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Paediatric meningitis in the conjugate vaccine era and a novel clinical decision model to predict bacterial aetiology

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SUMMARY

Objectives: The aims of this study were to assess aetiology and clinical characteristics in childhood meningitis, and develop clinical decision rules to distinguish bacterial meningitis from other similar clinical syndromes.

Methods: Children aged < 16 years hospitalised with suspected meningitis/encephalitis were included, and prospectively recruited at 31 UK hospitals. Meningitis was defined as identification of bacteria/viruses from cerebrospinal fluid (CSF) and/or a raised CSF white blood cell count. New clinical decision rules were developed to distinguish bacterial from viral meningitis and those of alternative aetiology.

Results: The cohort included 3002 children (median age 2·4 months); 1101/3002 (36·7%) had meningitis, including 180 bacterial, 423 viral and 280 with no pathogen identified. Enterovirus was the most common pathogen in those aged < 6 months and 10–16 years, with *Neisseria meningitidis* and/or *Streptococcus pneumoniae* commonest at age 6 months to 9 years. The Bacterial Meningitis Score had a negative predictive value of 95·3%. We developed two clinical decision rules, that could be used either before (sensitivity 82%, specificity 71%) or after lumbar puncture (sensitivity 84%, specificity 93%), to determine risk of bacterial meningitis.

Conclusions: Bacterial meningitis comprised 6% of children with suspected meningitis/encephalitis. Our clinical decision rules provide potential novel approaches to assist with identifying children with bacterial meningitis.

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Introduction

Acute meningitis has a broad range of infectious and non-infectious aetiologies, with viral and bacterial pathogens most common.[1] Bacterial meningitis is a severe disease with substantial morbidity,[2] and case-fatality rates are between 5% and 17% in children in Europe. Bacterial conjugate vaccines have significantly reduced the incidence of bacterial meningitis in the last 30 years. In the UK, the *Haemophilus influenzae* type b (Hib) conjugate vaccine was introduced in 1992, MenC vaccine in 1999, and infant MenB and adolescent MenACWY programmes in 2015. A pneumococcal conjugate vaccine was first introduced in the UK in 2006. The common causes of neonatal bacterial meningitis differ from older children and include Group B Streptococcus (GBS), *Escherichia coli,* and *Listeria monocytogenes*.[3]

Previous studies from Europe and the USA have reported that 81–96% of meningitis is non-bacterial,[4–6] and an increase in meningitis not caused by pneumococcus, Hib, or meningococcus has been reported globally.[1] Enteroviruses are responsible for most non-bacterial meningitis when a pathogen is identified, with previous European studies reporting that 52–77% of non-bacterial meningitis with an identified pathogen is caused by enteroviruses.[7,8]

Of children presenting to hospital with a febrile illness in high-income countries, very few have bacterial infections, making it increasingly challenging to identify those who need antibiotics. A European study reported invasive bacterial disease in only 4% of young febrile infants[9] and a further study found positive bacterial cultures in only 2.4% of children with suspected infection.[10] Although viral meningitis is usually self-limiting, most children are admitted to the hospital and receive intravenous antibiotics until a bacterial aetiology is excluded.

Previous studies from different countries, mostly completed prior to current vaccine programmes, have described some clinical and laboratory features of meningitis of different aetiologies and included well-established cerebrospinal fluid (CSF) parameters.[11,12] The Bacterial Meningitis Score (BMS) predicts a very low risk of bacterial meningitis in children with a raised CSF white blood cell (WBC) count, based on CSF parameters and presence/absence of seizures.[13]

The aims of this study were to analyse the aetiology of meningitis in hospitalised children in the UK, the clinical and laboratory features of meningitis of different aetiologies (or of suspected meningitis) in infants and children, to validate the BMS in the UK population and develop new clinical decision rules to distinguish bacterial meningitis from non-bacterial meningitis or viral illness.

Methods

Participant recruitment

From December 2012 to June 2016, children with suspected or confirmed meningitis or encephalitis were recruited to the prospective UK Childhood Meningitis and Encephalitis Study (UK-ChiMES) from 31 hospitals across the UK. All hospitals were tertiary paediatric centres or with dedicated paediatric services. Inclusion criteria were children aged < 16 years with suspected meningitis with lumbar puncture (LP) performed or LP indicated but deferred; children who had an LP performed as part of an evaluation of infection; and children with any clinical suspicion of encephalitis. Children were excluded if they had confirmed non-infectious/non-inflammatory central nervous system (CNS) disorders due to hypoxic, ischaemic, vascular, toxic or metabolic causes, or pre-existing indwelling ventricular devices, or were infants on the neonatal unit. Potential participants were identified by review of admission lists and microbiologic results by the research team. Relevant individuals and/or their parent/legal guardian were then approached to further explain the study and obtain written informed consent, if they agreed to be included.

Clinical data collection

Data were obtained from hospital records and interview with parent/legal guardian during hospital admission, and entered into a secure, web-based electronic database (OpenClinica, v3·1·2-Community). Data collected included medical history, clinical features, laboratory and radiology results, in-hospital treatment and sequelae at discharge. Investigation and management of individual patients was at the discretion of the treating clinician, and not specified by the study protocol.

Definitions

A raised CSF WBC count was defined as ≥20 × 10^6/L for participants aged 0–28 days and > 5 × 10^6/L for older infants and children. Definite bacterial meningitis was defined as identification of a bacterial pathogen in the CSF or raised CSF WBCs and a relevant (neurotropic) pathogen present in blood, or CSF Gram stain positive and corresponding pathogen present in blood. Definite viral meningitis was defined as raised CSF WBCs and a viral pathogen identified in CSF or blood. Aseptic meningitis was defined as raised CSF WBCs and no bacterial pathogen identified. Aseptic meningitis included atypical organisms and any non-bacterial cause identified. Possible meningitis included individuals with a pathogen known to cause bacterial meningitis identified in blood and no evaluable LP result, or a pathogen of uncertain significance in CSF and either no available or no raised CSF WBC, or a discharge diagnosis of meningitis but with no other features of confirmed or probable meningitis. The control group included all children who did not fulfill any of the meningitis or encephalitis definitions. Full definitions are provided in the Supplementary Methods.

Meningitis aetiology was defined by analysis of results from routine laboratory tests performed at hospital sites including CSF, blood or other bacterial culture and polymerase chain reaction (PCR) results, CSF WBC, CSF Gram stain, serum serology, and by discharge diagnosis. The diagnosis for children who did not have meningitis was determined by a review of results and final discharge diagnosis. All final determinations of diagnosis were independently reviewed by two paediatricians.

Outcomes

The primary outcome of this study was to determine the aetiology of meningitis in hospitalised children in the UK. The secondary outcomes included the description of clinical and laboratory features of children by aetiology and in children without meningitis; evaluation of the BMS, and development of novel clinical decision rules to distinguish children with bacterial meningitis from all children with suspected meningitis on admission to hospital, to enable targeted clinical management.

Statistical analysis

Analyses for primary outcomes were descriptive. The proportions of participants with meningitis of different aetiologies, and non-meningitis diagnoses were reported together with 95% binomial exact confidence intervals (CIs). Demographic data, mortality, investigations, length of hospital admission, antibiotic pre-treatment and management were analysed by aetiology. The median and interquartile range (IQR) for continuous variables, and frequency and proportion for categorical variables were reported. Clinical and laboratory features were described by meningitis aetiology.

Evaluation of the 'Bacterial Meningitis Score'

Participants were included in this analysis if aged between 29 days to < 16 years, and had CSF pleocytosis (CSF WBC > 5 × 10^6/L), and had not received antibiotics before LP, aligned with the inclusion criteria described for the BMS. Children were classified as very low risk of bacterial meningitis (negative) if all BMS criteria were not present (positive Gram stain, CSF protein ≥80 mg/dL, peripheral neutrophil count ≥10,000 cells/μL, seizure at or before presentation, CSF neutrophil count ≥1000 cells/μL). Participants were defined as having missing data if data were unreported for any BMS predictor and were excluded unless there was a positive BMS finding from another predictor.[4] The sensitivity, specificity, positive and negative predictive values (NPVs) for the BMS were reported. Additional exploratory analyses were performed including neonates (age 0–28 days, raised CSF WBC ≥20 × 10^6/L), including participants who were pretreated with antibiotics, and excluding participants with any missing data, regardless of the number of positive BMS findings from other available predictors.

Development of a new multivariable rule to predict probability of bacterial meningitis

We aimed to develop two prediction rules for bacterial meningitis separately among all children in this study: a pre-LP rule amongst all study participants; and a post-LP rule amongst those with CSF pleocytosis. Predictors with more than 50% missing data in the corresponding population were excluded, and to account for the missing data in the remaining analysis dataset multiple imputation by chained equations was used to generate 10 imputed datasets, assuming the data were missing at random. Bootstrapping was used to select predictors in pre-LP and post-LP rules, separately. The performance of the two rules was evaluated by calibration and the area under the receiver operating characteristic curve (AUROC). Analyses were carried out using R v3·6·3 or STATA v16·0, and the multiple imputation was carried out using the "mice" package in R. Full details of the statistical methods are included in the Supplementary Methods.

Ethics

The study was approved by the National Research Ethics Service Committee East Midlands – Nottingham 1 (Ref: 11/EM/0442) and by all participating hospitals.

Results

Description of study population

A total of 3002 children with suspected/confirmed meningitis and/or encephalitis were enroled. The majority of participants were male (n = 1727; 58%) and of white ethnicity (n = 2290; 76%); 1101/3002 (36·7%) had meningitis (Table 1). Overall 469 (16%) children were admitted to the intensive care unit (ICU), including 66 of 180 children (37%) with definite bacterial meningitis. There were 12 deaths, 3 in children with meningitis and 9 in those who did not have meningitis (Supplementary Table 2). 688 participants (23%) were neonates, and 996 (33%) were aged 29 days to 3 months (Table 2).

Meningitis aetiology

Definite bacterial meningitis was diagnosed in 180/3002 children (6%), with the highest rates in infants aged 6–11 months (30/211; 14%) (Table 2). The most common causes of bacterial meningitis were *Neisseria meningitidis, Streptococcus pneumoniae*, GBS and *E. coli*, with GBS and *E. coli* predominant in infants aged < 3 months, and *N. meningitidis* and *S. pneumoniae* occurring in all age groups. Overall, 794 children had aseptic meningitis, of which 423 had definite/probable viral meningitis. Enterovirus (EV) was the commonest cause of viral meningitis in all age groups (315/423; 75%) and human parechovirus (HPEV) the second most common viral pathogen (51/423; 12%) (Table 3). Although identified in cases across the age range, most HPEV cases occurred in infants aged < 3 months. In addition, 59 children had encephalitis of whom 28 had a confirmed non-infectious cause. Of 794 children with aseptic meningitis, 280 did not have an aetiology identified. In those aged ≥6 months, 41–48% of children with aseptic meningitis did not have an aetiology identified – infectious or non-infectious (Table 2). Amongst children who were investigated for suspected meningitis/encephalitis but did not have a CNS infection, the majority (1476/3002; 49%) had a different non-CNS infectious cause (Supplementary Table 3, Supplementary Fig. 1). For the entire cohort, including children with and without CSF pleocytosis, CSF PCR for EV was done in 62% of children, 60% for HSV, 52% for VZV and 42% for HPEV. In addition, 13–16% had blood and/or CSF PCR for *N. meningitidis* or *S. pneumoniae*.

Clinical and laboratory characteristics (Fig. 1; Supplementary Tables 4–11)

Infants with meningitis of different aetiologies, or those investigated for suspected meningitis, presented with similar constellations of symptoms and signs (Fig. 1a–c). Children ≥12 months with confirmed meningitis or suspected meningitis also had similar presenting clinical features (Fig. 1d). In infants and children with bacterial meningitis, a history of altered consciousness, vomiting and respiratory signs was frequently reported. A non-blanching rash was reported in 33% of children > 12 months with bacterial meningitis. In infants > 28 days with possible meningitis, a non-blanching rash was frequently reported. In children ≥1 year, headache, neck stiffness and photophobia were often reported in the meningitis groups (Fig. 1d); however, these features were much less common in infants aged 3–12 months, and were absent in those aged < 3 months (Fig. 1a–c).

In infants with bacterial meningitis, the median CSF WBC was 1023 × 10^6/L (IQR 85–2829) in those aged 0–28 days, 104 × 10^6/L (19–793) in infants aged 1 to < 3 months, 231 × 10^6/L (65–816) in those aged 3–11 months, and 505 × 10^6/L (122–1505) in children ≥12 months. In infants with aseptic meningitis, the median CSF WBC was 37 × 10^6/L (2–367 IQR) in those aged 0–28 days, 23 × 10^6/L (5–151) in infants aged 1 to < 3 months, 23 × 10^6/L (6–121) in those aged 3–11 months, and 18 × 10^6/L (3–68) in children ≥12 months (Supplementary Tables 8–11). In children ≥1 year, C-reactive protein (CRP) and CSF parameters appeared to most reliably distinguish between bacterial and non-bacterial meningitis (Supplementary Table 11).

Validation of the 'Bacterial Meningitis Score'

In infants and children aged > 28 days, who were not pretreated with antibiotics and did not have missing data, the sensitivity and specificity of the BMS was 82·9% (95% CI: 66·4–93·4) and 67·0% (95% CI: 59·7–73·8), respectively (Table 4). The positive predictive value (PPV) was 32·6% (95% CI: 23·0–43·3) and NPV was 95·3% (95% CI: 90·1–98·3) (Table 4). Six children (of 128 with a complete dataset) with bacterial meningitis did not have any positive predictors and thus would have not received antibiotic therapy if the BMS was applied. Inclusion of individuals with some missing data slightly increased the sensitivity and reduced the specificity of the BMS, with similar PPV and NPV. Inclusion of all children resulted in lower

Table 1
Baseline characteristics by diagnostic classification.

	Any bacterial meningitis	Definite bacterial meningitis	All aseptic meningitis	Definite/Probable viral meningitis	Aseptic meningitis with unknown aetiology	Encephalitis	Possible meningitis	Control	Total
n	**203**	180	**794**	423	280	59	**104**	**1901**	**3002**
Gender									
Male, n (%)	116 (57·1)	106 (58·9)	463 (58·3)	241 (57·0)	171 (61·1)	33 (55·9)	55 (52·9)	1093 (57·5)	1727 (57·5)
Ethnicity									
White, n (%)	160 (78·8)	141 (78·3)	619 (78·0)	347 (82·0)	210 (75·0)	39 (66·1)	84 (80·8)	1427 (75·1)	2290 (76·3)
Asian, n (%)	15 (7·4)	12 (6·7)	70 (8·8)	29 (6·9)	26 (9·3)	13 (22·0)	4 (3·8)	174 (9·2)	263 (8·8)
Black, n (%)	5 (2·5)	5 (2·8)	25 (3·1)	5 (1·2)	15 (5·4)	2 (3·4)	5 (4·8)	78 (4·1)	113 (3·8)
Mixed, n (%)	11 (5·4)	10 (5·6)	49 (6·2)	28 (6·6)	18 (6·4)	2 (3·4)	7 (6·7)	116 (6·1)	183 (6·1)
Other ethnic minority, n (%)	5 (2·5)	5 (2·8)	25 (3·1)	11 (2·6)	10 (3·6)	3 (5·1)	4 (3·8)	71 (3·7)	105 (3·5)
Unknown, n (%)	7 (3·4)	7 (3·9)	6 (0·8)	3 (0·7)	1 (0·4)	0 (0·0)	0 (0·0)	35 (1·8)	48 (1·6)
Past medical history									
Known infectious contact, n (%)	30 (14·8)	30 (16·7)	229 (28·8)	155 (36·6)	57 (20·4)	12 (20·3)	20 (19·2)	458 (24·1)	737 (24·6)
Previous illness with alteration in consciousness, n (%)	6 (3·0)	6 (3·3)	29 (3·7)	13 (3·1)	6 (2·1)	6 (10·2)	3 (2·9)	83 (4·4)	121 (4·0)
Developmental delay, n (%)	2 (1·0)	2 (1·1)	25 (3·1)	7 (1·7)	12 (4·3)	6 (10·2)	7 (6·7)	69 (3·6)	103 (3·4)
Learning difficulty, n (%)	2 (1·0)	2 (1·1)	12 (1·5)	1 (0·2)	6 (2·1)	4 (6·8)	5 (4·8)	49 (2·6)	68 (2·3)
Recent head trauma/neurosurgery, n (%)	9 (4·4)	9 (5·0)	17 (2·1)	3 (0·7)	7 (2·5)	4 (6·8)	0 (0·0)	32 (1·7)	58 (1·9)
Local anatomical defect, n (%)	4 (2·0)	4 (2·2)	15 (1·9)	7 (1·7)	5 (1·8)	2 (3·4)	2 (1·9)	37 (1·9)	58 (1·9)
Previous meningitis, n (%)	2 (1·0)	2 (1·1)	12 (1·5)	6 (1·4)	5 (1·8)	1 (1·7)	0 (0·0)	17 (0·9)	31 (1·0)
Immunocompromised, n (%)	1 (0·5)	1 (0·6)	6 (0·8)	1 (0·2)	4 (1·4)	1 (1·7)	0 (0·0)	12 (0·6)	19 (0·6)
Previous encephalitis, n (%)	1 (0·5)	1 (0·6)	7 (0·9)	1 (0·2)	3 (1·1)	2 (3·4)	1 (1·0)	1 (0·1)	10 (0·3)
Other medical problem, n (%)	88 (43·3)	83 (46·1)	317 (39·9)	151 (35·7)	130 (46·4)	27 (45·8)	35 (33·7)	809 (42·6)	1249 (41·6)
Vaccines up to date									
Yes, n (%)	149 (73·4)	135 (75·0)	506 (63·7)	229 (54·1)	193 (68·9)	56 (94·9)	79 (76·0)	1175 (61·8)	1909 (63·6)
No, n (%)	27 (13·3)	23 (12·8)	84 (10·6)	55 (13·0)	26 (9·3)	1 (1·7)	5 (4·8)	243 (12·8)	359 (12·0)
Not reported, n (%)	27 (13·3)	22 (12·2)	204 (25·7)	139 (32·9)	61 (21·8)	2 (3·4)	20 (19·2)	483 (25·4)	734 (24·5)
Outcomes									
Admitted to ICU, n (%)	66 (32·5)	66 (36·7)	95 (12·0)	31 (7·3)	38 (13·6)	17 (28·8)	35 (33·7)	273 (14·4)	469 (15·6)
Died, n (%)	1 (0·5)	1 (0·6)	2 (0·3)	1 (0·2)	1 (0·4)	0 (0·0)	0 (0·0)	9 (0·5)	12 (0·4)

Bold values represent the main groups.

Table 2
Summary table of outcome groups by age.

	Age groups								
Outcome groups	0–28 days	29 days to < 3 months	3–5 months	6–11 months	12–23 months	2–4 years	5–9 years	10–16 years	Total
n (% of total)	**688 (22·9)**	**996 (33·2)**	**343 (11·4)**	**211 (7·0)**	**226 (7·5)**	**203 (6·8)**	**182 (6·1)**	**153 (5·1)**	**3002 (100)**
Any bacterial meningitis, n (% of age group)	**35 (5·1)**	**49 (4·9)**	**30 (8·7)**	**31 (14·7)**	**22 (9·7)**	**20 (9·9)**	**11 (6·0)**	**5 (3·3)**	**203 (6·8)**
Definite bacterial meningitis, n (%)	33 (4·8)	37 (3·7)	23 (6·7)	30 (14·2)	21 (9·3)	20 (9·9)	11 (6·0)	5 (3·3)	180 (6·0)
Probable bacterial meningitis, n (%)	2 (0·3)	12 (1·2)	7 (2·0)	1 (0·5)	1 (0·4)	0	0	0	23 (0·8)
All aseptic meningitis, n (%)	**177 (25·7)**	**288 (28·9)**	**72 (21·0)**	**31 (14·7)**	**29 (12·8)**	**75 (36·9)**	**62 (34·1)**	**60 (39·2)**	**794 (26·4)**
Definite viral meningitis, n (%)	136 (19·8)	180 (28·9)	39 (21·0)	12 (14·7)	11 (12·8)	10 (36·9)	9 (34·1)	18 (39·2)	415 (13·8)
Probable viral meningitis, n (%)	1 (0·1)	2 (0·2)	1 (0·3)	0	2 (0·9)	2 (1·0)	0	0	8 (0·3)
Meningitis – Other Infection[1], n (%)	1 (0·1)	1 (0·1)	1 (0·3)	0	0	0	1[2] (0·5)	0	4 (0·1)
Aseptic meningitis: non-infectious cause, n (%)	0	1 (0·1)	5 (1·5)	1 (0·5)	1 (0·4)	6 (3·0)	8 (4·4)	6 (3·9)	28 (0·9)
Aseptic meningitis with unknown aetiology, n (%)	37 (5·4)	104 (10·4)	25 (7·3)	15 (7·1)	12 (5·3)	35 (17·2)	27 (14·8)	25 (16·3)	280 (9·3)
Encephalitis with/without meningitis, n (%)	2 (0·3)	0	1 (0·3)	3 (1·4)	3 (1·3)	22 (10·8)	17 (9·3)	11 (7·2)	59 (2·0)
Possible meningitis, n (%)	**22 (3·2)**	**15 (1·5)**	**14 (4·1)**	**11 (5·2)**	**8 (3·5)**	**10 (4·9)**	**15 (8·2)**	**9 (5·9)**	**104 (3·5)**
Control (not meningitis), n (%)	**454 (66·0)**	**644 (64·7)**	**227 (66·2)**	**138 (65·4)**	**167 (73·9)**	**98 (48·3)**	**94 (51·6)**	**79 (51·6)**	**1901 (63·3)**

[1]This new group was created as these participants have a mixed outcome that could not be classified into any one of the other groups. One was classified as both 'Definite Bacterial Meningitis' and 'Meningitis caused by atypical pathogen', while the remaining two were both 'Definite Bacterial Meningitis' and 'Definite Viral Meningitis' [2] Mycoplasma pneumoniae.
Bold values represent the main groups.

specificity and NPV. Inclusion of neonates did not substantially change the performance of the BMS in this population (Table 4).

Development of new multivariable rules to predict the probability of bacterial meningitis

For the post-LP rule in participants with CSF pleocytosis, we identified seven independent predictors for bacterial meningitis, including a combination of clinical, blood and CSF parameters: rash; blood lymphocyte count; blood CRP; total CSF WBC count, CSF neutrophil count, CSF glucose, and CSF protein (Fig. 2). For the pre-LP rule, we identified five non-CSF based independent predictors of bacterial meningitis: vomiting, history of altered consciousness, bulging fontanelle, blood lymphocyte count and blood CRP (Fig. 2). Both sets of predictors demonstrated high accuracy based on our interval validation (Supplementary Figs. 2 and 3). After dichotomising the continuous variables for ease of clinical usage, we devised pre- and post-LP points scoring systems (Supplementary Table 12). A total score can be calculated by adding the scores for each predictor present (Supplementary Table 12). Pre-LP, using a threshold of 2 points (≤2 vs. > 2), the sensitivity and specificity were 82% (95% CI: 76–87%) and 71% (95% CI: 69–73%), respectively. The sensitivity and specificity for the post-LP points score were 84% (95% CI: 75–90%) and 93% (95% CI: 90–95%), respectively, with a threshold of 4 points (≤4 vs. > 4).

Discussion

This is the first and largest UK-wide study to prospectively define the causes of childhood meningitis in the post vaccine era. These data, collected across 31 UK hospital sites, demonstrate that the majority of childhood meningitis in the UK is viral. Enteroviruses caused most aseptic meningitis when a cause was identified, with most EV infections occurring in infants aged < 3 months. No aetiology was identified in almost 50% of meningitis cases, particularly in older children.

Early identification of children with viral meningitis at presentation to hospital is important to avoid unnecessary antibiotics and hospital admission. In this current analysis, only 6% of children with suspected meningitis/encephalitis had bacterial meningitis. Our detailed analysis of this comprehensive clinical and laboratory dataset has identified that a relatively small number of predictors can be used to identify children with bacterial meningitis to develop a tool which could assist clinical decision making. This could significantly reduce unnecessary antibiotic treatment in children at low risk of bacterial meningitis.

Overall 18% of all meningitis cases were bacterial. Retrospective studies from the USA and other European countries have reported bacterial aetiologies for 4–15% of childhood meningitis.[4–6,14] These retrospective studies all identified children by searching patient records, laboratory records or hospital discharge coding, and all studies excluded neonates aged < 1 month.[4–6,14] The difference in the reported proportion of children with bacterial meningitis in this present study compared to a USA study,[4] which included 3295 children with meningitis and reported a bacterial cause for only 4% is likely due to different inclusion criteria. The USA study identified children retrospectively by discharge coding, and in contrast to the present study, children who presented to the emergency department but were not admitted to the hospital were included, and neonates were excluded.

No cause was identified for 35% of children with aseptic meningitis, compared with 30–76% reported by other studies from Europe and Canada.[7,15] Notably, there was an increase in the proportion of meningitis with no identified aetiology with increasing age, from 21% in neonates < 29 days, to approximately 35% in infants aged 29 days to 5 months, and over 40% in all older age groups. This

Table 3
Specific aetiology of meningitis cases by age group.

Aetiology	Age groups								
	0–28 days	29 days to < 3 months	3–5 months	6–11 months	12–23 months	2–4 years	5–9 years	10–16 years	Total (N = 631)
DEFINITE BACTERIAL MENINGITIS	33	37	23	30	21	20	11	5	180
N. meningitidis, n (%)	1	5	10	14	11	8	7	1	57 (31·7)
S. pneumoniae, n (%)	3	8	7	14	4	10	2	4	52 (28·9)
GBS, n (%)	16	13	2	–	1	–	–	–	32 (17·8)
E. coli, n (%)	11	10	–	–	1	–	–	–	22 (12·2)
H. influenzae, n (%)	–	1	1	1	1	–	–	–	4 (2·2)
Staphylococcus aureus, n (%)	–	–	1	–	1	1	–	–	3 (1·7)
Listeria monocytogenes, n (%)	1	–	–	–	–	–	1	–	2 (1·1)
Streptococcus pyogenes, n (%)	–	–	–	–	2	–	–	–	2 (1·1)
Other pathogens, n (%)	1	–	2	1	–	1	1	–	6 (3·3)
Viral meningitis (Definite or Probable)	137	182	40	12	13	12	9	18	423
Enterovirus, n (%)	107	150	31	7	6	2	6	6	315 (74·5)
Parechovirus, n (%)	24	21	3	–	1	1	–	1	51 (12·1)
HSV1, n (%)	2	2	1	1	2	3	1	3	15 (3·5)
HSV2, n (%)	–	–	1	1	–	1	–	–	3 (0·7)
HHV6, n (%)	1	3	2	–	3	–	–	–	9 (2·1)
VZV, n (%)	–	1	–	–	–	4	–	2	7 (1·7)
EBV, n (%)	1	1	–	–	–	1	1	3	7 (1·7)
Adenovirus, n (%)	–	1	–	1	–	1	1	–	4 (0·9)
CMV, n (%)	1	–	–	–	–	–	1	1	3 (0·7)
Measles, n (%)	–	–	–	–	–	–	–	2	2 (0·5)
Other aseptic meningitis (confirmed non-infectious cause)	–	1	5	1	1	6	8	6	28
ADEM, n (%)	–	1	1	–	–	4	1	4	11 (39·3)
Kawasaki disease, n (%)	–	–	4	1	1	–	–	–	6 (21·4)
Optic neuritis, n (%)	–	–	–	–	–	–	2	1	3 (10·7)
Transverse myelitis[1], n (%)	–	–	–	–	–	–	1	1	2 (7·1)
Guillain-Barre, n (%)	–	–	–	–	–	1	–	–	1 (3·6)

may suggest that clinicians have a lower threshold in investigating a cause in younger infants and children. This highlights the importance of early LP in children with suspected meningitis, ideally prior to antibiotic use, and the need for improved pan-viral diagnostics—including multiplex molecular diagnostic panels, and newer approaches, including host and/or pathogen transcriptomics and proteomics.[16]

We found that *N. meningitidis* was only slightly more frequent as a cause of bacterial meningitis than *S. pneumoniae*, in contrast with a previous study reporting laboratory confirmed data during an earlier period from 2004 to 11 in England and Wales, which reported that *N. meningitidis* (34%) was the most common cause of bacterial meningitis in children < 15 years, followed by *S. pneumoniae* (16%).[3] These differences are likely due to natural fluctuations in disease incidence. In the USA, the incidence of pneumococcal meningitis is higher than meningococcal meningitis.[17] GBS was the most common cause of neonatal bacterial meningitis in this study (48%) and of bacterial meningitis in infants 29 days to < 3 months of age (35%). A similar proportion was reported by a surveillance study in the UK and Ireland with GBS causing 50% of bacterial meningitis < 3 months in 2010–11.[18] Previous studies have reported a rise in GBS disease in recent years, with a study from England and Wales reporting an increase in all neonatal GBS disease from 1991 to 2010,[19] and another study reporting an increase in bacterial meningitis in infants aged < 3 months (7·4% per year) from 2004 to 2011 caused mostly by increased GBS disease.[3] Ongoing development of GBS vaccines for use in pregnancy is vital to further impact on this disease in young infants – and these data highlight the importance of that work and its potential impact.

Previous studies have investigated CSF and blood parameters including CSF cell counts, protein, glucose, and blood CRP and cell counts to distinguish bacterial from aseptic meningitis.[20] CSF results have not been reliably shown to discriminate although results of studies vary.[20] Studies also report variable results with blood cell counts.[20,21] A low or negative CRP has been shown to be a good predictor of non-bacterial meningitis, but studies report low specificity for raised CRP to predict bacterial meningitis.[20,21] Other previously investigated laboratory parameters include CSF neutrophil counts,[22] and CSF lactate and serum procalcitonin which are not routinely performed.[21]

Although typical clinical features of meningitis are well described,[11,23,24] few studies have directly compared clinical features in bacterial and aseptic meningitis.[12,21] In this study, a descriptive analysis of clinical and CSF parameters for bacterial and aseptic meningitis was consistent with previous typically described results.[11,23] Not surprisingly, children who were investigated for suspected meningitis also presented to the hospital with a similar constellation of clinical features to children with meningitis.

Previous studies investigating clinical decision rules to differentiate bacterial and viral meningitis from clinical, blood and CSF parameters reported that the BMS had the highest sensitivity and specificity,[13] including a systematic review of bacterial meningitis prediction rules.[25] The BMS was developed in 2002, and a meta-analysis was published in 2012 including eight non-UK, validation studies, most of which were retrospective.[13] We found a high NPV of the BMS of 95%, similar to previous studies. However, some children with bacterial meningitis would not have received treatment based on this tool – and the high risk of poor outcomes limits the use of any 'rule out' tool, with most clinicians having a low threshold to start antibiotic therapy. The new 'rules' developed in this study highlight the value of blood inflammatory markers (specifically lymphocyte count and CRP) and a small number of key clinical features in distinguishing bacterial from viral meningitis. The purpose of developing these rules was to aim for high specificity, to enable targeted use of adjunctive therapy, such as corticosteroids. However, only the post-LP rule had sufficiently high specificity and thus an LP would still be necessary for implementation. It would be important to further validate these rules in other populations. Interestingly, within the UK national guideline for sepsis clinical features including heart rate, respiratory rate, behaviour and temperature comprise some of the criteria used to assess risk and guide recommendations for prompt antibiotic management. In this

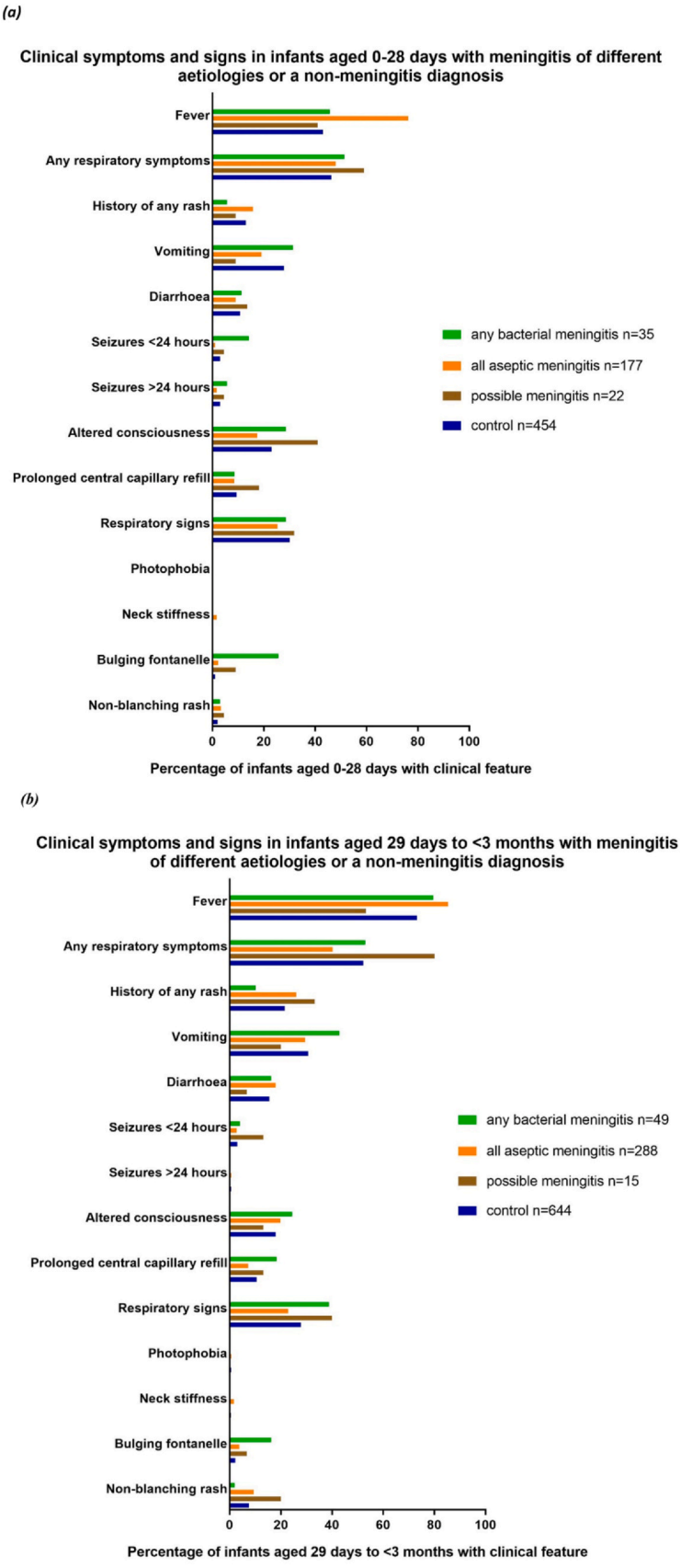
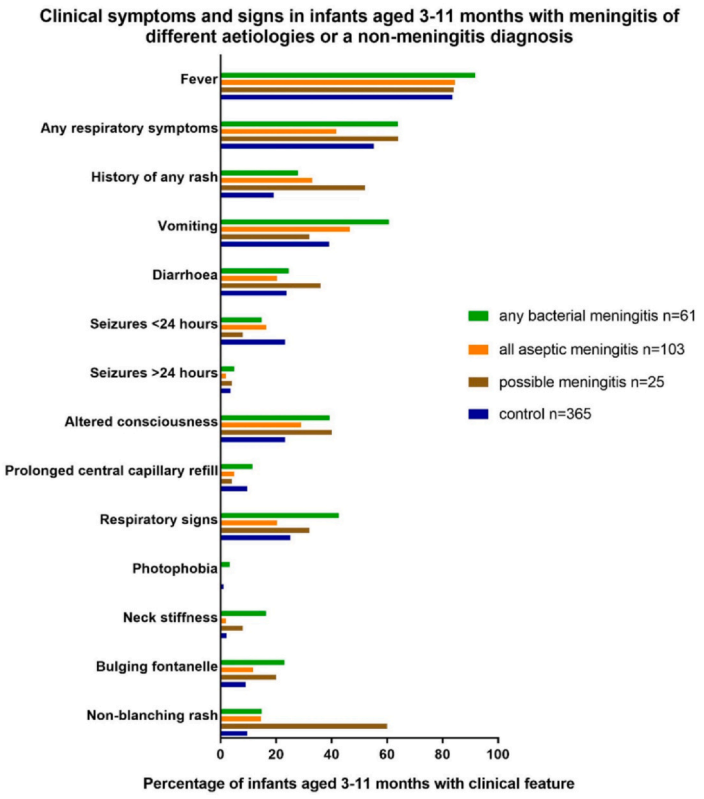


Fig. 1. Clinical features in children aged (a) 0–28 months; (b) 29 days to < 3 months; (c) 3–11 months and (d) 12 months and older with suspected meningitis. Note: Prolonged capillary refill was defined as ≥3 s.

(c)



(d)

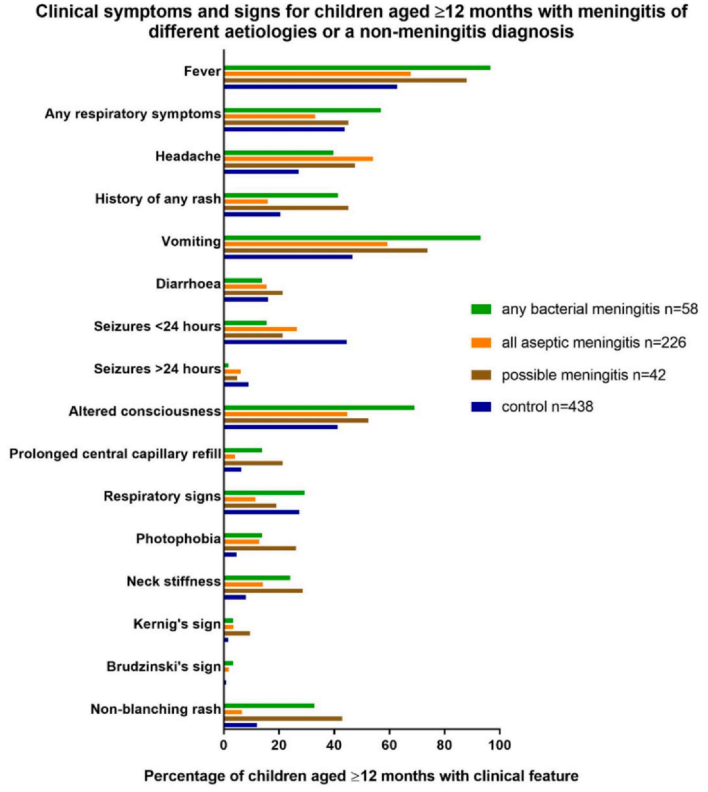


Fig. 1. (*continued*)

Table 4
Performance of Bacterial Meningitis Score in UK-ChiMES participants.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Children and infants aged >28 days				
Not pretreated, missing data excluded, N = 217	29/35 82·9% (66·4-93·4)	122/182 67% (59·7–73·8)	29/89 32·6% (23–43·3)	122/128 95·3% (90·1–98·3)
Not pretreated, missing data included, N = 296	49/55 89·1% (77·8-95·9)	122/241 50·6% (44·1–57·1)	49/168 29·2% (22·4–36·7)	122/128 95·3% (90·1–98·3)
Includes pretreated, missing data excluded, N = 336	56/76 73·7% (62·3-83·1)	166/260 63·8% (57·7–69·7)	56/150 37·3% (29·6–45·6)	166/186 89·2% (83·9–93·3)
Includes pretreated, missing data included, N = 466	96/116 82·8% (74·6-89·1)	166/350 47·4% (42·1–52·8)	96/280 34·3% (28·7–40·2)	166/186 89·2% (83·9–93·3)
All children and infants, including neonates				
Not pretreated, missing data excluded, N = 285	38/45 84·4% (70·5-93·5)	171/240 71·2% (65·1–76·9)	38/107 35·5% (26·5–45·4)	171/178 96·1% (92·1–98·4)
Not pretreated, missing data included, N = 380	67/74 90·5% (81·5-96·1)	171/306 55·9% (50·1–61·5)	67/202 33·2% (26·7–40·1)	171/178 96·1% (92·1–98·4)
Includes pretreated, missing data excluded, N = 418	69/92 75% (64·9-83·4)	221/326 67·8% (62·4–72·8)	69/174 39·7% (32·3–47·3)	221/244 90·6% (86·2–93·9)
Includes pretreated, missing data included, N = 566	119/142 83·8% (76·7-89·4)	221/424 52·1% (47·2–57)	119/322 37% (31·7–42·5)	221/244 90·6% (86·2–93·9)

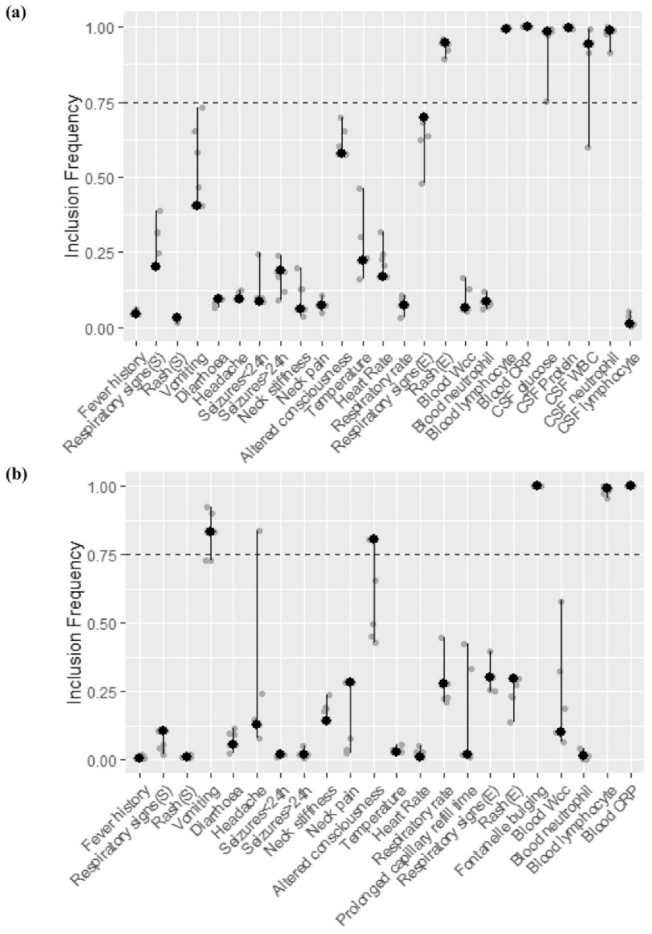


Fig. 2. The inclusion frequency of potential predictors for 10 imputed datasets among (a) children with CSF pleocytosis for post-LP rule development and (b) all children for pre-LP rule development. The grey dot for each variable represents the frequencies being included in the final prediction model after 500 bootstraps, based on one imputed dataset; a higher inclusion frequency means the variable is more likely to be a true predictor; the black dot indicates the median of the 10 inclusion frequencies from the 10 imputed datasets; the vertical line is the range of inclusion frequency among 10 imputed detests, and the horizontal dash line is the threshold for predictor selection. For blood and CSF variables, the cut-off was determined by receiver operating characteristic curves to maximise the accuracy in distinguishing participants with and without bacterial meningitis – details of the specific cut-offs for each variable is in Supplementary Table 12.

present study, these features were not helpful in distinguishing bacterial meningitis cases. Although many non-meningitis cases did have a serious bacterial infection elsewhere and would warrant antibiotic therapy, this was not the focus of the present study. Machine learning rather than the traditional statistical methods to develop prediction tools might be a better approach.

Limitations of this study include variation in laboratory investigations performed at different hospital sites and exclusion of participants with incomplete data for analysis. The requirements for recruitment to a prospective study also prevented all meningitis cases at hospital sites being included in the study, and so it is possible that the sample may not be completely representative of all paediatric meningitis, although the inclusion of over 30 hospitals across the UK partly mitigates this issue. There were also high rates of missing data for some variables investigated to distinguish bacterial from aseptic meningitis, including BMS predictors, and to formally diagnose encephalitis. However unreported variables are likely to represent information collected and tests typically performed for children presenting with suspected meningitis on arrival at the hospital in the UK. Frequent pre-treatment with antibiotics also reduced included participant numbers in the primary evaluation of the BMS, but exclusion of these children was required to ensure accurate comparisons between groups. We excluded neonates on the neonatal unit, and so the range of pathogens identified in this age group may not provide a complete picture of neonatal meningitis, specifically excluding some babies with early onset sepsis admitted directly to the neonatal unit after birth, before being discharged home.

In summary, this is the largest study of childhood meningitis in the UK to report prospectively collected data. It provides detailed contemporary knowledge about the current causes of meningitis, which is important to inform priorities for disease prevention and management, including the implementation of vaccine programmes, further research into improved diagnostic tests and vaccines, and improved clinical guidelines. There are still substantial numbers of bacterial meningitis cases, and early identification and management of these cases, and prevention strategies remain important. In addition to adequate investigation to promptly identify aetiology, robust methods are also needed to help clinicians assess the probability of whether a child has viral or bacterial meningitis on presentation to the hospital, to ensure prompt treatment of bacterial cases and reduce unnecessary antibiotics and hospital length of stay in viral meningitis. Clinical decision rules may aid in either identifying those who are most likely to have bacterial meningitis or identifying those who are unlikely to have it and might be used to reduce unnecessary antibiotic use and hospital stay. However, such rules remain difficult to implement because of the risk of failure to treat this serious infection. The study highlights the continued burden of bacterial meningitis and the need for ongoing efforts to optimise prevention through vaccination.

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Declaration of Competing Interest

MS has been an investigator on projects funded by GlaxoSmithKline, Merck, Moderna, Pfizer, Sanofi-Pasteur, Seqirus, Symvivo and VBI Vaccines. All funds have been paid to his institute, and he has not received any personal payments. **AJP** was a member of the World Health Organisation's Strategic Advisory Group of Experts on Immunisation until January 2022 and remains chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation (JCVI). **AJP** also reports providing advice to Shionogi on COVID-19, and funding from the National Institute for Health Research (NIHR), AstraZeneca, the Bill & Melinda Gates Foundation, Wellcome, the Medical Research Council, and the Coalition for Epidemic Preparedness Innovations (CEPI). Oxford University has entered into a partnership with AstraZeneca for the development of COVID-19 vaccines. **TS** is Director of The Pandemic Institute, which has received funding from Innova, CSL Seqirus, Aviva and DAM Health; was an advisor to the GSK Ebola Vaccine programme and the Siemens Diagnostic Programme; Co-Chaired the WHO Neuro-COVID task force and sat on the UK Government's Advisory Committee on Dangerous Pathogens, and the Medicines and Healthcare Products Regulatory Agency (MHRA) Expert Working Group on Covid-19 vaccines. **PH** has been an investigator on projects funded by GlaxoSmithKline, Merck, Moderna, Pfizer, Sanofi-Pasteur, Novavax, Valneva, Minervax and AZ. All funds have been paid to his institute, and he has not received any personal payments. He is a member of the UK JCVI. All other authors have no COI to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106145.

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