Meningitis In Infants ≤60 Days Of Age Diagnosis, Parent Experiences And Potential Improvements In Care And Communication

Eduardo Fleischer

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Meningitis in Infants ≤60 Days of Age
Diagnosis, Parent Experiences and Potential Improvements in Care and Communication

A Thesis Submitted to the Yale University School of Medicine
in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by Eduardo Fleischer
2020
ABSTRACT

Objectives: The aims of this body of work are several fold. Aim 1: To describe the cerebrospinal fluid (CSF) profile of infants ≤60 days old with bacterial meningitis and characterize the clinical and laboratory features of infants with bacterial meningitis who present with no CSF abnormalities. Aim 2: To evaluate the performance characteristics of the BioFire® FilmArray® Meningitis/Encephalitis panel (ME panel), the only Food and Drug Administration (FDA)-cleared multiplexed panel for the evaluation of CSF samples. Aim 3: To identify themes to be included in a parent-reported outcome measure for febrile infants ≤60 days old and to describe the process of developing a software application for use with parents of febrile infants ≤60 days old evaluated in the emergency department.

Methods: Aim 1: Clinical and laboratory data was abstracted from electronic medical records of infants ≤60 days old with culture-positive bacterial meningitis from 11 children’s hospitals in the U.S. in a 5-year period. Aim 2: A thorough review of the literature was performed to gather data required for the evaluation of the ME panel. Aim 3: Semi-structured qualitative interviews, as well as design impression and usability testing of the software application were conducted with parents of febrile infants ≤60 days old evaluated in the emergency department.

Results: Aim 1: The sensitivity of a CSF Gram stain was 71.9% (95% CI: 59.2–82.4), and the sensitivity of corrected CSF pleocytosis was 80.3% (95% CI: 68.7–89.1) among infants ≤60 days old with bacterial meningitis. Of 9 infants with meningitis who had a negative Gram stain result and no corrected CSF pleocytosis, 8 (88.9%) had either an abnormal peripheral WBC count (>15 000 or <5000 cells per μL) or bandemia >10%. Aim 2: The ME panel has a pooled sensitivity of 90.2% (95% CI: 86.2-93.1) and specificity of 97.7% (95% CI: 94.6-99.0). The overall sensitivity for 5 of the 6 bacterial organisms in the panel was 96.8% (95% CI: 92.7-99.0). Aim 3: After preliminary qualitative data analysis of interviews with parents, themes for the parent-reported outcome measure include feeling informed, involvement in decisions, stress, infant and family outcomes, which emerged as possibilities for further validation. Testing of the software application has identified elements in the structure, navigability and content to be modified prior to field testing.

Conclusions: Aim 1: Infants with no CSF pleocytosis and a negative Gram stain result are unlikely to have bacterial meningitis in the absence of other laboratory abnormalities. Aim 2: The ME panel is a rapid diagnostic tool with an overall high sensitivity and specificity for CNS infections, with potential to improve diagnosis and optimize utilization of healthcare resources. Aim 3: Semi-structured qualitative interviews have allowed for the preliminary identification of themes to be considered for validation in the generation of a parent-reported outcome measure of febrile infants ≤60 days of life. Design impression and usability testing of the application have enabled the identification of changes needed to optimize the effectiveness of the application for parents of febrile infants.
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I would also like to express my appreciation to Ms. Paula Schaeffer for her expertise and support in the qualitative study to better understand the experience of parents of febrile infants ≤60 days of age evaluated in the emergency department, with the aim to develop a parent-reported outcome measure. To Ms. Sylvia Perez and everyone at the Yale Information Technology Services (ITS) User Experience and Design Services team for their help in development of the software application for parents of febrile infants evaluated in the emergency department.

Most importantly I would like to express my deep gratitude and appreciation to my mentor, Dr. Paul Aronson who envisioned and designed all the projects described in this body of work. For giving the opportunity to be part of his research, for his time, guidance and mentorship. Working with Dr. Aronson has been the most impactful research experience I have had in my career. I feel incredibly fortunate that I had the opportunity and privilege to work and learn from him. Thank you for investing so much in me, my education and career.

Finally, I would like to thank my wife Valerie for being the best partner I could have ever imagined, my best friend and cheerleader (and for all of her help and support on all my projects), to my parents Samuel and Clara for their love, ever-present support, guidance, their hard work that enable me and my brothers to reach our dreams, and for being the role models they are every day. To my brothers Gini, Jonathan and Alan for being my best friends and always there for me. To my abuelita Riva for her undivided love and for being a wonderful role model, to my uncle Jacky for being an inspiration to go into medicine, my uncle David for his love and encouragement, Isa, Sabri and Alex for bringing so much joy to our lives, to Eyal and Leora for their constant help and support, to my grandparents Leo, Rika, Max and Riva for their love, sacrifice and doing everything possible so that my parents, brothers and myself could have the opportunities and life we have today. To all my family members.

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INTRODUCTION

Meningitis is an important cause of morbidity and mortality worldwide.\textsuperscript{1-3} Although vaccination efforts have made a significant impact in the incidence and epidemiology of cases in different regions of the world,\textsuperscript{3-5} in the U.S. alone, there are several thousand cases of meningitis seen annually in both children and adults.\textsuperscript{6,7} In other parts of the world, especially in developing countries, bacterial meningitis has an even higher impact in terms of incidence, morbidity and mortality.\textsuperscript{3,8}

Several infectious and non-infectious etiologies can cause meningitis.\textsuperscript{6} Among infectious etiologies, viral central nervous system (CNS) infections are more common in the US,\textsuperscript{6,7} although acute bacterial meningitis is the most rapidly fatal.\textsuperscript{9} Bacterial meningitis leads to oxidative damage and alterations in blood flow which cause ischemia and cortical necrosis. In addition, the immune response to invading bacteria contributes to hippocampal apoptosis.\textsuperscript{10} On the other hand, in immunocompetent hosts, viral meningitis is often benign and self-limited.\textsuperscript{11}

Early introduction of antibiotic treatment in bacterial meningitis is vital. Although there is limited data in pediatric patients, studies in adults have shown a 10%-30% increase risk of death or lasting sequelae per hour of treatment delay.\textsuperscript{12} Suspicion of bacterial meningitis is a medical emergency, as the mortality rate of untreated bacterial meningitis is near 100% and even after optimal treatment the disease can still be deadly.\textsuperscript{5} Evidence also suggests that approximately 20% of patients who survive bacterial meningitis have long-term disabling sequelae, with hearing loss, seizures, motor deficits and cognitive impairment being the most common.\textsuperscript{13}
Given the potential negative consequences of delaying the diagnosis or treatment, patients suspected of having meningitis are often hospitalized and started on antimicrobials while awaiting test results.\textsuperscript{6,7,14,15} These can be unnecessary in patients with viral meningitis, increasing costs, leading to suboptimal utilization of antimicrobials and their associated morbidity.\textsuperscript{16} Studies have also shown that in a significant percentage of pediatric patients (50-80\%) the causative pathogen is not identified, which can lead to extended hospitalizations and antimicrobial courses due to concern of a bacterial etiology, which may often be unnecessary.\textsuperscript{17}

The reasons why the causative pathogen is not identified in a large percentage of patients is likely multi-factorial. Although in part it may be due to the limited number of viral pathogens targeted by current diagnostic tools, it is potentially also a consequence of the limitations of diagnostic modalities currently used in the evaluation of patients suspected of having meningitis. This highlights the need for diagnostic tools with an enhanced capacity to identify the causative pathogens.

Clinical differentiation between viral and bacterial meningitis is challenging as the classical signs and symptoms such as headache, fever, photophobia and neck pain are not specific to a particular etiology.\textsuperscript{17,18} Cerebrospinal fluid (CSF) culture, Gram stain and other molecular and cellular analysis of the CSF are often the methods used for the diagnosis of meningitis.\textsuperscript{3,9}

The sensitivity of CSF culture has been reported to range between 60–90\% in patients with bacterial meningitis, although it varies depending on the organism, and it is lower in patients pretreated with antimicrobial agents.\textsuperscript{3,19} Gram stain of the CSF has a short turnaround time, excellent specificity, is inexpensive and well-validated.\textsuperscript{3,19}
However, its sensitivity for bacterial meningitis is estimated to be in the range of 35–90%,\textsuperscript{3,9,20-22} varying significantly depending on the organism, and is also decreased on patients pretreated with antimicrobials.\textsuperscript{3,9}

Polymerase chain reaction (PCR)-based approaches have been shown to be able to increase diagnostic yield, capable of identifying viral and bacterial pathogens in the CSF while having rapid turnaround times.\textsuperscript{9,19} In fact, viral PCR for enterovirus (EV) and herpes simplex virus (HSV) have become part of standard care.\textsuperscript{23} Other methods such as the latex agglutination test have been used to aid in the rapid diagnosis of bacterial meningitis however, its sensitivity also varies per organism, and it is decreased in antimicrobial pretreated samples.\textsuperscript{3} Its ability to provide additional diagnostic value may be limited.\textsuperscript{3,19}

Although CSF culture is considered the gold standard for diagnosis, and is essential to determine antibiotic susceptibilities of the causative pathogen,\textsuperscript{3} it can take up to 72 hours.\textsuperscript{6,7} In addition, patients can sometimes receive antimicrobials prior to the lumbar puncture (LP) decreasing the diagnostic yield of the CSF culture.\textsuperscript{3,19} Hence, physicians often have to make clinical decisions on the basis of the CSF profile\textsuperscript{24,25}.

Historically, it has been considered that evaluation of the CSF profile of a patient with bacterial meningitis would show a positive culture, stained smear, an elevated white blood cell count (WBC) with predominance of polymorphonuclear leukocytes, a reduced glucose concentration relative to serum, and an increased protein concentration.\textsuperscript{26,27} However, evidence suggests that patients with bacterial meningitis may have normal or uncharacteristic CSF profiles.\textsuperscript{3,19,28-33} Being able to confidently differentiate bacterial
from viral meningitis is essential to improve management, and prevent high risk outcomes and inefficient utilization of healthcare resources.\textsuperscript{25}

Young infants are particularly susceptible to meningitis\textsuperscript{7,8,34} and neonates are the age group most commonly affected by bacterial meninigitis.\textsuperscript{24} Deficiencies in humoral, cellular and complement immunity make infants in the first months of life particularly susceptible to bacterial pathogens.\textsuperscript{35} It is estimated that in 2015, 5.942 million children under the age of 5 died globally, with 2.681 million (45.1\%) deaths occurring in the first month of life.\textsuperscript{36} Sepsis and meningitis were the 3\textsuperscript{rd} leading cause of death in the first month of life with over 400,000 deaths, while they represented the 5\textsuperscript{th} leading cause of death in children under 5 years of age.\textsuperscript{36}

Clinically diagnosing meningitis in young infants can be particularly difficult as they do not necessarily present with the classic features of the disease.\textsuperscript{37} Neonates with bacterial meningitis can often present with symptoms such as irritability, poor feeding, respiratory distress, changes in skin or tone, while fever is only present in up to 39\% of cases.\textsuperscript{19} Hence, there is a low threshold to perform LPs in young infants. A recent meta-analysis by Biondi et al. looked into the prevalence of bacterial meningitis in febrile infants in the first and second month of life, with most studies analyzed being from patients evaluated in the emergency department. They found that 1.2\% of febrile infants in the first month of life, who underwent CSF testing, were diagnosed with bacterial meningitis, while only 0.4\% of those in the second month of life had the disease.\textsuperscript{38}

It has been a generally accepted practice to perform LPs in all infants in the first month of life that present with fever of an unknown source, while those in the second month of life are at a lower risk of bacterial infection and can be risk stratified.\textsuperscript{38} There is
ongoing research on the development and validation of clinical prediction rules to help guide physicians stratify the risk of a serious bacterial infection in infants ≤60 days of age.\textsuperscript{25,39}

The decision to perform invasive studies such as an LP is not always clear. In fact, there is significant variation on whether to perform an LP on well-appearing infants ≤60 days of life.\textsuperscript{40,41} Clinical prediction rules aim to provide physicians with evidence-based tools to simplify and increase accuracy in such circumstances,\textsuperscript{42} however even though traditionally, clinical success has focused on mortality, physiological measures and definable clinical events,\textsuperscript{43} over the last decades the concept of shared decision-making has gained strength in the medical field.\textsuperscript{44} The idea that optimal decisions are based on a shared decision-making structure, that respects the patient’s preferences, values and goals\textsuperscript{45} is rooted in medical ethics when Dr. Robert M. Veatch initially suggested this model over alternative approaches in 1972.\textsuperscript{46} In the field of outcomes research, patients’ experiences and values, are taken into account when evaluating decisions made in healthcare.\textsuperscript{43}

An important pillar of shared decision-making is the exchange of information between providers and patients.\textsuperscript{47} Patients should have a good understanding of the risks, benefits and treatment alternatives in order to effectively participate in the shared decision-making process.\textsuperscript{48} Perceived understanding of information and language barriers, have been identified as some of the obstacles to shared decision-making on whether to perform LPs on infants in the first 2 months of life.\textsuperscript{49}

Patient-reported outcome measures assess outcomes from the patient’s perspective and have been increasingly utilized in clinical practice to monitor and
improve care. Historically, quantitative methods have been used to inform the evaluation of clinical effectiveness in outcomes research. However, these are not necessarily ideal to measure some of the intricate elements of healthcare delivery, such as the patient’s perception of quality of care. Instead, qualitative methods may be better suited to examine these aspects of healthcare delivery.

In order to grasp the patient’s perspective, it is vital for patients to take part in the development of the patient-reported outcome measure. For pre-verbal pediatric patients, parent-reported outcome measures are utilized in order to capture the experience of the child and family.

This body of work will focus on (i) the study of the clinical and laboratory features of infants ≤60 days of life diagnosed with culture-positive bacterial meningitis. (ii) A review the scientific literature to evaluate the the BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel, a recently FDA-cleared rapid diagnostic tool with the potential to circumvent some of the current limitations in the diagnosis of meningitis. (iii) A description of the preliminary results obtained from in-depth, semi-structured interviews with parents of febrile infants ≤60 days of age, as the initial phase of a larger study aimed to develop a parent-reported outcome measure for the management of febrile infants in the emergency department. (iv) Introduce ongoing efforts in the development of a software application aimed to provide parents of febrile infants ≤60 days of age relevant and understandable information regarding risks and testing performed in the emergency department during the evaluation of febrile infants.

All four of these projects aim to address elements of the process of evaluating infants in the first 2 months of life with concern for meningitis, specifically they are
associated with the presentation, diagnosis, parental experience and decision-making components of these evaluations.
METHODS

I. Clinical and laboratory features of infants ≤60 days with culture-positive bacterial meningitis

Study design

This study was a planned secondary analysis of a cross-sectional study of infants ≤60 days of age with bacteremia and/or bacterial meningitis evaluated in the emergency department of 11 geographically diverse children’s hospital in the United States over a 5-year period between July 1, 2011 and June 30, 2016. The study was approved by each of the 11 children’s hospitals’ institutional review board.

Study sample

For the parent study, each hospital’s microbiology laboratory database or electronic medical record system was queried for positive blood or CSF culture results obtained in the ED from infants ≤60 days of age.

For this secondary analysis the following inclusion criteria had to be met: (i) infants ≤60 days of age evaluated in the emergency department, (ii) diagnosed with bacterial meningitis, (iii) a CSF culture positive for an *a priori*-defined bacterial pathogen as determined by expert consensus, these had to be common pathogens (e.g., Group B *Streptococcus*, *Escherichia coli*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Streptococcus bovis*, *Klebsiella pneumoniae*, *Neisseria meningitides*, *Pasteurella*, *Paenibacillus*) that were treated as a pathogen by the medical team (iv) with both CSF WBC and red blood cell (RBC) counts available. Exclusion criteria: (i) infants with ventriculoperitoneal shunts, (ii) infants with growth of a bacterial pathogen only from a CSF enrichment broth culture, except 1 infant who had CSF pleocytosis and growth of *Listeria monocytogenes* from the CSF.
Data collection

Medical records were used to extract the demographic, historical, physical examination and laboratory data, including results of a complete blood cell count, the CSF profile (Gram stain, WBC count and differential, RBC count, protein and glucose level) and bacterial culture results of urine, blood and CSF.

Definitions

Bacterial meningitis was defined as a CSF culture that grew a pathogen. The result of the CSF Gram stain was considered positive if bacteria were identified (e.g., Gram-positive cocci, Gram-negative rods). CSF pleocytosis was defined as a CSF WBC count ≥16 cells per mm$^3$ for infants ≤28 days and ≥10 cells per mm$^3$ for infants 29 to 60 days of age.$^{54}$ For infants with traumatic lumbar punctures (ie, CSF RBC count ≥10,000 cells per mm$^3$), an RBC/WBC correction factor of 1,000:1 was used to determine the corrected CSF WBC count.$^{55}$ An abnormal CSF profile was defined as a positive Gram stain result, CSF pleocytosis, neutrophil predominance on the CSF WBC differential (>50% neutrophils), an elevated CSF protein level (≥128 mg/dL for infants ≤28 days and ≥100 mg/dL for infants 29–60 days of age),$^{54}$ or a low CSF glucose level (<25 mg/dL for infants ≤28 days and <27 mg/dL for infants 29–60 days of age).$^{54}$ Ill-appearance was defined by any of the following descriptions on the physical examination in the emergency department: “ill-appearing,” “toxic,” “limp,” “un-responsive,” “gray,” “cyanotic,” “apnea,” “weak cry,” “poorly perfused,” “grunting,” “listless,” “lethargic,” or “irritable.”$^{52}$
Statistical analysis

The sensitivity for bacterial meningitis of the CSF Gram stain and corrected CSF pleocytosis, alone and in combination was calculated. Proportions were compared by using the \( \chi^2 \) test or Fisher’s exact test. Statistical analyses were performed by using Stata version 15.0 (Stata Corp, College Station, TX).

Methods conducted by me

I contributed to the design of the study, interpreted the data, performed the literature review to inform the writing of the manuscript, drafted the initial manuscript, and reviewed and revised the manuscript critically for important intellectual content.

Methods conducted by others

Dr. Aronson conceptualized and designed the study, supervised data collection locally and nationally, performed the data analyses, interpreted the data, helped draft the initial manuscript, and reviewed and revised the manuscript critically for important intellectual content. Dr. Neuman and Dr. Wang contributed to the design of the study, collected local data, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content. Dr. Nigrovic, Dr. Desai, Dr. DePorre, Dr. Leazer, Dr. Marble, and Dr. Sartori collected local data, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content.

II. Review of the literature and evaluation of the BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel

Study design
A thorough review of the literature was conducted to gather information related to multiplexed arrays, rapid diagnostics, case reports and published studies that have used and evaluated the BioFire® FilmArray® ME Panel. Google Scholar was the search engine utilized to gather all the reviewed scientific literature about the ME panel. Inclusion criteria was any published work that referenced the ME panel. Search terms included “BioFire”, “FilmArray”, “ME panel”, “multiplexed arrays”.

Data collection

Data was collected from published scientific literature. For calculations and statistical analysis, data was extracted from a published systemic review and meta-analysis of the ME panel by Tansarli et al.23

Statistical analysis

Statistical analyses were performed using Stata version 15.0 (Stata Corp, College Station, TX) and Microsoft® Excel® (2013).

Methods conducted by me

I gathered and reviewed the published scientific literature, assisted with the statistical analyses, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript critically for important intellectual content.

Methods conducted by others

Dr. Aronson supervised the gathering and review of published scientific literature, performed statistical analyses, interpreted the data, helped draft the initial manuscript, and reviewed and revised the manuscript critically for important intellectual content.
III. Qualitative study to better understand the experience of parents of febrile infants ≤60 days of age evaluated in the emergency department

Study design

This qualitative study was performed through the recruitment and interviews of parents of febrile infants ≤60 days of age that presented to Yale-New Haven Children’s Hospital over an approximate 4 month period between August and December of 2019. This study was approved by the hospital’s institutional review board, and a written informed consent was obtained from each of the participants during enrollment in the study. A small monetary ($25 gift card) incentive was provided to those who agreed to participate.

Study sample

Through monitoring of the electronic medical record system and notifications from physicians working in the emergency department at Yale New Haven Children’s Hospital, parents that presented with febrile infants ≤60 days of age (fever defined as a temperature ≥ 100.4 °F) were approached and informed consent was obtained from those who agreed to participate. In order to ensure diversity of socio-demographic backgrounds, purposeful sampling was performed. In addition, parents whose primary language was Spanish were also enrolled.

Data collection

Semi-structured interviews were conducted with those enrolled in the study, and these interviews were audio-recorded, transcribed, and qualitatively analyzed until thematic saturation was achieved. Demographic data was obtained from each parent enrolled and included: age, gender, race/ethnicity, number of children, prior visits to the
emergency department with a febrile infant, highest level of education, and health literacy by asking the parent’s confidence in completing medical forms by his/herself.

Information relevant to the infants was gathered through the electronic medical record and included: gender, age, whether an LP was performed, whether the patient was admitted, results of urine, blood and CSF cultures (if performed), and viral test results (if performed).

**Interviews**

The semi-structured interviews were performed by Dr. Paul Aronson (pediatric emergency physician at Yale New Haven Children’s hospital) and/or myself. All interviews were conducted individually except in the occasions where both parents of an infants participated jointly. All interviews performed in English were transcribed word-by-word by professional transcribers. All interviews conducted in Spanish were transcribed and translated by me. An interview guide was used to conduct the interviews. Interview questions aimed to understand the parents’ experience with the evaluation of febrile infants ≤60 days of age in the emergency department, factors related to parents’ stress during the process, and the outcomes important to parents (Table 1).

**Data Analysis**

Dr. Aronson, Ms. Paula Schaeffer (a research associate with expertise in qualitative research) and myself, reviewed the transcripts separately and subsequently discussed our analysis to reach a consensus. We developed an initial coding guide based on topics that arose during interviews; the guide was iteratively revised during the
process of data analysis. The data was then coded using the grounded theory approach until thematic saturation was obtained (after 21 interviews).

**Methods conducted by me**

I contributed in the monitoring of the electronic medical record, enrollment of parents in the study, performing and recording of interviews, transcription and translation of interviews conducted in Spanish, analysis and coding of interviews and initial interpretation of obtained results.

**Methods conducted by others**

Dr. Aronson conceptualized and designed the study, supervised data collection, developed the interview guide, contributed to the monitoring of the electronic medical record, enrollment of parents in the study, performing and recording of interviews, analysis and coding of interviews and initial interpretation of obtained results. Ms. Paula Schaeffer collaborated on the development of the interview guide and in the analysis of interviews.

**IV. Development of a software application to provide relevant information to parents of febrile infants in the emergency department**

**Study design**

This study is part of an ongoing research project. The parts described in this body of work were done in two phases. The first in September of 2019 and the second in January and February of 2020. Both phases were conducted with Yale New Haven Children’s Hospital’s pediatric emergency physicians and nurses, as well as with parents of febrile infants ≤60 days of life evaluated in the emergency department. For the phase two
(usability testing), a small monetary ($35 gift card for parents, $10 for physicians and nurses) incentive was provided to those who agreed to participate.

**Study sample**

Design impression testing of a software application was performed through an online survey distributed to pediatric emergency medicine physicians, nurses and parents of febrile infants ≤60 days of life evaluated in the emergency department. The objective was to assess if the visual format of the application supported the message it intends to communicate. During design impression testing, participants had 5 seconds to observe some of the different designs presented in the application and provide their immediate “gut” reaction to the layout (not the content), by listing their perceptions about the message the design intended to communicate. Subsequently, a randomized list of both “positive” and “negative” adjectives was provided to participants for them to select which ones they considered best described the displayed designs. This data was then used to rate the application design as overall “positive” or “negative”.

Usability testing of the software application was performed through in-person sessions with pediatric emergency medicine physicians, nurses and parents of febrile infants. These sessions included a qualitative and a quantitative analysis component. For the qualitative assessment participants were given an iPad and a Yale ITS UX Researcher provided a scenario in order to assess their ability to navigate the application and find relevant information. Participants were asked to “think aloud” while using the application. Subsequently the investigators asked a set of questions related to the format and content of the application. Quantitative assessment was then performed by gathering the rating of each participant regarding the application’s ease of use on a scale of 1 (very
difficult) to 7 (very easy), and by having each participant complete the System Usability Scale, a 10-item validated questionnaire for usability testing, scored from 0-100,\textsuperscript{58} with high scores being indicative of increasing usability.\textsuperscript{59,60}

**Data collection**

Information was collected based on overall design impression of the software application, easiness of use, understanding of content, real-time navigation and overall general feedback.

**Methods conducted by me**

I contributed to recruiting and enrolling parents to participate in the studies, collaborated in the usability testing sessions, and translated the initial version of the software application from English to Spanish.

**Methods conducted by others**

Dr. Aronson conceptualized and designed the study, created the content and format for the software application, supervised data collection, contacted and enrolled parents, physicians and nurses, performed the usability testing sessions, gathered and interpreted the data. Yale Information Technology Services (ITS) User Experience and Design services team provided the technical expertise to design and develop the software application, and interpreted the design impression testing and usability testing data.
STATEMENT OF PURPOSE

As described above, there is a low-threshold to perform CSF testing in infants ≤60 days of life when there is a possibility of bacterial meningitis, due to their increased susceptibility and subtle presentation. Given that physicians often rely on the CSF profile when making management decisions, and that the CSF profile of patients with bacterial meningitis can sometimes be normal, an improved understanding of the clinical and laboratory features of infants ≤60 days of life with bacterial meningitis could help in the management of those who undergo CSF evaluation. For the first part of this body of work, the aim is to describe the CSF profile of infants ≤60 days of life with culture-positive bacterial meningitis that were evaluated in the emergency department, and to describe the clinical and other laboratory characteristics of those that presented without other CSF abnormalities.

The case for faster and more sensitive tools to elucidate the causative pathogen in meningitis, as well as the need for new tools that can help providers make more informed decisions when differentiating between viral and bacterial meningitis, has also been demonstrated above. The second part of this body of work is focused on the evaluation of the benefits and limitations of the BioFire® FilmArray® ME Panel, a recently FDA-cleared technology that shows promise in enhancing our ability to overcome some of the existing limitations in our current diagnostic approach. In addition, promising alternative new methods that also have the potential to significantly change our methodology in the diagnosis of meningitis are briefly explored.

Third, the decision to perform CSF studies in febrile infants ≤60 days of life is not necessarily an easy one. The prevalence of bacterial meningitis in this population is
approximately 1% of those with CSF studies performed. In addition, there is significant variability on whether to perform an LP on a well-appearing infant in the first 2 months of life. Ongoing research aimed at better understanding and stratifying patients to rule-out bacterial meningitis is essential to avoid unnecessary procedures, hospitalizations, antimicrobial exposure and healthcare costs. At the same time, it is evident that in addition to the clinical ramifications that must be considered when taking the decision to perform invasive CSF studies, it is essential to take into account the parent’s values, preferences and goals. To our knowledge, no parent-reported outcome measure for febrile infants currently exists. The initial phase for the development of such outcome measure, is the basis of the project described in the third part of this body of work.

We hypothesize that (i) there are a set of factors that parents of febrile infants ≤60 days of life evaluated in the emergency department value when defining a good outcome. (ii) These set of factors could be identifiable through in-depth, semi-structured interviews with parents, and qualitative data thematic analysis. The end-goal of this project is to identify themes and items to be included in a parent-reported outcome measure of febrile infants ≤60 days of life.

Finally, as described above, parents’ perceived understanding of information and language barriers in the exchange of information between providers and parents, have been identified as barriers for shared decision-making in the emergency department setting during the evaluation of febrile infants in the first 2 months of life. The final part of this body of work is focused on the development and initial testing of a software application to be provided to parents of febrile infants while in the emergency department. The aim is for this application to serve as an additional (not as a substitute)
source of information about what are the risks, testing and possibilities associated with the presentation and management of their infant. This could significantly impact the experience of parents in the emergency department, by having a trustable informational resource, specifically written for individuals not involved in the medical field. This could potentially help overcome some of the identified barriers in the shared decision-making process. The main objective of this part of the project is to test the design, content, and navigability of the application with those involved in the shared decision-making process (i.e., pediatric emergency medicine physicians, nurses and parents).
RESULTS

I. Clinical and laboratory features of infants ≤60 days with culture-positive bacterial meningitis

Over the study period, 10,635 infants ≤60 days of age had CSF cultures obtained, and 76 (0.7%) had positive culture results. Ten of these 76 infants (13.2%) were excluded: 3 had ventriculoperitoneal shunts, and 7 did not have CSF cell counts performed. Of the remaining 66 study infants with bacterial meningitis, 44 (66.7%) were ≤28 days, and 22 (33.3%) were 29 to 60 days of age.

The most commonly isolated pathogens were Group B Streptococcus (GBS) (n = 41 [62.1%]), Escherichia coli (n = 8 [12.1%]), and Listeria monocytogenes (n = 4 [6.1%]). The distribution of pathogens was different between infants ≤28 days and those 29 to 60 days of age (P = .03). Forty-eight infants (72.7%) had concomitant positive blood culture results with the same bacterial pathogen.

Overall, 62 of 66 infants with bacterial meningitis had an abnormal CSF parameter (93.9%; 95% confidence interval [CI]: 85.2–98.3) (Table 2). The sensitivity of the CSF Gram stain for bacterial meningitis was 71.9% (95% CI: 59.2–82.4). After correction of CSF WBCs for CSF RBCs, the sensitivity of CSF pleocytosis for bacterial meningitis was 80.3% (95% CI: 68.7–89.1). The sensitivity of combining a positive Gram stain result with corrected CSF pleocytosis was 86.4% (95% CI: 75.7–93.6). The proportion of infants with a positive Gram stain result or corrected CSF pleocytosis was the same among infants ≤28 days and infants 29 to 60 days of age (86.4% vs 86.4%; P = 1.0) (Table 2). Among infants who were not ill appearing, the sensitivity of combining a positive Gram stain result with corrected CSF pleocytosis was 81.3% (95% CI: 63.6–92.8).
A total of 9 infants with bacterial meningitis had a negative CSF Gram stain result and no CSF pleocytosis (3 of whom had no pleocytosis only after correction of CSF WBCs for CSF RBCs). Six infants (66.7%) were ≤28 days, and 3 (33.3%) were 29 to 60 days of age. Pathogens isolated from the CSF of these infants were GBS (5 infants), *Escherichia coli* (2 infants), *Staphylococcus aureus* (1 infant), and *Klebsiella oxytoca* (1 infant). Five infants (55.6%) had concomitant bacteremia. No infants had low CSF glucose levels, whereas 5 (55.6%) had an elevated CSF protein level (Table 3).

Of the 9 infants, 8 (88.9%) had either an abnormal peripheral WBC count (>15 000 or <5000 cells per mL) or bandemia >10% (Table 3). The other infant was 42 days old and had *Escherichia coli* bacteremia and meningitis and no CSF pleocytosis after correction of CSF WBCs for RBCs. The infant was not ill appearing, had a normal peripheral WBC count, and had an absolute neutrophil count of 4599 neutrophils per mm$^3$, without a band count performed.

II. Review of the literature and evaluation of the BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel

In October, 2015, the FilmArray® Meningitis/Encephalitis Panel (ME) (BioFire Salt Lake City, UT) was the first FDA-cleared multiplex PCR panel for the evaluation of CSF samples. The ME panel is a multiplexed PCR able to identify 14 organisms, which include 7 viruses, 6 bacteria, and 1 fungus (Table 4). The ME panel consists of automated nucleic acid extraction, purification, reverse transcription, PCR, DNA melting analysis and automatic results analysis. A minimum of 0.2 mL of CSF volume is needed, the ME panel is capable of analyzing 12 samples at a time, and less than 2 minutes of hands-on technician time are required. Most important for clinicians is that results are obtained in approximately 1 hour. Notably, the ME panel is intended to be
used jointly with additional clinical, epidemiological and laboratory data, including CSF culture. Additionally, the panel is not intended for CSF specimens collected from indwelling CNS medical devices or from patients in whom there is concern for a nosocomial infection, as pathogens which often cause these infections are not included in the ME panel.

There have been multiple investigations that have evaluated the ME panel for the detection and identification of pathogens in pediatric and adult patients assessed for meningitis/encephalitis. The largest prospective study to date by Leber et al, evaluated 1,560 CSF samples, and the sensitivity of the ME panel ranged from 85.7% for HHV-6 to 100% for 9 of the 14 organisms. However, there were limited numbers of samples for many of the organisms and two (Listeria monocytogenes and Neisseria meningitides) were not detected in the study. The specificity of the ME panel was reported to be 99.2% or greater for all 14 organisms.

A recent meta-analysis by Tansarli et al. identified 8 studies (prospective and retrospective focused solely on pediatric or both pediatric and adult patients) that provide data required to estimate the performance of the ME panel through the evaluation of discordant results between the ME panel and reference methods. Using the data from the meta-analysis, we calculated the overall performance characteristics of the ME panel from the 8 studies (Table 5). Additionally, we calculated the combined performance characteristics for the ME panel: pooled sensitivity 90.2% (95% CI: 86.2-93.1), specificity 97.7% (95% CI: 94.6-99.0), positive predictive value (PPV) 85.1% (95% CI: 81.6-88.2), negative predictive value (NPV) 98.5% (95% CI: 97.9-98.9), likelihood ratio positive (LR+) 38.8 (95% CI: 16.6-90.8), likelihood ratio negative (LR-) 0.10 (95% CI:...
Due to the limited number of studies and sample sizes, the authors of the meta-analysis were not able to calculate sensitivities and specificities of the ME panel for individual organisms in the panel.\textsuperscript{23}

From the data gathered by Tansarli et al. from these 8 studies, we also calculated that the overall sensitivity for 5 of the 6 bacterial organisms in the ME panel was 96.8\% (95\% CI: 92.7-99.0). As the 1 positive case of \textit{Listeria monocytogenes} was not able to be corroborated, we were not able to include this organism in the calculation of overall sensitivity for the bacterial pathogens in the panel.\textsuperscript{23}

Young infants <3 months of age are particularly susceptible to ME.\textsuperscript{7,8,34} Although many studies evaluating the ME panel have included infants in the first 3 month of life, 2 of the investigations specifically focused on this age group.\textsuperscript{78,80} Arora et al. evaluated the ME panel in 62 infants ≤3 months of age and reported a sensitivity of 100\% and specificity of 93.4\%. Blaschke et al., however, reported mixed results for infants ≤60 days of age, including two false positive bacterial pathogens detected by the ME panel. Additionally, larger number of infants had viruses detected with the ME panel than with conventional methods, but it was unclear if these detections were true positive or false positive results.

The duration of antimicrobial therapy with the implementation of the ME panel has also been evaluated. A study in a pediatric population found a shorter duration of antimicrobial therapy after the implementation of the ME panel (2 vs. 3 days).\textsuperscript{73} Additionally, in a study focused on partially-treated bacterial meningitis in adult and pediatric patients, the total duration of antimicrobial treatment was shorter with implementation of the ME panel (9.5 days vs. 15.2 days).\textsuperscript{81} A shorter time to narrowing
antimicrobials and a decrease in the number of acyclovir doses has also been reported with use of the ME panel,\textsuperscript{79} as has an increase in use of narrow spectrum regimens.\textsuperscript{81} Other studies, however, have provided conflicting results, including a study of adult patients that reported no difference in the duration of antimicrobial therapy with the use of the ME panel.\textsuperscript{82} As a possible mechanism for these findings, some investigations found that significant proportion of patients with negative ME panel results were still continued on antimicrobial therapy.\textsuperscript{72,82} The potential impact of the implementation of the ME panel on hospital length of stay has also been analyzed. While some studies have reported a shorter duration of hospitalization with use of the ME panel,\textsuperscript{73,79,83} others have found no difference.\textsuperscript{81,82}

III. Qualitative study to better understand the experience of parents of febrile infants $\leq$ 60 days of age evaluated in the emergency department

Of the 21 febrile infants whose parents were enrolled in the study, 8 (38.1\%) were $\leq$ 28 days of age, while the remaining 13 (61.9\%) were 29-60 days of life. The median age of the infants was 35 days (range 3 to 60 days). Of the 21 patients, there were 9 females (42.9\%) and 12 male infants (57.1\%). LPs were attempted on 15 (71.4\%) of them and were successful on 12 (80.0\%). The presentation to the emergency department lead to a hospital admission in 19/21 (90.5\%), while 1 of the 2 patients discharged was admitted after presenting for a second time to the emergency department. Of the 21 infants evaluated, 1 was diagnosed with culture-positive bacterial meningitis (due to \textit{Neisseria meningitides}).

Out of the total 21 parental interviews, 11 (52.4\%) were conducted on mothers, 3 (14.3\%) were conducted on fathers, and 7 (33.3\%) with both the mother and father jointly. A total of 4 parents (19.0\%) had interviews in Spanish as this was the language
preferred by the parents, of these 4 Spanish speaking parents, 3 (75.0%) were mothers and 1 (25.0%) was a father. The remaining 17 parents (81.0%) had interviews conducted in English. The median number of days from the emergency department visit to the day the interview was conducted was 1 (range 0 to 9 days).

Several concepts were identified when evaluating for a set of items to be considered in the generation of a parent-reported outcome measure. Although the analysis process of all the interviews has not yet been completed, there are a few areas that were recurrent through many of our interviews and will likely be associated with some of the themes to go onto the process of determining the items for inclusion in the parent-reported outcome measure. Some of these identified in a preliminary analysis include: (1) feeling informed, (2) involvement in decisions, (3) stress, (4) infant outcomes and (5) family outcomes (Table 6).

IV. **Development of a software application to provide relevant information to parents of febrile infants in the emergency department**

Design impression testing of the application was successfully completed through the input of pediatric emergency medicine physicians, nurses and parents that had presented to the emergency department with a febrile infants ≤60 days of age. A total of 10 participants completed the testing, and their “gut” impressions were, overall, positive, as interpreted by Yale ITS. Therefore, the designs of the application were determined to be ready for incorporation into a prototype of the application. The software application was then developed. Subsequently, usability testing has so far been conducted with 2 pediatric emergency medicine physicians, 1 pediatric emergency nurse, and 4 parents of febrile infants. Additionally, 2 other parents are scheduled to perform usability testing this upcoming week. Overall, the application has been highly rated for its usability, and all
the participants felt the application would be helpful for parents. Three main concepts for revisions have been identified in the preliminary results of usability testing. The layout in some areas of the application must be adjusted as some of the participants in the study noted they failed to realize there was additional content in parts of the application. There have also been suggestions in terms of navigability between pages of the application that will likely be implemented in the next iteration. Finally, some of the information provided in the application will likely be edited following the feedback provided by physicians, nurses and parents that have participated in the testing of the application.
DISCUSSION

I. Clinical and laboratory features of infants ≤60 days with culture-positive bacterial meningitis

In this multicenter cross-sectional study, the majority of young infants with bacterial meningitis who were evaluated in the ED had either a positive Gram stain result or corrected CSF pleocytosis. Of the few infants with bacterial meningitis without these laboratory markers, all but 1 had either an abnormal peripheral WBC count or bandemia.

We found that CSF pleocytosis had a sensitivity of 80.3%, which is higher than reported in some recent studies. Our study builds on this previous work by revealing a higher sensitivity (86.4%) when CSF pleocytosis was combined with a positive CSF Gram stain result.

The bacterial meningitis score combines clinical and laboratory features to accurately identify infants with CSF pleocytosis at low risk for bacterial meningitis. However, although this validated score has 100% sensitivity in infants ≤60 days of age, it has a specificity of 1.6% and should not be applied clinically in this age group. Therefore, these youngest infants with CSF pleocytosis are often treated presumptively for bacterial meningitis until the results of CSF bacterial cultures are available. Although a minority of infants with bacterial meningitis in our study had normal CSF profiles, they frequently had either an abnormal peripheral WBC count or bandemia. Our results, combined with the overall low prevalence of bacterial meningitis (1%) among infants who undergo CSF testing, reveal that infants with no CSF pleocytosis and a negative Gram stain result are unlikely to have bacterial meningitis in the absence of other laboratory abnormalities.
Traumatic lumbar punctures artificially elevate the CSF WBC count by introducing peripheral blood into the spinal space (which could have resulted in the positive CSF culture result for the infant with no CSF pleocytosis, a normal Gram stain result, and growth of *Escherichia coli* in the blood and CSF). Correcting CSF WBCs for the presence of RBCs reduces the sensitivity for bacterial meningitis, whereas it increases the specificity.\(^{55}\) In our study, applying a CSF RBC/WBC correction factor of 1,000:1 classified 3 additional infants with bacterial meningitis as having no CSF pleocytosis. However, the peripheral WBC count, band count, or CSF protein level was abnormal in these infants. When applying a CSF RBC/WBC correction to young infants with traumatic lumbar punctures, clinicians should consider additional laboratory parameters when making management decisions.

**Limitations**

Our study has several limitations. First, we only included infants with a positive CSF bacterial culture result. We excluded 13 infants with bacteremia and CSF pleocytosis but negative CSF culture results after antimicrobial pretreatment because of potential misclassification of these infants as having bacterial meningitis. Second, CSF pleocytosis and an abnormal peripheral WBC count or elevated band count are not specific for bacterial meningitis, and we do not know the overall number of infants with these laboratory abnormalities. Therefore, our findings are most applicable when clinicians have clinical concern for bacterial meningitis, but the infant has a normal CSF profile. Third, our study was conducted at pediatric emergency departments, and our findings may not be generalizable to other settings. Fourth, we could not assess
abnormalities in newer biomarkers because only 4 infants had a procalcitonin level measured, and 12 had a C-reactive protein measurement obtained.

II. Review of the literature and evaluation of the BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel

Multiplexed PCR technologies allow for the simultaneous detection and identification of microorganisms in a single test reaction. Currently there are multiple FDA-cleared/approved multiplex PCR respiratory, gastrointestinal and blood panels.\textsuperscript{61,62} Although for years there have been FDA-approved PCR technologies to test for either enteroviruses or herpes simplex virus 1/2, in October, 2015, the ME panel was the first and so far only FDA-cleared multiplexed PCR for the identification of bacteria, virus and fungi in the CSF.

Benefits and Limitations of the ME Panel

There are multiple potential benefits and limitations of the ME panel (Table 7). Potential clinical benefits include the detection of CSF viruses and bacteria with high sensitivity and specificity, as noted previously.\textsuperscript{23} Additional clinical benefits reported in the literature include shorter time to pathogen identification,\textsuperscript{73,75,86} detection of organisms in CSF missed by other conventional studies such as Gram stain\textsuperscript{87,88} or culture,\textsuperscript{71,80,89-91} identification of organisms in samples of patients pretreated with antimicrobial agents,\textsuperscript{71,80,81,87,88} and enhanced implementation of chemoprophylaxis for close contacts.\textsuperscript{81}

There is also a possible economic impact of using the ME panel. Given the adverse consequences of delayed or misdiagnosed meningitis/encephalitis, patients suspected of ME are often hospitalized for empiric antimicrobial therapy while awaiting the results of CSF culture.\textsuperscript{14,15,83} Fast turnaround times of the ME panel (approximately 1 hour) have
the potential to optimize resource utilization by decreasing unnecessary hospitalizations, number of other diagnostic tests, length of stay, and length of empiric antimicrobial therapy. Theoretical models in pediatric and adult patients have suggested that the ME panel can lead to cost savings when compared with current practice standards. A study in adult patients found a significant difference between the median costs per treatment course of antimicrobials for patients who received standard of care testing compared with those in which the ME panel was used. Another study estimated cost savings of approximately $1,750 per case with the use of the ME panel in patients with suspected CNS infections, due to faster turnaround times compared with conventional methods. These potential cost savings must be evaluated while also taking into account the cost of purchase of the ME panel, the testing itself, and the service of the equipment. The elevated cost of performing each test has been considered a limitation for the implementation of the ME panel in low-income countries.

There are important limitations of the ME panel. Some investigators have raised concerns for false positives and false negatives with use of the ME panel. Case reports have described how false positive and/or false negative ME panel results led to delayed diagnosis of the causative pathogen. Studies have also suggested that the ME panel should not replace the cryptococcal antigen test and culture for patients with suspicion of C. neoformans/C. gattii ME. Specifically, some potential false negative results of C. neoformans/C. gattii on ME panel have occurred in patients with low burden of disease and/or in patients on antifungal treatment. Additionally, studies have suggested the possibility that positive antigen results after
initiation of therapy may indicate persistence of antigen and not actual detection of live organisms.\textsuperscript{63,66,99} False negative results for viruses may be due to specimens containing low viral loads\textsuperscript{86} and to the lower ability of the ME panel to detect viruses when compared to some singleplex assays.\textsuperscript{75,94,100,101} With regards to false positive results, there are concerns for the potential of contamination during collection and processing of CSF samples.\textsuperscript{23,66}

It is also important to highlight that all herpesviruses in the ME panel (HSV-1, HSV-2, CMV, VZV, HHV-6) can establish latent infections. Therefore, a positive result in the ME panel may be due to a primary infection, or alternatively to a latent infection present in the cells retrieved in the specimen (either the CSF or from peripheral blood in a traumatic tap) or reactivation of the virus (with or without true disease).\textsuperscript{66,94,102} This accentuates the importance of evaluating the full clinical scenario when interpreting ME panel results.\textsuperscript{23,66,103,104} In addition, HHV-6 can be integrated into human chromosomes and transmitted vertically giving a positive ME panel result.\textsuperscript{86,103}

Clinicians should consider the entire clinical scenario including immune status of the patient, symptoms, laboratory, and imaging data when dealing with a positive FilmArray test\textsuperscript{95,103}. For example, most cases of HHV-6 encephalitis occur 2-6 weeks after hematopoietic stem cell transplants and in other immunocompromised states \textsuperscript{64,103}. In the initial investigator use only (IUO) version of the FilmArray, Epstein-Barr Virus (EBV) which can also establish latency or be reactivated, was one of the targets of the panel. Due to concerns for the discordance of results and the possibility of misleading clinicians, it was taken out of the commercial version approved by the FDA \textsuperscript{66}. Some have also
questioned the significance of a positive result for other viruses in the panel (such as HHV-6 and CMV)\textsuperscript{64,74,104}.

Promising Additional Rapid Diagnostic Technologies

Multiplexed PCR panels, like the BioFire® FilmArray® ME Panel, are one of several rapid diagnostic approaches that have the potential to overcome some of the existing limitations in the diagnosis of CNS infections. Some of these diagnostics employ different PCR-based techniques to improve the diagnostic yield such as, the utilization of nested-PCR (as in the BioFire® FilmArray®), loop-mediated isothermal amplification (LAMP),\textsuperscript{105} and 16s ribosomal RNA sequencing (broad-range PCR).\textsuperscript{106} Others employ different approaches for the identification of microorganisms such as matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF),\textsuperscript{107} and metagenomics next-generation sequencing.\textsuperscript{108} All of these offer promising avenues to improve our current strategies to diagnose CNS infections, but require further research.

III. Qualitative study to better understand the experience of parents of febrile infants ≤60 days of age evaluated in the emergency department

The preliminary results of the in-depth, semi-structured interviews with parents of febrile infants, show the emergence of concepts that will potentially be used in the subsequent stage of the project (identification and validation of themes) once the analysis of the current qualitative data is finalized (and results are no longer preliminary).

The concept of feeling informed was an interesting one that presented with some variability. Although many parents felt providers were in constant communication, and that they had a good understanding of what was going on, others mentioned an element of surprise when they were told they were going to be admitted. Interestingly, some also
noted that providers often repeated the information, which they found to be helpful. Although it is difficult to assess the level of understanding parents had at the time, it seems most parents felt they were informed by their providers.

When considering the amount of information that is provided to parents regarding testing and risks, it is also important to realize the emotional states parents often described while being in the hospital. Experienced emergency department providers have likely seen these presentations many times in their careers, however understanding the emotions parents are describing can potentially be an essential pillar when aiming to enhance shared decision-making and improve the parents’ experience during the medical evaluation of their children.

Given that the approach to febrile infants in the first month of life can be different with regards to CSF studies when compared to those in the second month of life, it was expected to observe variability in the parents’ perspective regarding their involvement in making some of the decisions associated with their children. Interestingly however, there was also variability within parents of infants in the second month of life. While some felt their opinion was considered and listened too, others felt less part of the decision.

When analyzing the factors that either increased or decreased the level of stress, parents often cited the compassionate and kind care of providers (with a special emphasis given to nurses) as one of the main factors allowing them to feel less stressed. Parents also appreciated when the staff would place emphasis not only on the patient but also on the parents’ experience. On the other hand, uncertainty, the wait and watching the testing being done on their children (especially when the blood draws, LPs or IVs were
unsuccessful) were some of the main factors that worsened their stress levels while in the hospital.

Given the multiple potential etiologies of fever in infants, it was also expected for variability to be observed in parental perceptions on whether their babies were doing well or not well at the time the interviews were conducted. Interestingly many parents expressed improvement on their perception of their baby’s health when compared to their initial presentation, however some noted evident changes in their baby’s health-status when compared to baseline.

Another interesting concept that can often be overlooked is the impact that this experience can have in families. Not just the emotional toll and potentially traumatic experience of witnessing the tests required to be performed on their infants, but also on other things that can become and additional sources of stress and worry for parents. These include the need to find childcare for other their children while being in the hospital, the need to miss work, or financial concerns associated with the care received.

In 1964 Green and Solnit described the concept of the vulnerable child syndrome (VCS). They reported cases of healthy children that experienced life-threatening events in which their parents expected fatal results, and how this impacted the psychological development and parent-child relationship in the long term. Others have studied the impact of the VCS in emergency department usage.

The potential impact of the parents’ experience during the evaluation of a febrile infant to rule-out bacterial meningitis could have more significant and long-term consequences that we are currently aware. We tried to explore how such experience
would influence the parents’ future reactions to changes in the health-status of their children. However, a better understanding of the long-term impact that the evaluation of a febrile infant can have in the parent-child relationship and the long-term consequences (if any) this experience can have in the development of the child, could provide further insights into the appropriate information and resources that physicians could provide to parents to offer optimal care.

It is important to note that the results of this project presented in this body of work need to be finalized before generating a final list of themes and items to be validated for inclusion in a parent-reported outcome measure.

Limitations

Interviews were conducted at a single, tertiary-care children’s hospital. However, we enrolled parents from different race/ethnicities, ages, genders, and levels of education and preferred language. In addition, interviews were conducted in only two languages with most of them being done in English. This means our results might not be generalizable to the entire population of parents of febrile infants. Our goal is for this to serve as an initial study upon which further research could be done to eventually create a parent-reported outcome measure that better represents the diversity of our society.

In addition, parents were interviewed shortly after being admitted or discharged from the hospital. Although this may have provided a fresh perspective, their answers might have also been influenced by the emotional state associated with their presentation. For this reason, the validation of results with parents (months after the original interviews were conducted) and other healthcare providers will be important.
IV. Development of a software application to provide relevant information to parents of febrile infants in the emergency department

Usability testing is an important step when creating interactive, user-centered tools to evaluate the effectiveness, efficiency, and appropriate responses in projected users. After completion of the usability testing part of the project, important changes will be implemented to the structure, navigability and content of the application based on obtained results. Following these changes, field testing of the application will be performed in order to evaluate the impact of this tool in the medical encounter, specifically on parents’ knowledge and experiences, and to facilitate a shared decision-making process between physicians and parents.
CONCLUSION

Most infants ≤60 days of age with bacterial meningitis have either CSF pleocytosis or a positive Gram stain result. Among infants with normal CSF profiles, bacterial meningitis is rare, and clinicians should consider the results of additional laboratory parameters in making treatment decisions.

The BioFire® FilmArray® Meningitis/Encephalitis Panel is the first FDA-cleared multiplexed PCR capable of simultaneously detecting and identifying 14 organisms in CSF samples. This newer rapid diagnostic tool has an overall high sensitivity and specificity for CNS infections and has the potential to improve diagnosis and optimize utilization of healthcare resources for patients undergoing evaluation of meningitis. However, the ME panel should not be used as the sole diagnostic tool in patients with suspected bacterial meningitis, and clinicians should interpret ME panel results in combination with clinical, epidemiological and laboratory data. Additionally, both false positive and false negative results have been reported. A negative ME panel test does not indicate the absence of infection, as only 14 organisms are included in the panel, and a positive test may not necessarily reflect the true disease-causing organism, such as with latent viral infections. More research is needed to guide laboratories and clinicians in determining the optimal use of the ME panel in clinical decision-making for patients undergoing evaluation for CNS infections.

Semi-structured qualitative interviews have allowed for the preliminary identification of important themes to be considered for validation in the generation of a parent-reported outcome measure for febrile infants ≤60 days of life. Further analysis and
interpretation of the obtained results is essential to determine the appropriate set of themes to be included for validation.

Design impression and usability testing of an application to provide relevant information to parents during the evaluation of febrile infants in the emergency department has already provided valuable data to implement changes in the structure and content of the application. Completing the usability testing will be important in order to ensure the application is capable of effectively achieving its intended objective.

The evaluation process of young infants suspected of having meningitis can be complex. Clinicians must consider all of these factors in decision-making: 1) variation of clinical presentations; 2) importance of acting in a timely fashion; 3) determination of the optimal testing strategy; 4) limitations of current diagnostics; 5) invasiveness of the lumbar puncture; 6) amount and level of information parents need to effectively participate in shared decision-making. The four projects described in this thesis aim to address several of these areas that are important for the evaluation, diagnosis, parental experience, and decision-making during the evaluation of infants ≤60 days of age with concern for meningitis.

Further work is essential to better understand the presentation of infants in the first 2 months of life with bacterial meningitis. Additional research is fundamental to continue assessing the impact of new diagnostic technologies, such as the ME panel, in overall patient care. The development of a parent-reported outcome measure will give medical providers the ability to assess and continuously improve on the care they provide during the evaluation of infants suspected of having meningitis. Further testing and
implementation of the described software application will facilitate communication and shared decision-making with parents of febrile infants during the evaluation process.

The concepts and ideas explored on these projects could also have potential applications in other populations, such as in different age groups. In addition, the process of understanding parental experiences or the implementation of software applications in patient care could also serve as valuable resources for parents of children being evaluated for other medical conditions.
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**Table 1. Interview Guide used for Parents of Febrile Infants ≤60 Days of Age Evaluated in the Emergency Department**

<table>
<thead>
<tr>
<th>Interview Topic</th>
<th>Interview Questions</th>
<th>Associated Prompts</th>
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<tbody>
<tr>
<td><strong>Rapport building</strong></td>
<td>Tell me about your baby. What are some of your favorite things to do with your baby?</td>
<td></td>
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<tr>
<td><strong>Experience</strong></td>
<td>- Why did you decide to bring your baby to the emergency room?</td>
<td>- Did you have any expectations about what would happen in the emergency room?</td>
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<td></td>
<td>- What were you hoping would happen in the emergency room?</td>
<td>- What were you expecting to happen in the emergency room that would help your baby?</td>
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<tr>
<td></td>
<td>- What was your experience like in the emergency room from when you arrived to when you were discharged/admitted to the hospital?</td>
<td>- What was the experience like with the nurses and doctors? Tell me more about that</td>
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<td></td>
<td>- What was good about the experience?</td>
<td>- What was the experience like when your baby was having tests done? Tell me more about that</td>
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<tr>
<td></td>
<td>- What parts of the experience could have been better?</td>
<td>- Did your baby have a spinal tap? If YES, what was that experience like?</td>
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<td></td>
<td>- How informed did you feel about what was happening in the emergency room?</td>
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<td></td>
<td>- How involved did you feel in making decisions for your baby?</td>
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<td></td>
<td>- How would you describe your feelings in the emergency room while your baby was being evaluated?</td>
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<td></td>
<td>- What was stressful about being in the emergency room?</td>
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<td></td>
<td>- What made the experience less stressful?</td>
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<td></td>
<td>- What can nurses and doctors do to make the experience less stressful?</td>
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<td></td>
<td>- Could you describe what a good experience in the emergency room with your baby would look like?</td>
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<td></td>
<td>- Could you suggest any changes that would make the experience better for the next family with a baby with fever?</td>
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<tr>
<td>If admitted:</td>
<td>- What has your experience been like being admitted to the hospital?</td>
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<td></td>
<td>- How do you feel about your baby being in the hospital?</td>
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<tr>
<td>If discharged from the ED:</td>
<td>- What has your experience been like being home with your baby?</td>
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<tr>
<td></td>
<td>- How do you feel about being at home with your baby?</td>
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<tr>
<td><strong>Satisfaction</strong></td>
<td>How satisfied do you feel about the medical care given to your baby in the emergency room? Please explain</td>
<td>- What helped your satisfaction the most?</td>
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<td></td>
<td></td>
<td>- What could have made you more satisfied?</td>
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<tr>
<td><strong>Infant Outcomes</strong></td>
<td>How is your baby doing now? Tell me more about that</td>
<td>- How is your baby acting?</td>
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<td></td>
<td>How do you know that your baby is doing well/not well?</td>
<td>- How is your baby feeding?</td>
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<tr>
<td></td>
<td>What information do you use to know if your baby is doing well?</td>
<td>- How is your baby sleeping?</td>
</tr>
<tr>
<td></td>
<td>What is most important to you in deciding that your baby is doing well?</td>
<td></td>
</tr>
<tr>
<td><strong>Family Outcomes</strong></td>
<td>- How has your baby’s illness affected your family?</td>
<td>- Did you or a family member have to miss work? Please explain</td>
</tr>
<tr>
<td></td>
<td>- Are you worried about the costs of the emergency room visit/admission? Please explain</td>
<td>- Did you need to find childcare? Please explain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Did your baby’s illness cause you or your family any financial problems? Please explain</td>
</tr>
<tr>
<td><strong>Ending Questions</strong></td>
<td>Is there anything else you would like to add?</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2. Cerebrospinal Fluid Parameters of Infants ≤60 Days of Age with Bacterial Meningitis

<table>
<thead>
<tr>
<th></th>
<th>Positive CSF Gram Stain Result, n/N (%)</th>
<th>CSF Pleocytosis (Corrected), n (%)</th>
<th>Neutrophil-Predominant CSF Among Infants with CSF Pleocytosis (Corrected), n/N (%)</th>
<th>Elevated CSF Protein Levels, n/N (%)</th>
<th>Low CSF Glucose Levels, n/N (%)</th>
<th>CSF Pleocytosis (Corrected) or Positive CSF Gram Stain Result, n (%)</th>
<th>Any Abnormal CSF Parameter, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=66)</td>
<td>46/64 (71.9)a</td>
<td>53 (80.3)</td>
<td>46/63 (73.0)c</td>
<td>31/63 (49.2)c</td>
<td>57 (86.4)</td>
<td>62 (93.9)</td>
<td></td>
</tr>
<tr>
<td>By Age Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤28 days (n=44)</td>
<td>29/43 (67.4)a</td>
<td>35 (79.6)</td>
<td>29/33 (87.9)b</td>
<td>18/42 (42.9)c</td>
<td>38 (86.4)</td>
<td>40 (90.9)</td>
<td></td>
</tr>
<tr>
<td>Age 29-60 days (n=22)</td>
<td>17/21 (81.0)a</td>
<td>18 (81.8)</td>
<td>17/18 (94.4)</td>
<td>13/21 (61.9)c</td>
<td>19 (86.4)</td>
<td>21 (95.5)</td>
<td></td>
</tr>
<tr>
<td><em>P</em></td>
<td>0.38</td>
<td>1.0</td>
<td>0.65</td>
<td>0.14</td>
<td>0.15</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** CSF, cerebrospinal fluid

- a Two infants had missing CSF Gram stain results
- b Two infants with corrected CSF pleocytosis had no CSF WBC differential
- c Three infants did not have a CSF protein or glucose level measurement
- d *P* value for comparison of parameter by age group (≤28 vs. 29-60 days)
Table 3. Characteristics of the 9 Infants with Bacterial Meningitis Who Had a Negative Gram Stain Result and No Corrected CSF Pleocytosis

<table>
<thead>
<tr>
<th>Age, d</th>
<th>History of Prematurity, Yes or No&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ill-appearing, Yes or No</th>
<th>WBC Count, Cells per µL</th>
<th>ANC, Cells per mm&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Bands, %</th>
<th>CSF WBC Count, Corrected, Cells per mm&lt;sup&gt;3&lt;/sup&gt;</th>
<th>CSF RBC Count, Cells per mm&lt;sup&gt;3&lt;/sup&gt;</th>
<th>CSF Protein Level, mg/dL</th>
<th>CSF Glucose Level, mg/dL</th>
<th>Blood Culture Result</th>
<th>CSF Culture Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>No</td>
<td>No</td>
<td>23,900&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6,955</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>684</td>
<td>58</td>
<td>No growth</td>
<td><em>K. oxytoca</em></td>
</tr>
<tr>
<td>11</td>
<td>No</td>
<td>No</td>
<td>17,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9,520</td>
<td>11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4</td>
<td>2</td>
<td>73</td>
<td>52</td>
<td>GBS</td>
<td>GBS</td>
</tr>
<tr>
<td>15</td>
<td>No</td>
<td>Yes</td>
<td>12,000</td>
<td>4,320</td>
<td>22&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>53,805</td>
<td>199</td>
<td>51</td>
<td><em>S. aureus</em></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td>19</td>
<td>No</td>
<td>No</td>
<td>3,310&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1,324</td>
<td>1</td>
<td>0</td>
<td>243,500</td>
<td>313</td>
<td>55</td>
<td>No growth</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>23</td>
<td>No</td>
<td>No</td>
<td>13,600</td>
<td>4,216</td>
<td>20&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4</td>
<td>0</td>
<td>52</td>
<td>42</td>
<td>GBS</td>
<td>GBS</td>
</tr>
<tr>
<td>28</td>
<td>Yes</td>
<td>Yes</td>
<td>4,870&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1,768</td>
<td>0</td>
<td>0</td>
<td>3,065</td>
<td>86</td>
<td>58</td>
<td>No growth</td>
<td>GBS</td>
</tr>
<tr>
<td>36</td>
<td>Yes</td>
<td>No</td>
<td>5,630</td>
<td>1,278</td>
<td>14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3</td>
<td>225</td>
<td>197</td>
<td>52</td>
<td>GBS</td>
<td>GBS</td>
</tr>
<tr>
<td>42</td>
<td>No</td>
<td>No</td>
<td>10,950</td>
<td>4,599</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>62,778</td>
<td>589</td>
<td>41</td>
<td><em>E. coli</em></td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>43</td>
<td>Yes</td>
<td>Yes</td>
<td>21,500&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17,200</td>
<td>0</td>
<td>8</td>
<td>6</td>
<td>86</td>
<td>39</td>
<td>No growth</td>
<td>GBS</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell, ANC, absolute neutrophil count, -, not applicable.

<sup>a</sup>Prematurity was defined as gestational age <37 weeks.

<sup>b</sup>Abnormal values: WBC > 15,000 or <5,000 cells per µL.

<sup>c</sup>Abnormal values: band percentage > 10%.

<sup>d</sup>Band count not performed at this site.
Table 4. Targets of the BioFire® FilmArray® ME Panel

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Bacteria</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td><em>Escherichia coli K1</em></td>
<td><em>Cryptococcus neoformans</em></td>
</tr>
<tr>
<td>Enterovirus (EV)</td>
<td><em>Haemophilus influenza</em></td>
<td></td>
</tr>
<tr>
<td>Herpes Simplex Virus-1 (HSV-1)</td>
<td><em>Listeria monocytogenes</em></td>
<td></td>
</tr>
<tr>
<td>Herpes Simplex Virus-2 (HSV-2)</td>
<td><em>Neisseria meningitides</em></td>
<td></td>
</tr>
<tr>
<td>Human Herpesvirus 6 (HHV-6)</td>
<td><em>Streptococcus agalactiae</em></td>
<td></td>
</tr>
<tr>
<td>Human Parechovirus (HPeV)</td>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>Varicella-Zoster Virus (VZV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Studies of the BioFire® FilmArray® ME Panel included in the 2019 Meta‐Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Total Number of Samples in the Study</th>
<th>Type of Study</th>
<th>Overall Sensitivity</th>
<th>Overall Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Positive Likelihood Ratio (LR+)</th>
<th>Negative Likelihood Ratio (LR−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leber et al.</td>
<td>Pediatrics and Adults</td>
<td>1560</td>
<td>Prospective</td>
<td>94.2%</td>
<td>97.7%</td>
<td>74.8%</td>
<td>99.6%</td>
<td>41.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Arora et al.</td>
<td>Pediatrics</td>
<td>62</td>
<td>Prospective</td>
<td>100.0%</td>
<td>93.4%</td>
<td>55.6%</td>
<td>100.0%</td>
<td>15.3</td>
<td>0</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>Pediatrics and Adults</td>
<td>42</td>
<td>Prospective</td>
<td>60%</td>
<td>100%</td>
<td>100.0%</td>
<td>86.7%</td>
<td>N/A</td>
<td>0.40</td>
</tr>
<tr>
<td>Radmard et al.</td>
<td>Pediatrics and Adults</td>
<td>705</td>
<td>Retrospective</td>
<td>85.7%</td>
<td>98.3%</td>
<td>36.8%</td>
<td>99.9%</td>
<td>52.2</td>
<td>0.13</td>
</tr>
<tr>
<td>Hanson et al.</td>
<td>Pediatrics and Adults</td>
<td>342</td>
<td>Retrospective</td>
<td>91.8%</td>
<td>88.3%</td>
<td>88.4%</td>
<td>91.7%</td>
<td>7.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Messacar et al.</td>
<td>Pediatrics</td>
<td>138</td>
<td>Retrospective</td>
<td>91.1%</td>
<td>97.9%</td>
<td>95.3%</td>
<td>95.9%</td>
<td>43.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Graf et al.</td>
<td>Pediatrics</td>
<td>133</td>
<td>Retrospective</td>
<td>92.5%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>93.0%</td>
<td>N/A</td>
<td>0.07</td>
</tr>
<tr>
<td>Piccirilli et al.</td>
<td>Pediatrics and Adults</td>
<td>63</td>
<td>Retrospective</td>
<td>85.7%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>77.8%</td>
<td>N/A</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Table 6. Themes that Emerged After a Preliminary Review of Interviews Performed to Parents of Febrile Infants

<table>
<thead>
<tr>
<th>Theme Identified</th>
<th>Representative Answers</th>
</tr>
</thead>
</table>
| Feeling Informed | - “We felt like we knew everything that they were going to do from front to back. There wasn’t anything they were doing that they weren’t telling us about. As they were going along, they were kind of explaining everything, even the simple things like using the light to try and find the vein and everything like that. It was very descriptive and everything in letting us know exactly what they were doing.”  
  - “So I think the news of being admitted was a little shocking to both of us because he said it and neither of us said anything for a few seconds because I think we were just so surprised. Just because – not that they hadn’t been communicating, but we both just had that thought that we were going to be sent home and everything was going to be like, oh, this is nothing. But then yeah, no, everything went very smoothly with being admitted.”  
  - “Almost like they – in a good way, they were repeating themselves, which is good because being that I was exhausted and I was pretty much up the night before. Some things I heard, some things I didn’t. It just depends on who was talking. So it was nice to get the repeat story and information. Then like, you know, the doctor would tell us something and then we would Google it and look it up and have more questions when they came back. So I think we both felt very informed.” |
| Involvement in Decisions | - “Yes, I think that they definitely didn’t make them for me. They just gave me the pros and cons on like what, especially with the spinal tap, the benefits of it and you know the negative effects and the pros definitely outweighed the cons so we went with that.”  
  - “I feel like that’s the way it’s been in the hospital. They just tell you instead of asking. I mean, they’re the doctors and nurses. But it kind of just feels like, oh, he’s now admitted for three days without – I don’t know if I should be consulted, but they’re just like oh, he’s now admitted. So there’s never really like, a…do you want him admitted?”  
  - “Oh yeah. Definitely. It was all of our decision. You know? They would’ve done – if we really wanted to do the spinal tap at that time, they would’ve done it. They gave us what they thought was best and what they had discussed and they let us make our own choice.” |
| Stress | - “The nurses were wonderful. They gave me a break. They watched the baby and I could leave the room and catch my breath and make my phone calls and prepare to be staying so that was great. We got right up here really quickly for a bed request. The transition was really smooth, so that’s always good and then the staff up here were great too so everything went well.”  
  - “Just really to me, it was the not knowing. You know, they can’t give us an answer if they don’t know. You’ve got to wait for the cultures to come back, which is totally understandable. The other thing that kind of worried me, which they did go over and like I said, they did a great job, was the spinal fluid tap. You know, that scares me because I know there’s a lot of nerves...” |
around the area and things like that. So that was very scary. But I mean, they were great. They let us stay in the room while they did it. They had a good team in there doing it. So you know, that always makes a world of difference, especially when us as new parents coming in and dealing with this, the whole thing is scary.”

### Infant Outcomes
- “He’s good. His fever is 99.5 this morning. He’s just been very sort of snuggly and quiet. He’s you know I think a little off, I can tell from his personality – from the last 48 hours. He seems tired, but other than that, the temperature is down, there’s not other symptoms, so we’re in close contact with the pediatrician’s office just to make sure everything is okay.”
- “She’s doing much better. Her fever has completely come down. The rash that she came in for is also completely gone, which is good. We’re hoping we’re going home today. She said as long as she stays stable, we should be able to go home this afternoon.”
- “He’s been doing fine. But definitely I can tell that the antibiotics already start to have some effect on him. He’s a little bit more fussy. Yeah.”

### Family Outcomes
- “Yeah, I mean, it’s a really good question. I think there will be a residual just automatic response next time she gets a fever. Even if it’s like a couple months out and it’s totally normal for a cold or an ear infection. I think there’s going to be like that residual, last time we went through this, it was terrible. But like, I personally am a psychologist and in my training, I did my focus for a couple years was on pediatric behavioral health. And so I worked in hospitals and you know, I was on the staff side to some degree for a while. So I remember right, sick kids on whatever spectrum of sick, even if they’re chronically ill, having something that’s normal for them and not feeling medicalized is really healthy for them. That’s really important for them to not just be a kid with a medical diagnosis.”
- “Well it was a lot. So I think yesterday was the first day that I kind of felt normal. So throughout the admission and I think the couple days after, me personally, I was just having spontaneous crying fits and I knew cognitively that everything was okay, you know? Odds of relapse are super small, but just the emotional load, I just couldn’t shake it. It was really heavy. It really dug in there I think. For my husband, he was just beside himself in the hospital and yeah, he was able to resume in normal, daily activities when we got home. I think he detached from the emotional fear a little bit faster than I did. But he definitely was still feeling it. He just processed it differently. Then we have grandparents on both sides and they were both really concerned obviously and shocked because nobody expected it and the fact that she got this, I guess according to the pediatrician was just really, really rare. My three-year-old daughter, we explained it to her, you know, like bacteria and the bad germs/good germs. You know, needing medicine and all of that. So she kind of got a concrete understanding of it, just something for her to latch onto knowledge-wise to help her make sense of why her sister was in the hospital and why we were gone for a short while.”
Table 7. Potential Benefits and Limitations of the BioFire® FilmArray® ME Panel

<table>
<thead>
<tr>
<th>Potential Benefits</th>
<th>Potential Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Faster turnaround time, diagnosis and definitive treatment/treatment discontinuation 70,71,74</td>
<td>-Concern for false positive and false negative tests 23,66,94-97,112</td>
</tr>
<tr>
<td>-Pathogen identification in culture-negative CSF samples from patients with suspected bacterial meningitis 71,80,89-91</td>
<td>-Not all pathogens able to cause CNS infections are detected by the panel 63,66,70,71,78,79,86,112</td>
</tr>
<tr>
<td>-Detection of organisms in CSF obtained after antimicrobial pretreatment 71,80,81,87,88</td>
<td>-Unable to provide antimicrobial susceptibilities 63,66</td>
</tr>
<tr>
<td>-Enables simultaneous identification of co-infections on the same sample 9,101</td>
<td>-Not intended for CSF samples obtained from indwelling CNS medical devices 63</td>
</tr>
<tr>
<td>-Ability to test for multiple organisms simultaneously 63</td>
<td>-Positive results do not exclude the possibility of a co-infection with an organism not in the panel 63</td>
</tr>
<tr>
<td>-Facilitates proper administration of chemoprophylaxis for close contacts 81</td>
<td>-Relatively high cost of purchase ($35,550-$50,000), service ($4,000/year) and per test ($~200) 68,83,93</td>
</tr>
<tr>
<td>-Relatively small amount of CSF sample (minimum 0.2 mL) required 63</td>
<td>-Lower ability to detect viruses when compared to some singleplex assays 75,94,100,101</td>
</tr>
<tr>
<td>-Limited hands-on time and technical expertise necessary 23,68</td>
<td>-Positive results for herpesviruses may be due to latency or reactivation of the virus with or without disease 66,94</td>
</tr>
</tbody>
</table>