Do All Children Who Present With a Complex Febrile Seizure Need a Lumbar Puncture?

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Study objective: We assess the prevalences of bacterial meningitis and herpes simplex virus meningoencephalitis (HSV-ME) in children with a complex febrile seizure and determine these prevalences in the subgroup of children with a clinical examination result not suggestive of meningitis or encephalitis.

Methods: This multicenter retrospective study was conducted in 7 pediatric emergency departments (EDs) in the region of Paris, France. Visits of patients aged 6 months to 5 years for a complex febrile seizure from January 2007 to December 2011 were analyzed. We defined a subgroup of patients whose clinical examination result was not suggestive of meningitis or encephalitis. Bacterial meningitis and HSV-ME were sequentially sought for by analyzing bacteriologic and viral data at the visit, looking for data from a second visit to the hospital after the index visit, and telephoning the child's parents.

Results: From a total of 1,183,487 visits in the 7 pediatric EDs, 839 patients presented for a complex febrile seizure, of whom 260 (31.0%) had a lumbar puncture. The outcomes bacterial meningitis and HSV-ME were ascertainable for 715 (85%) and 657 (78.3%) visits, respectively, and we found 5 cases of bacterial meningitis (0.7% [95% confidence interval [CI] 0.2% to 1.6%]) and no HSV-ME (0% [95% CI 0% to 0.6%]). Among the 630 visits of children with a clinical examination result not suggesting meningitis or encephalitis, we found no bacterial meningitis (0% [95% CI 0% to 0.7%]) and no HSV-ME (0% [95% CI 0% to 0.8%]).

Conclusion: In children with a complex febrile seizure, bacterial meningitis and HSV-ME are unexpected events when the clinical examination after complex febrile seizure is not suggestive of meningitis or encephalitis. [Ann Emerg Med. 2017;70:52-62.]

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INTRODUCTION

Background and Importance

Febrile seizures are defined as seizures occurring in children aged 6 months to 5 years, in a context of fever, without a history of an unprovoked seizure or concurrent central nervous system infection.[1,2] They affect 2% to 5% of children in Europe and North America.[3,4] They are categorized as complex if at least one of the following features is present: focal seizure, prolonged seizure (>15 minutes), or multiple seizures (>1/24 hours). Because a seizure in the context of fever may be associated with bacterial meningitis[5] or herpes simplex virus meningoencephalitis (HSV-ME),[6] deciding whether a lumbar puncture should be performed to rule out these central nervous system infections in children presenting with a complex febrile seizure may be a challenge.

Before the availability of immunization against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (prepneumococcal conjugate vaccine era), the global prevalence of bacterial meningitis in children with "seizure and fever" was found to be 0.8%[7] and was approximately 5 times higher after a complex than a simple febrile seizure.[8] However, a recent meta-analysis including 2 postvaccine-era studies found a pooled prevalence of bacterial meningitis in children with a complex febrile seizure of 0.6%.[9] Currently, the scarce guidelines on the performance of a lumbar puncture

Editor's Capsule Summary

What is already known on this topic

Complex febrile seizure in children is an uncommon (<1%) presenting symptom of bacterial meningitis or herpes meningoencephalitis. Many debate the need for emergency lumbar puncture in these children.

What question this study addressed

What is the current prevalence of bacterial meningitis and herpes meningoencephalitis in children with complex febrile seizure who have no other clinical findings suggestive of these conditions?

What this study adds to our knowledge

In a multicenter retrospective study conducted in Paris, France, among 839 children aged 6 months to 5 years with complex febrile seizure, 0.7% had bacterial meningitis and none had herpes meningoencephalitis. Among children free of other suggestive clinical findings of either, none had these diseases.

How this is relevant to clinical practice

These data support the development of guidelines limiting lumbar puncture for complex febrile seizure in the absence of other concerning signs in urban vaccinated populations.

in children with complex febrile seizure are heterogeneous,[10-13] and thus clinical practices are also.[14] In the context of a complex febrile seizure, potential contributing reasons for this heterogeneity are a low risk of bacterial meningitis, an unknown risk of HSV-ME, an unknown risk of bacterial meningitis or HSV-ME in the subgroup of patients for whom the clinical examination does not suggest these infections, and the fact that complex febrile seizure include some very different clinical situations such as brief generalized multiple seizures and status epilepticus.[15]

Goals of This Investigation

We hypothesized that among children with complex febrile seizure, the subpopulation presenting with a clinical examination result not suggestive of meningitis or encephalitis had prevalence for these infections of close to zero. The objective of this study was to calculate the proportion of bacterial meningitis and HSV-ME in children with a complex febrile seizure, and to determine these proportions according to the feature of the seizure and in the subgroup of children with a clinical examination result not suggestive of meningitis or encephalitis.

MATERIALS AND METHODS

Study Design

We retrospectively reviewed the records of all visits of patients aged 6 months to 5 years in 7 pediatric emergency departments (EDs) in the Paris region in France between January 2007 and December 2011 for a complex febrile seizure and determined the proportion of bacterial meningitis and HSV-ME in this population. In France, conjugate immunizations against *H influenzae* type b or *S pneumoniae* were introduced in 1992 and 2003, respectively, and the respective national immunization coverage was higher than 95% and 90%, respectively, during the enrollment period.[16]

The study was approved by the local ethics committee for the protection of human subjects, and the computerized data collection was approved by the French Data Protection Authority.

Febrile seizure and complex febrile seizure were defined as above. The index visit was defined as the visit that was included in the study. Fever was defined as any temperature greater than or equal to 38.0°C [100.4°F].

Setting and Selection of Participants

From the 7 pediatric EDs, 2 were located in university pediatric hospitals, 2 in university general hospitals and 3 in teaching general hospitals. The 5 general hospitals had an independent pediatric department that allowed them to have a separate pediatric ED staffed by pediatricians. They all used the same electronic medical records software, Urqual (McKesson Corp, Paris, France), but each hospital was independent. All visits from January 2007 to December 2011 with an available electronic medical record were evaluated for inclusion. The record exhaustiveness of this system is higher than 99% because accidental downtimes are rare and brief.

Visits were eligible if the patients had come to the ED within 24 hours after a complex febrile seizure. Although we had initially planned to include children aged 3 months to 5 years, as stipulated in the clinical trial registry, we decided to limit the study group to those aged 6 months to 5 years to comply with the American Academy of Pediatrics definition.[1] Visits of patients with a simple febrile seizure, a medical history of nonfebrile seizure, or conditions known to be associated with an increased risk of seizure (eg, cerebral malformation, genetic syndromes, trauma in the previous 24 hours) or predisposing to bacterial meningitis or HSV-ME (eg, sickle cell disease, malignant tumor, immunosuppressive treatment) were excluded. Any history of fever concomitant

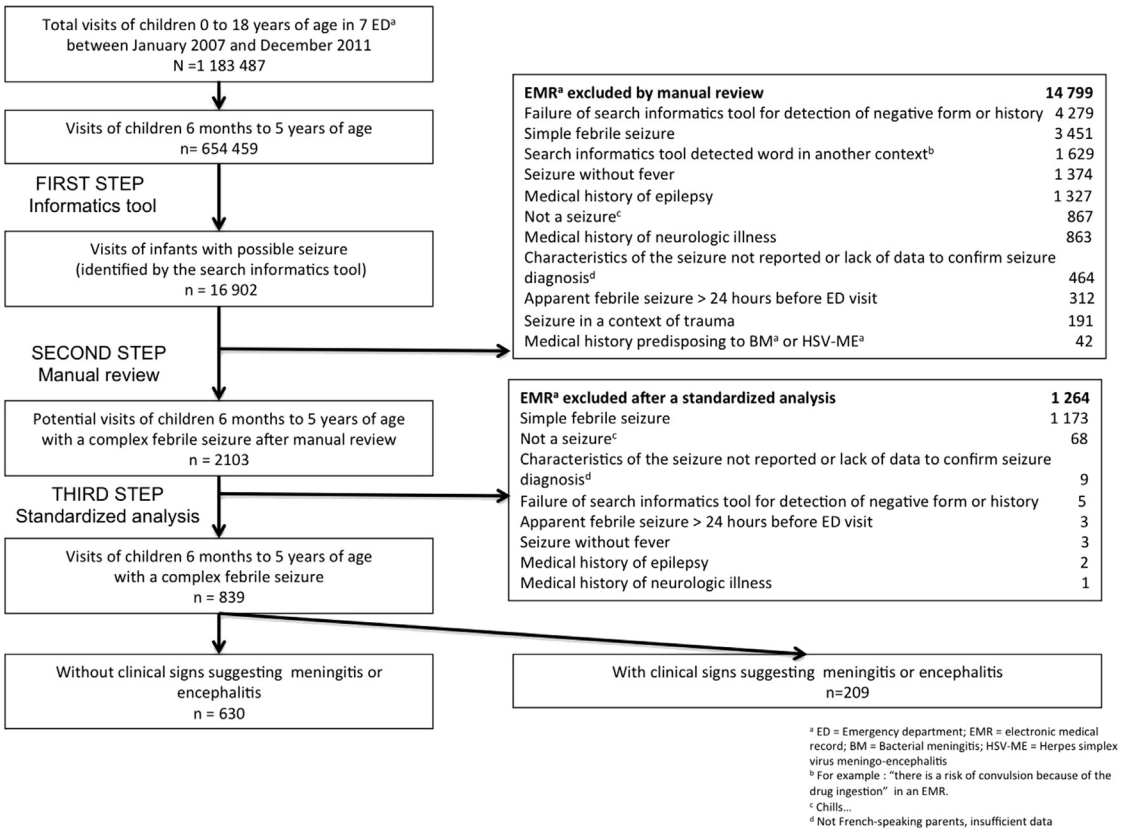

Figure 1. Selection of visits included in the study.

with the seizure was sufficient to include the patient even if the fever was not documented in the ED.

Data Collection and Processing

Visit selection was carried out in 3 steps (Figure 1). First, all visits of patients aged 6 months to 5 years and with a potential seizure were identified with a search informatics tool that used regular expressions (a sequence of characters that forms a search pattern), allowing the search in all fields of the electronic medical record of a list of key words (the French translations of "seizure," "febrile seizure," "clonic," "tonic," "shaking," "jerks," and "twitch") and their misspellings. The tool did not include records that contained these words in the medical history field and in a negative form. The complete process is detailed in Appendix E1 (available online at http://www.annemergmed.com). This methodology has already been reported.[17,18] We tested the sensitivity and specificity of this tool; the test characteristics of the tool are shown in Appendix E2 (available online at http://www.annemergmed.com). Second, one of the authors (R.G.) manually reviewed the retrieved records to identify visits for a potential complex febrile seizure. Third, this sample population was randomly split in 2 groups, and each group was assigned to one research assistant.

These 2 assistants analyzed the selected records with a sequenced standardized questionnaire. They were blind to the objectives of the study. They identified the presence or absence of a list of words in the patient's records (Appendix E3, available online at http://www.annemergmed.com). For example, more than 30 words describing the features of meningeal syndrome, neurologic examination, and mental status were gathered in the questionnaire to identify whether the clinical examination result was suggestive of bacterial meningitis or encephalitis (Appendix E3, available online at http://www.annemergmed.com). The clinical examination result was defined as suggestive of meningitis or encephalitis when at least one word of the list was in the record in an affirmative form. When all the words were in the negative form or not available in the record, we considered that the clinical examination result was not suggestive of meningitis or encephalitis. When notes from both an attending physician and a trainee were present in the electronic medical record, we gathered data from the attending physician. The first 50 records that were abstracted by each research assistant were reviewed with a physician. A quality assurance control was performed by one of the authors (R.G.), who randomly double-checked 10% of cases to ensure that assistants were following the

detailed instructions. Moreover, 15% of the electronic medical records were randomly reviewed by an attending emergency pediatrician (S.L.), who performed a global assessment of all the presenting characteristics to determine the features of the seizure and whether the patient had a clinical examination result suggesting meningitis or encephalitis. We assessed the interrater agreement for the features of the seizures and the suggestiveness of the clinical examination to confront this global assessment with the classification obtained by the sequenced questionnaire performed by the research assistants.

Finally, we identified visits of children with a complex febrile seizure and the subgroup of those without a clinical examination result suggesting meningitis or encephalitis.

Outcome Measures

The main outcomes were the proportion of bacterial meningitis and HSV-ME diagnosed up to 7 days after the index complex febrile seizure. Bacterial meningitis and HSV-ME were first sought by analysis of bacteriologic and viral data at the visit and during the hospitalization if this happened. If this information was not available, we looked for a second visit for any reason to the same hospital that occurred from the index visit to December 31, 2014, to determine whether the diagnosis of bacterial meningitis or HSV-ME was mentioned in the records, and finally, if neither of these 2 sources of information was available, we telephoned the child's parents to determine the evolution after the index visit. When a lumbar puncture had been performed, HSV-ME was defined as a positive herpes simplex virus-polymerase chain reaction (HSV-PCR) result, and bacterial meningitis was defined as bacterial growth from cerebrospinal fluid, cerebrospinal fluid pleocytosis and bacterial growth from any blood specimen, or a positive latex agglutination test result in cerebrospinal fluid. Cerebrospinal fluid pleocytosis was defined as cerebrospinal fluid WBC count greater than 7 cells/mm.[19] The correction for blood-contaminated cerebrospinal fluid was: "corrected cerebrospinal fluid WBC count=cerebrospinal fluid WBC count–(cerebrospinal fluid RBC count/700)".[20]

We used 2 additional approaches to increase the exhaustiveness and reliability of the outcome. First, to ascertain that infants lost to follow-up had not been treated in another hospital and received a diagnosis of bacterial meningitis, we verified whether they had been registered in the database of the French Surveillance Network of Bacterial Meningitis (ACTIV). This network monitors features and evolution of bacterial meningitis in France[21] and its functioning has already been described.[18] We did not look for national registries of dead infants to complete our search. A second approach was used to ensure the reliability of our outcome. As in a previous study, we called this a "reverse strategy,"[18] ie, we identified all children aged 6 months to 5 years who presented to the 7 participating EDs during the same period and selected those who had an ED discharge diagnosis code (*International Classification of Diseases, 10th Revision*) consistent with or suggestive of meningitis or encephalitis (Appendix E4, available online at http://www.annemergmed.com). We did not verify whether these discharge diagnoses were later confirmed, so most of them might have not actually been bacterial meningitis or herpes simplex virus meningoencephalitis. Then we searched in the records of these children to determine whether a febrile seizure had been a previous feature of their evolution.

Primary Data Analysis

Data are reported as means or medians for continuous variables and as proportions for categorical variables. Lumbar puncture, pleocytosis, bacterial meningitis, and HSV-ME rates are given as proportions with 95% confidence intervals (CIs), calculated by using a binomial distribution. The exact method of Clopper-Pearson was used. We used the κ test to assess the interrater agreement for the features of the seizures and the suggestiveness of the clinical examination. Proportions of bacterial meningitis and HSV-ME are also reported according to the feature of the complex febrile seizure.

The analyses were performed with SPSS (version 18; SPSS Inc, Chicago, IL) and with R (version 2.7.0; The R Foundation, Vienna, Austria). We followed methodology suggestions for a chart review study,[22] and we used the Strengthening the Reporting of Observational Studies in Epidemiology methodology to report the results.[23] $P<.05$ was considered statistically significant.

We assumed that the proportion of bacterial meningitis and HSV-ME in the group of children presenting with a complex febrile seizure and a clinical examination result not suggestive of meningitis or encephalitis would be 0%. Thus, to obtain a proportion of 0% with a 95% CI of within 1%, we computed with R software that we would need to include 367 children with a complex febrile seizure and a normal clinical examination result. Because we assumed that at least 50% of children with complex febrile seizure would have a clinical examination result not suggestive of meningitis or encephalitis, we planned to include 734 visits of children presenting with a complex febrile seizure. In accordance with these assumptions and a pilot sample, we estimated that we needed a whole sample of 1,000,000 visits in pediatric EDs to reach that number. We calculated that the aimed sample would be obtained with 5-year visits to the 7 pediatric EDs.

RESULTS

From 2007 to 2011, there were 1,183,487 visits in the 7 participating ED, including 654,459 visits for children aged 6 months to 5 years. The search informatics tool identified at the first step 16,902 visits of children for a potential seizure (Figure 1). Then the manual review yielded 2,103 visits for a potential complex febrile seizure. After a standardized analysis of these visits, we found 839 visits for a complex febrile seizure (ie, 15.3% of the 5,463 visits for febrile seizure). The interrater agreement test for the 15% sample (attending pediatrician versus research assistants) showed κ=0.80 (95% CI 0.66 to 0.94) for focal seizure, κ=0.89 (95% CI 0.81 to 0.98) for multiple seizure, κ=0.90 (95% CI 0.82 to 0.99) for prolonged seizure, and κ=0.79 (95% CI 0.66 to 0.92) for clinical examination suggesting meningitis or encephalitis.

Characteristics of Study Subjects

The descriptive characteristics of the 839 visits are shown in Table 1. The most frequent presenting feature of complex febrile seizure was multiple episodes (n=468; 55.8%). From the 839 visits, the clinical examination was suggestive of meningitis or encephalitis in 209 (24.9%). (Details about

Table 1. Descriptive characteristics of visits of children aged 6 months to 5 years, with a complex febrile seizure, and visiting 7 EDs between January 2007 and December 2011.

Characteristics	All Visits for Complex Febrile Seizures, n=839	Visits for Complex Febrile Seizures Without Clinical Signs Suggesting meningitis or encephalitis, n=630
Center, No. (%)		
A	302 (36.0)	219 (34.8)
B	135 (16.1)	102 (16.2)
C	94 (11.2)	82 (13.0)
D	79 (9.4)	59 (9.4)
E	46 (5.5)	32 (5.1)
F	85 (10.1)	63 (10.0)
G	98 (11.7)	73 (11.6)
Year of visit, No. (%)		
2007	145 (17.3)	119 (18.9)
2008	177 (21.1)	129 (20.5)
2009	172 (20.5)	134 (21.3)
2010	172 (20.5)	126 (20.0)
2011	173 (20.6)	122 (19.4)
Male patient, No. (%)	463 (55.2)	349 (55.4)
Age, median (interquartile range), mo	20 (14–29)	21 (15–30)
ED documentation of immunization status, No. (%)		
Not documented*	506 (60.3)	385 (61.2)
Updated	274 (32.7)	205 (32.5)
Not updated	59 (7.0)	40 (6.3)
Medical history of febrile seizure, No. (%)	264 (31.5)	207 (32.9)
Clinical examination result suggesting meningitis or encephalitis, No. (%)	209 (24.9)	0‡
Meningeal syndrome†	53 (6.3)	
Abnormal mental status†	98 (11.7)	
Abnormal neurologic examination result†	110 (13.1)	
Patients who received antibiotics before the ED visit, No. (%)	35 (4.2)	28 (4.4)
Disposition after the ED visit, No. (%)		
Discharged home	220 (26.2)	195 (31.0)
Hospitalization	619 (73.8)	435 (69.0)
Lumbar puncture performed, No. (%)	260 (31.0)	147 (23.3)
Complex febrile seizure by features		
Multiple	468 (55.8)	415 (65.9)
Prolonged	163 (19.4)	125 (19.8)
Focal	112 (13.3)	58 (9.2)
Focal and prolonged	48 (5.7)	11 (1.7)
Focal and multiple	30 (3.6)	12 (1.9)
Prolonged and multiple	13 (1.5)	7 (1.1)
Focal, prolonged and multiple	5 (0.6)	2 (0.3)

*Not documented in the ED record of the index visit.
†The clinical abnormalities defining each group are shown in Appendix E3, available online at http://www.annemergmed.com.
‡By definition.

the data gathering for the variables used to define the clinical examination are shown in Table E1, available online at http://www.annemergmed.com.) The characteristics of the 630 visits in which the clinical examination result was not suggestive of meningitis or encephalitis are also shown in Table 1.

A lumbar puncture was performed in 260 children (31.0% [95% CI 27.9% to 34.2%]). The proportions of children who underwent a lumbar puncture among those with and without a clinical examination result suggestive of meningitis or encephalitis were, respectively, 54% (113/209) and 23% (147/630). The median number of cells in cerebrospinal fluid was 1.5/mm^3 (interquartile range 0 to 4/mm^3; range 0 to 3,350/mm^3). Herpes simplex virus-polymerase chain reaction was performed in 55 cerebrospinal fluid samples; no results were positive. Pleocytosis was observed in 22 cerebrospinal fluid samples, including 5 cases with bacterial growth. Among the 17 patients with pleocytosis and no bacterial growth in cerebrospinal fluid, one, a 23-month-old boy, died at home the following day after the ED visit and the other 16 had a favorable outcome. The child who died had visited the ED for a left-sided hemicorporal febrile seizure. He had not received any antibiotics before the visit and was described as irritable at initial clinical examination. A lumbar puncture was performed and found a WBC count of 79 cells/mm^3, a negative latex agglutination test result, and no bacterial growth. He was discharged without any antibiotic treatment and was found dead the following morning in his bed. No evidence of any infection (meningitis or other) was found in the test results (blood and lumbar puncture) performed after his death. The death was attributed to a refractory status epilepticus.

None of the other 16 patients had been treated with antibiotics or antiviral medications on arrival to the ED. In regard to the risk of meningitis, 12 of them had a blood culture test and 6 had a latex agglutination test, all of which were negative. In regard to the risk of HSV-ME, 13 patients had a HSV-PCR result that was negative. Finally, 3 patients had an enterovirus in cerebrospinal fluid. All 16 patients were hospitalized for between 24 hours and 10 days and had a favorable outcome: 3 had a discharge diagnosis of presumptive nonherpetic meningoencephalitis, 3 of enteroviral meningitis, and 9 of presumptive viral meningitis.

The outcome bacterial meningitis was ascertainable for 715 of 839 visits (85.2%): 260 by a lumbar puncture, 357 through data obtained during a second visit, and 98 by a telephone call to parents (Figure 2). Five cases of bacterial meningitis were found; thus, the bacterial meningitis proportion was 0.7% (95% CI 0.2% to 1.6%). The characteristics of these 5 cases are described in Table 2. *S pneumoniae* was found in 4 cerebrospinal fluid samples and group B *Neisseria meningitidis* in 1 cerebrospinal fluid sample. In 4 cases, the patients were younger than 12 months. All 5 patients presented with a combined or isolated feature of prolonged seizure. A 6-month-old child died after 7 days of hospitalization.

None of the 124 children lost to follow-up was registered in the database of the French Surveillance Network of Bacterial Meningitis (ACTIV) as having bacterial meningitis. A good reliability of the database was verified because all 5 cases of bacterial meningitis diagnosed in our population were registered in this database.

The outcome HSV-ME was ascertainable for 657 of 839 visits (78.3%) (Figure 3). No HSV-ME was found; thus, the HSV-ME proportion was 0% (95% CI 0% to 0.6%).

The proportions of bacterial meningitis and HSV-ME in children according to the features of the complex febrile seizure are shown in Table 3. Among the 468 cases presenting only with multiple seizures, the proportions of bacterial meningitis and of HSV-ME were, respectively, 0% (95% CI 0% to 0.9%) and 0% (95% CI 0% to 1.0%).

Neither bacterial meningitis nor HSV-ME was found among the 630 visits in which the clinical examination result was not suggestive of meningitis or encephalitis; thus, the bacterial meningitis and HSV-ME proportions in this subgroup of patients were 0% (95% CI 0% to 0.7%) and 0% (95% CI 0% to 0.8%) (Figures E1 and E2, available online at http://www.annemergmed.com).

In regard to the reverse strategy, we found no visits of patients with a history of febrile seizure among 623 electronic medical records with a discharge diagnostic code of meningitis or encephalitis.

The rates of hospital admission and lumbar puncture performance were different among centers, ranging from 60.3% to 91.8% and from 13.0% to 51.9%, respectively (Table E2, available online at http://www.annemergmed.com).

LIMITATIONS

This study has some limitations. First, because of a retrospective design, all children with a complex febrile seizure and presenting to the ED might not have been included. This bias was reduced by a customized computerized identification of potential eligible patients. Although our list of words was comprehensive, it may have missed some unusual descriptions. Thus, we cannot be confident of the complete exhaustiveness of all the cases.

Second, we were not able to directly determine the outcome bacterial meningitis of 124 children (14.8%). However, the absence of these infants in a wide national registry of bacterial meningitis makes it very unlikely that they developed bacterial meningitis. There was no registry

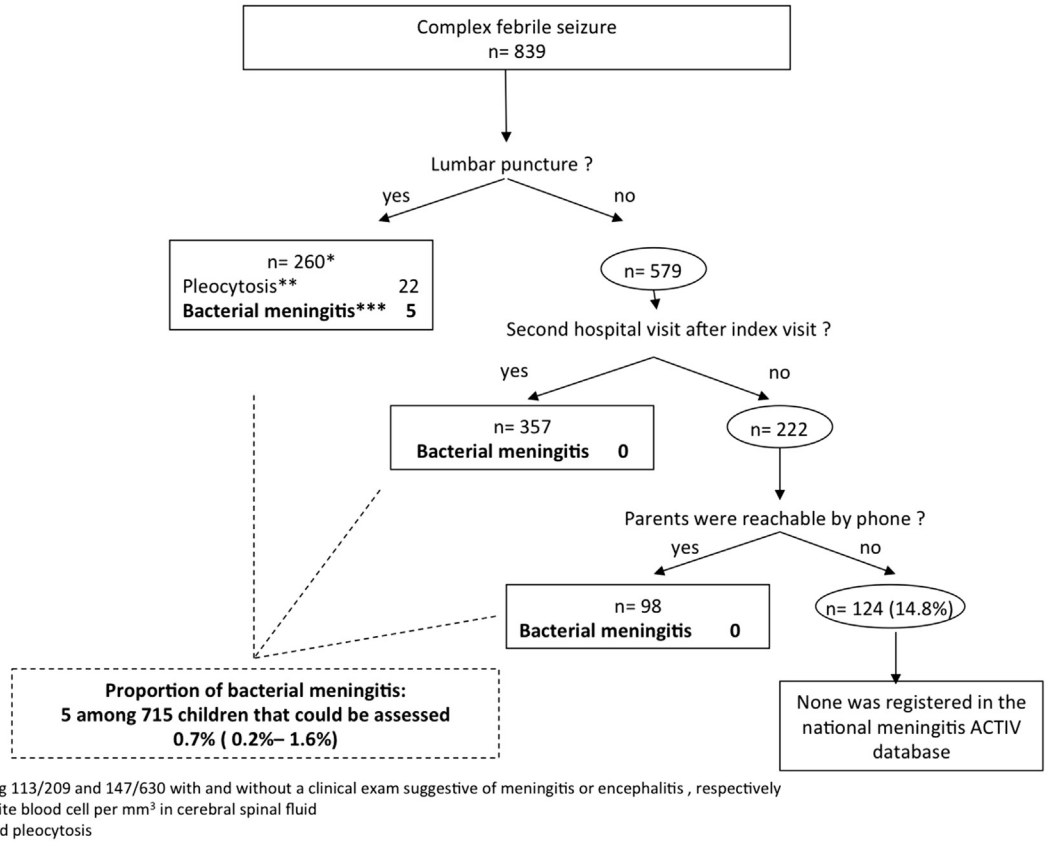

Figure 2. Proportion of bacterial meningitis among infants aged 6 months to 5 years, visiting in 7 EDs between January 2007 and December 2011, and with a complex febrile seizure.

of HSV-ME, so this second outcome was not ascertainable for 182 children (21.7%). Moreover, we were not able to link these patients with a national death registry. If a case of bacterial meningitis or herpes simplex virus was missed in patients without follow-up, it might change our results. Thus, our results should be interpreted with the caveat of 14.8% and 21.7% lost to follow-up.

Third, because this was a retrospective study, there is a potential risk that a case of bacterial meningitis or HSV-ME was inadvertently excluded during the selection process by the knowledge of the results of the clinical examination or the lumbar puncture. This potential bias was limited by making the assistants blind to the objectives of the study and by using a sequenced standardized questionnaire.

Fourth, we assumed that data not available in the electronic medical records were either normal or negative. By making this choice, we have might misclassified patients with an actual clinical examination result suggestive of meningitis or encephalitis that was not reported in the electronic medical record and thus overestimated the frequency of patients with a clinical examination result nonsuggestive of meningitis or encephalitis. We made this choice because our aim was to avoid excluding inadvertently any patient who had bacterial meningitis or MEH from the group of children with a clinical examination result nonsuggestive of meningitis or encephalitis.

Fifth, the study was not powered for subanalyses by seizure features. As with any subanalysis, the results must be interpreted with caution because of an increased risk of type I error. Moreover, because of the small size of the groups of children with a focal or prolonged seizure, the CIs are broad.

Sixth, although our results may be generalized to similar developed countries with high immunization coverage for *H influenzae* type b and *S pneumoniae*, caution is recommended when they are extrapolated to settings in which immunization coverage is much lower.

DISCUSSION

To our knowledge, this is the first multicenter European study dealing specifically with the assessment of the prevalence of bacterial meningitis and HSV-ME in children presenting a complex febrile seizure. We found no HSV-ME (0%; 95% CI 0% to 0.6%) and a very low risk of bacterial meningitis (0.7%; 95% CI 0.2% to 1.6%).

Table 2. Characteristics of the 5 visits of children with bacterial meningitis.

Patient	Age, Months	Sex	Medical History of Febrile Seizure	Features of the Seizure	Clinical Examination Suggesting Meningitis or Encephalitis	Number of Cells in CSF/mm^3	Bacteriologic Culture	Outcome, Alive
1	6	Male	No	Focal and prolonged	Yes, neck stiffness, bulging fontanel, drowsy,	803	CSF: pneumococcus	Yes
2	6	Male	No	Prolonged	Yes, bulging fontanel, unconsciousness, Glasgow Coma Scale 4	28	CSF: pneumococcus	No; died after 7 days of hospitalization
3	6	Female	No	Focal, prolonged and multiple	Yes, irritability	3,350	CSF: pneumococcus	Yes
4	8	Male	No	Focal and prolonged	Yes, bulging fontanel, unconscious	1,845	CSF: meningococcus b	Yes
5	21	Male	No	Prolonged	Yes, meningeal syndrome, neck stiffness	40	CSF: pneumococcus	Yes

CSF, Cerebrospinal fluid.

Moreover, we found neither bacterial meningitis nor HSV-ME in the subgroup of children with a clinical examination result nonsuggestive of meningitis or encephalitis.

For decades, children with febrile seizure have undergone lumbar puncture to rule out bacterial meningitis.[24] Before the 1990s, a lumbar puncture was performed from 67%[25] to more than 90%[26] of children presenting with a febrile seizure. The risk of bacterial meningitis is not the same in simple and complex febrile seizure.[9,27] In a study conducted on 205 infants aged 6 to 11 months who were treated in the ED for a first simple febrile seizure, we found no case of bacterial meningitis.[18] During the last 2 decades, 3 retrospective single-center studies conducted in the United States found a prevalence of bacterial meningitis between 0.5% and 1.5% in complex febrile seizure.[6,19,28] In a review of 390 visits of children to a pediatric ED who had complex febrile seizure between 2002 and 2006 and a lumbar puncture rate of 53%, Seltz et al[6] found a bacterial meningitis prevalence of 1.5% (95% CI 0.6% to 3.3%). In another similar review of 193 patients treated for a first complex febrile seizure from 2005 to 2010 and who had a lumbar puncture rate of 70.5%, Fletcher and Sharieff[28] found a bacterial meningitis prevalence of 0.5% (95% CI 0% to 1.5%). In a third study including 526 children with a first complex febrile seizure who were treated between 1995 and 2008 in a pediatric ED and had a 64.6% lumbar puncture rate, the bacterial meningitis prevalence found by Kimia et al[19] was 0.9% (95% CI 0.2% to 2.8%). Thus, the 0.7% prevalence of bacterial meningitis in our French cohort is in line with the reported prevalence in the United States.

In retrospective studies, potential biases are incomplete exhaustiveness of the target cases and patients lost to follow-up. Studies that selected patients by using a diagnostic code may not be exhaustive.[6,28] We sought to reduce this bias by performing a comprehensive search, using customized computerized identification of all potential eligible patients. Because complex seizures are not frequent, the feasibility of a large prospective multicenter study in pediatric EDs is so difficult to set up that it will probably not take place. That is why large retrospective data can contribute to the body of evidence. In regard to follow-up, we not only systematically looked for a second visit after the index visit but also called parents when there was not one. Thus, only 124 of 839 infants (14.8%) were lost to initial follow-up. Moreover, none of these 124 infants was registered in the French Active Surveillance Network national bacterial meningitis database. Besides, using a reverse strategy we found no history of seizure and fever among 623 electronic medical records of patients with a discharge diagnostic code of meningitis or encephalitis.

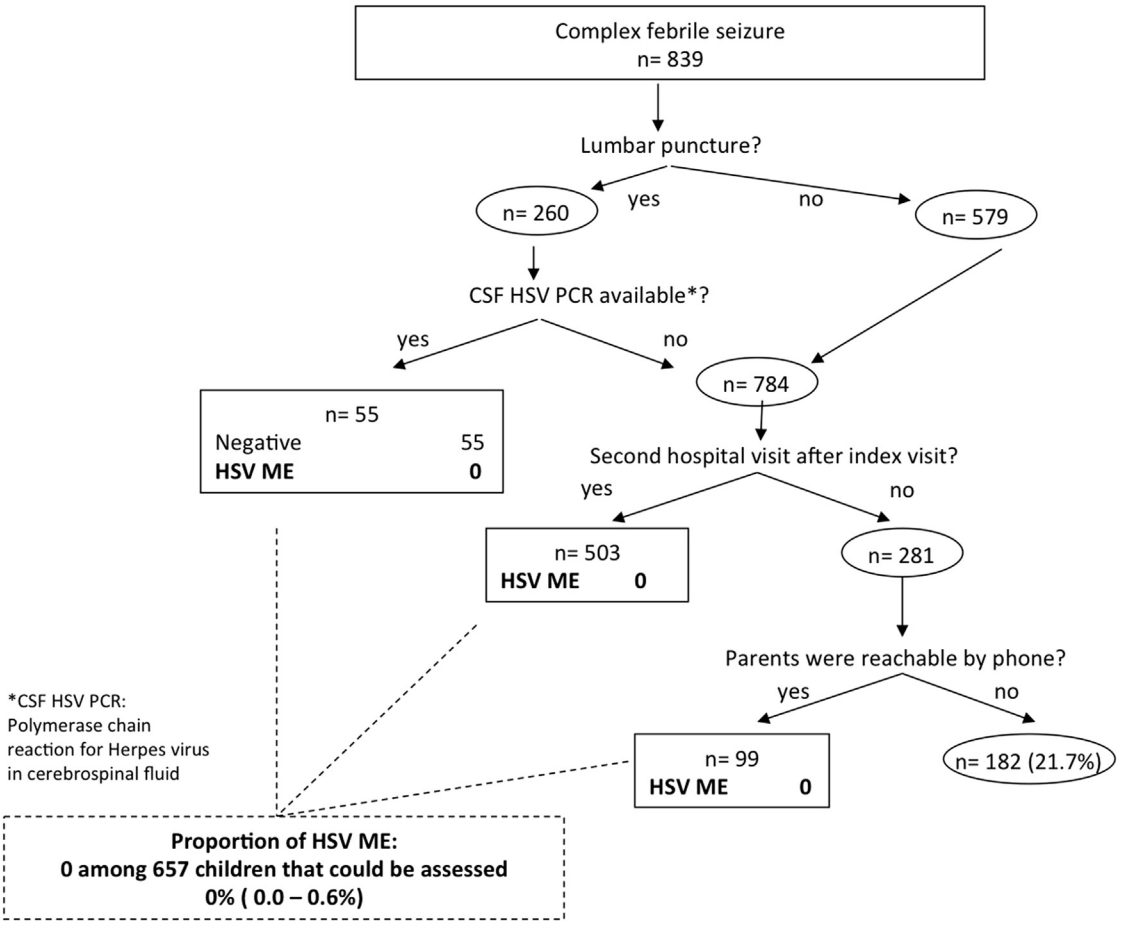

Figure 3. Proportion of HSV-ME among infants aged 6 months to 5 years, visiting in 7 EDs between January 2007 and December 2011, and with a complex febrile seizure.

Currently, recommendations about the performance of a lumbar puncture in children with complex febrile seizure are heterogeneous,[4,11-13,29,30] and so are clinical practices.[14] In our sample, 69% of children did not undergo a lumbar puncture, but clinical practices were heterogeneous among centers. Because complex febrile seizures include different types of patients with various degrees of severity of manifestations, recommendations should probably consider clinical characteristics such as age, clinical examination result, and features of the seizure as key elements.

In our study, 4 of 5 children with bacterial meningitis were younger than 12 months. Also, in the study by Kimia et al,[19] 2 of the 3 children with bacterial meningitis were younger than 12 months. In the study by Seltz et al,[6] the bacterial meningitis proportion difference between children younger than 18 months (2.8%) and older than 18 months (0.5%) did not reach statistical significance. Nonetheless,

Table 3. Proportions of bacterial meningitis and HSV-ME according to the features of 839 cases of complex febrile seizure.

		Bacterial Meningitis			HSV Meningoencephalitis		
Features of the Complex Febrile Seizure	**Number (%)**	**Lost to Follow-up (%)**	**Number of Bacterial Meningitis**	**Proportion of Bacterial Meningitis (95% CI), %**	**Lost to Follow-up (%)**	**Number of HSV-ME**	**Proportion of HSV-ME (95% CI)**
Multiple	468 (55.8)	78 (16.7)	0/390	0 (0–0.9)	101 (21.6)	0/367	0 (0–1.0)
Prolonged	163 (19.4)	25 (15.3)	2/138	1.4 (0.2–5.1)	40 (24.5)	0/123	0 (0–3.0)
Focal	112 (13.3)	18 (16.1)	0/94	0 (0–3.8)	22 (19.6)	0/90	0 (0–4.0)
Focal and prolonged	48 (5.7)	0 (0)	2/48	4.2 (0.5–14.3)	10 (20.8)	0/38	0 (0–9.3)
Focal and multiple	30 (3.6)	2 (6.7)	0/28	0 (0–12.3)	5 (16.7)	0/25	0 (0–13.7)
Multiple and prolonged	13 (1.5)	1 (7.7)	0/12	0 (0–26.5)	3 (23.1)	0/10	0 (0–30.8)
Focal, multiple, and prolonged	5 (0.6)	0 (0)	1/5	20 (0.5–71.6)	1 (20.0)	0/4	0 (0–60.2)

current data do not suggest performing a lumbar puncture routinely in all children younger than 12 months.

We found no bacterial meningitis in children for whom the clinical examination result was not suggestive of meningitis or encephalitis. In a case series during the prevaccine area, from 111 children who had bacterial meningitis and presented with seizures before hospital admission, only 8 had a "normal" level of consciousness, of whom 6 had nuchal rigidity, 1 a prolonged focal seizure, and 1 multiple seizures and petechial rash.[27] In the study by Seltz et al,[6] all 6 patients with bacterial meningitis had an abnormal mental status. In the study by Fletcher and Sharieff,[28] the only child with bacterial meningitis was intubated. Finally, in the study by Kimia et al,[19] 2 of the 3 children with bacterial meningitis had an abnormal clinical examination result; the remaining child received a diagnosis of meningitis, although there was no cerebrospinal fluid cell count because of blood in the fluid nor bacterial growth in the cerebrospinal fluid sample. Therefore, data suggest that in a child presenting with a complex febrile seizure and a clinical examination result not suggesting meningitis or encephalitis, the probability of bacterial meningitis is extremely low. Furthermore, an early lumbar puncture in these children may miss more than 40% of cases if performed too early.[7,8] An alternative might be an ED observation of 2 to 4 hours[31] to rapidly prompt the performance of a lumbar puncture if any deterioration in the clinical examination result occurs.

In our study, all children with bacterial meningitis experienced a prolonged seizure. This in line with the fact that bacterial meningitis has been associated with febrile status epilepticus[15] and prolonged seizures.[6,19,28] We found that the prevalence of bacterial meningitis in children with one brief focal seizure and fever was 0% (95% CI 0% to 3.8%). Contrary to data from the prevaccine era,[32] none of the children with bacterial meningitis reported in the 3 postvaccine-era studies[6,19,28] experienced brief focal seizures. However, the number of patients of this subgroup was low and a cautious interpretation is mandatory. Finally, the prevalence of bacterial meningitis in children with generalized, brief, multiple seizures in our study was 0% (95% CI 0% to 0.9%). A low risk of bacterial meningitis has been reported in this subgroup of patients.[19,28] Among children with multiple brief generalized seizures, Kimia et al[19] and Seltz et al,[6] respectively, found only 1 and 2 children with bacterial meningitis. Hence, data suggest a greater risk of bacterial meningitis only for prolonged seizures.

The prevalence of HSV-ME is probably very low in children with a complex febrile seizure because we found no case in our study and Seltz et al[6] found only 1 case among 193 children. In a 3-year prospective survey of children aged 2 to 23 months in Britain and Ireland, 19 children had HSV-ME and all of them experienced seizures and had an abnormal level of consciousness.[33]

We conclude that in an urban vaccinated population, bacterial meningitis and HSV-ME are rare events in children with complex febrile seizure. We found neither bacterial meningitis nor HSV-ME in the subgroup of children with a clinical examination result not suggestive of meningitis or encephalitis. These results lend support to the development of guidelines limiting lumbar puncture in this subgroup of children.

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APPENDIX E1

Methodology used to identify visits of patients aged 6 months to 5 years and with a potential seizure by means of an informatics tool: an example with the word "seizure."

We describe hereafter the steps to select all the electronic medical records (EMRs) of patients with a potential seizure. The example is given with the word "seizure." The same methodology was applied with the words "febrile seizure," "clonic," "tonic," "shaking," "jerks," and "twitch."

Step 1:

We created a regular expression (a sequence of characters that forms a search pattern) for the word "seizure": "[s|S].*[z|Z].*."

Step 2:

The regular expression was applied to each field of all EMRs to construct a list with all the terms that correspond to this regular expression. For example, some of the words of the list with the regular expression "[s|S].*[z|Z].*" are as follows:

Seizure
skyzophrenic
skizure
szre
-Seizure
squeeze
seizure

Step 3:

From this list, we performed a manual selection of the terms that matched the word "seizure" to create a list of relevant key words. All the other words were deleted.

Seizure
~~sckyzophrenic~~
skizure
szre
-Seizure
~~squeeze~~
seizure

Step 4:

The list of selected key words was applied to all EMR fields. The EMRs including at least one key word were selected.

Step 5:

To perform a more specific search, we also applied a negative regular expression: EMRs that had the words only in this negative form were not included. When a key word was in the "medical history" field, the EMRs were not included.

APPENDIX E2

Informatics tool test characteristics

Methods:

We first randomly selected 22 days between January 1, 2007, and December 31, 2011 (approximately 1% of the days included during 5 years). We manually reviewed the EMRs of visits of children aged 3 months to 5 years during those 22 days in one center and identified the visits related to a seizure (febrile and afebrile). Then the tool was applied to that sample of EMRs to identify the potential visits related to a seizure. We assessed the performance of the tool with these results.

Results:

Among the 1,449 EMRs manually reviewed, 10 visits were related to a seizure.

The tool identified 16 EMRs (including the 10 visits related to a seizure).

The sensitivity was 100% (95% CI 69.2% to 100%); the specificity was 99.6% (95% CI 99.1% 99.8%). The 2×2 table is presented below.

		Visits Related to a Seizure (Manual Review)	
		Yes	No
EMR selected by the tool	Yes	10 (TP)	6 (FP)
	No	0 (FN)	1,433 (TN)

APPENDIX E3

Standardized questionnaire

You only have to report the presence or absence of a list of words in the patient's records. You do not have to interpret any of these answers. If the word is in an affirmative form in the record, you have to tick YES. If the word is in a negative form in the record, you have to tick NO. If the word is not in the record, you have to tick NOT AVAILABLE.

1. Birth date			
2. Sex: Boy or Girl			
3. Date of the visit			
4. Hour of the visit			
5. Exclusion Criteria: If Yes: why?			
6. Medical history of febrile seizure	☐YES	☐No	☐Not available
If YES :			
• Number of febrile seizure…(99 if Not available).			
7. Updated immunization status	☐YES	☐No	☐Not available
8. Patients with antibiotics before the ED visit	☐YES	☐No	☐Not available
If YES, which antibiotic :			
If YES, duration of the antibiotics ?			
9. Description of the seizure			
• Multiple during the 24 last hours.	☐YES	☐No	☐Not available
If YES: Number of seizure			
• Description of the first seizure			
• Generalized, interesting the 4 limbs,	☐YES	☐No	☐Not available
• Focalized	☐YES	☐No	☐Not available
• If Yes :			
i. Left Upper limb	☐YES	☐No	☐Not available
ii. Right upper limb	☐YES	☐No	☐Not available
iii. Left lower limb	☐YES	☐No	☐Not available
iv. Right lower limb	☐YES	☐No	☐Not available
• Head or eye deviation	☐YES	☐No	☐Not available
• Seizure	☐YES	☐No	☐Not available
• Clonic	☐YES	☐No	☐Not available
• Tonic	☐YES	☐No	☐Not available
• Loss of consciousness	☐YES	☐No	☐Not available
• Hypotonic, loss of muscle tone during the seizure	☐YES	☐No	☐Not available
• Hypertonia	☐YES	☐No	☐Not available
• Cyanosis	☐YES	☐No	☐Not available
• Eyes revulsion	☐YES	☐No	☐Not available
• Duration of the seizure avalaible	☐YES	☐No	
• If YES : duration (number or word)			
Description of the second seizure			
Idem			
Description of the third seizure			
Idem			
Description of the fourth seizure			
Idem			
10. Anticonvulsant medication intervention	☐YES	☐No	☐Not available
If YES: Which treatment			
If YES, Does the seizure stop after the medication intervention	☐YES	☐No	☐Not available
CLINICAL EXAM AFTER THE SEIZURE.			
11. Clinical signs associated with meningitis	☐YES	☐No	☐Not available
• Neck stiffness	☐YES	☐No	☐Not available
• Kernig sign	☐YES	☐No	☐Not available
• Brudzinsky sign	☐YES	☐No	☐Not available
• Hypotonia	☐YES	☐No	☐Not available
• Photophobia	☐YES	☐No	☐Not available
• Bulging fontanelle	☐YES	☐No	☐Not available
• Purpura	☐YES	☐No	☐Not available
• Septic, sepsis,	☐YES	☐No	☐Not available
• Shock	☐YES	☐No	☐Not available

Continued.

12. Normal Mental Status or normal consciousness	☐YES	☐No	☐Not available
• Normal overall condition	☐YES	☐No	☐Not available
• Confused	☐YES	☐No	☐Not available
• Abnormal reactivity	☐YES	☐No	☐Not available
• Irritability	☐YES	☐No	☐Not available
• Inconsolable, or not normal crying	☐YES	☐No	☐Not available
• Moaning	☐YES	☐No	☐Not available
• Restless, disturb	☐YES	☐No	☐Not available
• Drowsy, sleepy	☐YES	☐No	☐Not available
• Unconscious, coma	☐YES	☐No	☐Not available
• Sleepy	☐YES	☐No	☐Not available
• Lethargic	☐YES	☐No	☐Not available
13. Normal neurologic exam	☐YES	☐No	☐Not available
• Paralysis, paresis	☐YES	☐No	☐Not available
• If Yes :			
i. Left Upper limb	☐YES	☐No	☐Not available
ii. Right upper limb	☐YES	☐No	☐Not available
iii. Left lower limb	☐YES	☐No	☐Not available
iv. Right lower limb	☐YES	☐No	☐Not available
• Babinski sign or plantar reflex in extension	☐YES	☐No	☐Not available
• Not symmetric tendon reflexes	☐YES	☐No	☐Not available
• Todd paresis	☐YES	☐No	☐Not available
• Direct light reflex not normal	☐YES	☐No	☐Not available
• Strabismus	☐YES	☐No	☐Not available
• Nystagmus	☐YES	☐No	☐Not available
• Localizing signs	☐YES	☐No	☐Not available
• Hypertension intracranial signs	☐YES	☐No	☐Not available
• Gait disturbance	☐YES	☐No	☐Not available
• Balance impaired	☐YES	☐No	☐Not available
14. Performance of lumbar puncture	☐YES	☐No	
15. If Yes: Were CSFs obtained ?	☐YES	☐No	
• Aspect: ☐Clear ☐Trouble ☐Purulent ☐Hematic ☐hemorrhagic ☐Opalescent ☐Other:			
• Glycorrhachia:			
• CSF proteins:			
• Number of cells:			
• Number of neutrophils			
• Number of red blood cells			
• Gram Stain: ☐Coccus ☐Bacillus-☐Gram-positive ☐Gram-Negative ☐Other: texte			
• Positive latex agglutination test	☐Yes	☐No	☐Not available
• Culture:	☐Positive	☐Negative	
• If positive, write down the results:			
• Blood specimen	☐Yes	☐No	
If Yes: Culture			
16. Disposition after the ED visit: ☐Discharged home ☐Hospitalization ☐Transfer ☐Other:			

APPENDIX E4

Discharge diagnostic codes used in the "reverse strategy."

The discharge diagnostic codes that we looked for were bacterial meningitis, viral meningitis, pneumococcal meningitis, meningococcal meningitis, *Haemophilus* meningitis, herpes viral meningitis, streptococcal meningitis, bacterial meningoencephalitis, herpes viral encephalitis, encephalitis, myelitis, encephalomyelitis, bacterial meningoencephalitis, and cerebral abscess.

Table E1. Details of the data-gathering for the variables used to define the clinical examination.

	Clinical Examination Result Not Suggestive of Bacterial Meningitis or MEH, n=630 (%)			Clinical Examination Result Suggestive of Bacterial Meningitis or MEH, n=209 (%)		
	Negative Form	**Unavailable**	**Positive Form**	**Negative Form**	**Unavailable**	**Positive Form**
Meningeal syndrome	132 (21)	498 (79)	0	39 (18.7)	168 (80.4)	2 (1.0)*
Neck stiffness	220 (34.9)	410 (65.1)	0	68 (32.5)	124 (59.3)	17 (8.1)*
Kernig's sign	11 (1.7)	619 (98.3)	0	5 (2.4)	202 (96.7)	2 (1.0)*
Brudzinski's sign	7 (1.1)	623 (98.9)	0	2 (1.0)	206 (98.6)	1 (0.5)*
Hypotonia	6 (1.0)	624 (99.0)	0	4 (1.9)	186 (89.0)	19 (9.1)*
Photophobia	4 (0.6)	626 (99.4)	0	1 (0.5)	207 (99.0)	1 (0.5)*
Bulging fontanel	24 (3.8)	606 (96.2)	0	11 (5.3)	191 (91.4)	7 (3.3)*
Purpura	354 (56.2)	276 (43.8)	0	124 (59.3)	75 (35.9)	10 (4.8)*
Septic, sepsis	0	630 (100)	0	0	208 (99.5)	1 (0.5)*
Coloration gray	0	630 (100)	0	0	208 (99.5)	1 (0.5)*
Shock	0	630 (100)	0	0	209 (100)	0*
Abnormal mental status	105 (16.7)	525 (83.3)	0	27 (12.9)	170 (81.3)	12 (5.7)*
Normal overall condition	0	380 (60.3)	250 (39.7)	1 (0.5)*	169 (80.9)	39 (18.7)
Abnormal reactivity	42 (6.7)	588 (93.3)	0	6 (2.9)	200 (95.7)	3 (1.4)*
Normal contact	0	590 (93.7)	40 (6.3)	6 (2.9)*	189 (90.4)	14 (6.7)
Irritability	1 (0.2)	629 (99.8)	0	0	171 (81.8)	38 (18.2)*
Inconsolable or not normal crying	0	630 (100)	0	0	209 (100)	0*
Moaning	0	630 (100)	0	0	200 (95.7)	9 (4.3)*
Restless	0	630 (100)	0	0	207 (99.0)	2 (1.0)*
Sleepy	1 (0.2)	629 (99.8)	0	1 (0.5)	190 (90.9)	18 (8.6)*
Confused	0	630 (100)	0	0	209 (100)	0*
Unconscious, coma	0	630 (100)	0	0	202 (96.7)	7 (3.3)*
Difficult to awaken	82 (13)	548 (87.0)	0	24 (11.5)	181 (86.6)	4 (1.9)*
Lethargic	0	0	0	0	209 (100)	0*
Obsessed	0	0	0	0	208 (99.5)	1 (0.5)*
Unresponsiveness	0	0	0	1 (0.5)	207 (99.0)	1 (0.5)*
Abnormal neurologic examination result	127 (20.2)	503 (79.8)	0	17 (8.1)	190 (90.9)	2 (1.0)*
Normal neurologic impression	0	561 (89.0)	69 (11.0)	7 (3.3)*	190 (90.9)	12 (5.7)
Paralysis, paresis	196 (31.1)	434 (68.9)	0	61 (29.2)	66 (31.6)	82 (39.2)*
Todd's paresis	0	630 (100)	0		207 (99.0)	2 (1.0)*
Babinski's sign	128 (20.4)	502 (79.7)	0	59 (28.2)	137 (65.6)	12 (5.7)*
Asymmetric tendon reflex	193 (30.6)	437 (69.4)	0	96 (45.9)	97 (46.4)	16 (7.7)*
Abnormal direct light reflex	168 (26.7)	462 (73.3)	0	85 (40.7)	118 (56.5)	6 (2.9)*
Strabismus	4 (0.6)	626 (99.4)	0	5 (2.4)	183 (87.6)	1 (0.5)*
Nystagmus	54 (8.6)	576 (91.4)	0	21 (10.0)	183 (87.6)	5 (2.4)*
Localizing signs	65 (10.4)	565 (89.7)	0	16 (7.7)	186 (89.0)	7 (3.3)*
Hypertension intracranial signs	1 (0.2)	629 (99.8)	0	1 (0.5)	207 (99.0)	1 (0.5)*
Gait disturbance	49 (7.8)	581 (92.2)	0	14 (6.7)	191 (91.4)	4 (1.9)*
Balance impaired	13 (2.1)	617 (97.9)	0	5 (2.4)	204 (97.6)	0*
Sensitivity disorder	32 (5.1)	598 (94.9)	0	10 (4.8)	99 (95.2)	0*

*The features used to define that a patient had a clinical examination result suggestive of meningitis or encephalitis.

Table E2. Descriptive characteristics by center of 839 visits of patients aged 6 months to 5 years, with a complex febrile seizure, and with visits to 7 EDs between January 2007 and December 2011.*

Center	A (N=302)	B (N=135)	C (N=94)	D (N=79)	E (N=46)	F (N=85)	G (N=98)
Male patient	161 (53.3)	79 (58.5)	49 (52.1)	52 (65.8)	28 (60.9)	41 (48.2)	53 (54.1)
Age, median (25p–75p), mo	19 (14–28)	20 (15–27)	22 (14.75–32)	22 (15–30)	23.5 (15–35.25)	20 (15–31.5)	21 (13–32.5)
Lumbar puncture performed	85 (28.1)	56 (41.5)	21 (22.3)	41 (51.9)	6 (13.0)	21 (24.7)	30 (30.6)
Hospitalization	182 (60.3)	106 (78.5)	74 (78.7)	57 (72.2)	41 (89.1)	69 (81.2)	90 (91.8)
Center visits							
Total ED visits for patients 0–18 y between 2007 and 2011	367,591	214,706	133,246	148,069	93,872	92,017	133,986
ED visits for patients 6 mo to 5 y between 2007 and 2011	210,148	117,697	76,183	82,019	43,789	50,356	74,267

N, Number of visits by center; *n*, number of patients with the corresponding characteristic; *p*, percentile.
*Data are presented as No.(%) unless otherwise indicated. University pediatric hospitals: A and E; university general hospitals: C and D; teaching general hospitals: B, F, and G.

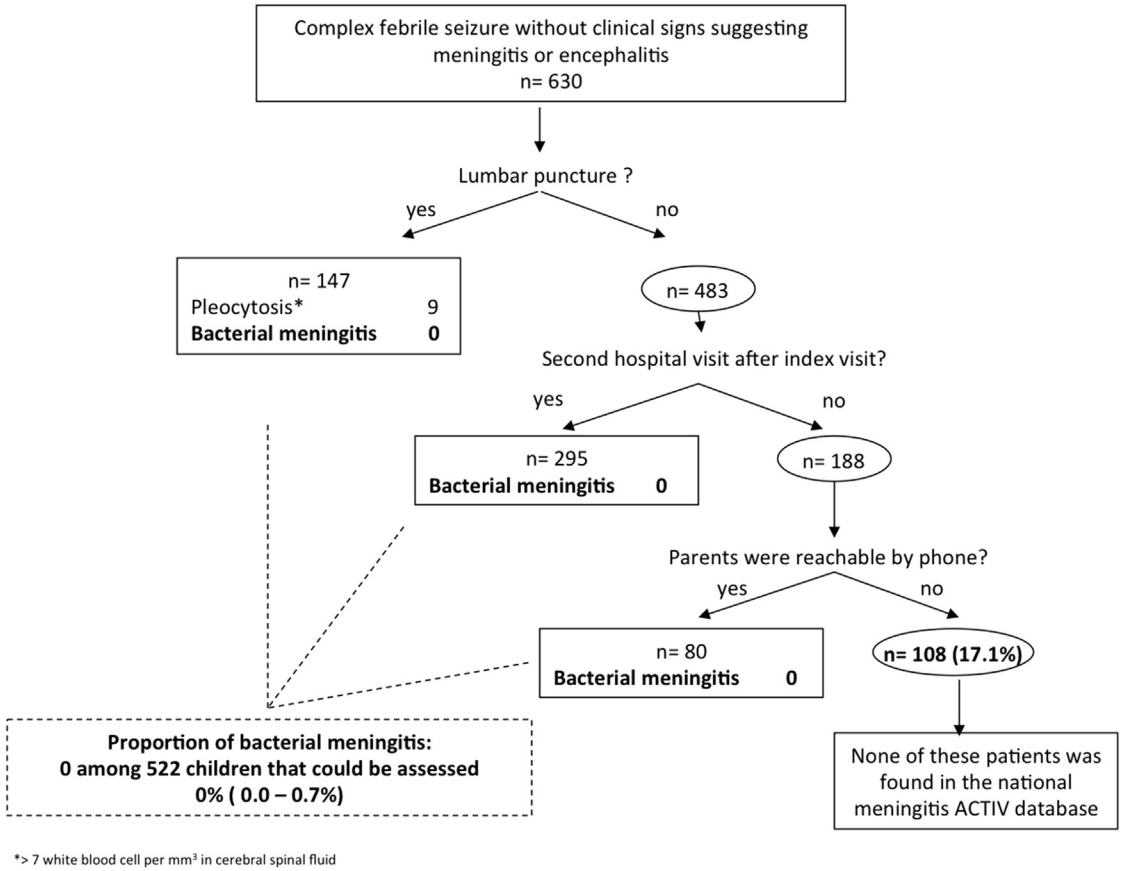

Figure E1. Proportion of bacterial meningitis among infants aged 6 months to 5 years, visiting 7 EDs between January 2007 and December 2011, and with a complex febrile seizure without clinical signs suggesting meningitis or encephalitis.

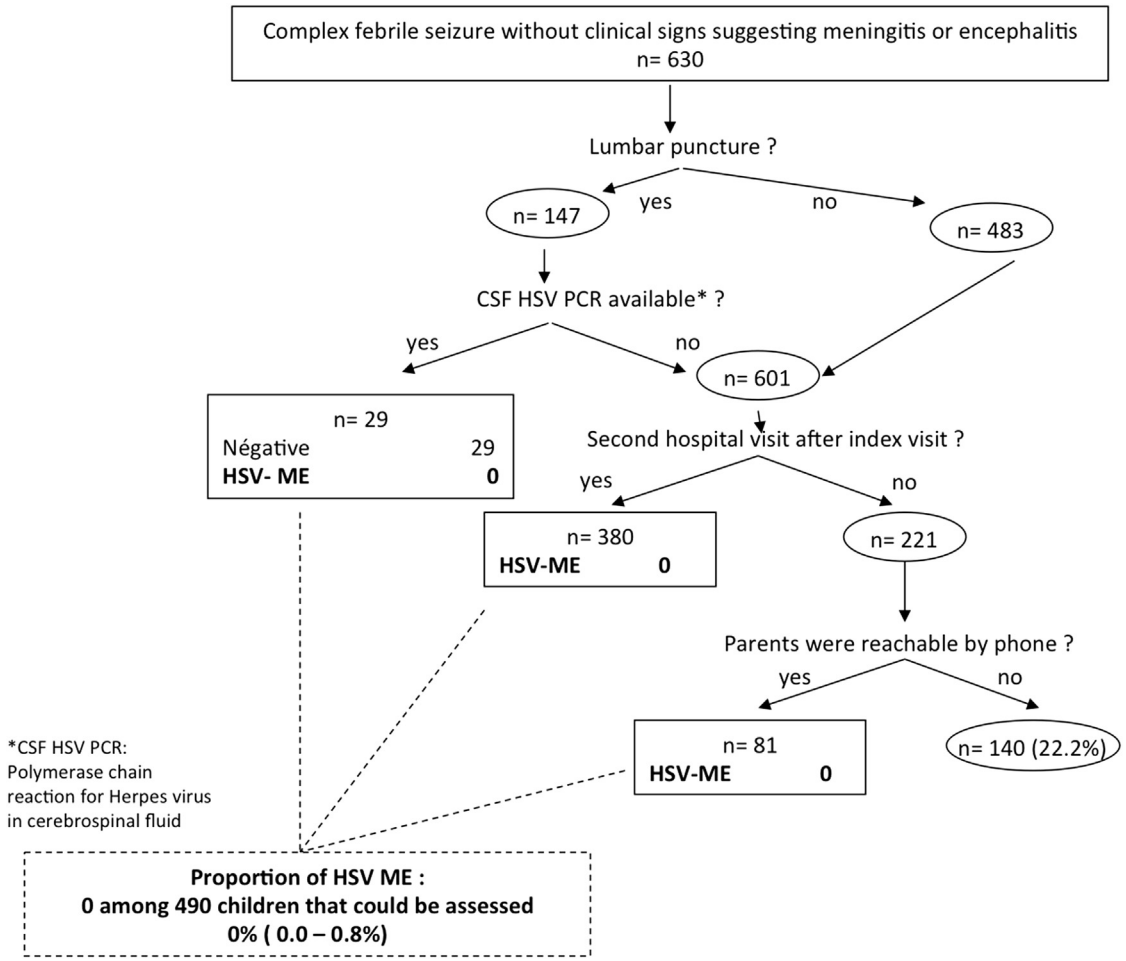

Figure E2. Proportion of HSV-ME among infants aged 6 months to 5 years, visiting 7 EDs between January 2007 and December 2011, and with a complex febrile seizure without clinical signs suggesting meningitis or encephalitis.