 in AUC and 9-42% in sensitivity.

At the task of predicting death, the MeningiSSS (AUC = 0.70) together with the Herson–Todd Scale (AUC = 0.79), and the Niklasson Scale (AUC = 0.72) were graded as “fair”, the Simple Luanda Scale (AUC = 0.63) as “poor” and the Aronin Scale (AUC = 0.53) as “failed” in the ROC analysis. Here, the MeningiSSS had the highest sensitivity at 75% compared with the other predictive scales having a sensitivity of 0-40%.

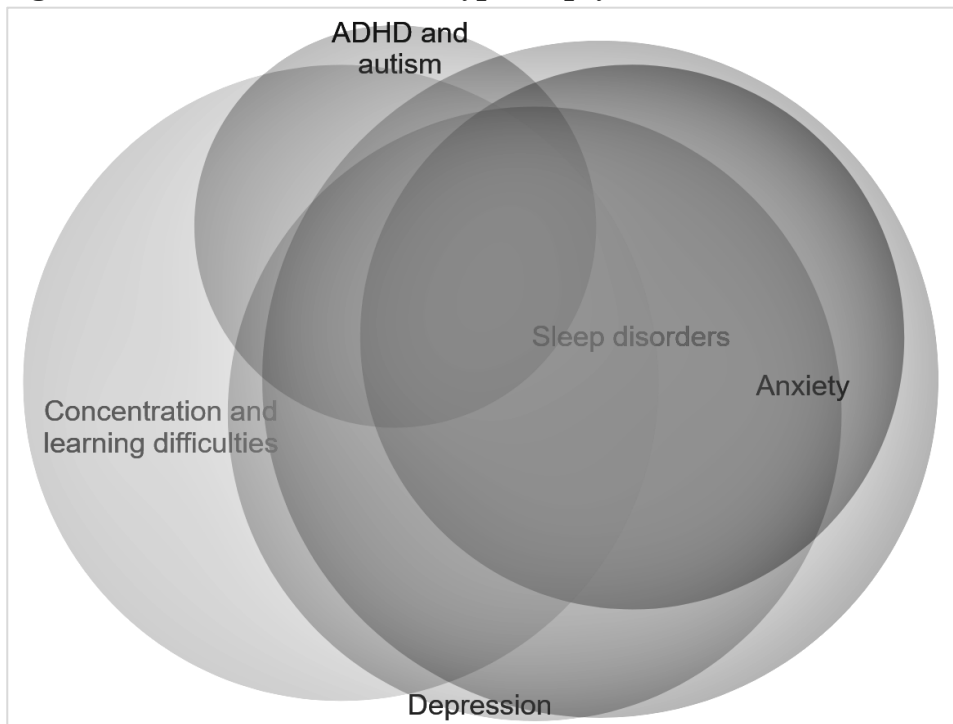
None of the predictive scores performed well at identifying children later suffering from intracerebral injury or other types of complications during the hospital. At this task, all were graded as either “poor” or “failed”.

## Paper V

In the final paper, we studied children having survived bacterial meningitis to identify possible long-term disabilities. During the observational period spanning a mean duration of 19 years and 2 months, 56% (CI: 45-67) of patients contracted a permanent disability that could not be attributed to pre-existing illnesses. In addition, another 16% (CI: 9-25) experienced transient disabilities.

Psychiatric disease was diagnosed in 30% (CI: 21-41) of patients during the observational period and another 5% (CI: 2-13) had ongoing investigations for symptoms of psychiatric disease at the time when the data was collected. Combined, this makes psychiatric disease the most common disability following childhood bacterial meningitis. The most common psychiatric disease was anxiety disorders noted in 23% (CI: 15-34), followed by depression noted in 19% (CI: 11-29), sleep disorders noted in 15% (CI: 8-25), and neurodevelopmental disorders noted in 8% (CI: 4-16) of whom Attention deficit hyperactivity disorder (ADHD) accounted for 7% (CI: 3-14). Notably, in many cases the patient had more than one psychiatric disability (Figure 6).

**Figure 6. The five most common types of psychiatric disabilities.**



*In this figure, the five most common psychiatric disabilities are shown using a Venn diagram, illustrating the degree of overlap.*

Concentration or learning disabilities were present in 21% (CI: 13-31) of patients, resulting in 8% (4-16) of children needing special education. Other commonly occurring disabilities included hearing impairments noted in 36% (CI: 25-48) of patients without previous hearing impairments undergoing a hearing test, equivalent to 30% (CI: 20-40) of the entire group of patients without previous hearing impairments. In addition, 23% (CI: 15-34) of patients developed permanent neurological deficits and 11% (CI: 5-19) developed epilepsy.

Whereas neurological deficits and hearing impairments were mostly detected during the scheduled follow-up, psychiatric disabilities were not. Furthermore, psychiatric disabilities were not discovered during the regular child health visits either. Child health records were obtained for 46 children still undergoing regular child health visits at the time they had bacterial meningitis. Of these, 16 children later developed psychiatric disease. In two out of these 16 children, disabilities were known at discharge or detected early during the scheduled follow-up at the paediatric clinic. Of the remaining 14 children later developing psychiatric disease, only two were suspected of having a delayed general development during the regular child health visits. No action was taken in neither case, despite both children failing several developmental tests.

The duration from discharge until disabilities were first brought to the attention of a health care provider differed when comparing different permanent disabilities with each other. The longest duration was seen for psychiatric disabilities with a mean duration of 14 years (CI: 11:1-16:11). This was followed by concentration or learning disabilities at 12 years and 3 months (CI: 8:1-16:5), epilepsy at 7 years and 6 months (CI: 0:11-15:0), other neurological deficits at 1 year and 4 months (CI: 0:8-2:0), and hearing impairments at 10 months (CI: 4-22) after discharge.

Although some clinical findings were significantly associated with the child later developing certain permanent disabilities, these associations were not strong enough to predict which child would develop permanent disabilities.

# Discussion

## Can vaccinations prevent bacterial meningitis?

In papers I and II, we showed that introduction of general infant Hib vaccination in the Västerbotten Region was followed by a reduction of bacterial meningitis and sepsis in children caused by *H. influenzae*. Likewise, when general infant pneumococcal vaccination was introduced in the region, incidence of bacterial meningitis and sepsis in children due to this pathogen were also reduced, as were incidence of several bacterial respiratory tract infections.

The effects of general infant Hib or pneumococcal vaccinations has been studied extensively. Vast evidence support that these actions are effective in protecting children against bacterial meningitis caused by these pathogens (8-10, 12, 128-132). Previous publications also support the claim that these vaccinations provide protection against sepsis and less severe infections including many respiratory tract infections (128-132, 225-234). In this aspect, our results shown in papers I and II are not surprising. However, there are aspects of our findings that are especially interesting and merit further discussion: the long-term impacts of vaccinations shown in paper I and how the simultaneous reduction of respiratory tract infections shown in paper II relate to reduced occurrence of bacterial meningitis.

*What are the long-term impacts of general infant Hib and pneumococcal vaccinations on incidence of bacterial meningitis in children?*

In paper I, we noted a marked decline in bacterial meningitis caused by *H. influenzae* by 95.3% in children aged one month to four years shortly following introduction of general infant Hib vaccination in the Västerbotten Region. This reduction is similar to those reported elsewhere (10, 12, 128-130). Additionally, we noted an increase of bacterial meningitis caused by *S. pneumoniae* in the same period. This has previously been reported for bacterial meningitis and invasive pneumococcal disease in some locations (131, 235-236), whereas in others no association have been noted (237-238). Although causality has never been proven, pre-clinical studies have noted an antagonistic relationship with *H. influenzae* stimulating the host's immune system response against *S. pneumoniae* when both were co-colonizing the nasopharyngeal epithelium (239-240).

Vaccinations have been shown to reduce nasopharyngeal carriage of the specific pathogen being targeted, resulting in a shift of the nasopharyngeal bacterial flora with other pathogens expanding their colonization (86-87, 132, 225-226, 241). This phenomenon is perhaps best exemplified by the serotype replacement often occurring when a low-valent pneumococcal vaccine is used for pneumococcal vaccination. Here, reduction in serotypes included in the specific vaccine are followed by an increase in non-vaccine serotypes (8, 87, 242-245). On the other hand, bacteria can sometimes be in symbiosis with each other. This relationship can either be mutually beneficial or so that one type of bacteria facilitates or enables another type of bacteria to colonize the same location, as seen in polymicrobial biofilm formations or co-infections with *S. pneumoniae* and *M. catarrhalis*. Here, a reduction in carriage of one type of bacteria will result in reduced carriage of the other type as well (246-248). As these examples show, the overall impact on occurrence of a specific type of infection such as bacterial meningitis does not only depend on the vaccine's ability to elicit an immune response resulting in immunity, or how well it reduces nasopharyngeal carriage of the intended target. Rather, the vaccine's impact on the composition of the bacterial flora is also an important factor to consider (86-87, 132, 225-226, 241).

The net effect of an altered composition of the normal bacterial flora can be either positive or negative depending on what bacteria utilize the opportunity and increase in nasopharyngeal carriage. Bacteria constituting the normal flora is often those best adapted to colonize this location. However, this does not imply that these bacteria necessarily are also most adept at causing infections. Despite the fact that some of the bacteria included in the normal flora are among those responsible for causing infections in humans, the normal bacterial flora is often considered a protection against more aggressive pathogens (249-252). Therefore, there is a risk that the net effect may be negative if a shift in normal bacterial flora results in an increase in carriage of more invasive pathogens (253).

In paper I, the 95.3% decrease in bacterial meningitis in children aged one month to four years cause by *H. influenzae* following introduction of general infant Hib vaccination only resulted in a total reduction of bacterial meningitis in the same age group by 82.3% due to an increase of bacterial meningitis caused by *S. pneumoniae*. Considering the discussion above, it is not unlikely that general infant Hib vaccination may have increased nasopharyngeal carriage of *S. pneumoniae* resulting in increased bacterial meningitis caused by this pathogen.

Following introduction of general infant pneumococcal vaccination in the region, we noted a decline in bacterial meningitis caused by *S. pneumoniae* by 67.5% in children aged one month to four years. Similar reductions have also been reported in multiple studies before (8-10, 131-132). Contrary to what happened when general infant Hib vaccination was introduced, we noted no increase in bacterial meningitis caused by other pathogens, nor did we note any resurgence of *H. influenzae*. Furthermore, incidence of bacterial meningitis caused by *N. meningitidis* remained at a low level not requiring further action to be taken at this time.

In paper I, we did not perform serotyping of pneumococcal specimens. This is unfortunate since it would have been desirable to determine the degree of serotype replacement as well. Studies have reported serotype replacements occurring within just a few years of introducing pneumococcal vaccination, thereby resulting in a diminished reduction in incidence of pneumococcal infections (8, 87, 242-244). There are examples where serotype replacement has even resulted in the net effect of pneumococcal vaccinations being close to zero (245). Since this is a widespread problem, it is likely that some degree of serotype replacement has occurred following introduction of general infant pneumococcal vaccination in the Västerbotten Region as well. Given the low incidence of pneumococcal meningitis in vaccinated children in our material, one can speculate that the problem might not be of equal magnitude as seen in other regions. However, without studying serotype distribution of pneumococcal specimens specifically, it is not possible to estimate the extent of serotype replacement. Also, without this information, one cannot give recommendations regarding whether it is necessary to switch to a higher valent vaccine or not.

Combined, these findings presented in paper I are encouraging and speaks to a long-term protective effect occurring in younger children, one of the major risk groups for severe infections (65). These findings also demonstrate that vaccinations can be as effective in preventing childhood bacterial meningitis in Arctic regions as elsewhere. This is important since many Arctic regions have substantially higher occurrence of bacterial meningitis and other severe infections in children compared with other regions. Additionally, effects of vaccinations have been lesser in some Arctic regions compared with more temperate areas (139-147). Therefore, our results showing reductions comparable to those occurring in more temperate areas are promising.

*Can reductions of respiratory tract infections be a means of preventing bacterial meningitis in children?*

There is a correlation between upper respiratory tract infections and bacterial meningitis (4, 28-43). This is likely due to the close proximity to the subarachnoid space (13-15) and the relatively weak barrier against invading pathogens compared to elsewhere (13, 16-23). Preventing upper respiratory tract infections is therefore an important key in preventing cases of bacterial meningitis.

In paper II, we noted significant reductions of acute otitis media, bacterial sinusitis, and pneumonia in children in the Västerbotten Region following general infant pneumococcal vaccination. As we used ICD diagnoses to identify these respiratory tract infections, there is always a risk of misdiagnosis of viral infections as bacterial or reclassification occurring during the study period (254). However, since we did not note any compensatory increase in respiratory tract infections given an ICD diagnosis of viral infections, we do not believe this to be the case in our paper.

Upper respiratory tract infection are common primary foci in cases of bacterial meningitis. Studies have shown that 20-34% of all cases of bacterial meningitis are preceded by an upper respiratory tract infection, most commonly acute otitis media or sinusitis (28, 34, 37-38).

Although the risk of complications in the individual child having an upper respiratory tract infection is marginal (255-257), the sheer number of upper respiratory infections occurring in children each year means that even a minimal risk at an individual level can have significant impact on incidence at a population level (255-256). Acute otitis media is the most common bacterial infection in children and 50-85% of children have at least one episode of acute otitis media during their first years of life (255). In Sweden, 200,000 cases of acute otitis media occur each year, mostly in younger children (256). Although the complication rate is low, the risk of bacterial meningitis when having acute otitis media has been estimated to be 0.002% (255). For bacterial sinusitis, it has been noted that 0.7% of cases of sinusitis being admitted to the hospital also had bacterial meningitis (257).

When considering that all three historically predominant causative pathogens for bacterial meningitis in children colonize the epithelium of the upper respiratory tract (27), and that those bacteria colonizing the upper respiratory tract often are those that cause infections here (27), impact on nasopharyngeal carriage by vaccinations becomes highly interesting. As previously discussed, vaccinations have been shown to reduce nasopharyngeal carriage of important pathogens (86-87, 132, 225-226, 241). As seen in paper II and elsewhere, reduced incidence of acute otitis media and bacterial sinusitis have also been noted following general infant pneumococcal vaccination (230-233). It is plausible that reduced occurrence of bacterial upper respiratory tract infections could result in a reduction in bacterial meningitis as well. However, no previous study has investigated incidence changes in upper respiratory tract infections and bacterial meningitis related to general infant pneumococcal vaccination simultaneously. Therefore, our findings showing reduction of bacterial respiratory tract infections and bacterial meningitis in children in the same region at the same time is highly interesting.

Pneumonia, being a lower respiratory tract infection, does not involve risk of direct transmission to the central nervous system. However, bacteraemia is common in pneumonia allowing for the possibility of haematogenous spread instead (258-260). Pneumonia has also been shown to be a common primary focus in cases of bacterial meningitis (261-262). In paper II, we noted a decrease of pneumonia in children aged 0 to four years by 28.6%, but no significant reductions in other age groups. A large nation-wide register study conducted in Sweden have shown reductions in children under two years of age by 36% and aged two to four years by 20%, results very similar to our findings (263). However, in children aged five to 17 years, the national study reported a significant decrease by 16% (263), compared with our study only noting a non-significant decrease by 1.6%. This difference may be due to several factors. Our study was limited to one region whereas this was a national study. Given the previous discussion regarding less effects noted in some Arctic regions following vaccinations (139-147), regional differences need to be considered and may at least partially explain this difference. Furthermore, there are several differences in the methods used. Most importantly, the national study uses a register that only includes hospitalised patients, whereas the register used by us includes both hospitalised patients and patients receiving outpatient care. Furthermore, although trying to compensate for changes in admission rates, it is possible that reduced hospital bed capacity may be partially responsible for explaining some of the difference since this does not impact outpatient care to the same extent. Finally, there are some differences in what ICD diagnoses were used, mainly, they also included the ICD diagnosis codes J10-12 representing influenzae and viral pneumonia, whereas we reported those separately.

## **How can clinical practice be improved?**

Clinical practice is seldom improved by a single major advancement, rather by a multitude of minor achievements. In papers III to V, we have described just that; findings that in themselves are not ground-breaking but if combined and implemented could possibly help improve clinical practice. In these papers, we described different means of meeting the several difficult challenges of treating children with bacterial meningitis.

### *How can correct identification of bacterial meningitis in children be improved?*

First, we addressed the challenge presented when the child seeks medical attention for their symptoms or complaints. Each year, several children with severe infections are not receiving correct treatment since their condition is mistaken for a less severe infection (264). The challenge of separating bacterial and viral infections apart in children presenting with complaints of fever can be difficult (265-267). Due to the severity of the condition, there is no room for error in the task of identifying children having bacterial meningitis. If undetected, bacterial meningitis can progress rapidly and in short time result in severe disabilities or death (1-2).

In paper III, we reviewed clinical presentation of bacterial meningitis in children and identified several differences when comparing children aged one month to four years with older children. Most importantly, it appears that younger children more often are severely ill at admission, and also more often presents with symptoms less specific to the central nervous system. This is unlike older children that typically present with well-known symptoms such as headache and neck stiffness. Similar findings have been reported in other studies (150-151). This difference is important to consider when consulting on younger children at the emergency department with complaints of fever. Potentially, these less specific symptoms could increase the risk of misdiagnosis, as seen in other conditions when clinical presentation differ from what is described in textbooks (268-270). This claim is supported by studies showing that incorrect diagnoses are generally more common in younger children (270-272).

To reduce the risk of misdiagnosis, several clinical decision rules have been suggested to aid in the correct identification of bacterial meningitis and other severe infections in children (156, 159-162). In our attempts to validate clinical decision rules for identifying bacterial meningitis in children, we unfortunately noted that none reached 100% sensitivity. Furthermore, in many studies investigating identification of severe infections in children, doctor's or parents' concern were among the strongest predictive factors (273-276). Although clinical decision rules can be an aid, one must always keep in mind that these are not perfect and therefore also trust in one's own clinical experience and the concern of parents.

*Can risk assessment improve clinical practice by aiding in difficult treatment decisions during the hospital stay in children with bacterial meningitis?*

When having correctly diagnosed the child with bacterial meningitis comes the next set of challenges. Initial treatment of bacterial meningitis, in children as well as in adults, are directed by clinical guidelines (167-172). These provide support regarding choice of antibiotic regime and use of corticosteroids or antiviral treatment (167-172). However, for some treatment decisions, they do not provide sufficient support. One of the most difficult decisions in the treatment of bacterial meningitis is to decide if the patient needs an invasive procedure to manage the intracerebral pressure (179-186). When needed, this procedure must be performed within a few hours otherwise there is high risk of severe neurological disabilities or death due to intracerebral neuronal injury caused by a rapidly increasing intracerebral pressure (174-186). However, as discussed in the introduction, this procedure is not without complications and often require transfer to another hospital.

In paper IV, we tried to address this challenge by developing a predictive score called the Meningitis Swedish Survival Score (MeningiSSS) based on previously identified individual risk factors for adverse outcome. When comparing this with other previously existing predictive score (202-204), it had better results at most predictive tasks. Most importantly, it was able to identify all children that later had to undergo invasive procedures to manage the intracerebral pressure. The MeningiSSS could therefore possibly be used in clinical practice to identify these children already at admission to the hospital. Our data do not support placement of such a device based on the MeningiSSS indicating high risk of it being needed, rather, to plan ahead so that the procedure can be performed hastily if required later. This could for example involve transfer of the patient to another hospital with neurosurgical capacity.

Transporting patients between hospitals always involve some degree of risk and the advantages of transfer must therefore surpass the risk (187-188). Here, the MeningiSSS could have the potential to identify such cases. However, before considering implementing the MeningiSSS into clinical practice, external validation of the MeningiSSS using another patient cohort needs to be undertaken to prove its predictive capability. Provided this is successful, the MeningiSSS could aid the clinician when deciding upon difficult treatment decisions in children with bacterial meningitis.

*How to address the risk of long-term disabilities in children with bacterial meningitis?*

Permanent disabilities affect a large proportion of surviving children. In previous literature, up to half of patients are reported to suffer from permanent disabilities following bacterial meningitis in childhood. These mostly involve hearing impairments, epilepsy, and neurological disabilities (190-195). Although we noted a slightly higher occurrence of epilepsy, possibly due to a longer observational period, our result in paper V are mostly consistent with these findings.

Recently, focus has shifted more towards less noticeable disabilities as described in the introduction (190-191, 196-200). In paper V, we noted a high occurrence of several psychiatric diagnoses in patients having had bacterial meningitis as a child. Since we did not have a comparison group in this paper, we need to instead compare our findings with the occurrence of psychiatric disease in the general population. Here, it is important to note that the reported occurrence of psychiatric disease varies in between different countries, likely due to differences in stigma associated with psychiatric disease (277-278). Therefore, it is most accurate to compare our findings with studies of psychiatric disease conducted in Sweden.

In paper V, we noted that 30-35% of patients suffered from some type of psychiatric disease during the observational period. This is considerably higher than in the general population in Sweden (279-282). As the comparison studies mostly investigate occurrence of psychiatric disease in the adult population, it is important to consider the age distribution within our study population. At the end of the observational period, the median age in our study was 29 years, ranging from two to 44 years of age, with 71% being 18 years or older. Hence, using data from the adult population in Sweden is not an unjust comparison either.

In a large questionnaire study conducted in two Swedish regions, the overall rate of self-reported symptoms of mental disorders including harmful alcohol use were 13-20% in persons aged 20-64 years and 17-26% in persons aged 20-34 years (279). The Västerbotten Region where our study was conducted is a mainly rural region. Notably, rates were generally lower in the rural region included in the questionnaire study. Here, only 13-15% of persons aged 20-64 years and 17-22% of persons aged 20-34 years reported symptoms of mental disorders including harmful alcohol use (279). When comparing our results in paper V with this study, the differences in study methods are important to consider. Being a questionnaire study, it is likely to overestimate the prevalence of psychiatric disease. Questionnaire studies are prone to response bias whereby persons experiencing symptoms are more likely to respond than those that are not (283). The response rate in this study was only 52%. This means that a considerable proportion decided not to respond allowing for a high degree of response bias. Furthermore, the questionnaire study did not define psychiatric disease using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria nor were participants assessed by a physician. Therefore, patients with symptoms not fulfilling the criteria for psychiatric disease may also have been included into the statistics. The possible impact of this is apparent when considering that 10-47% of the participants reporting symptoms of mental disorders including harmful alcohol use in the questionnaire study had not been into contact with any healthcare facility for their concerns. Finally, whereas we studied the accumulated occurrence over a longer period, this study uses a point-prevalence design reporting occurrence during the last year. Generally, this study design would result in a lower occurrence compared to our study design. However, as most patients with psychiatric disease in our study appeared to have permanent disabilities, with 86% of these patients still being in contact with a psychiatric clinic at the end of the observational period, this should reduce the impact of difference in study design.

A register study including a cohort of more than five million adults in Sweden investigated accumulated occurrence of psychiatric disease during a period of eight to 17 years, depending on region (280). Here, 9.9% of participants had been in contact with a primary healthcare clinic for anxiety disorders and 12.4% for depression. In addition, 0.5% had received the diagnosis of ADHD (280). The corresponding rates in our study were 23% (CI: 15-34), 19% (CI: 11-29) and 7% (CI: 3-14), respectively. As this register study also used accumulated occurrence over a longer period, this study is more like ours in this aspect. However, this study uses a register based on primary healthcare. Therefore, it is likely to also include patients with less severe conditions than in our study. This is exemplified by almost all patients in our study having received their diagnosis by a psychiatric clinic, whereas only one in five patients in the register study had any contact with a psychiatric clinic.

In addition to the previously discussed study reporting an occurrence of ADHD by 0.5% in the adult population in Sweden (280), two other recent studies have investigated occurrence of ADHD in Sweden (281-282). Both these reported a lower occurrence compared with the 7% (CI: 3-14) occurrence of ADHD noted in our patient cohort. In the first population-based cohort study, 27,092 children aged 12 year were included. Here, a combination of diagnosis registers and parental questionnaires were employed to assess occurrence of ADHD (281). Using this method, the occurrence of ADHD was estimated to be 2% in these children (281). Next, a nation-wide register study included all patients with an ICD diagnosis of ADHD in Sweden during 2007-2011 (282). In total, this study identified 71,127 patients with ADHD resulting in a prevalence of 0.48% for the entire population (282). As both these studies are based on ICD diagnoses and comprehensive registers, the reported prevalence of ADHD would be comparable with our findings to a large extent.

Finally, we can compare our results with official population data using the openly accessible database provided by the National Board of Health and Welfare contain information on registered ICD diagnoses in the specialised health care in Sweden (284). This database covers the last ten years of the observational period used in paper V. For the Västerbotten Region, the mean occurrence of having a registered ICD diagnosis of psychiatric disease (F00-F99) or ADHD (F90) were 3.4% and 0.6% during this period, respectively. In children aged 0 to 14 years, the corresponding occurrence was 1.7% and 1.0% whereas in persons aged 15 to 29 years it was 5.4% and 1.6%, respectively.

When considering the diversity of psychiatric disabilities noted in this paper, it does not appear as if these children contract a specific localised neuronal injury resulting in a specific type of psychiatric disease. Rather, these children display a variety of psychiatric disabilities including depression and anxiety as well as concentration or learning disabilities. Furthermore, there were a considerable overlap and most children with psychiatric disabilities had more than one type of disability. This would suggest a general vulnerability as seen in post-concussion syndrome following repeated concussions due to head trauma (285-286) or exemplified by the general behavioural changes and other long-term mental health issues noted in one in ten children following cerebral malaria (287).

During childhood, the brain is constantly evolving with new abilities being learned in a rapid pace and therefore more vulnerable to injury (288-290). Although children have a high plasticity in their central nervous system (291-292), it is apparent that it is not fully able to compensate the injuries sustained by bacterial meningitis in childhood.

The single most important finding in paper V was perhaps how long the time-period was from when the child had bacterial meningitis and until it was diagnosed with either a psychiatric disease or having concentration or learning disabilities. This time-period spanned, in mean, 14 years for psychiatric disease and 12 years and 3 months for concentration or learning disabilities. Based solely on our findings, we cannot determine whether these disabilities were present all along and remained undiscovered or if they debuted later. Furthermore, we cannot determine for how long these patients suffered silently until they decided to seek medical attention. As bacterial meningitis is an acute illness rather than a condition with an ongoing destructive process (1-2), it is plausible that these disabilities were present all along and that they were discovered first when the child could not cope with increasing demands. From previous studies, we know that psychiatric disabilities often remain undiagnosed and thereby go untreated for several years (293-296). Whilst medications and other interventions can improve the situation for many patients suffering from psychiatric disease, undiagnosed psychiatric disabilities have a severe negative impact on quality of life, school results, work, and social life (294-300).

When considering how common psychiatric disabilities were following childhood bacterial meningitis, the predictive difficulties, long time-period until diagnosis and the devastating effects of undetected illness, it becomes apparent that clinical practice needs to change. Today, no major clinical guideline recommends routine psychiatric or neuropsychiatric follow-up in children having had bacterial meningitis (167-172). In light of our findings discussed earlier, these need to be revised to include a long-term strategy for detecting psychiatric disabilities to reduce potential suffering for the affected child.

### *What are the limitations of our findings?*

As for all studies, there are limitations that impact the interpretation of our findings.

Papers I and II are both epidemiological studies and therefore share many of their limitations. First, it is important to note that our study design can only prove time-correlations between introduction of general infant vaccinations within the region and changes in incidences noted within papers I and II. Although it appears to be a strong link, we cannot prove causality using this study design. Within the papers, we discussed impact of possible confounder including effects of other health interventions, changes in health determinants, availability of health care, or diagnostic practice. As we did not find any evidence of changes in these possible confounders, we do not believe they had a major impact on our results. We also discussed the risk of changes in care-seeking patterns. We do not believe this would affect incidence of bacterial meningitis or sepsis. However, despite us not seeing any signs of altered care-seeking patterns in paper II, it is possible that this affected our results regarding incidence of respiratory tract infections to some extent. Notably, changes in treatment guidelines for acute otitis media towards more restrictive usage of antibiotics issued in 2010 might have had an impact.

Although Sweden is a country well known for keeping comprehensive registers, there is always a risk of missing cases resulting in underreporting. Furthermore, the risk of incorrect diagnoses might overestimate incidence. In paper I, we tried to reduce these risks by using two sources of data and by adopting a case validation process. This was unfortunately not possible in paper II. However, this error is likely to be constant over time and will therefore not impact the interpretations related to changes in incidences when comparing different periods with each other.

In papers III-V focusing on clinical aspects of bacterial meningitis, the retrospective study design results in a very important limitation. Since our findings rely on information obtained from medical records, any information not registered there will therefore be missed. Hence, there is a risk that our retrospective study design results in us underestimating the occurrence of symptoms or signs at admission as well as complications or disabilities associated with bacterial meningitis in childhood.

In paper III we tested several clinical decision rules aimed at either identifying bacterial meningitis specifically or severe infections in general. However, as we did this there were several other clinical decision rules that were not included in the study. This was mostly due to us wanting to investigate clinical decision rules aimed specifically at bacterial meningitis. However, this also means that many of the clinical decision rules in use today were not included. This unfortunately means that our results are less transferable to many clinical settings today.

When creating the predictive score in paper IV, we took several steps to minimise the risk of overfitting the model to our own patient cohort. These included using a limited number of predefined outcomes and basing the predictive score on known risk factors identified in a previous systematic review article. However, the selection of a specific cut-off level used for our predictive score was based on the results obtained when testing it using our dataset. This will not impact the results obtained in the ROC-analysis. Nevertheless, it may result in the score not having equally high sensitivity and specificity as when tested using another patient cohort. Therefore, it would be important to conduct an external validation using another sample before considering clinical use of our predictive score.

Finally, the lack of control group to compare our results with regarding the occurrence of psychiatric disabilities noted in paper V is important to consider. Not having a control group means we must use previous studies as comparison. This is a limitation since previous studies did not utilise the exact methods as we did, meaning their results are not directly comparable with ours. Consequently, we cannot estimate the exact increase in risk of psychiatric disabilities, only conclude that psychiatric disabilities are common following childhood bacterial meningitis.

## Conclusions

Vaccinations are excellent at protecting children against severe infection, also in the Arctic region. This is exemplified by the marked decline in incidence of bacterial meningitis in children in the Västerbotten Region following introduction of general infant Hib and pneumococcal vaccinations. In addition, positive effects were also noted for other less severe infections such as sepsis, pneumonia, sinusitis, and acute otitis media.

Bacterial meningitis in children, despite being rare nowadays, can still cause great suffering for the individual child. Since bacterial meningitis nowadays is so uncommon, many clinicians may only come across a few cases during an entire career. It is therefore important to be aware that this severe disease can present itself very differently depending on several factors, most importantly age. While clinical decision rules provide some support, none is perfect. Identifying these patients among children with less severe infections is therefore a challenge not to be taken lightly.

The next challenge, arising when a child affected by bacterial meningitis has been identified, is deciding on treatment strategies. Here, one of the most difficult decisions is whether to perform an invasive procedure to manage the intracerebral pressure. At this task, the predictive score developed and tested by us, the MeningiSSS, surpassed existing predictive scores. It was able to predict the need of invasive procedures to manage the intracerebral pressure with high certainty, making the MeningiSSS potentially very helpful in difficult treatment decisions.

Finally, in children having survived the acute effects of the infection, permanent disabilities may be more common than previously thought. This is especially true for psychiatric disabilities, possibly affecting more than one third of survivors. Due to late detection of psychiatric disabilities, specific long-term follow-up strategies for detecting psychiatric disabilities need to be developed to reduce suffering caused by undetected psychiatric disabilities.

# Remaining questions and future research

In this thesis, some of the knowledge gaps outlined in the aims and introduction have been at least partially diminished in size. Still, many questions remain.

We have been able to demonstrate that the desirable long-term effects of general infant Hib and pneumococcal vaccinations seen in many temperate areas can also be obtained in Arctic regions. However, the Västerbotten Region is only a very small part of the entire Arctic. Whereas some areas have reported higher occurrences of severe infections and lesser effects of vaccinations, this has not been studied at all in many Arctic regions. It would be important to investigate this further and assess the true burden of disease due to severe infections in children in the Arctic, as well as what preventive effects can be attributed to general infant vaccinations. Are bacterial meningitis and other severe infections more common or less common in children in other Arctic regions today? Do you need to consider alternative vaccination schedules or other preventive measures in the Arctic region?

In the third paper, we showed that clinical presentation can vary considerably and demonstrated shortcomings in several clinical decision rules. But can't you create a clinical decision rule that is better? How? Will it be used? Would a clinical decision rule ever be good enough to trust completely? How do you know when to trust it and when to rely on your experience or your gut feeling?

The predictive score developed and tested by us in paper IV might be an improvement. However, before clinical use it would need to be validated in a separate cohort. How can this be accomplished? Would it perform equally well? And what about adults, are these results transferable to adults also? If it were to be implemented into clinical practice, does the benefits of being able to perform an invasive procedure to manage the intracerebral pressure in these select cases really justify the added risk of transfer?

Finally, as we demonstrated in the last paper, psychiatric disease as well as concentration or learning disabilities are common following childhood bacterial meningitis. But what would happen if you performed neuropsychiatric tests on all children shortly after discharge? Would we find these disabilities, or do they develop later? Could a prospective study answer this? If disabilities exist early on, would we then be able to improve the quality of life for these children or would it just label them as "having problems"?

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