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Assessment of healthcare delivery in the early management of bacterial meningitis in UK young infants.

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TITLE: Assessment of healthcare delivery in the early management of bacterial meningitis in UK young infants.

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ABSTRACT

OBJECTIVE:

To define early presenting features of bacterial meningitis in young infants in England and to review the adequacy of individual case management as compared with relevant national guidelines and an expert panel review

DESIGN:

Retrospective medical case note review and parental recall using standardised questionnaires

SETTING:

England and Wales

PARTICIPANTS:

Infants aged <90 days with bacterial meningitis diagnosed between September 2010 and June 2013

RESULTS:

Of the 97 cases recruited across England and Wales, 66 (68%) were admitted from home and 31 (32%) were in hospital prior to disease onset. Almost all symptoms reported by parents appeared at the onset of the illness, with very few new symptoms appearing subsequently. Overall, 20/66 (30%) infants were assessed to have received inappropriate pre-hospital management. The median time from onset of first symptoms to first help was 5 hours (IQR: 2-12) and from triage to receipt of first antibiotic dose was 2.0 hours (IQR: 1.0-3.3) hours, significantly shorter in infants with fever or seizures at presentation compared to those without (1.7 [IQR, 1.0-3.0] vs. 4.2 [1.8-6.3] hours, p=0.02). Overall, 26 (39%) infants had a poor outcome in terms of death or neurological complication; seizures at presentation was the only significant independent risk factor (OR, 7.9; 95% CI: 2.3- 207.0). For cases in hospital already, the median time from onset to first dose of antibiotics was 2.6 (IQR: 1.3-9.8) hours and 12/31 (39%) of infants had serious neurological sequelae at hospital discharge.

CONCLUSIONS:

Young infants with bacterial meningitis have non-specific symptoms and signs, with no clear progression of illness over time, highlighting the difficulties in early recognition by parents and healthcare professionals alike. We propose a targeted campaign for education and harmonisation of practice with evidence-based management algorithms.

STRENGTH AND LIMITATIONS

- The strength of this study lies in the detailed analysis of a large cohort of geographically-representative infants with bacterial meningitis

- We did not find any significant differences between the recruited and non-recruited cases in relation to age, sex, region of the country and causal bacteria (data not shown).

- On the other hand, because we relied on paediatricians using their discretion to contact parents, this may have led to exclusion of families of infants who died or developed severe sequelae.

- Conversely, some parents may have agreed to participate simply because they were concerned about their child's condition or about suboptimal healthcare.

- Another potential limitation is that we relied on parents' recall for onset and progression of early clinical features.

- There is evidence however that parents are able to accurately recall such events for other serious infections[6].

INTRODUCTION

Bacterial meningitis in young infants remains a significant cause of mortality and long-term morbidity [1]. During 2010-11, we conducted national, prospective-population-based surveillance of bacterial meningitis in infants younger than three months of age in the United Kingdom and Ireland and found that 26% of 329 infants had poor outcomes at discharge[2]. Among survivors of neonatal meningitis in the 1980's, 50% had neurological sequelae at five years of age[3] and similar rates (40%) have been reported in survivors of neonatal bacterial meningitis in the 1990s[4].

The pathogens responsible for bacterial meningitis in young infants are different to those causing meningitis in other age groups[5], with group B streptococci (GBS) and *Escherichia coli* responsible for more than half the cases; neither are currently vaccine-preventable[1].

It is recognised that the early presentations of meningitis in young infants can be subtle and non-specific. This poses a substantial challenge for parents and healthcare workers. In our national surveillance, for example, half the infants with bacterial meningitis did not have fever at presentation and only 5% had the classic triad of fever, bulging fontanelle and seizures[2].

Studies of invasive meningococcal disease have been able to delineate the onset of specific symptoms and signs and chart their progression over the course of the illness[6]. This information has helped improve knowledge and increase awareness of meningococcal infections among parents and healthcare workers (http://www.meningitis.org/health-professionals/doctors-in-training). Early recognition of meningococcal infection coupled with rapid antibiotic treatment and more aggressive management of children with sepsis has subsequently led to improved outcomes[7-9]. In adults with sepsis, earlier antibiotics have been

associated with higher survival rates[10], but in infants the evidence base is poor even though they have the highest incidence of bacterial meningitis[5].

We hypothesised that earlier recognition may lead to earlier healthcare interventions which in turn might improve the outcomes of bacterial meningitis in young infants. We, therefore, undertook a detailed assessment of the timing, course and progression of bacterial meningitis in young infants across England and Wales. We also compared their initial and subsequent clinical management with relevant national guidelines.

METHODS

We undertook a detailed review of the clinical presentation and management of bacterial

meningitis in young infants in England and Wales diagnosed between September 2010 and

July 2013 from the perspectives of parents and healthcare workers. We aimed to recruit 100

eligible infants (**TABLE 1**)[11-13]. Cases were identified from LabBase2 (a national

surveillance database used by National Health Service hospitals laboratories to voluntarily

electronically report clinically significant infections to Public Health England)[14], through

parents of cases who reported directly to the meningitis support charities, and via a network

of hospital paediatricians.

Group	Definition
Eligible infants	Infants <90 days of age in whom a bacterium was isolated from CSF, or where a significant bacterial pathogen was isolated from blood together with CSF pleocytosis (defined as ≥20 cells / mm^3 for infants 0-28 days of age and ≥10 cells/ mm^3 for infants 29-89 days of age)[11-13]
Age at diagnosis	Early onset (0-6 days) and late onset (7-89 days)
Home admission	Infants admitted to hospital from home
In-patients	Infants already in hospital at the time, either in the neonatal unit, birthing centre or postnatal ward.
Time from onset to first help	The time from when parents noticed the first clinical feature to the time they sought any type of help (phone call or visit).
Time from onset to first dose of antibiotics	The time from appearance of first clinical feature to first dose of antibiotics
Time from triage to first dose of antibiotics	The time from when infant was triaged by a nurse to the time of administration of the first dose of antibiotics.
"In hours" (www.hscic.gov.uk)	Triage in hospital between hours of 0900 and 1800.
Appropriateness	Advice given prior to admission was judged as appropriate or inappropriate. Choice of empiric antibiotics and duration of antibiotics were appropriate if in conformity with existing guidelines. For example, the use of any antibiotics other than amoxicillin and cefotaxime/ ceftriaxone in any infant admitted from home would be classified as inappropriate.

Table 1: Definitions

A study pack containing study details, a consent form and a questionnaire was sent to the

local paediatrician to forward to parents. If families did not respond, we asked the

paediatrician to send a second pack. Parents of all participants completed a questionnaire with

details about onset and progression of specific symptoms. Participating parents also gave

informed written consent for the study investigators to access their infant's medical records.

All stages of care, including pre-hospital management, initial hospital assessment, ongoing

care and post-admission follow-up were assessed through an in-depth review of hospital

notes.

Assessment of management: Expert panel and national guidelines.

An expert panel consisting of a general paediatrician, neonatologist, paediatric infectious

diseases consultant and a paediatric specialist registrar reviewed the data to determine

appropriateness of pre-hospital management, delays in recognition, empiric antibiotics,

antibiotic duration and follow-up. These were judged according to any national guidelines

available at the time. The NICE feverish illness in children aged <5 years guideline [15] was

used to assess the appropriateness of advice/actions prior to hospital admission in febrile

infants; in the absence of fever, the expert panel proposed a standard best practice. The

Bacterial Meningitis and Meningococcal Septicaemia in Children guideline [16] was used to

assess the appropriateness of empiric antibiotics, length of treatment, and timing of audiology

testing for all cases. The management of infants presenting in the first 72 hours of life was

assessed against the NICE antibiotics for early onset neonatal infection guideline[17].

Data collection

Parents completed a questionnaire, which recorded the time of first appearance and

progression of pre-defined clinical features (online supplement on request). Information on

any illnesses in the previous two weeks was also requested. Hospital medical notes and GP

letters in the medical notes were used to corroborate parental recollection of onset, timing and

progression of events.

Data analysis

The data are mainly descriptive. We plotted the appearance and course of symptoms from the time of onset of first symptoms. The timing of each subsequent feature was then recorded and rounded to the nearest hour. For children admitted from home, we calculated the number of hours from the onset of illness to seeking any medical help ("first help" = hospital attendance, GP attendance or phone contact with a health professional) and to hospital admission. We compared the prevalence of symptoms at onset and at hospital presentation (infants admitted from home) or at diagnosis (in-patients). We also compared presenting features and clinical management in infants admitted from home and in-patients. Continuous data that did not follow a normal distribution are described as medians with interquartile ranges (IQR) and compared using the Mann Whitney U or Kruskal Wallis test, as appropriate. Proportions were compared using chi-squared or Fisher's Exact Test, as appropriate. To identify independent risk factors for poor outcomes (death or serious complications), potential explanatory factors were included in a backward, stepwise multivariable logistic regression model and the least significant parameter was then sequentially removed until only those parameters with p <0.05 remained.

RESULTS

A total of 224 infants with bacterial meningitis were identified and study information

forwarded to the parents **(Figure 1)**. The parents of 103 infants (46%) agreed to participate

but six cases were subsequently excluded because they did not meet the inclusion criteria.

Demographic data on parents and infants are shown in tables 2A and 2B. Cases were

recruited from 48 hospitals representing all English regions (**TABLE 2B**). Sixty-six (68%)

infant were at home when they became unwell and 31 (32%) were inpatients. Most parents

(92/97, 95%) completed the study questionnaire.

Parameter	Mothers	Fathers
Parental age distribution: 20-40 years	68 (70%)	69 (71%)
Median parental age (IQR)	29 (26-33)	32 (26-36)
Parent's highest academic level: Mothers (n=79): fathers (n=77)		
Post graduate	16 (20%)	7 (9%)
Graduate	16 (20%)	15 (19%)
A levels	20 (25%)	13 (17%)
GCSEs	27 (34%)	42 (55%)
Parents accommodation: mothers (n=87); fathers (n=77)		
Own house/ flat	45 (52%)	45 (58%)
Rented house/ flat	35 (40%)	26 (34%)
Council house/ flat	7 (8%)	6 (8%)

Table 2A: Basic demographics of parents

CASES ADMITTED FROM HOME (n=66)

The median age at diagnosis of bacterial meningitis was 14 days (IQR, 3-25), higher in cases

admitted from home (17 [11-34] days) compared to cases already in hospital (1 [0-7];

p=0.0001). The most common features at onset of illness were poor feeding (n=44, 65%),

lethargy (n=30, 45%) and fever (n=30, 44%). The majority of symptoms reported by parents

appeared at the onset of infection (**Figure 2A**) and these symptoms persisted, with very few

new symptoms appearing over the subsequent 24 hours (Fig 2B). However, there were small

but significant differences in the proportion of infants with more specific symptoms at

hospital admission compared with the onset of the illness: irritability (p=0.036), abnormal

breathing (p=0.023), abnormal movement/ seizures (p=0.024) (Figure 2C).

Twenty parents (30%) took their infants straight to the hospital: the A&E department (n=15, 22.5%) or the urgent care centre (n=5, 7.5%). The other parents (n=46, 70%) sought help by phoning the GP (n=21, 32%), calling the 24-hour NHS direct telephone service (n=15, 23%), or contacting the community midwife (n=10, 15%); of these, 13 (28%) were advised to stay at home.

The median time from onset of first features to first help was 5.0 hours (IQR: 2.0-12.0). The time to first help was not associated with early- or late-onset disease, gestation at birth, presence of fever or seizure, region of the country, type of housing or level of maternal academic qualifications. The majority of parents (47/62, 76%) presented to hospital within 24 hours of onset of symptoms, although 15 (24%) parents presented to hospital after 24 hours. Of these, 13 of 15 (93%) had fever (n=8) or seizures (n=4) or both (n=1) at the time they presented to hospital. Eight of the 15 (53%) had attended their GP surgery before going to hospital, of these three were reviewed at the A&E/walk-in centre and sent home and two were initially seen by a community midwife (all five infants were seen <24 hours from onset). The remaining 7/15 (47%) infants were brought to hospital by their parents more than 24 hours from the onset of symptoms.

Overall, 20/66 (30%) infants were assessed to have received inappropriate pre-hospital management. Examples included parents being told that their child's fever was due to a change in milk formula, or to an umbilical hernia, or where prune juice was recommended for fever and irritability (supplement table 1). In eight cases there appeared to be a delay in seeking help by parents despite the presence of worrying clinical features.

Parameter	Value
Male	52 (54%)
Term (≥37 weeks)	74 (76%)
Preterm (<37 weeks)	23 (24%)
32-36	14 (14%)
28-31	5 (5%)
<28	4 (4%)
BIRTH ORDER: Singleton	88 (91%)
Twins	9 (9%)
Age distribution: Early-onset: 0-6 days	30 (31%)
Late onset : 7-28 days	44 (45%)
29-89 days	23 (24%)
ROUTE OF ADMISSION: Home	66 (68%)
In-patient	31 (32%)
Ethnicity: White	81(84%)
Asian	6 (6%)
Black	4 (4%)
Unknown	6 (6%)
Region of England: North of England	26 (26%)
Midlands and East of England	18 (19%)
London and integrated regions	13 (13%0
South of England	39 (41%)
Infants mode of feeding at diagnosis: Breastfeeding	32 (38%)
Mixed feeding	13 (20%)
Bottle feeding	32 (33%)
BACTERIA: Identified from CSF only	23 (24%)
Identified from CSF and blood	40 (41%)
Identified from blood only	34 (35%)
GBS	65 (63%)
E. coli	11 (11%)
Listeria monocytogenes	4 (4%)
Neisseria meningitidis 4 (4%)	4 (4%)
Other Gram negative bacteria*	10 (10%)
Other Gram positive bacteria**	5 (5%)
Pseudomonas spp. 3, *Klebsiella spp.* 2, *Salmonella spp.* 2, *Citrobacter* 1, *Pasteurella spp.*1, *Haemophilus influenzae* 1. **Streptococcus pneumoniae* 2, *Streptococcus bovis* 2 and α-haemolytic streptococcus 1.	
Alive	96
Dead (after 28 hours in PICU after developing meningitis in the 4th week of life).	1

Table 2B: Basic demographics of all infants

A+E management

Around half of the infants (n=36, 55%) were triaged in A&E during normal working hours.

The median time from triage to receipt of the first antibiotic dose was 2.0 hours (IQR: 1.0-

3.3; > 1 hour in 43 infants, 73%), but was significantly shorter in infants with fever or

seizures at presentation than those without these features (1.7 [IQR, 1.0-3.0] vs. 4.2 [1.8-6.3]

hours, p=0.02). There was no significant difference in median time from triage to first

antibiotic dose in infants, early or late-onset disease, by region of the country, time of day at

presentation or whether a fluid bolus was given. The median time from onset to GP visit,

hospital attendance and first dose of antibiotics varied by route of admission (Table 3). Onset

to antibiotics time was significantly longer in those who were first seen by the GP.

Category	Onset to GP	Onset to hospital visit	Onset to first dose of antibiotics
Infants who went from Home direct to hospital	Not applicable	5.7 hours (2-8.4)	8 (4.8-13.5)
Infants who went from Home to hospital via GP	10.5 hours (3-33)	11 hours (5.2-17)	13 hours (6.8-25)
Infants who went to hospital via GP, were sent home and went to hospital a second time	9 hours (3.5-48)	52 hours (36-96)	57.5 hours (38-98.2)
P value	0.8	P=0.0001	P=0.0001

Table 3: Median time in hours (IQR) from onset to GP, hospital visit and first dose of antibiotics by route taken prior to hospital admission. (GP: General Practitioner).

Overall, 26 (39%) infants had a poor outcome in terms of death (one case) or neurological

complication (25, 38%). These included motor disorder or developmental delay (n=12, 18%),

seizures (n=7, 11%), hydrocephalus (n=5, 8%), hearing loss (n=5, 8%), cerebral infarct or

ischaemia on MRI (n=3, 5%) or visual deficits (n=3, 5%). There was no statistically

significant difference between the median time (IQR) from onset of illness to first help in

infants with poor outcomes and those who recovered (6.25 [1-24] hours vs. 4.75 [2-10],

p=0.8). Similarly the rate of poor outcome was not significantly different between the 15

infants who presented to hospital >24 hours after onset of symptoms and those who presented

<24hrs (8/15 [53%] vs. 18/47 [38%]; p=0.3). The interval between triage to first antibiotic

dose was also not associated with poor outcome.

A number of pre-defined, potential explanatory factors (age, gender, time from onset to first

help, delay in antibiotics, pre-hospital inappropriate advice, inappropriate empiric antibiotics,

presence of fever, presence of seizures) were explored in univariate and multivariate analyses

to identify risk factors for poor outcome; only the presence of seizures at presentation (OR,

7.9; 95% CI: 2.3- 207.0) was found to be an independent risk factor (supplement table 2).

In-patient infants (n=31)

As with those infants presenting from home, parents of in-patient infants at the time of diagnosis reported that the majority of symptoms were all present at the onset of the illness (**Figure 3A**) and remained present until diagnosis, with only a few new symptoms appearing during the course of the illness (**Figure 3B**). The only significant difference between symptoms at onset and those at diagnosis was the proportion with breathing difficulty (p<0.001) (**Figure 3C**).

Two-thirds of infants (21/31, 68%) had onset of symptoms within 72 hours of birth and were, therefore, assessed against the NICE early-onset antibiotic guidelines. According to these guidelines, the maternal "red flags" (mainly chorioamnionitis/ maternal sepsis in 5), baby "red flags" (respiratory distress after 4 hours of age in 9, shock in 4, seizures in 2 and need for ventilation at term in 1) or both, were present in 5/21 (24%), 15/21 (71%) and 17/21 (81%), respectively. At the time of diagnosis 17/31 (55%) of these infants received a fluid bolus, 12/31 (39%) had seizures and 8/31 (26%) had a fever.

The median time from onset of symptoms to first antibiotic dose was 2.6 hours (IQR, 1.3-8.5), with 74% (23/31) receiving their first dose >1 hour after onset of symptoms and 4 infants (13%) receiving the first dose >24 hours after onset.

Outcomes among in-patient infants: Overall, 12/31 (39%) of infants had a serious neurological complication at hospital discharge, including developmental delay or motor disorder (n=9, 29%), abnormal hearing (n=5, 16%), hydrocephalus/VP shunt (n=5, 16%), seizures (n=2, 6%) and abnormal MRI: cortical grey and white matter injury (n=1, 3%) and two infants were treated for cerebral abscesses. No significant risk factors for poor outcomes were identified in either the univariate or multivariate analyses (supplement table 2).

HOME vs. IN-PATIENT infants

The main differences between infants admitted from home and in-patient cases were age,

presence of fever on presentation, timing of LP and time to discharge from outpatient follow-

up (**Table 4**).

Variable	All cases	Home (n=66)	In-patient (n=31)	P value
Median age at disease (days)	14 (3-25)	17 (11-34)	1(0-7)	**0.0001**
Early onset (<7 days)	30 (31%)	8(12%)	22(71%)	**<0.0001**
Male	52(54%)	34(52%)	18(58%)	0.5
Prematurity	23(24%)	8(12%)	15(48%)	**<0.0001**
Out-of- hours presentation	47(48%)	30(45%)	17(55%)	0.4
Fever on presentation	48(51%)	40(61%)	8(26%)	**0.001**
Seizure at presentation	33 (34%)	21(32%)	12(39%)	0.5
Received fluid bolus at presentation	53(55%)	36(55%)	17(55%)	0.7
Antibiotics delay (hours)	2 (1.3-4)	2 (1-3.3)	2.6 (1.3-9.8)	0.09
LP done post first dose of antibiotics	57 (59%)	30 (45%)	27 (87%)	**<0.0001**
Antibiotics to LP time>24 hours	33 (59%)	14 (47%)	19 (70%)	0.07
Median time to LP and no bacteria in CSF (hours)	46 (24-92.5)	24 (15.2-52.8)	65 (44-100.8)	**0.017**
Median time to LP and bacteria in CSF (hours)	7.3 (1.5-2.4)	3 (1-24)	9.5 (2-24)	0.3
Empiric antibiotics not in conformity with national guidelines	52 (54%)	35(53%)	17 (55%)	0.9
Discharge to first OPD review (months)	2.5 (2.0-3.5)	2.5 (2.0-4.0)	2.5 (2.0-2.5)	0.6
Discharge from follow up age <12 months	13 (14%)	12/65 (18%)	1/31 (3%)	**0.03**
Discharge from follow up age <24 months	31 (32%)	26/65 (40%)	5/31 (16%)	**0.02**
Hearing test performed in survivors*	74 (77%)	53/65 (82%)	21/31 (68%)	0.1
Neurological complications	40 (42%)	26/65 (40%)	14/31(45%)	0.6
Discharge to audiology test (days)	25(0-32)	24 (10-42)	26 (0-28)	0.2
Informed of meningitis support charities	12/97 (13)	11/66(17%)	2/31(6)	0.2

Table 4. Comparison of infants admitted from home and infants in hospital at the time of diagnosis (EO: early onset, OPD, out-patient department, LP: Lumbar puncture). * There were 22 survivors without report of hearing test. 12 (13%) had no record of hearing test at review, 5 (5%) were transferred to another hospital where data was not available and 4 (12%) had the review <1 month after discharge and 1 (1%) missed two appointments.

Empiric antibiotics.

The empiric antibiotics used in 35 (53%) and 17/31 (55%) of infants admitted from home and

in-patient cases respectively were not in conformity with the appropriate NICE guidelines

(Supplement table 3).

FOLLOW-UP AND HEARING TESTS AFTER DISCHARGE.

The median time to first out-patient follow-up was 2.5 (IQR; 2-3.5) months and was not

different amongst infants admitted from home and in-patient cases (**Table 4**). However,

infants from home were more likely to be discharged from follow-up before 2 years of age. A

hearing test was performed in 74/96 (77%) survivors (Table 4). The median time from

discharge to hearing test was 25 days (IQR: 0-32), with 30 (41%) and 14 (19%) infants

having the hearing test ≥4 and ≥6 weeks after hospital discharge respectively.

Discussion

This is the first study to assess in detail the course of the illness in young infants with bacterial meningitis and the early healthcare they receive. Parental reporting of the early features of bacterial meningitis is a unique aspect of this study. We have shown that in infants with bacterial meningitis most of the symptoms and signs are present from the onset of the illness and there is little progression, with no or few additional symptoms developing as the illness progresses. Notably, up to 40% of infants did not develop fever at any time during their illness. In keeping with previous studies, only seizures at presentation were significantly associated with a poor outcome[2].

The course of bacterial meningitis in young infants appears to be different to that of children with meningococcal meningitis. With a similar study design, Thompson, Ninis and colleagues demonstrated that meningococcal disease progresses in a stereotypical manner in all children, with a prodromal phase, early sepsis phase and meningism only as a late feature[6]. In terms of the healthcare-seeking behaviour for those infants admitted from home, 70% of parents had sought medical help prior to A&E attendance. Of concern, a significant proportion had received inappropriate advice suggesting that further training of frontline healthca0re staff in recognising serious illness in children is required[18]. On the other hand, many of the parents presented to hospital more than 24 hours after the initial healthcare contact, most likely because their child's condition deteriorated, thus highlighting the importance of providing appropriate safety-netting advice to parents if they are advised to return home.

On admission to hospital, the median time from triage to first antibiotic dose was 2 hours, lower than that recently reported for childhood septicaemia (3 hours)[19] but higher than the recommended threshold of 1 hour[20]. We identified a number of reasons for this delay,

including uncertainty in recognition (especially in those with non-specific presentations), over-reliance on the presence of fever, waiting for urine samples before giving antibiotics and waiting for handover between shifts. Presentation in-hours or out-of-hours did not influence time to first antibiotic, which is reassuring given that half of infant presented out of hours. That infants with fever or seizure received antibiotics more quickly than those without these features suggests that these delays can potentially be avoided. Miner et al showed that delay to antibiotics time is significantly shorter in patients who received it in the emergency department[21]. With appropriate education strategies, it is therefore possible to significantly improve antibiotic delivery time for infants[22].

Most in-patient infants developed meningitis within 72 hours of birth, suggesting vertical transmission of infection. The recent NICE guidelines for early-onset antibiotics provides guidance on maternal, birth and infant risk factors that should lead to specific and timely antibiotic therapy[17]. Notably, 80% of infants had such risk factors, suggesting this to be a useful tool. However the time to antibiotic administration and choice of antibiotic was still very variable. Adult studies from USA and France reported low compliance to established guidelines[23, 24].

There is still a need to reinforce to clinicians the importance of performing a timely hearing test in infants with bacterial meningitis. There is no record of such a test in 23% of cases and even when done it was ≥ 4weeks in 40%. National guidelines emphasize the need for early diagnosis of deafness to allow early interventions such as cochlear implantation [16]. Follow-up of infants with bacterial meningitis is also believed to be important as it should allow early identification of those with neurodevelopmental impairment (likely to be around 50% of survivors)[4, 25] and timely intervention and support[16].

Summary

The impact of bacterial meningitis on young infants and their families is significant. This may reflect its delayed recognition and management. We propose a targeted campaign for education of new parents, primary care health workers (including telephone advice providers) and hospital doctors regarding the non-specific features, the lack of progression of clinical features and the lack of fever in young infants with bacterial meningitis. There is also need to explore ways of harmonising clinical practice with evidence-based management algorithms, including timely investigation and administration of appropriate antibiotics and adequate follow up of infants with bacterial meningitis.

Ethical Approval

Ethical approval was given by Cambridgeshire 2 REC (Ref: 10/H0308/64). Paediatricians were approached by email asking if there would be willing to take part in the study. If in agreement, a National Institute for Health Research Coordinated System for gaining NHS Permission (NIHR CSP) application was made and the hospital listed once approval was granted.

Competing interests

Contributorship statement:

Ifeanyichukwu O Okike completed the ethics application form, finalised the data collection tool, coordinated the study, entered all data into an Access database, data interpretation, performed the analysis and wrote the initial manuscript, reviewed and revised the manuscript and submitted the final manuscript.

Shamez N Ladhani helped with case ascertainment from the Public Health England, supported the data analysis and data interpretation, reviewed and revised the manuscript and approved the final manuscript.

Mark Anthony co-conceived and designed the study including the grant application, was a member of the expert panel who reviewed the management of cases, took part in data interpretation, reviewed and revised the manuscript and approved the final manuscript.

Nelly Ninis co-conceived and designed the study including the grant application, was a member of the expert panel who reviewed the management of cases, took part in data interpretation, reviewed and revised the manuscript and approved the final manuscript.

Paul T Heath was the Chief Investigator, co-conceived and designed the study including the grant and ethics application, was a member of the expert panel who reviewed the management of cases, contributed to the data analysis and data interpretation, reviewed and revised the manuscript and approved the final manuscript.

Acknowledgement

Transparency declaration:

 The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

Copyright/licence for publication

Data sharing: We are happy to share our anonymised raw data which is not included in the manuscript. All requests should be made to the corresponding author.

What this paper adds

Section 1: What is already known on this subject

- The incidence of bacteria meningitis is higher in young infants than in any other age group and is often associated with a poor outcome - this has not changed over the last 3 decades

- The early clinical presentation of meningitis in young infants can be subtle and non-specific

Section 2: What this study adds

- The majority of symptoms and signs in young infants with bacterial meningitis are present at the onset of the illness, with little progression over time.

Inadequate pre-hospital management and delayed antibiotic administration in hospital were found in a significant proportion of cases.

SUPPLEMENTARY TABLE

No	Details	Source	Action & advice
1	74 days old, Fever, poor feeding, irritable, odd cry, bulging fontanel	Walk in centre	Umbilical hernia. Paracetamol. Sent home
2	13 days old, grunting, quiet	Parents/ GP	Sought help after 12hours. Appointment made for 4hrs later
5	6days old febrile, poor feeding, irritable	Parents/ GP	Sought help after 6 hours. Was told to make an appointment next morning.
8	53days old, febrile, irritable, bulging fontanelle	GP	Did not check temperature or anterior fontanelle. Reassured (teething or a virus). Advised to stay at home.
10	14days old, Irritable, constant crying, stiff	Parents/GP	Sought help after 2 days. GP told mum it was reflux. Pleaded with GP to examine baby. Temp 38.3. Diagnosis: Formula allergy due to crying & recent change in formula.
23	30days old, Poor feeding, vomiting, quiet / lethargic, more sleepy.2hours later fast breathing, irritable, odd cry, cold hands & feet, floppy	Parents/ GP	Seen at Walk in centre 4 hours from onset. Diagnosis: Gastroenteritis. Sent to hospital for a 2nd opinion.
24	50days old, Quiet , lethargic, irritable, odd cry, poor eye contact	Hospital	GP sent infant to hospital. Features as noted with umbilical discharge: Sent home
25	36days old, bulging fontanelle	NHS direct/ Hospital	NHS direct: just monitor since no fever. At hospital: Loose stool and breathing problems. ↓activity, more sleepy, cough resolved, grunting, poor feeding, ↓urine output. Pulse 150.Diagnosis: resolving viral URTI. Plan: home. Advice: return if febrile.
27	34days old, Fever, poor feeding, fast breathing, irritable, odd cry, more sleepy, bulging fontanelle	Walk in centre	Febrile: diagnosis of viral infection and discharged
28	3days old, poor feeding, irritable, odd cry, more sleepy than normal	Community midwife	Advised: see how the baby goes through the night (40 hours delay to hospital)
31	5days old, Poor feeding, tremors of hands, sleepy	Community midwife	Visited and advised: Tremor was a way of regulating body temperature. Stay at home
36	11days old, febrile, Fever, poor feeding, vomiting, slow breathing, quiet/ lethargic, irritable, odd cry, poor eye contact, more sleepy	Parents/ GP	Sought help after 24 hours. GP appointment for 5.5hours from call.
39	12days old, Fever, poor feeding, irritable, odd cry, abnormal movement	NHS direct	Advise: give prune juice, reassured to stay at home (45 mls of prune juice given)

51	2days old, Poor feeding, irritable, jaundice, eyes rolling, grunting	Community midwife	At this time baby also was vomiting, odd cry, abnormal movement, more sleepy. Reassured to stay at home (by telephone)
52	14days old, Fever at the GP	GP	Temperature 38.3C (axilla). Baby was fine, sent home
55	11days old fever, poor feeding	midwife	Constipation due to formula. In Accident and Emergency after 13.5hours
56	11days old, irritable, odd cry, jerky movement, fever	Ambulance	(NHS direct to hospital time 3h 6mins). Reassured it is a cold. Took 30minutes to complete paper work & 1 hour to hospital
64	53days old, Fever, poor feeding, quiet/ lethargic, more sleepy, Temperature 39.5C, odd cry, fast breathing.	GP	Seen at 1800: Temperature 38.5C. Advice: give paracetamol, monitor temperature, doctor will call at 10pm
67	59d, Fever, poor feeding, vomiting, pale, irritable, odd cry, poor eye contact, abnormal movement, bulging fontanelle, wont sleep, won't settle.	GP/ parents	Sought help after 12 hours. Seen at 2100: advised to water him and go home and if symptoms continue to call again: She refused and pointed to the doctor that AF was bulging and so be referred to local hospital
68	73days old, Fever, poor feeding, fast breathing, mottled skin, quiet/lethargic, poor eye contact, more sleepy	GP	Saw GP. Was told it was change from breast to bottle feeds. Next day called NHS direct. Advised to go to AE

Table 1: Inappropriate advice given (I think this table is easy to identify by readers given the number of infants). We can keep and provide if asked.

	All cases			Home			In-patient		
Parameter	No complications	complications	P-value	No complications	complications	P-value	No complications	complications	P value
Median age at presentation	14 (3-31)	12 (3-23)	0.4	19 (13-37)	16(9-25)	0.3	1(0-3)	2(1-8)	0.3
Early onset	16 (28)	14(35)	0.5	3(8)	5(19)	0.2	13(76)	9(64)	0.7
Male	29 (51)	23(58)	0.5	20(50)	14(54)	0.8	9 (53)	9(64)	0.7
Prematurity	11 (19)	12 (30)	0.2	4(10)	4(15)	0.7	7(41)	8(57)	0.4
OOH presentation	31(54)	16(40)	0.2	21(53)	9(35)	0.2	10(59)	7(50)	0.6
Inappropriate advice	NA	NA	NA	16(40)	14(54)	0.3	NA	NA	NA
Fever or seizure	39 (68)	32(80)	0.2	30(75)	24(92)	0.1	9(53)	8(57)	0.8
Fever	30(53)	18(47)	0.5	25(63)	15(63)	0.7	5(29)	3(21)	0.7
Seizure	13(23)	20(51)	**0.005**	7(18)	14(56)	**0.002**	6(35)	6(43)	0.7
Fluid bolus	30(53)	24(67)	0.5	22(55)	15(68)	0.8	8(47)	9(64)	0.5
Bacteria in CSF	41(72)	23(58)	0.1	31(78)	17(65)	0.3	10(58)	6(43)	0.6
Non-conformity antibiotics	31(54)	21(53)	0.9	21(53)	14(54)	0.8	10(59)	7(50)	0.6
Antibiotics delay >6h *	7/55 (13)	5/32(16)	0.8	2/38(5)	2/21 (10)	0.6	5/17 (29)	3/11 (27)	1.0
Onset to help ≥12h	NA	NA	NA	7/40 (18)	10/26(38)	**0.06**	NA	NA	NA
Maternal age	30(26-35)	29(24-32)	0.2	29(26-34)	29(24-32)	0.8	31(27-40)	27(23-33)	**0.07**

Table 2: Univariate analysis of death (1 case) and serious complications. OOH= out of hours

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Pathogen	HOME	IN-PATIENT
GBS : Home (24) in-patient (10)	Cefotaxime/ ceftriaxone alone 9 Benzyl penicillin and gentamicin 7 Amoxicillin and gentamicin 3 Cefuroxime and metronidazole 1 Cefotaxime and flucloxacillin 1 Cefotaxime and gentamicin 1 Benzyl penicillin 1 and Co-amoxiclav 1	Cefotaxime/ ceftriaxone alone 4 Benzyl penicillin and gentamicin 2 flucloxacillin and gentamicin 2 Amoxicillin and gentamicin 1 Vancomycin and gentamicin 1
E. coli (5)	Benzyl penicillin and gentamicin 4 Benzyl penicillin and cefotaxime 1	Cefotaxime/ ceftriaxone 1 Tazocin and Vancomycin 1
N. meningitidis (3)	Cefotaxime/ ceftriaxone 3	
L. monocytogenes (2)	Cefotaxime 1	Cefotaxime 1
Pasteurella spp (1)	Benzyl penicillin and gentamicin 1	
Salmonella agama (1)	Flucloxacillin and gentamicin 1	
Klebsiella spp. (1)		Teicoplanin 1
S. bovis (1)		Cefotaxime 1
H. influenzae (1)		Cefotaxime and gentamicin 1

Table 3: Isolated bacteria in cases where empiric antibiotics was not in conformity with existing guidelines and antibiotics started empirically

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┌─────────────────────────────────────────┐      ┌─────────────────────────────────────┐
│  Study pack sent to Paediatricians: 322  │─────▶│ Not cases (24) or deemed            │
└─────────────────────────────────────────┘      │ inappropriate to send to            │
                     │                            │ parents (27*): 51                   │
                     ▼                            └─────────────────────────────────────┘
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│  Eligible to be sent to parents: 271     │      ┌─────────────────────────────────────┐
└─────────────────────────────────────────┘─────▶│ Invitations not confirmed as        │
                     │                            │ sent: 44                            │
                     ▼                            │ Duplicates: 2                       │
┌─────────────────────────────────────────┐      │ Return slip received but not        │
│  Invitations confirmed to have been      │      │ confirmed as a case: 1              │
│  sent to parents: 224                    │      └─────────────────────────────────────┘
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                     │                ─────▶    ┌─────────────────────────────────────┐
                     ▼                          │ Consent form not                    │
┌─────────────────────────────────────────┐    │ returned: 121                       │
│  Consented to take part in study: 103    │    └─────────────────────────────────────┘
└─────────────────────────────────────────┘
                     │                ─────▶    ┌─────────────────────────────────────┐
                     ▼                          │ Viral meningitis: 4,                │
┌─────────────────────────────────────────┐    │ No organism: 2                      │
│  Eligible for analysis: 97               │    └─────────────────────────────────────┘
└─────────────────────────────────────────┘
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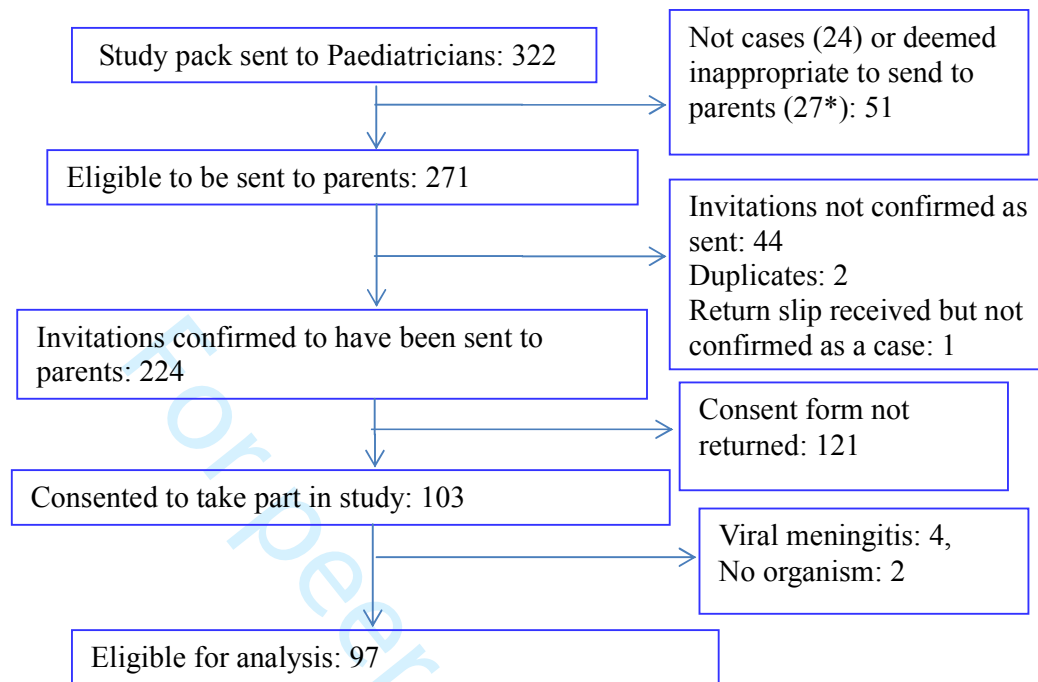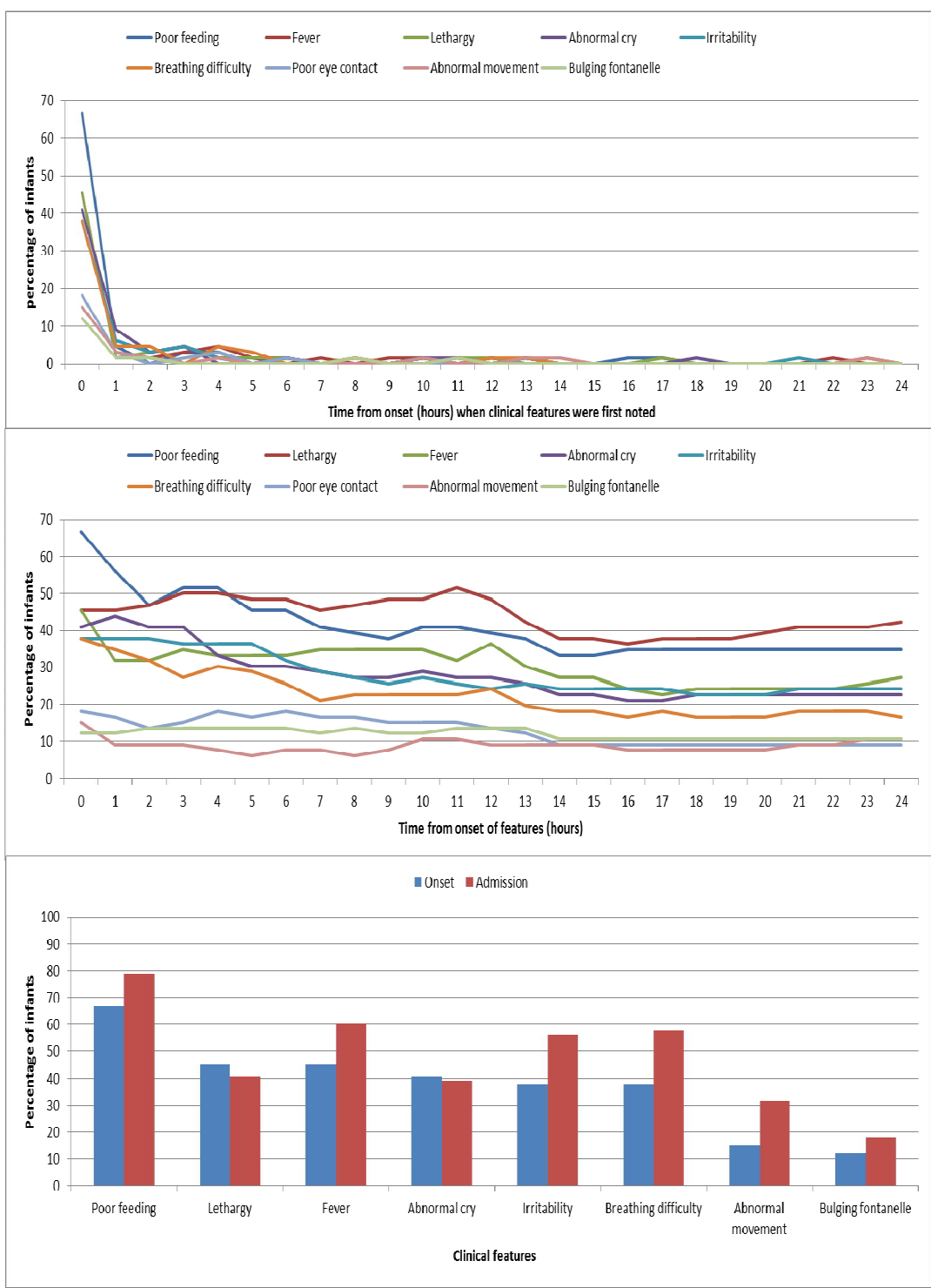
Figure 1: Recruitment algorithm. (*: died (8), moved away (5), foster care (2), language barrier (2)).
Recruited cases were from 2010 (n=25), 2011 (n=39), 2012 (n=22) and 2013 (n=11)

FIGURES:

Figure 2A. Time (hours) at which parents first noticed a specific clinical feature. Figure 2B: Number of features present at each hour as reported by parents Figure 2C: Clinical features present at onset and time of admission
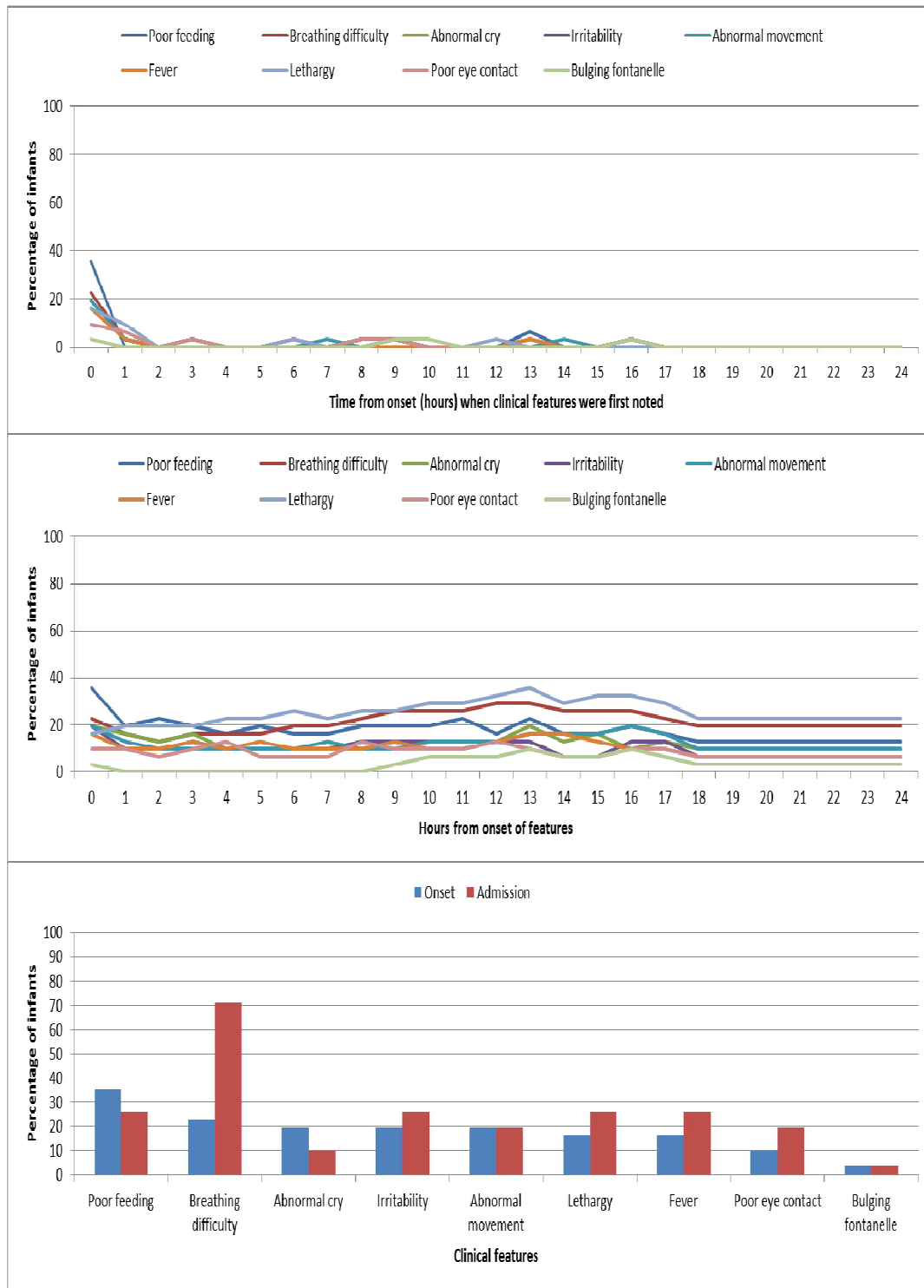
Figure 3A: Time (hours) at which parents first noticed a specific clinical feature (in-patient cases). Figure 3B: Number of features present at each hour as reported by parents (in-patient cases) Figure 3C: Clinical features present at onset and time of admission (in-patient cases)

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Study pack sent to Paediatricians: 322

Not cases (24) or deemed inappropriate to send to parents (27*): 51

Eligible to be sent to parents: 271

Invitations not confirmed as sent: 44
Duplicates: 2
Return slip received but not confirmed as a case: 1

Invitations confirmed to have been sent to parents: 224

Consent form not returned: 121

Consented to take part in study: 103

Viral meningitis: 4,
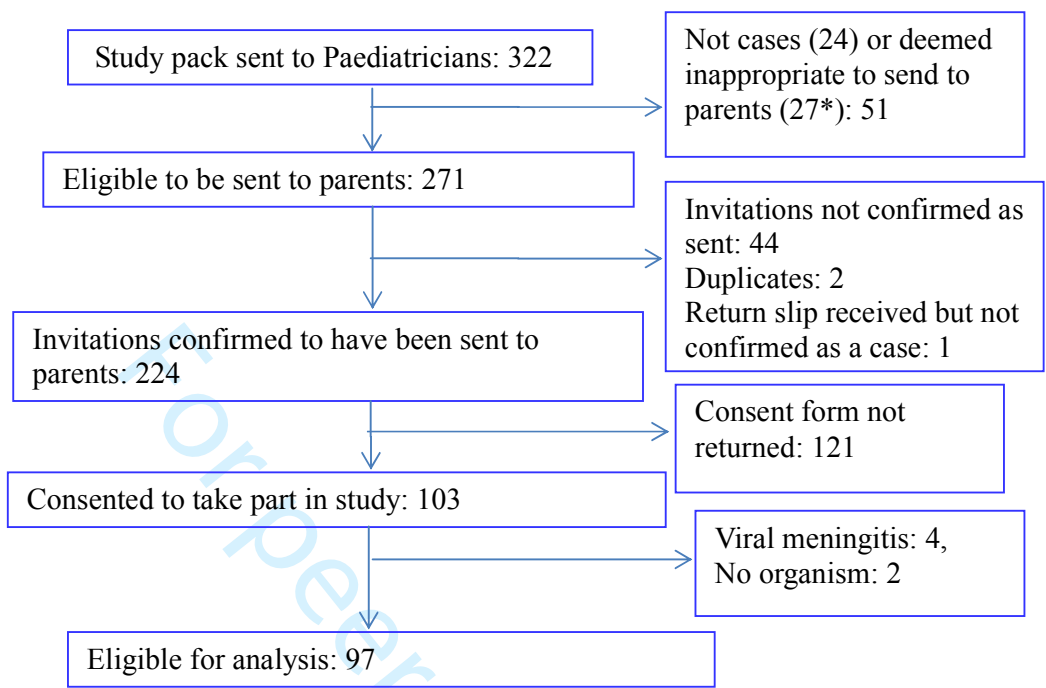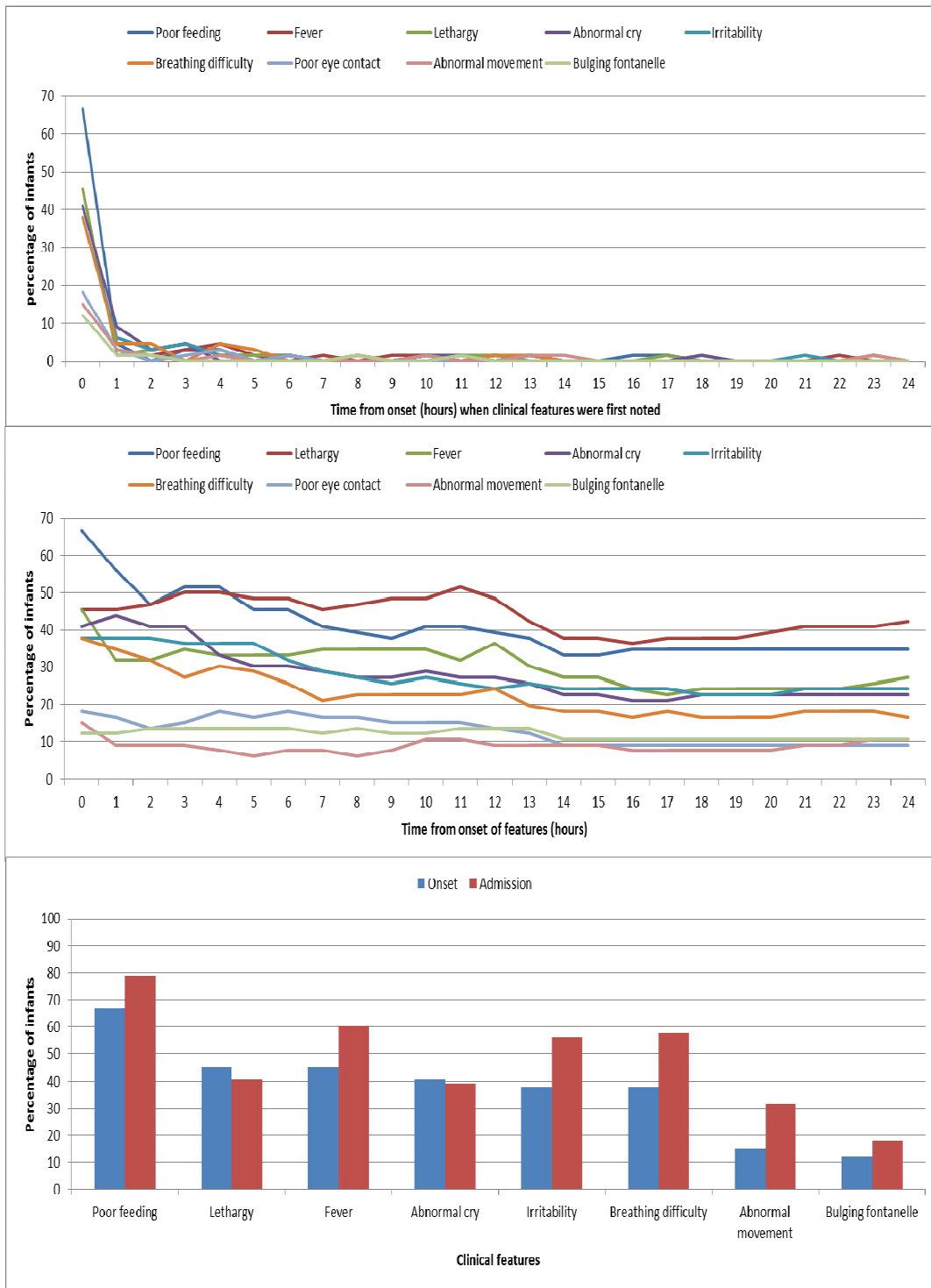No organism: 2

Eligible for analysis: 97

Figure 1: Recruitment algorithm. (*: died (8), moved away (5), foster care (2), language barrier (2)).
Recruited cases were from 2010 (n=25), 2011 (n=39), 2012 (n=22) and 2013 (n=11)

FIGURES:

Figure 2A. Time (hours) at which parents first noticed a specific clinical feature. Figure 2B: Number of features present at each hour as reported by parents Figure 2C: Clinical features present at onset and time of admission
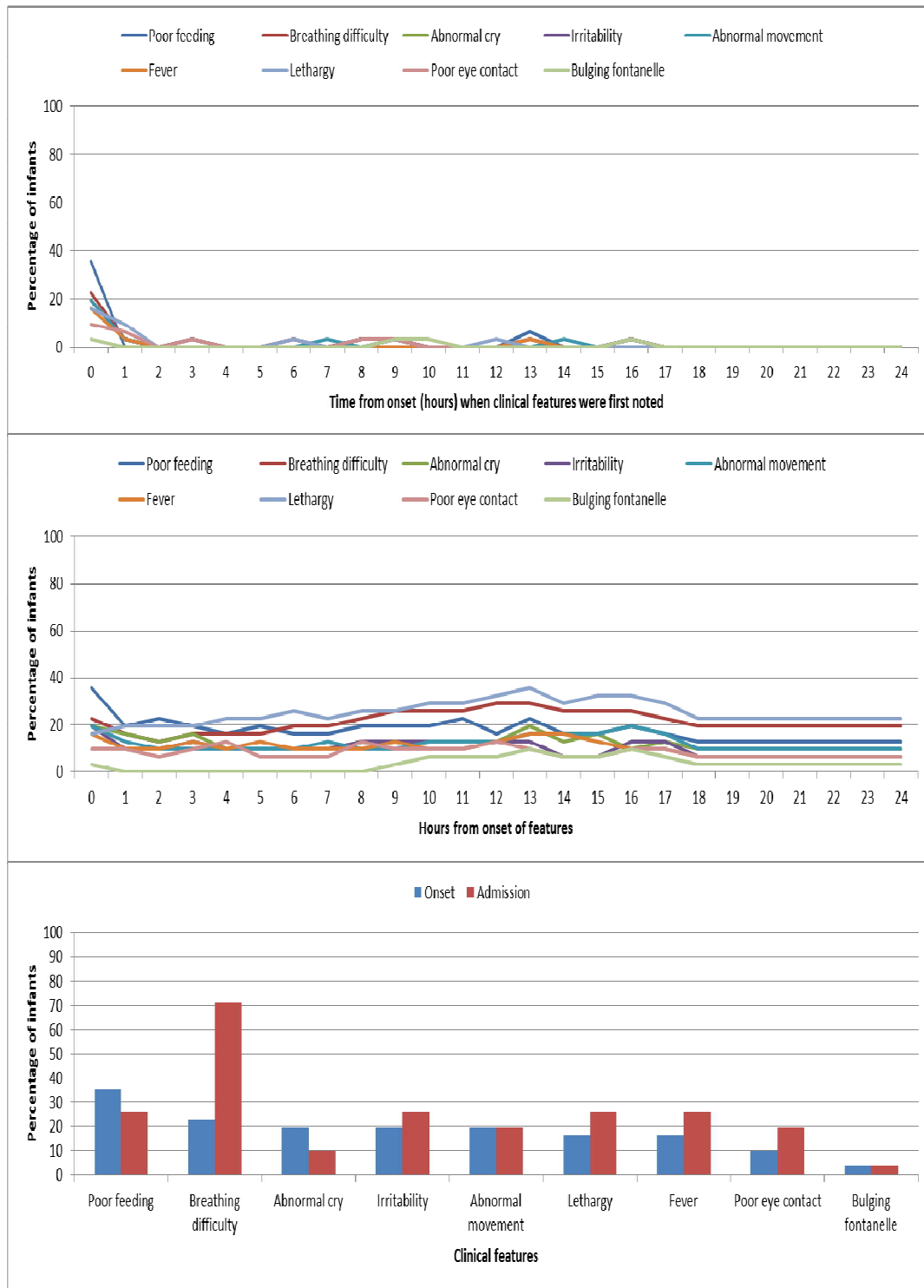
Figure 3A: Time (hours) at which parents first noticed a specific clinical feature (in-patient cases). Figure 3B: Number of features present at each hour as reported by parents (in-patient cases) Figure 3C: Clinical features present at onset and time of admission (in-patient cases)

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SUPPLEMENTARY TABLE

Table 1: Inappropriate advice given (I think this table is easy to identify by readers given the number of infants). We can keep and provide if asked.

Note: this table has been removed by the editors because it contains more than two direct identifiers and could breach patients' right to anonymity.

	All cases			Home			In-patient		
Parameter	No complications	complications	P-value	No complications	complications	P-value	No complications	complications	P value
Median age at presentation	14 (3-31)	12 (3-23)	0.4	19 (13-37)	16(9-25)	0.3	1(0-3)	2(1-8)	0.3
Early onset	16 (28)	14(35)	0.5	3(8)	5(19)	0.2	13(76)	9(64)	0.7
Male	29 (51)	23 (58)	0.5	20(50)	14(54)	0.8	9 (53)	9(64)	0.7
Prematurity	11 (19)	12 (30)	0.2	4(10)	4(15)	0.7	7(41)	8(57)	0.4
OOH presentation	31(54)	16(40)	0.2	21(53)	9(35)	0.2	10(59)	7(50)	0.6
Inappropriate advice	NA	NA	NA	16(40)	14(54)	0.3	NA	NA	NA
Fever or seizure	39 (68)	32(80)	0.2	30(75)	24(92)	0.1	9(53)	8(57)	0.8
Fever	30(53)	18(47)	0.5	25(63)	15(63)	0.7	5(29)	3(21)	0.7
Seizure	13(23)	20(51)	**0.005**	7(18)	14(56)	**0.002**	6(35)	6(43)	0.7
Fluid bolus	30(53)	24(67)	0.5	22(55)	15(68)	0.8	8(47)	9(64)	0.5
Bacteria in CSF	41(72)	23(58)	0.1	31(78)	17(65)	0.3	10(58)	6(43)	0.6
Non-conformity antibiotics	31(54)	21(53)	0.9	21(53)	14(54)	0.8	10(59)	7(50)	0.6
Antibiotics delay >6h *	7/55 (13)	5/32(16)	0.8	2/38(5)	2/21 (10)	0.6	5/17 (29)	3/11 (27)	1.0
Onset to help ≥12h	NA	NA	NA	7/40 (18)	10/26(38)	**0.06**	NA	NA	NA
Maternal age	30(26-35)	29(24-32)	0.2	29(26-34)	29(24-32)	0.8	31(27-40)	27(23-33)	**0.07**

Table 2: Univariate analysis of death (1 case) and serious complications. OOH= out of hours

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Pathogen	HOME	IN-PATIENT
GBS : Home (24) in-patient (10)	Cefotaxime/ ceftriaxone alone 9 Benzyl penicillin and gentamicin 7 Amoxicillin and gentamicin 3 Cefuroxime and metronidazole 1 Cefotaxime and flucloxacillin 1 Cefotaxime and gentamicin 1 Benzyl penicillin 1 and Co-amoxiclav 1	Cefotaxime/ ceftriaxone alone 4 Benzyl penicillin and gentamicin 2 flucloxacillin and gentamicin 2 Amoxicillin and gentamicin 1 Vancomycin and gentamicin 1
E. coli (5)	Benzyl penicillin and gentamicin 4 Benzyl penicillin and cefotaxime 1	Cefotaxime/ ceftriaxone 1 Tazocin and Vancomycin 1
N. meningitidis (3)	Cefotaxime/ ceftriaxone 3	
L. monocytogenes (2)	Cefotaxime 1	Cefotaxime 1
Pasteurella spp (1)	Benzyl penicillin and gentamicin 1	
Salmonella agama (1)	Flucloxacillin and gentamicin 1	
Klebsiella spp. (1)		Teicoplanin 1
S. bovis (1)		Cefotaxime 1
H. influenzae (1)		Cefotaxime and gentamicin 1

Table 3: Isolated bacteria in cases where empiric antibiotics was not in conformity with existing guidelines and antibiotics started empirically

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BMJ Open

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UK and Ireland prospective study of bacterial meningitis less than 90 days of life. Study number_____

Study of bacterial meningitis in infants less than 90 days of age.

St. George's, University of London in conjunction with the Health Protection Agency

1. Title:

Bacterial meningitis in infants less than 90 days of age: Assessment of healthcare delivery.

2. Purpose:

What is the current management of meningitis in infants < 90 days of age?

Our aims are to conduct a comprehensive study of bacterial meningitis in infants less than 90 days of age, to define the optimal management of meningitis in this age group, to describe the current management with reference to this and thus to define opportunities for improving the outcome.

3. Objectives:

To describe the clinical presentation of cases of meningitis in this age group.

What strategies can be identified that might improve the outcome from meningitis in this age group?

What is the neurodevelopmental outcome of meningitis in infants < 90 days of age when these children reach 2 years of age?

4. Background:

Meningitis is associated with significant mortality and morbidity in newborn infants. The most recent national surveillance study in the UK and Ireland was 10 years ago (1) and the first study 20 years ago. The Holt study (1996-7) identified an overall mortality of 10% (1). A more recent national GBS study (2000-1) indicated a mortality of 12.4% (15/121) for GBS meningitis specifically (the leading cause of neonatal meningitis) (2). A case-control study from the 1996-7 study cohort determined the neurodevelopmental outcome at 5 years of age (3). Overall it showed that about 50% of cases had some form of disability (24% with serious disability) and that the risk of serious disability was 16-fold higher than that of GP-matched controls. When compared to the previous national meningitis cohort (1985-7) the mortality had fallen significantly but there was no change in the rate of sequelae (26% with serious disability). Data from other studies confirm that despite declines in mortality, morbidity from neonatal meningitis did not change significantly between the 1970s and 1990s (reviewed in (4)). There have been no UK studies since that time. In addition, none of the previous studies specifically looked at the timing and progression of presenting symptoms and signs or assessed how these infants were managed. It is conceivable that earlier recognition and better or more prompt management may have an impact on their outcome.

[1]

[1] Healthcare delivery protocol version 1. 8 June 2010

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UK and Ireland prospective study of bacterial meningitis less than 90 days of life. Study number_____

This is the focus of this research. However, because there are no published guidelines on the management of neonatal meningitis we will formulate standards of clinical practice by using an expert panel convened for the study and based on reviews of the relevant literature. The standards will relate to multiple steps in the diagnosis and management process from first assessment, initial symptoms, initial management in the first and subsequent hours, through to follow-up. The expert panel will consist of recognized experts from the USA, Australia and the UK and will reflect the relevant fields of paediatric infectious diseases, paediatric accident and emergency, neonatology and microbiology. Ultimately then we will measure and report clinical practice against the study standards and through this hope to identify areas where management might be improved.

None of the previous studies have specifically looked at the timing and progression of presenting symptoms and signs in infants with meningitis or at their early management. It is conceivable that earlier recognition and better and more prompt management may have an impact on the mortality and also the morbidity. This study will focus on these aspects and will complement another study (the burden of disease study REC **Ref: 10/H0308/45**) which is addressing the national incidence of meningitis and the responsible pathogens.

To obtain such data we ideally need to review the hospital notes and also to gather detailed information from the parents on the events leading up to the illness. These will require parental consent. For logistic reasons (the need to visit hospitals) we will therefore recruit infants in England only. The same study will be undertaken by colleagues in the Republic of Ireland (subject to a separate ethics application). Cases of meningitis will be identified through microbiologists (via routine notifications and referral of isolates to the HPA and via regular email reminders to microbiologists to alert us to cases) and through parents, via websites and communications from Group B Strep Support (a parent's support charity) and Meningitis charities (Meningitis Research Foundation, Meningitis UK and Meningitis Trust). Once we are aware of a potential case via these sources we will send a parents' information pack to the paediatrician responsible for the case requesting that they send this on to the parents on our behalf. There will be a return slip with a prepaid return envelope that the Paediatrician sends to us once the pack has been sent to parents (for accountability purposes).

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In the pack will be an information booklet, the parents' questionnaire, a consent form and a pre-paid return envelope. If parents are interested in participating, we will ask them to complete the consent form and the questionnaire and return them to use in the envelope provided. It will be clear that they have the options of consenting to allow us to access the hospital notes and/or to completing the questionnaire and/or to making contact with them before the 2nd birthday of the child to arrange a neurodevelopmental assessment.

1. Holt DE, Halket S, de Louvois J, Harvey D. Neonatal meningitis in England and Wales: 10 years on. Arch Dis Child Fetal Neonatal Ed. 2001 Mar;84(2):F85-9.

2. Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days. Lancet. 2004 Jan 24;363(9405):292-4.

3. de Louvois J, Halket S, Harvey D. Neonatal meningitis in England and Wales: sequelae at 5 years of age. Eur J Pediatr. 2005 Dec;164(12):730-4.

4. Heath PT, Nik Yusoff NK, Baker CJ. Neonatal meningitis. Arch Dis Child Fetal Neonatal Ed. 2003 May;88(3):F173-8

4. Plan, Methods and Techniques:

We propose to recruit babies in England and the Republic of Ireland who had bacterial meningitis when aged less than 90 days.

Recruitment in England.

Cases of meningitis will be identified through microbiologists and parents.

Microbiologists: The Health Protection Agency (HPA) routinely receives notifications of cases of bacteremia and meningitis and, separately, referral of isolates from microbiologists in England and Wales. To enable follow up of potential cases the HPA will provide the Study Research Fellow (who will hold an Honorary contract with the HPA) with sufficient identifying data on such cases to allow contact to be made with the relevant paediatrician. This may include: patient initials, date of birth, gender, NHS number, date of notification and name of the referring hospital or laboratory. This will be supplemented by regular reminder emails from the study team to microbiologists based at hospitals with larger neonatal units.

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Parents: To ensure as complete ascertainment as possible we will also receive notifications from parents who will become aware of the study though several parent support groups / charities. These include Group B Strep Support (http://www.gbss.org.uk), a UK charity offering information on group B streptococcal disease to health professionals and affected families (coordinated by Jane Plumb), the Meningitis Research Foundation (contact: Linda Glennie), the Meningitis Trust (contact: Jane Blewitt) and Meningitis UK (contact: Catherine Fougere-Masters). Parental reporting was successfully used in our previous national GBS study (Lancet. 2004 Jan 24;363(9405):292-4). Information about the study will be made available on the respective websites and communications of these groups. Parents who make contact with these support groups, either spontaneously or as a result of the study, will be asked for permission to pass on sufficient identifying data to the study team to allow contact to be made with the relevant paediatrician.

Once a case has been notified by the other sources, the Research Fellow will send the relevant paediatrician a letter requesting them to approach the family on our behalf. This will be done by sending the family our information pack (which we will have provided to the paediatrician). They will be asked to write the subjects' home address on the envelope and will also have the option of including a cover letter (we will provide the paediatrician with a draft that they may use if they wish).

The information pack will include details about the study, a parent questionnaire, a consent form and a reply paid envelope together with contact details of the study team. Families will be asked to complete and return the consent form and the questionnaire; they can make contact with the study team by telephone or email if they require further clarification. The consent form will provide the options of: consent to access the hospital notes and/or to complete the parental questionnaire and/or to make contact with the family before the 2nd birthday of the child to arrange a neurodevelopmental assessment. We will only inform the baby's GPs if parents consent to this.

When the consent form is returned to the study team indicating their consent for access to the hospital notes, the research fellow will make contact with the Paediatrician/Paediatric Secretary requesting that they make the notes available for a visit by the Research Fellow to allow him to complete the Healthcare delivery proforma. This is a standardized case report form which has been extensively reviewed by the study team and piloted on patient notes.

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Data to be collected includes demographics, indicators of standards of care, disease severity and outcome. Each subject will be given an encrypted unique identifier which will maintain anonymity but enable record linkage.

The parent questionnaire has been developed following extensive review by representatives of the parent support charities (MRF, MUK, MT, GBSS) and piloting by parents who were identified by these parent support charities. It is estimated that it will take approximately 30 minutes to complete. Parent may also complete the questionnaire with the research fellow over the telephone or in person if they wish. The questionnaire will collect detailed information about the events leading up to the diagnosis.

Where families do not respond to the first letter from the paediatrician within 1 month, we will ask the paediatrician to send them a second identical information pack. This method of recruitment has been used previously by a study looking at meningococcal disease outcomes in children and adolescents (MOSAIC) project reference 07GA07.

It is likely that a proportion of cases identified through microbiologists and the HPA will be uncontactable or refuse to participate. This may be a source of bias, as is it possible that the degree or severity of sequelae may influence participation in the study (although the direction of bias is unclear). We will therefore collect anonymised data from the HPA about unrecruited cases and compare data with recruited cases.

Paediatricians- at the end of the BPSU study

At the end of the BPSU study (Cambridgeshire 2 REC Ref: **10/H0308/45)** , we will send a one off email to the British Paediatric Allergy, Immunity and Infection Group (BPAIIG) who will disseminate to members as a form of advert for the study. From the group any Paediatrician who sees a case of meningitis in babies less than 90 days of age can then contact the study team (but without any patient identifiable data) and we will send them the information pack for onward forwarding to parents.

Recruitment from the Republic of Ireland.

A Microbiology SpR under the supervision of Professor Cafferkey (a co-applicant) will be responsible for the study in Ireland. Using similar methods the Microbiology SpR will identify cases of meningitis in infants <90 days of age, send the study information pack to the responsible paediatrician, collate returned consent forms and completed parent questionnaires and extract data from subject notes. Completed proformas and parental questionnaires will be anonymised and sent to the study research fellow for inclusion in the study database. Ethics approval in Ireland will be sought for this component.

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Case definitions and reporting instructions:

Any case where the clinician has made a clinical diagnosis of bacterial meningitis in babies less than 90 days of age.

Analytical case definitions:

Confirmed case: Isolation# of a significant* bacterial pathogen from CSF;

OR

Isolation# of a significant* bacterial pathogen from blood cultures AND CSF pleocytosis (≥20 cells /mm3 for babies 0-28days old and ≥10 cells/mm3 for babies 29

Probable case: The presence of clinical signs of meningitis~ AND CSF pleocytosis (≥20 cells / mm3 for babies 0-28days old and ≥10 cells/mm3 for babies 29-90days old) AND where appropriate IV antibiotics are given for > 7 days BUT where no significant pathogen is isolated from blood or CSF.

#Isolation refers to a positive culture. In the cases of Neisseria meningitidis, listeria monocytogenes and Group B streptococcus a positive PCR from blood or CSF is acceptable and in the case of Streptococcus pneumoniae a positive PCR from CSF is acceptable.

*Positive CSF or blood cultures for organisms generally considered to be contaminants will be excluded e.g. corynebacterium, propionibacterium, diphtheroids. In the case of coagulase negative staphylococcal (CoNS) meningitis, a definite case will be defined where the CoNS is cultured from a CSF specimen together with CSF pleocytosis (≥20 cells / mm3 for babies 0-28days old and ≥10 cells/mm3 for babies 29-90days old) and clinical signs

Clinical signs of meningitis are: fever or hypothermia or temperature instability PLUS 1 or more neurological findings e.g. coma, seizures, neck stiffness, apnoea, bulging fontanel

Exclusion Criteria
1. Any baby with any type of intraventricular shunt device: Ventricular-peritoneal (VP), ventricular-atrial (VA) or external ventricular device (EVD
2. Any baby with a spina bifida or its spectrum.

> **Age range for cases:**   From birth to 90 chronological days.

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Reporting instructions: Please report any infant seen in the last month who meets the case definition.

Cases of meningitis will be identified through microbiologists and parents.

Microbiologists: The Health Protection Agency (HPA) routinely receives notifications of cases of bacteraemia and meningitis and, separately, referral of isolates from microbiologists in England and Wales. To enable follow up of potential cases the HPA will provide the Study Research Fellow (who will hold an Honorary contract with the HPA) with sufficient identifying data on such cases to allow contact to be made with the relevant paediatrician. This may include: patient initials, date of birth, gender, NHS number, date of notification and name of the referring hospital or laboratory. This will be supplemented by regular reminder emails from the study team to microbiologists based at hospitals with larger neonatal units.

Parents: To ensure as complete ascertainment as possible we will also receive notifications from parents who will become aware of the study though several parent support groups / charities. These include Group B Strep Support (http://www.gbss.org.uk), a UK charity offering information on group B streptococcal disease to health professionals and affected families (coordinated by Jane Plumb), the Meningitis Research Foundation (contact: Linda Glennie), the Meningitis Trust (contact: Jane Blewitt) and Meningitis UK (contact: Kate Rowland). Parental reporting was successfully used in our previous national GBS study (Lancet. 2004 Jan 24;363(9405):292-4). Information about the study will be made available on the respective websites and communications of these groups. Parents who make contact with these support groups, either spontaneously or as a result of the study, will be asked for permission to pass on sufficient identifying data to the study team to allow contact to be made with the relevant paediatrician. Alternatively parents can contact the study team via the study website.

At the end of the BPSU study (Cambridgeshire 2 REC Ref: **10/H0308/45)** , we will send a one off email to the British Paediatric Allergy, Immunity and Infection Group (BPAIIG) who will disseminate to members as a form of advert for the study. From the group any Paediatrician who sees a case of meningitis in babies less than 90 days of age can then contact the study team and we will send them the information pack for onward forwarding to parents.

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(ii) Approached

Once a case has been notified by the other sources, the Research Fellow will send the relevant paediatrician a letter requesting them to approach the family on our behalf. This will be done by sending the family our information pack (which we will have provided to the paediatrician). They will be asked to write the subjects' home address on the envelope and will also have the option of including a cover letter (we will provide the paediatrician with a draft that they may use if they wish).

The information pack will include details about the study, a parent questionnaire, a consent form and a reply paid envelope together with contact details of the study team.

(iii) Recruited.

Families will be asked to complete and return the consent form and the questionnaire; they can make contact with the study team by telephone or email if they require further clarification. The consent form will provide the options of: consent to access the hospital notes and/or to complete the parental questionnaire and/or to make contact with the family before the 2nd birthday of the child to arrange a neurodevelopmental assessment.

5. Statistical methods

We will compare proportions using Chi-square or Fishers exact test and use SPSS, EpiInfo and Confidence Interval Analysis (2.0.0) for analyses.

6. Compliance with guidelines

The study will be conducted in accordance with the 1996 ICH GCP guidelines, the 2000 Declaration of Helsinki, and the Data Protection Act 1998.

7. Ethical approval

Approval for the study has been sought through the Cambridgeshire 2 REC
(**ref: 10/H0308/64**).

8. Funding

Appropriate funding from the Meningitis Research Foundation has been granted.

9. Target dates

Proposed duration of study: 18 months

Proposed starting date: July 2010

Appendix 1 – Healthcare delivery professional proforma
Appendix 2- Healthcare delivery parent proforma
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Assessment of healthcare delivery in the early management of bacterial meningitis in UK young infants: An observational study

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TITLE: Assessment of healthcare delivery in the early management of bacterial meningitis in UK young infants: An observational study

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Word count: 3380

Keywords: bacterial, meningitis, young infants, healthcare delivery, assessment

ABSTRACT

OBJECTIVE:

To define early presenting features of bacterial meningitis in young infants in England and to review the adequacy of individual case management as compared with relevant national guidelines and an expert panel review.

DESIGN:

Retrospective medical case note review and parental recall using standardised questionnaires.

SETTING:

England and Wales.

PARTICIPANTS:

Infants aged <90 days with bacterial meningitis diagnosed between July 2010 and July 2013.

RESULTS:

Of the 97 cases recruited across England and Wales, 66 (68%) were admitted from home and 31 (32%) were in hospital prior to disease onset. Almost all symptoms reported by parents appeared at the onset of the illness, with very few new symptoms appearing subsequently. Overall, 20/66 (30%) infants were assessed to have received inappropriate pre-hospital management. The median time from onset of first symptoms to first help was 5 hours (IQR: 2-12) and from triage to receipt of first antibiotic dose was 2.0 hours (IQR: 1.0-3.3) hours, significantly shorter in infants with fever or seizures at presentation compared to those without (1.7 [IQR, 1.0-3.0] vs. 4.2 [1.8-6.3] hours, p=0.02). Overall, 26 (39%) infants had a poor outcome in terms of death or neurological complication; seizures at presentation was the only significant independent risk factor (OR, 7.9; 95% CI: 2.3- 207.0). For cases in hospital already, the median time from onset to first dose of antibiotics was 2.6 (IQR: 1.3- 9.8) hours and 12/31 (39%) of infants had serious neurological sequelae at hospital discharge. Hearing test was not performed in 23% and, when performed delayed by ≥4 weeks in 41%.

CONCLUSIONS:

Young infants with bacterial meningitis have non-specific symptoms and signs, with no clear progression of illness over time, highlighting the difficulties in early recognition by parents and healthcare professionals alike. A substantial proportion of infants received inappropriate pre- and post-hospital management. We propose a targeted campaign for education and harmonisation of practice with evidence-based management algorithms.

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STRENGTH AND LIMITATIONS

- The strength of this study lies in the detailed analysis of a large cohort of geographically representative young infants with bacterial meningitis; this is the first study of its kind in the United Kingdom.

- We did not find any significant differences between the recruited and non-recruited cases in relation to age, sex, region of the country and causal bacteria (data not shown).

- Because we relied on paediatricians using their discretion to contact parents, however, this may have led to exclusion of families of infants who died or developed severe sequelae where the paediatrician was reluctant to contact the family about the study.

- Conversely, some parents may have agreed to participate simply because they were concerned about their child's long-term outlook or about suboptimal healthcare.

- Another potential limitation is that we relied on parents' recall for onset and progression of early clinical features. There is, however, evidence from other serious infections such as meningococcal disease that parents are able to accurately recall in detail such life-changing events.

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INTRODUCTION

Bacterial meningitis in young infants remains a significant cause of mortality and long-term morbidity [1]. During 2010-11, we conducted national, prospective-population-based surveillance of bacterial meningitis in infants younger than three months of age in the United Kingdom and Ireland and found that 26% of 329 infants had poor outcomes at discharge[2]. Among survivors of neonatal meningitis in the 1980's, 50% had neurological sequelae at five years of age[3] and similar rates (40%) have been reported in survivors of neonatal bacterial meningitis in the 1990s[4].

The pathogens responsible for bacterial meningitis in young infants are different to those causing meningitis in other age groups[5], with group B streptococci (GBS) and *Escherichia coli* responsible for more than half the cases; neither are currently vaccine-preventable[1].

It is recognised that the early presentations of meningitis in young infants can be subtle and non-specific. This poses a substantial challenge for parents and healthcare workers. In our national surveillance, for example, half the infants with bacterial meningitis did not have fever at presentation and only 5% had the classic triad of fever, bulging fontanelle and seizures[2].

Studies of invasive meningococcal disease have been able to delineate the onset of specific symptoms and signs and chart their progression over the course of the illness[6]. This information has helped improve knowledge and increase awareness of meningococcal infections among parents and healthcare workers (http://www.meningitis.org/health-professionals/doctors-in-training). Early recognition of meningococcal infection coupled with rapid antibiotic treatment and more aggressive management of children with sepsis has subsequently led to improved outcomes[7-9]. In adults with sepsis, earlier antibiotics have been

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associated with higher survival rates[10], but in infants the evidence base is poor even though they have the highest incidence of bacterial meningitis[5].

We hypothesised that earlier recognition may lead to earlier healthcare interventions which in turn might improve the outcomes of bacterial meningitis in young infants. We, therefore, undertook a detailed assessment of the timing, course and progression of bacterial meningitis in young infants across England and Wales. We also compared their initial and subsequent clinical management with relevant national guidelines.

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METHODS

We undertook a detailed review of the clinical presentation and management of bacterial

meningitis in young infants in England and Wales diagnosed between July 2010 and July

2013 from the perspectives of parents and healthcare workers. We aimed to recruit 100

eligible infants (**TABLE 1**)[11-13]. Cases were identified from LabBase2 (a national

surveillance database used by National Health Service hospitals laboratories to voluntarily

electronically report clinically significant infections to Public Health England)[14]..

Group	Definition
Eligible infants	Infants <90 days of age in whom a bacterium was isolated from the cerebrospinal fluid (CSF), or where a significant bacterial pathogen was isolated from blood together with CSF pleocytosis (defined as $\geq$20 cells / mm^3 for infants 0-28 days of age and $\geq$10 cells/ mm^3 for infants 29-89 days of age)[11-13]
Age at diagnosis	Early onset (0-6 days) and late onset (7-89 days)
Home admission	Infants admitted to hospital from home
In-patients	Infants already in hospital at the time, either in the neonatal unit, birthing centre or postnatal ward.
Time from onset to first help	The time from when parents noticed the first clinical feature to the time they sought any type of help (phone call or visit).
Time from onset to first dose of antibiotics	The time from appearance of first clinical feature to first dose of antibiotics.
Time from triage to first dose of antibiotics	The time from when infant was triaged by a nurse to the time of administration of the first dose of antibiotics.
"In hours" (www.hscic.gov.uk)	Triage in hospital between hours of 0900 and 1800.
Appropriateness	Advice given prior to admission was judged as appropriate or inappropriate. Choice of empiric antibiotics and duration of antibiotics were appropriate if in conformity with existing guidelines. For example, the use of any antibiotics other than amoxicillin and cefotaxime/ ceftriaxone in any infant admitted from home would be classified as inappropriate.

Table 1: Definitions

A study pack containing study details, a consent form and a questionnaire was sent to the

local paediatrician to forward to parents. If families did not respond, we asked the

paediatrician to send a second pack. Parents of all participants completed a questionnaire with

details about onset and progression of specific symptoms. Participating parents also gave

informed written consent for the study investigators to access their infant's medical records.

All stages of care, including pre-hospital management, initial hospital assessment, ongoing

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care and post-admission follow-up were assessed through an in-depth review of hospital notes.

Assessment of management: Expert panel and national guidelines.

An expert panel consisting of a general paediatrician, neonatologist, paediatric infectious diseases consultant and a paediatric specialist registrar reviewed the data to determine appropriateness of pre-hospital management, delays in recognition, empiric antibiotics, antibiotic duration and follow-up. These were judged according to any national guidelines available at the time. The NICE feverish illness in children aged <5 years guideline [15] was used to assess the appropriateness of advice/actions prior to hospital admission in febrile infants; in the absence of fever, the expert panel proposed a standard best practice. The Bacterial Meningitis and Meningococcal Septicaemia in Children guideline [16] was used to assess the appropriateness of empiric antibiotics, length of treatment, and timing of audiology testing for all cases. The management of infants presenting in the first 72 hours of life was assessed against the NICE antibiotics for early onset neonatal infection guideline[17]. We adhered to the STROBE guidelines for reporting observational studies.

Data collection

Parents completed a questionnaire, which recorded the time of first appearance and progression of pre-defined clinical features (online supplement on request). Information on any illnesses in the previous two weeks was also requested. Hospital medical notes and GP letters in the medical notes were used to corroborate parental recollection of onset, timing and progression of events.

Data analysis

The data are mainly descriptive. We plotted the appearance and course of symptoms from the time of onset of first symptoms. The timing of each subsequent feature was then recorded and rounded to the nearest hour. For children admitted from home, we calculated the number of hours from the onset of illness to seeking any medical help ("first help" = hospital attendance, GP attendance or phone contact with a health professional) and to hospital admission. We compared the prevalence of symptoms at onset and at hospital presentation (infants admitted from home) or at diagnosis (in-patients). We also compared presenting features and clinical management in infants admitted from home and in-patients. Continuous data that did not follow a normal distribution are described as medians with interquartile ranges (IQR) and compared using the Mann Whitney U or Kruskal Wallis test, as appropriate. Proportions were compared using chi-squared or Fisher's Exact Test, as appropriate. To identify independent risk factors for poor outcomes (death or serious complications), potential explanatory factors were included in a backward, stepwise multivariable logistic regression model and the least significant parameter was then sequentially removed until only those parameters with p <0.05 remained.

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RESULTS

A total of 224 infants with bacterial meningitis were identified and study information

forwarded to the parents **(Figure 1)**. The parents of 103 infants (46%) agreed to participate

but six cases were subsequently excluded because they did not meet the inclusion criteria.

Demographic data on parents and infants are shown in tables 2A and 2B. Cases were

recruited from 48 hospitals representing all English regions (**TABLE 2B**). Sixty-six (68%)

infant were at home when they became unwell and 31 (32%) were inpatients. Most parents

(92/97, 95%) completed the study questionnaire.

Parameter	Mother	Father
Median parental age (IQR)	29 (26-33)	32 (26-36)
Parent's highest academic level: Mothers (n=79): fathers (n=77)		
Post graduate	16 (20%)	7 (9%)
Graduate	16 (20%)	15 (19%)
A levels	20 (25%)	13 (17%)
GCSEs	27 (34%)	42 (55%)
Parents accommodation: mothers (n=87); fathers (n=77)		
Own house/ flat	45 (52%)	45 (58%)
Rented house/ flat	35 (40%)	26 (34%)
Council house/ flat	7 (8%)	6 (8%)

Table 2A: Basic demographics of parents

CASES ADMITTED FROM HOME (n=66)

The median age at diagnosis of bacterial meningitis was 14 days (IQR, 3-25), higher in cases

admitted from home (17 [11-34] days) compared to cases already in hospital (1 [0-7];

p=0.0001). The most common features at onset of illness were poor feeding (n=44, 65%),

lethargy (n=30, 45%) and fever (temperature $\geq 38^0$C) [n=30, 44%]. The majority of

symptoms reported by parents appeared at the onset of infection (**Figure 2A**) and these

symptoms persisted, with very few new symptoms appearing over the subsequent 24 hours

(**Figure 2B**). However, there were small but significant differences in the proportion of

infants with more specific symptoms at hospital admission compared with the onset of the

illness: irritability (p=0.036), abnormal breathing (p=0.023), abnormal movement/ seizures

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(p=0.024) (Figure 2C).

Twenty parents (30%) took their infants straight to the hospital: the A&E department (n=15, 22.5%) or the urgent care centre (n=5, 7.5%). The other parents (n=46, 70%) sought help by phoning the GP (n=21, 32%), calling the 24-hour NHS direct telephone service (n=15, 23%), or contacting the community midwife (n=10, 15%); of these, 13 (28%) were advised to stay at home.

The median time from onset of first features to first help was 5.0 hours (IQR: 2.0-12.0). The time to first help was not associated with early or late-onset disease, gestation at birth, presence of fever or seizure, region of the country, type of housing or level of maternal academic qualifications. The majority of parents (47/62, 76%) presented to hospital within 24 hours of onset of symptoms. 13 of 15 (93%) infants who presented after 24 hours had fever (n=8) or seizures (n=4) or both (n=1) at the time they presented to hospital. Eight of the 15 (53%) had attended their GP surgery before going to hospital, of these three were reviewed at the A&E/walk-in centre and sent home and two were initially seen by a community midwife (all five infants were seen <24 hours from onset). The remaining 7/15 (47%) infants were brought to hospital by their parents more than 24 hours from the onset of symptoms.

Overall, 20/66 (30%) infants were assessed to have received inappropriate pre-hospital management. Twelve infants with fever warranted further investigation according to the NICE guidelines and, in a further eight cases, there was a delay in seeking help despite the presence of worrying clinical features. Examples of inappropriate advice given to parents included being told that their child's fever was due to a change in milk formula, or to an umbilical hernia, or where prune juice was recommended for fever and irritability.

Parameter	Value
Male	52 (54%)
Term (≥37 weeks)	74 (76%)
Preterm (<37 weeks)	23 (24%)
32-36	14 (14%)
28-31	5 (5%)
<28	4 (4%)
BIRTH ORDER: Singleton	88 (91%)
Twins	9 (9%)
Age distribution: Early-onset: 0-6 days	30 (31%)
Late onset : 7-28 days	44 (45%)
29-89 days	23 (24%)
ROUTE OF ADMISSION: Home	66 (68%)
In-patient	31 (32%)
Ethnicity: White	81(84%)
Asian	6 (6%)
Black	4 (4%)
Unknown	6 (6%)
Region of England: North of England	26 (26%)
Midlands and East of England	18 (19%)
London and integrated regions	13 (13%0
South of England	39 (41%)
Infants mode of feeding at diagnosis: Breastfeeding	32 (38%)
Mixed feeding	13 (20%)
Bottle feeding	32 (33%)
BACTERIA: Identified from CSF only	23 (24%)
Identified from CSF and blood	40 (41%)
Identified from blood only	34 (35%)
GBS	65 (63%)
E. coli	11 (11%)
Listeria monocytogenes	4 (4%)
Neisseria meningitidis	4 (4%)
Other Gram negative bacteria*	10 (10%)
Other Gram positive bacteria**	5 (5%)
**Pseudomonas spp.* 3, *Klebsiella spp.* 2, *Salmonella spp.* 2, *Citrobacter* 1, *Pasteurella spp.*1, *Haemophilus influenzae* 1. **Streptococcus pneumoniae* 2, *Streptococcus bovis* 2 and α-haemolytic streptococcus 1.	
Alive	96
Dead (after 28 hours in PICU after developing meningitis in the 4th week of life).	1

Table 2B: Basic demographics of all infants

A+E management

Around half of the infants (n=36, 55%) were triaged in A&E during normal working hours.

The median time from triage to receipt of the first antibiotic dose was 2.0 hours (IQR: 1.0-

3.3; > 1 hour in 43 infants, 73%), but was significantly shorter in infants with fever or

seizures at presentation than those without these features (1.7 [IQR, 1.0-3.0] vs. 4.2 [1.8-6.3]

hours, p=0.02). There was no significant difference in median time from triage to first

antibiotic dose in infants, by early or late-onset disease, region of the country, time of day at

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presentation or whether a fluid bolus was given. The median time from onset to GP visit,

hospital attendance and first dose of antibiotics varied by route taken before admission (Table

3). Onset to antibiotics time was significantly longer in those who were first seen by the GP.

Category	Onset to GP	Onset to hospital visit	Onset to first dose of antibiotics
Infants who went from Home direct to hospital	Not applicable	5.7 hours (2-8.4)	8 hours (4.8-13.5)
Infants who went from Home to hospital via GP	10.5 hours (3-33)	11 hours (5.2-17)	13 hours (6.8-25)
Infants who went to hospital via GP, were sent home and went to hospital a second time	9 hours (3.5-48)	52 hours (36-96)	57.5 hours (38-98.2)
P value	0.8	0.0001	0.0001

Table 3: Median time in hours (IQR) from onset to GP, hospital visit and first dose of antibiotics by route taken prior to hospital admission. (GP: General Practitioner).

Overall, 26 (39%) infants had a poor outcome in terms of death (one case) or neurological

complication (25, 38%). These included motor disorder or developmental delay (n=12, 18%),

seizures (n=7, 11%), hydrocephalus (n=5, 8%), hearing loss (n=5, 8%), cerebral infarct or

ischaemia on MRI (n=3, 5%) or visual deficits (n=3, 5%). The median time in hours (IQR)

from onset of illness to first help in infants with poor outcomes was longer than in those who

recovered without sequelae (6.25 [1-24] hours vs. 4.75 [2-10], p=0.8) but this was not

statistically significant. The rate of poor outcome was also not statistically different between

the 15 infants who presented to hospital >24 hours after onset of symptoms and those who

presented <24hrs (8/15 [53%] vs. 18/47 [38%]; p=0.3). The interval between triage to first

antibiotic dose was also not associated with poor outcome.

A number of pre-defined, potential explanatory factors (age, gender, time from onset to first

help, delay in antibiotics, pre-hospital inappropriate advice, inappropriate empiric antibiotics,

presence of fever, presence of seizures) were explored in univariate and multivariate analyses

to identify risk factors for poor outcome; only the presence of seizures at presentation (OR,

7.9; 95% CI: 2.3- 207.0) was found to be an independent risk factor (supplement table 1).

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In-patient infants (n=31)

As with those infants presenting from home, parents of in-patient infants at the time of diagnosis reported that the majority of symptoms were all present at the onset of the illness (**Figure 3A**) and remained present until diagnosis, with only a few new symptoms appearing during the course of the illness (**Figure 3B**). The only significant difference between symptoms at onset and those at diagnosis was the proportion with breathing difficulty (p<0.001) (**Figure 3C**).

Two-thirds of infants (21/31, 68%) had onset of symptoms within 72 hours of birth and were, therefore, assessed against the NICE early-onset antibiotic guidelines. According to these guidelines, the maternal "red flags" (mainly chorioamnionitis/maternal sepsis in 5), baby "red flags" (respiratory distress after 4 hours of age in 9, shock in 4, seizures in 2 and need for ventilation at term in 1) or both, were present in 5/21 (24%), 15/21 (71%) and 17/21 (81%), respectively. At the time of diagnosis 17/31 (55%) of these infants received a fluid bolus, 12/31 (39%) had seizures and 8/31 (26%) had a fever.

The median time from onset of symptoms to first antibiotic dose was 2.6 hours (IQR, 1.3-8.5), with 74% (23/31) receiving their first dose >1 hour after onset of symptoms and 4 infants (13%) receiving the first dose >24 hours after onset.

Outcomes among in-patient infants

 Overall, 12/31 (39%) of infants had a serious neurological complication at hospital discharge, including developmental delay or motor disorder (n=9, 29%), abnormal hearing (n=5, 16%), hydrocephalus/VP shunt (n=5, 16%), seizures (n=2, 6%) and abnormal MRI: cortical grey and white matter injury (n=1, 3%) and two infants were treated for cerebral

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abscesses. No significant risk factors for poor outcomes were identified in either the

univariate or multivariate analyses (supplement table 1).

HOME vs. IN-PATIENT INFANTS

The main differences between infants admitted from home and in-patient cases were age,

presence of fever on presentation, timing of LP and time to discharge from outpatient follow-

up (**Table 4**).

Variable	All cases	Home (n=66)	In-patient (n=31)	P value
Median age at disease (days)	14 (3-25)	17 (11-34)	1(0-7)	**0.0001**
Early onset (<7 days)	30 (31%)	8(12%)	22(71%)	**<0.0001**
Male	52(54%)	34(52%)	18(58%)	0.5
Prematurity	23(24%)	8(12%)	15(48%)	**<0.0001**
Out-of- hours presentation	47(48%)	30(45%)	17(55%)	0.4
Fever on presentation	48(51%)	40(61%)	8(26%)	**0.001**
Seizure at presentation	33 (34%)	21(32%)	12(39%)	0.5
Received fluid bolus at presentation	53(55%)	36(55%)	17(55%)	0.7
Antibiotics delay (hours)	2 (1.3-4)	2 (1-3.3)	2.6 (1.3-9.8)	0.09
LP done post first dose of antibiotics	57 (59%)	30 (45%)	27 (87%)	**<0.0001**
Antibiotics to LP time>24 hours	33 (34%)	14 (47%)	19 (70%)	0.07
Median time to LP and no bacteria in CSF (hours)	46 (24-92.5)	24 (15.2-52.8)	65 (44-100.8)	**0.017**
Median time to LP and bacteria in CSF (hours)	7.3 (1.5-2.4)	3 (1-24)	9.5 (2-24)	0.3
Empiric antibiotics not in conformity with national guidelines	52 (54%)	35(53%)	17 (55%)	0.9
Discharge to first OPD review (months)	2.5 (2.0-3.5)	2.5 (2.0-4.0)	2.5 (2.0-2.5)	0.6
Discharge from follow up age <12 months	13 (14%)	12/65 (18%)	1/31 (3%)	**0.03**
Discharge from follow up age <24 months	31 (32%)	26/65 (40%)	5/31 (16%)	**0.02**
Hearing test performed in survivors*	74 (77%)	53/65 (82%)	21/31 (68%)	0.1
Neurological complications	40 (42%)	26/65 (40%)	14/31(45%)	0.6
Discharge to audiology test (days)	25(0-32)	24 (10-42)	26 (0-28)	0.2
Informed of meningitis support charities	12/97 (13)	11/66(17%)	2/31(6)	0.2

Table 4. Comparison of infants admitted from home and infants in hospital at the time of diagnosis (EO: early onset, OPD, out-patient department, LP: Lumbar puncture). * There were 22 survivors without report of hearing test. 12 (13%) had no record of hearing test at review, 5 (5%) were transferred to another hospital where data was not available and 4 (12%) had the review <1 month after discharge and 1 (1%) missed two appointments.

Empiric antibiotics.

The empiric antibiotics used in 35/66 (53%) and 17/31 (55%) of infants admitted from home

and in-patient cases respectively were not in conformity with the appropriate NICE

guidelines (Supplement table 2).

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FOLLOW-UP AND HEARING TESTS AFTER DISCHARGE.

The median time to first out-patient follow-up was 2.5 months (IQR; 2-3.5) and was not

different amongst infants admitted from home and in-patient cases (**Table 4**). However,

infants from home were more likely to be discharged from follow-up before 2 years of age. A

hearing test was performed in 74/96 (77%) survivors (Table 4). The median time from

discharge to hearing test was 25 days (IQR: 0-32), with 30 (41%) and 14 (19%) infants

having the hearing test ≥4 and ≥6 weeks after hospital discharge respectively.

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Discussion

This is the first study to assess in detail the course of the illness in young infants with bacterial meningitis and the early healthcare they receive. Parental reporting of the early features of bacterial meningitis is a unique aspect of this study. We have shown that in infants with bacterial meningitis most of the symptoms and signs as reported by parents are present from the onset of the illness and there is little progression, with no or few additional symptoms developing as the illness progresses. Notably, up to 40% of infants did not develop fever at any time during their illness. In keeping with previous studies, only seizures at presentation were significantly associated with a poor outcome[2].

The course of bacterial meningitis in young infants appears to be different to that of children with meningococcal meningitis. With a similar study design, Thompson, Ninis and colleagues demonstrated that meningococcal disease progresses in a stereotypical manner in all children, with a prodromal phase, early sepsis phase and meningism only as a late feature[6]. In terms of the healthcare-seeking behaviour for those infants admitted from home, 70% of parents had sought medical help prior to A&E attendance. Of concern, a significant proportion had received inappropriate advice suggesting that further training of frontline healthcare staff in recognising serious illness in children is required[18]. On the other hand, many of the parents who presented to hospital more than 24 hours after the initial healthcare contact, are most likely because their child's condition deteriorated, thus highlighting the importance of providing appropriate safety-netting advice to parents if they are advised to return home.

On admission to hospital, the median time from triage to first antibiotic dose was 2 hours, lower than that recently reported for childhood septicaemia (3 hours)[19] but higher than the recommended threshold of 1 hour[20]. We identified a number of reasons for this delay,

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including uncertainty in recognition (especially in those with non-specific presentations),

over-reliance on the presence of fever, waiting for urine samples before giving antibiotics and

waiting for handover between shifts. Presentation in-hours or out-of-hours did not influence

time to first antibiotic, which is reassuring given that half of infant presented out of hours.

That infants with fever or seizure received antibiotics more quickly than those without these

features suggests that these delays can potentially be avoided. Miner et al showed that delay

to antibiotics time is significantly shorter in patients who received it in the emergency

department[21]. With appropriate education strategies, it is therefore possible to significantly

improve antibiotic delivery time for infants[22].

Most in-patient infants developed meningitis within 72 hours of birth, suggesting vertical

transmission of infection. The recent NICE guidelines for early-onset antibiotics provides

guidance on maternal, birth and infant risk factors that should lead to specific and timely

antibiotic therapy[17]. Notably, 80% of infants had such risk factors, suggesting this to be a

useful tool. However the time to antibiotic administration and choice of antibiotic was still

very variable. Adult studies from USA and France reported low compliance to established

guidelines[23, 24].

There is still a need to reinforce to clinicians the importance of performing a timely hearing

test in infants with bacterial meningitis. There is no record of such a test in 23% of cases and

even when done it was $\geq$ 4weeks in 40%. National guidelines emphasize the need for early

diagnosis of deafness to allow early interventions such as cochlear implantation [16]. Follow-up

of infants with bacterial meningitis is also believed to be important as it should allow early

identification of those with neurodevelopmental impairment (likely to be around 50% of

survivors)[4, 25] and timely intervention and support[16].

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Summary

The impact of bacterial meningitis on young infants and their families is significant. Case fatality rates and severe complications among survivors remains unacceptably high, at least partly due to delayed recognition and management. Unlike children with meningococcal disease, for example, we were unable to identify any distinctive features at disease onset or of symptom progression that might aid earlier recognition or trigger earlier healthcare presentation. We propose a targeted campaign for education of new parents, primary care health workers (including telephone advice providers) and hospital doctors regarding the non-specific features, the lack of progression of clinical features at least in the first 24 hours and the lack of fever in young infants with bacterial meningitis. There is also need to explore ways of harmonising clinical practice with evidence-based management algorithms, including timely investigation and administration of appropriate antibiotics and adequate follow up of infants with bacterial meningitis.

Ethical Approval

Ethical approval was given by Cambridgeshire 2 REC (Ref: 10/H0308/64). Paediatricians were approached by email asking if there would be willing to take part in the study. If in agreement, a National Institute for Health Research Coordinated System for gaining NHS Permission (NIHR CSP**)** application was made and the hospital listed once approval was granted.

Competing interests

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Group B vaccines, has received honoraria to teaching on meningitis from Novartis. All other

authors declare no conflicts of interests. The ICMJE Form for Disclosure of Potential

conflicts of Interest has been submitted.

Contributorship statement:

Ifeanyichukwu O Okike completed the ethics application form, finalised the data collection

tool, coordinated the study, entered all data into an Access database, data interpretation,

performed the analysis and wrote the initial manuscript, reviewed and revised the manuscript

and submitted the final manuscript.

Shamez N Ladhani helped with case ascertainment from the Public Health England,

supported the data analysis and data interpretation, reviewed and revised the manuscript and

approved the final manuscript.

Mark Anthony co-conceived and designed the study including the grant application, was a

member of the expert panel who reviewed the management of cases, took part in data

interpretation, reviewed and revised the manuscript and approved the final manuscript.

Nelly Ninis co-conceived and designed the study including the grant application, was a

member of the expert panel who reviewed the management of cases, took part in data

interpretation, reviewed and revised the manuscript and approved the final manuscript.

Paul T Heath was the Chief Investigator, co-conceived and designed the study including the

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grant and ethics application, was a member of the expert panel who reviewed the

management of cases, contributed to the data analysis and data interpretation, reviewed and

revised the manuscript and approved the final manuscript.

Transparency declaration:

 The lead author affirms that the manuscript is an honest, accurate, and transparent account of

the study being reported; that no important aspects of the study have been omitted; and that

any discrepancies from the study as planned (and, if relevant, registered) have been explained

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Data sharing: We are happy to share our anonymised raw data which is not included in the manuscript. All requests should be made to the corresponding author.

What this paper adds

Section 1: What is already known on this subject

- The incidence of bacteria meningitis is higher in young infants than in any other age group and is often associated with a poor outcome - this has not changed over the last three decades

- The early clinical presentation of meningitis in young infants can be subtle and non-specific

Section 2: What this study adds

- The majority of symptoms and signs in young infants with bacterial meningitis are present at the onset of the illness, with little progression over time.

- Inadequate pre-hospital management, delayed antibiotic administration in hospital and post discharge management were found in a significant proportion of cases.

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FIGURE LEGENDS

 Figure 1: Recruitment algorithm. (*: died (8), moved away (5), foster care (2), language barrier (2)).
Recruited cases were from 2010 (n=25), 2011 (n=39), 2012 (n=22) and 2013 (n=11)

Figure 2A: Time (hours) at which parents first noticed a specific clinical feature. Figure 2B: Number of features present at each hour as reported by parents Figure 2C: Clinical features present at onset and time of admission
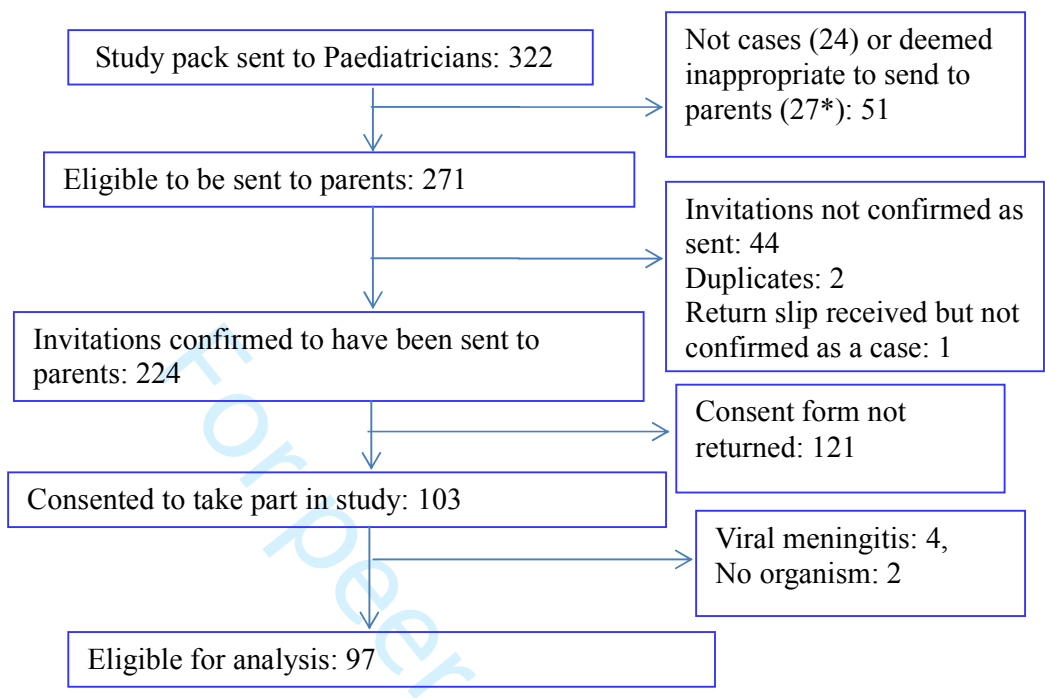
Figure 3A: Time (hours) at which parents first noticed a specific clinical feature (in-patient cases). Figure 3B: Number of features present at each hour as reported by parents (in-patient cases) Figure 3C: Clinical features present at onset and time of admission (in-patient cases)

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Study pack sent to Paediatricians: 322

Not cases (24) or deemed inappropriate to send to parents (27*): 51

Eligible to be sent to parents: 271

Invitations not confirmed as sent: 44
Duplicates: 2
Return slip received but not confirmed as a case: 1

Invitations confirmed to have been sent to parents: 224

Consent form not returned: 121

Consented to take part in study: 103

Viral meningitis: 4,
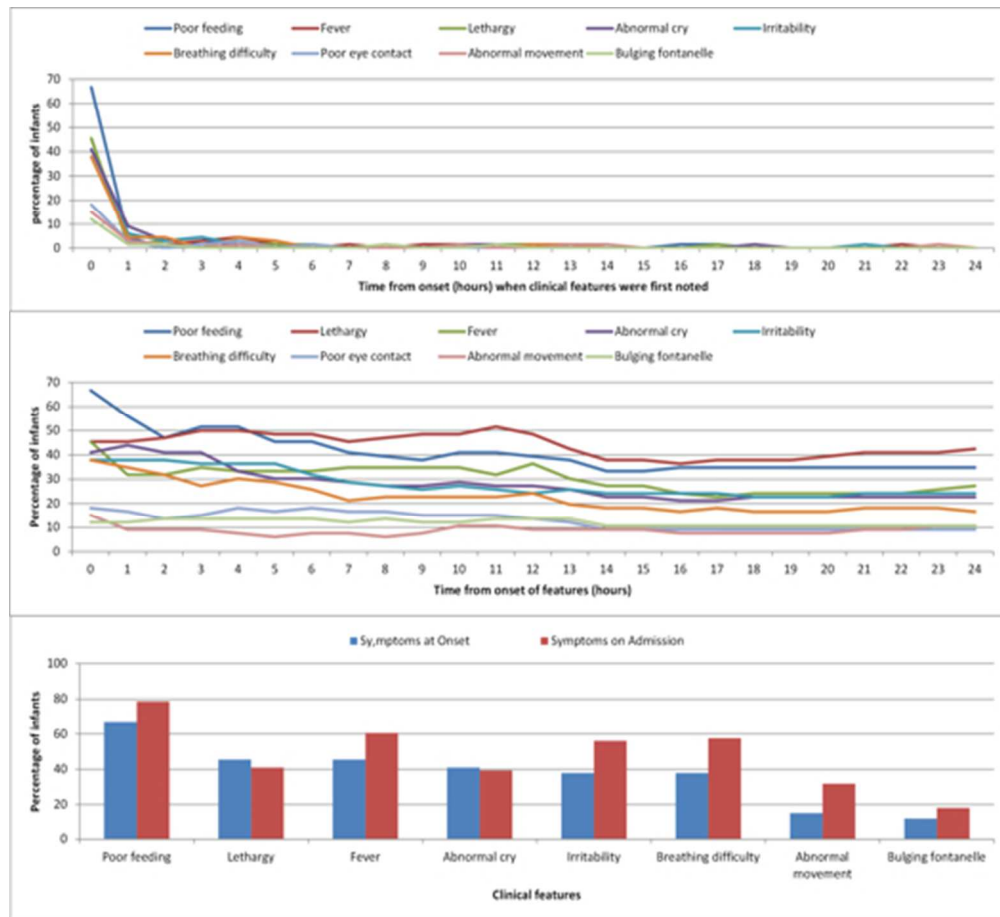No organism: 2

Eligible for analysis: 97

Figure 2A: Time (hours) at which parents first noticed a specific clinical feature. Figure 2B: Number of features present at each hour as reported by parents Figure 2C: Clinical features present at onset and time of admission
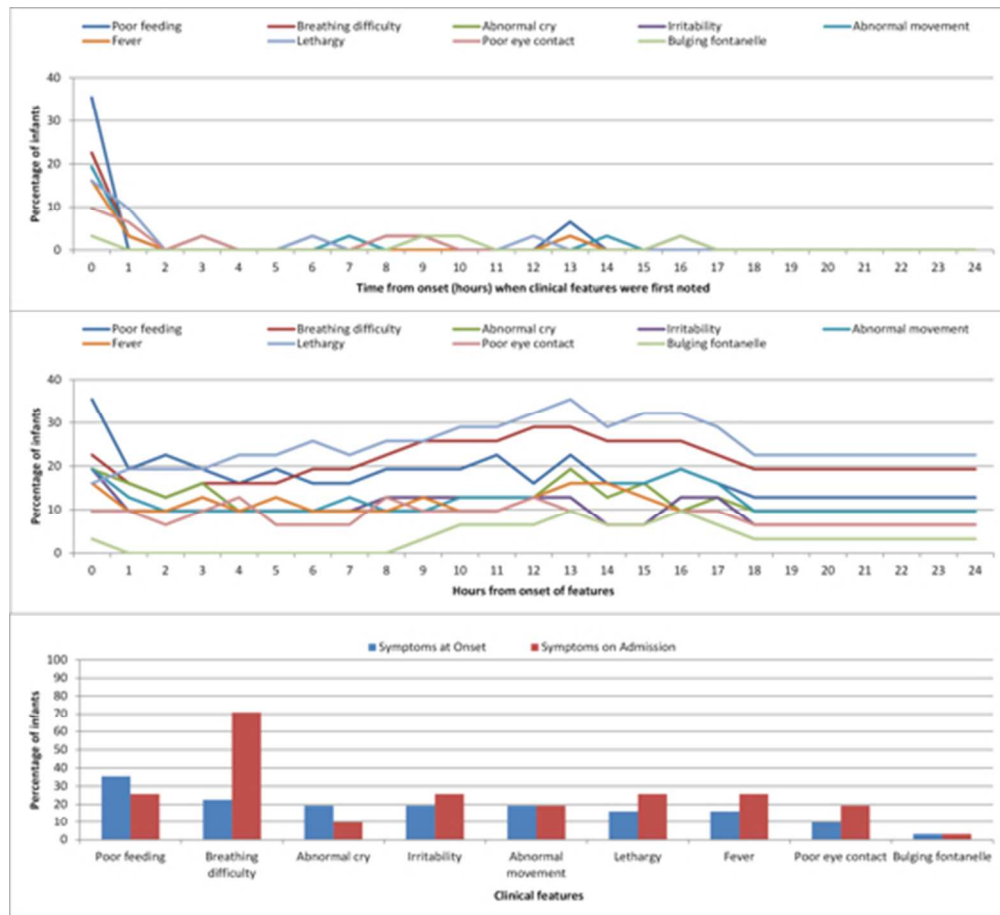
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Figure 3A: Time (hours) at which parents first noticed a specific clinical feature (in-patient cases). Figure 3B: Number of features present at each hour as reported by parents (in-patient cases) Figure 3C: Clinical features present at onset and time of admission (in-patient cases)

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SUPPLEMENTARY TABLE

Parameter	All cases			Home			In-patient		
	No complications	complications	P-value	No complications	complications	P-value	No complications	complications	P value
Median age at presentation	14 (3-31)	12 (3-23)	0.4	19 (13-37)	16(9-25)	0.3	1(0-3)	2(1-8)	0.3
Early onset	16 (28)	14(35)	0.5	3(8)	5(19)	0.2	13(76)	9(64)	0.7
Male	29 (51)	23(58)	0.5	20(50)	14(54)	0.8	9 (53)	9(64)	0.7
Prematurity	11 (19)	12 (30)	0.2	4(10)	4(15)	0.7	7(41)	8(57)	0.4
OOH presentation	31(54)	16(40)	0.2	21(53)	9(35)	0.2	10(59)	7(50)	0.6
Inappropriate advice	NA	NA	NA	16(40)	14(54)	0.3	NA	NA	NA
Fever or seizure	39 (68)	32(80)	0.2	30(75)	24(92)	0.1	9(53)	8(57)	0.8
Fever	30(53)	18(47)	0.5	25(63)	15(63)	0.7	5(29)	3(21)	0.7
Seizure	13(23)	20(51)	**0.005**	7(18)	14(56)	**0.002**	6(35)	6(43)	0.7
Fluid bolus	30(53)	24(67)	0.5	22(55)	15(68)	0.8	8(47)	9(64)	0.5
Bacteria in CSF	41(72)	23(58)	0.1	31(78)	17(65)	0.3	10(58)	6(43)	0.6
Non-conformity antibiotics	31(54)	21(53)	0.9	21(53)	14(54)	0.8	10(59)	7(50)	0.6
Antibiotics delay >6h	7/55 (13)	5/32(16)	0.8	2/38(5)	2/21 (10)	0.6	5/17 (29)	3/11 (27)	1.0
Onset to help ≥12h	NA	NA	NA	7/40 (18)	10/26(38)	**0.06**	NA	NA	NA
Maternal age	30(26-35)	29(24-32)	0.2	29(26-34)	29(24-32)	0.8	31(27-40)	27(23-33)	**0.07**

Supplementary Table 1: Univariate analysis of death (1 case) and serious complications. OOH= out of hours, h=hours, CSF= cerebrospinal fluid

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Pathogen	HOME	IN-PATIENT
GBS : Home (24) in-patient (10)	Cefotaxime/ ceftriaxone alone 9 Benzyl penicillin and gentamicin 7 Amoxicillin and gentamicin 3 Cefuroxime and metronidazole 1 Cefotaxime and flucloxacillin 1 Cefotaxime and gentamicin 1 Benzyl penicillin 1 and Co-amoxiclav 1	Cefotaxime/ ceftriaxone alone 4 Benzyl penicillin and gentamicin 2 flucloxacillin and gentamicin 2 Amoxicillin and gentamicin 1 Vancomycin and gentamicin 1
E. coli (5)	Benzyl penicillin and gentamicin 4 Benzyl penicillin and cefotaxime 1	Cefotaxime/ ceftriaxone 1 Tazocin and Vancomycin 1
N. meningitidis (3)	Cefotaxime/ ceftriaxone 3	
L. monocytogenes (2)	Cefotaxime 1	Cefotaxime 1
Pasteurella spp (1)	Benzyl penicillin and gentamicin 1	
Salmonella agama (1)	Flucloxacillin and gentamicin 1	
Klebsiella spp. (1)		Teicoplanin 1
S. bovis (1)		Cefotaxime 1
H. influenzae (1)		Cefotaxime and gentamicin 1

Supplementary Table 2: Isolated bacteria in cases where empiric antibiotics was not in conformity with existing guidelines and antibiotics started empirically

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	Not applicable (convenient cohort)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	In results
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not done

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 and 26
		(b) Give reasons for non-participation at each stage	9 and 26
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	14 and 15
Outcome data	15*	Report numbers of outcome events or summary measures over time	12, 13 and 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13 and 14
		(*b*) Report category boundaries when continuous variables were categorized	Throughout text
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16,17 and 18, 3 for strength & limitations
Generalisability	21	Discuss the generalisability (external validity) of the study results	16,17 and 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Assessment of healthcare delivery in the early management of bacterial meningitis in UK young infants: An observational study

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TITLE: Assessment of healthcare delivery in the early management of bacterial meningitis in UK young infants: An observational study

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Word count: 3380

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ABSTRACT

OBJECTIVE:

To define early presenting features of bacterial meningitis in young infants in England and to review the adequacy of individual case management as compared with relevant national guidelines and an expert panel review.

DESIGN:

Retrospective medical case note review and parental recall using standardised questionnaires.

SETTING:

England and Wales.

PARTICIPANTS:

Infants aged <90 days with bacterial meningitis diagnosed between July 2010 and July 2013.

RESULTS:

Of the 97 cases recruited across England and Wales, 66 (68%) were admitted from home and 31 (32%) were in hospital prior to disease onset. Almost all symptoms reported by parents appeared at the onset of the illness, with very few new symptoms appearing subsequently. Overall, 20/66 (30%) infants were assessed to have received inappropriate pre-hospital management. The median time from onset of first symptoms to first help was 5 hours (IQR: 2-12) and from triage to receipt of first antibiotic dose was 2.0 hours (IQR: 1.0-3.3) hours, significantly shorter in infants with fever or seizures at presentation compared to those without (1.7 [IQR, 1.0-3.0] vs. 4.2 [1.8-6.3] hours, p=0.02). Overall, 26 (39%) infants had a poor outcome in terms of death or neurological complication; seizures at presentation was the only significant independent risk factor (OR, 7.9; 95% CI: 2.3- 207.0). For cases in hospital already, the median time from onset to first dose of antibiotics was 2.6 (IQR: 1.3-9.8) hours and 12/31 (39%) of infants had serious neurological sequelae at hospital discharge. Hearing test was not performed in 23% and, when performed delayed by ≥4 weeks in 41%.

CONCLUSIONS:

In young infants, the non-specific features associated with bacterial meningitis appear to show no progression from onset to admission whereas there were small but significant differences in the proportion of infants with more specific symptoms at hospital admission compared with at the onset of the illness Young infants with bacterial meningitis have non-specific symptoms and signs, with no clear progression of illness over

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time, highlighting the difficulties in early recognition by parents and healthcare professionals alike. A substantial proportion of infants received inappropriate pre- and post-hospital management. We propose a targeted campaign for education and harmonisation of practice with evidence-based management algorithms.

STRENGTH AND LIMITATIONS

- The strength of this study lies in the detailed analysis of a large cohort of geographically representative young infants with bacterial meningitis; this is the first study of its kind in the United Kingdom.

- We did not find any significant differences between the recruited and non-recruited cases in relation to age, sex, region of the country and causal bacteria (data not shown).

- Because we relied on paediatricians using their discretion to contact parents, however, this may have led to exclusion of families of infants who died or developed severe sequelae where the paediatrician was reluctant to contact the family about the study.

- Conversely, some parents may have agreed to participate simply because they were concerned about their child's long-term outlook or about suboptimal healthcare.

- Another potential limitation is that we relied on parents' recall for onset and progression of early clinical features. There is, however, evidence from other serious infections such as meningococcal disease that parents are able to accurately recall in detail such life-changing events.

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INTRODUCTION

Bacterial meningitis in young infants remains a significant cause of mortality and long-term morbidity [1]. During 2010-11, we conducted national, prospective-population-based surveillance of bacterial meningitis in infants younger than three months of age in the United Kingdom and Ireland and found that 26% of 329 infants had poor outcomes at discharge[2]. Among survivors of neonatal meningitis in the 1980's, 50% had neurological sequelae at five years of age[3] and similar rates (40%) have been reported in survivors of neonatal bacterial meningitis in the 1990s[4].

The pathogens responsible for bacterial meningitis in young infants are different to those causing meningitis in other age groups[5], with group B streptococci (GBS) and *Escherichia coli* responsible for more than half the cases; neither are currently vaccine-preventable[1].

It is recognised that the early presentations of meningitis in young infants can be subtle and non-specific. This poses a substantial challenge for parents and healthcare workers. In our national surveillance, for example, half the infants with bacterial meningitis did not have fever at presentation and only 5% had the classic triad of fever, bulging fontanelle and seizures[2].

Studies of invasive meningococcal disease have been able to delineate the onset of specific symptoms and signs and chart their progression over the course of the illness[6]. This information has helped improve knowledge and increase awareness of meningococcal infections among parents and healthcare workers (http://www.meningitis.org/health-professionals/doctors-in-training). Early recognition of meningococcal infection coupled with rapid antibiotic treatment and more aggressive management of children with sepsis has subsequently led to improved outcomes[7-9]. In adults with sepsis, earlier antibiotics have been

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associated with higher survival rates[10], but in infants the evidence base is poor even though

they have the highest incidence of bacterial meningitis[5].

We hypothesised that earlier recognition may lead to earlier healthcare interventions which in

turn might improve the outcomes of bacterial meningitis in young infants. We, therefore,

undertook a detailed assessment of the timing, course and progression of bacterial meningitis

in young infants across England and Wales. We also compared their initial and subsequent

clinical management with relevant national guidelines.

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METHODS

We undertook a detailed review of the clinical presentation and management of bacterial

meningitis in young infants in England and Wales diagnosed between July 2010 and July

2013 from the perspectives of parents and healthcare workers. We aimed to recruit 100

eligible infants (**TABLE 1**)[11-13]. Cases were identified from LabBase2 (a national

surveillance database used by National Health Service hospitals laboratories to voluntarily

electronically report clinically significant infections to Public Health England)[14]..

Group	Definition
Eligible infants	Infants <90 days of age in whom a bacterium was isolated from the cerebrospinal fluid (CSF), or where a significant bacterial pathogen was isolated from blood together with CSF pleocytosis (defined as ≥20 cells / mm^3 for infants 0-28 days of age and ≥10 cells/ mm^3 for infants 29-89 days of age)[11-13]
Age at diagnosis	Early onset (0-6 days) and late onset (7-89 days)
Home admission	Infants admitted to hospital from home
In-patients	Infants already in hospital at the time, either in the neonatal unit, birthing centre or postnatal ward.
Time from onset to first help	The time from when parents noticed the first clinical feature to the time they sought any type of help (phone call or visit).
Time from onset to first dose of antibiotics	The time from appearance of first clinical feature to first dose of antibiotics.
Time from triage to first dose of antibiotics	The time from when infant was triaged by a nurse to the time of administration of the first dose of antibiotics.
"In hours" (www.hscic.gov.uk)	Triage in hospital between hours of 0900 and 1800.
Appropriateness	Advice given prior to admission was judged as appropriate or inappropriate. Choice of empiric antibiotics and duration of antibiotics were appropriate if in conformity with existing guidelines. For example, the use of any antibiotics other than amoxicillin and cefotaxime/ ceftriaxone in any infant admitted from home would be classified as inappropriate.

Table 1: Definitions

A study pack containing study details, a consent form and a questionnaire was sent to the

local paediatrician to forward to parents. If families did not respond, we asked the

paediatrician to send a second pack. Parents of all participants completed a questionnaire with

details about onset and progression of specific symptoms. Participating parents also gave

informed written consent for the study investigators to access their infant's medical records.

All stages of care, including pre-hospital management, initial hospital assessment, ongoing

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care and post-admission follow-up were assessed through an in-depth review of hospital

notes.

Assessment of management: Expert panel and national guidelines.

An expert panel consisting of a general paediatrician, neonatologist, paediatric infectious

diseases consultant and a paediatric specialist registrar reviewed the data to determine

appropriateness of pre-hospital management, delays in recognition, empiric antibiotics,

antibiotic duration and follow-up. These were judged according to any national guidelines

available at the time. The NICE feverish illness in children aged <5 years guideline [15] was

used to assess the appropriateness of advice/actions prior to hospital admission in febrile

infants; in the absence of fever, the expert panel proposed a standard best practice. The

Bacterial Meningitis and Meningococcal Septicaemia in Children guideline [16] was used to

assess the appropriateness of empiric antibiotics, length of treatment, and timing of audiology

testing for all cases. The management of infants presenting in the first 72 hours of life was

assessed against the NICE antibiotics for early onset neonatal infection guideline[17]. We

adhered to the STROBE guidelines for reporting observational studies.

Data collection

Parents completed a questionnaire, which recorded the time of first appearance and

progression of pre-defined clinical features (online supplement on request). Information on

any illnesses in the previous two weeks was also requested. Hospital medical notes and GP

letters in the medical notes were used to corroborate parental recollection of onset, timing and

progression of events.

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Data analysis

The data are mainly descriptive. We plotted the appearance and course of symptoms from the time of onset of first symptoms. The timing of each subsequent feature was then recorded and rounded to the nearest hour. For children admitted from home, we calculated the number of hours from the onset of illness to seeking any medical help ("first help" = hospital attendance, GP attendance or phone contact with a health professional) and to hospital admission. We compared the prevalence of symptoms at onset and at hospital presentation (infants admitted from home) or at diagnosis (in-patients). We also compared presenting features and clinical management in infants admitted from home and in-patients. Continuous data that did not follow a normal distribution are described as medians with interquartile ranges (IQR) and compared using the Mann Whitney U or Kruskal Wallis test, as appropriate. Proportions were compared using chi-squared or Fisher's Exact Test, as appropriate. To identify independent risk factors for poor outcomes (death or serious complications), potential explanatory factors were included in a backward, stepwise multivariable logistic regression model and the least significant parameter was then sequentially removed until only those parameters with p <0.05 remained.

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RESULTS

A total of 224 infants with bacterial meningitis were identified and study information

forwarded to the parents **(Figure 1)**. The parents of 103 infants (46%) agreed to participate

but six cases were subsequently excluded because they did not meet the inclusion criteria.

Demographic data on parents and infants are shown in tables 2A and 2B. Cases were

recruited from 48 hospitals representing all English regions (**TABLE 2B**). Sixty-six (68%)

infant were at home when they became unwell and 31 (32%) were inpatients. Most parents

(92/97, 95%) completed the study questionnaire. The median time (IQR) from diagnosis to

return of questionnaire was 286 days (84-252).

Parameter	Mother	Father
Median parental age (IQR)	29 (26-33)	32 (26-36)
Parent's highest academic level: Mothers (n=79): fathers (n=77)		
Post graduate	16 (20%)	7 (9%)
Graduate	16 (20%)	15 (19%)
A levels	20 (25%)	13 (17%)
GCSEs	27 (34%)	42 (55%)
Parents accommodation: mothers (n=87); fathers (n=77)		
Own house/ flat	45 (52%)	45 (58%)
Rented house/ flat	35 (40%)	26 (34%)
Council house/ flat	7 (8%)	6 (8%)

Table 2A: Basic demographics of parents

CASES ADMITTED FROM HOME (n=66)

The median age at diagnosis of bacterial meningitis was 14 days (IQR, 3-25), higher in cases

admitted from home (17 [11-34] days) compared to cases already in hospital (1 [0-7];

p=0.0001). The most common features at onset of illness were poor feeding (n=44, 65%),

lethargy (n=30, 45%) and fever (temperature $\geq 38^0$C) [n=30, 44%]. The majority of

symptoms reported by parents appeared at the onset of infection (**Figure 2A**) and these

symptoms persisted, with very few new symptoms appearing over the subsequent 24 hours

(**Figure 2B**). However, there were small but significant differences in the proportion of

infants with more specific symptoms at hospital admission compared with the onset of the

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illness: irritability (p=0.036), abnormal breathing (p=0.023), abnormal movement/ seizures (p=0.024) (Figure 2C).

Twenty parents (30%) took their infants straight to the hospital: the A&E department (n=15, 22.5%) or the urgent care centre (n=5, 7.5%). The other parents (n=46, 70%) sought help by phoning the GP (n=21, 32%), calling the 24-hour NHS direct telephone service (n=15, 23%), or contacting the community midwife (n=10, 15%); of these, 13 (28%) were advised to stay at home.

The median time from onset of first features to first help was 5.0 hours (IQR: 2.0-12.0). The time to first help was not associated with early or late-onset disease, gestation at birth, presence of fever or seizure, region of the country, type of housing or level of maternal academic qualifications. The majority of parents (47/62, 76%) presented to hospital within 24 hours of onset of symptoms. 13 of 15 (93%) infants who presented after 24 hours had fever (n=8) or seizures (n=4) or both (n=1) at the time they presented to hospital. Eight of the 15 (53%) had attended their GP surgery before going to hospital, of these three were reviewed at the A&E/walk-in centre and sent home and two were initially seen by a community midwife (all five infants were seen <24 hours from onset). The remaining 7/15 (47%) infants were brought to hospital by their parents more than 24 hours from the onset of symptoms.

Overall, 20/66 (30%) infants were assessed to have received inappropriate pre-hospital management. Twelve infants with fever warranted further investigation according to the NICE guidelines and, in a further eight cases, there was a delay in seeking help despite the presence of worrying clinical features. Examples of inappropriate advice given to parents included being told that their child's fever was due to a change in milk formula, or to an umbilical hernia, or where prune juice was recommended for fever and irritability.

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Parameter	Value
Male	52 (54%)
Term (≥37 weeks)	74 (76%)
Preterm (<37 weeks)	23 (24%)
32-36	14 (14%)
28-31	5 (5%)
<28	4 (4%)
BIRTH ORDER: Singleton	88 (91%)
Twins	9 (9%)
Age distribution: Early-onset: 0-6 days	30 (31%)
Late onset : 7-28 days	44 (45%)
29-89 days	23 (24%)
ROUTE OF ADMISSION: Home	66 (68%)
In-patient	31 (32%)
Ethnicity: White	81(84%)
Asian	6 (6%)
Black	4 (4%)
Unknown	6 (6%)
Region of England: North of England	26 (26%)
Midlands and East of England	18 (19%)
London and integrated regions	13 (13%0
South of England	39 (41%)
Infants mode of feeding at diagnosis: Breastfeeding	32 (38%)
Mixed feeding	13 (20%)
Bottle feeding	32 (33%)
BACTERIA: Identified from CSF only	23 (24%)
Identified from CSF and blood	40 (41%)
Identified from blood only	34 (35%)
GBS	65 (63%)
E. coli	11 (11%)
Listeria monocytogenes	4 (4%)
Neisseria meningitidis	4 (4%)
Other Gram negative bacteria*	10 (10%)
Other Gram positive bacteria**	5 (5%)
**Pseudomonas spp.* 3, *Klebsiella spp.* 2, *Salmonella spp.* 2, *Citrobacter* 1, *Pasteurella spp.*1, *Haemophilus influenzae* 1. ***Streptococcus pneumoniae* 2, *Streptococcus bovis* 2 and α-haemolytic streptococcus 1.	
Alive	96
Dead (after 28 hours in PICU after developing meningitis in the 4th week of life).	1

Table 2B: Basic demographics of all infants

A+E management

Around half of the infants (n=36, 55%) were triaged in A&E during normal working hours.

The median time from triage to receipt of the first antibiotic dose was 2.0 hours (IQR: 1.0-

3.3; > 1 hour in 43 infants, 73%), but was significantly shorter in infants with fever or

seizures at presentation than those without these features (1.7 [IQR, 1.0-3.0] vs. 4.2 [1.8-6.3]

hours, p=0.02). There was no significant difference in median time from triage to first

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antibiotic dose in infants, by early or late-onset disease, region of the country, time of day at presentation or whether a fluid bolus was given. The median time from onset to GP visit, hospital attendance and first dose of antibiotics varied by route taken before admission (Table 3). Onset to antibiotics time was significantly longer in those who were first seen by the GP.

Category	Onset to GP	Onset to hospital visit	Onset to first dose of antibiotics
Infants who went from Home direct to hospital	Not applicable	5.7 hours (2-8.4)	8 hours (4.8-13.5)
Infants who went from Home to hospital via GP	10.5 hours (3-33)	11 hours (5.2-17)	13 hours (6.8-25)
Infants who went to hospital via GP, were sent home and went to hospital a second time	9 hours (3.5-48)	52 hours (36-96)	57.5 hours (38-98.2)
P value	0.8	0.0001	0.0001

Table 3: Median time in hours (IQR) from onset to GP, hospital visit and first dose of antibiotics by route taken prior to hospital admission. (GP: General Practitioner).

Overall, 26 (39%) infants had a poor outcome in terms of death (one case) or neurological complication (25, 38%). These included motor disorder or developmental delay (n=12, 18%), seizures (n=7, 11%), hydrocephalus (n=5, 8%), hearing loss (n=5, 8%), cerebral infarct or ischaemia on MRI (n=3, 5%) or visual deficits (n=3, 5%). The median time in hours (IQR) from onset of illness to first help in infants with poor outcomes was longer than in those who recovered without sequelae (6.25 [1-24] hours vs. 4.75 [2-10], p=0.8) but this was not statistically significant. The rate of poor outcome was also not statistically different between the 15 infants who presented to hospital >24 hours after onset of symptoms and those who presented <24hrs (8/15 [53%] vs. 18/47 [38%]; p=0.3). The interval between triage to first antibiotic dose was also not associated with poor outcome.

A number of pre-defined, potential explanatory factors (age, gender, time from onset to first help, delay in antibiotics, pre-hospital inappropriate advice, inappropriate empiric antibiotics, presence of fever, presence of seizures) were explored in univariate and multivariate analyses to identify risk factors for poor outcome; only the presence of seizures at presentation (OR, 7.9; 95% CI: 2.3- 207.0) was found to be an independent risk factor (supplement table 1).

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In-patient infants (n=31)

As with those infants presenting from home, parents of in-patient infants at the time of

diagnosis reported that the majority of symptoms were all present at the onset of the illness

(**Figure 3A**) and remained present until diagnosis, with only a few new symptoms appearing

during the course of the illness (**Figure 3B**). The only significant difference between

symptoms at onset and those at diagnosis was the proportion with breathing difficulty

(p<0.001) (**Figure 3C**).

Two-thirds of infants (21/31, 68%) had onset of symptoms within 72 hours of birth and were,

therefore, assessed against the NICE early-onset antibiotic guidelines. According to these

guidelines, the maternal "red flags" (mainly chorioamnionitis/maternal sepsis in 5), baby "red

flags" (respiratory distress after 4 hours of age in 9, shock in 4, seizures in 2 and need for

ventilation at term in 1) or both, were present in 5/21 (24%), 15/21 (71%) and 17/21 (81%),

respectively. At the time of diagnosis 17/31 (55%) of these infants received a fluid bolus,

12/31 (39%) had seizures and 8/31 (26%) had a fever.

The median time from onset of symptoms to first antibiotic dose was 2.6 hours (IQR, 1.3-

8.5), with 74% (23/31) receiving their first dose >1 hour after onset of symptoms and 4

infants (13%) receiving the first dose >24 hours after onset.

Outcomes among in-patient infants

 Overall, 12/31 (39%) of infants had a serious neurological complication at hospital

discharge, including developmental delay or motor disorder (n=9, 29%), abnormal hearing

(n=5, 16%), hydrocephalus/VP shunt (n=5, 16%), seizures (n=2, 6%) and abnormal MRI:

cortical grey and white matter injury (n=1, 3%) and two infants were treated for cerebral

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abscesses. No significant risk factors for poor outcomes were identified in either the

univariate or multivariate analyses (supplement table 1).

Home vs. in-patient infants

The main differences between infants admitted from home and in-patient cases were age,

presence of fever on presentation, timing of LP and time to discharge from outpatient follow-

up (**Table 4**).

Variable	All cases	Home (n=66)	In-patient (n=31)	P value
Median age at disease (days)	14 (3-25)	17 (11-34)	1(0-7)	**0.0001**
Early onset (<7 days)	30 (31%)	8(12%)	22(71%)	**<0.0001**
Male	52(54%)	34(52%)	18(58%)	0.5
Prematurity	23(24%)	8(12%)	15(48%)	**<0.0001**
Out-of- hours presentation	47(48%)	30(45%)	17(55%)	0.4
Fever on presentation	48(51%)	40(61%)	8(26%)	**0.001**
Seizure at presentation	33 (34%)	21(32%)	12(39%)	0.5
Received fluid bolus at presentation	53(55%)	36(55%)	17(55%)	0.7
Antibiotics delay (hours)	2 (1.3-4)	2 (1-3.3)	2.6 (1.3-9.8)	0.09
LP done post first dose of antibiotics	57 (59%)	30 (45%)	27 (87%)	**<0.0001**
Antibiotics to LP time>24 hours	33 (34%)	14 (47%)	19 (70%)	0.07
Median time to LP and no bacteria in CSF (hours)	46 (24-92.5)	24 (15.2-52.8)	65 (44-100.8)	**0.017**
Median time to LP and bacteria in CSF (hours)	7.3 (1.5-2.4)	3 (1-24)	9.5 (2-24)	0.3
Empiric antibiotics not in conformity with national guidelines	52 (54%)	35(53%)	17 (55%)	0.9
Discharge to first OPD review (months)	2.5 (2.0-3.5)	2.5 (2.0-4.0)	2.5 (2.0-2.5)	0.6
Discharge from follow up age <12 months	13 (14%)	12/65 (18%)	1/31 (3%)	**0.03**
Discharge from follow up age <24 months	31 (32%)	26/65 (40%)	5/31 (16%)	**0.02**
Hearing test performed in survivors*	74 (77%)	53/65 (82%)	21/31 (68%)	0.1
Neurological complications	40 (42%)	26/65 (40%)	14/31(45%)	0.6
Discharge to audiology test (days)	25(0-32)	24 (10-42)	26 (0-28)	0.2
Informed of meningitis support charities	12/97 (13)	11/66(17%)	2/31(6)	0.2

Table 4. Comparison of infants admitted from home and infants in hospital at the time of diagnosis (EO: early onset, OPD, out-patient department, LP: Lumbar puncture). * There were 22 survivors without report of hearing test. 12 (13%) had no record of hearing test at review, 5 (5%) were transferred to another hospital where data was not available and 4 (12%) had the review <1 month after discharge and 1 (1%) missed two appointments.

Empiric antibiotics

The empiric antibiotics used in 35/66 (53%) and 17/31 (55%) of infants admitted from home

and in-patient cases respectively were not in conformity with the appropriate NICE

guidelines (Supplement table 2).

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Follow-up and hearing tests after discharge

The median time to first out-patient follow-up was 2.5 months (IQR; 2-3.5) and was not different amongst infants admitted from home and in-patient cases (**Table 4**). However, infants from home were more likely to be discharged from follow-up before 2 years of age. A hearing test was performed in 74/96 (77%) survivors (Table 4). The median time from discharge to hearing test was 25 days (IQR: 0-32), with 30 (41%) and 14 (19%) infants having the hearing test ≥4 and ≥6 weeks after hospital discharge respectively.

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Discussion

This is the first study to assess in detail the course of the illness in young infants with bacterial meningitis and the early healthcare they receive. Parental reporting of the early features of bacterial meningitis is a unique aspect of this study. We have shown that in infants with bacterial meningitis most of the symptoms and signs as reported by parents are present from the onset of the illness and there is little progression, with no or few additional symptoms developing as the illness progresses. Notably, up to 40% of infants did not develop fever at any time during their illness. In keeping with previous studies, only seizures at presentation were significantly associated with a poor outcome[2].

The course of bacterial meningitis in young infants appears to be different to that of children with meningococcal meningitis. With a similar study design, Thompson, Ninis and colleagues demonstrated that meningococcal disease progresses in a stereotypical manner in all children, with a prodromal phase, early sepsis phase and meningism only as a late feature[6]. In terms of the healthcare-seeking behaviour for those infants admitted from home, 70% of parents had sought medical help prior to A&E attendance. Of concern, a significant proportion had received inappropriate advice suggesting that further training of frontline healthcare staff in recognising serious illness in children is required[18]. On the other hand, many of the parents who presented to hospital more than 24 hours after the initial healthcare contact, are most likely because their child's condition deteriorated, thus highlighting the importance of providing appropriate safety-netting advice to parents if they are advised to return home.

On admission to hospital, the median time from triage to first antibiotic dose was 2 hours, lower than that recently reported for childhood septicaemia (3 hours)[19] but higher than the recommended threshold of 1 hour[20]. We identified a number of reasons for this delay,

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including uncertainty in recognition (especially in those with non-specific presentations), over-reliance on the presence of fever, waiting for urine samples before giving antibiotics and waiting for handover between shifts. Presentation in-hours or out-of-hours did not influence time to first antibiotic, which is reassuring given that half of infant presented out of hours. That infants with fever or seizure received antibiotics more quickly than those without these features suggests that these delays can potentially be avoided. Miner et al showed that delay to antibiotics time is significantly shorter in patients who received it in the emergency department[21]. With appropriate education strategies, it is therefore possible to significantly improve antibiotic delivery time for infants[22].

Most in-patient infants developed meningitis within 72 hours of birth, suggesting vertical transmission of infection. The recent NICE guidelines for early-onset antibiotics provides guidance on maternal, birth and infant risk factors that should lead to specific and timely antibiotic therapy[17]. Notably, 80% of infants had such risk factors, suggesting this to be a useful tool. However the time to antibiotic administration and choice of antibiotic was still very variable. Adult studies from USA and France reported low compliance to established guidelines[23, 24].

There is still a need to reinforce to clinicians the importance of performing a timely hearing test in infants with bacterial meningitis. There is no record of such a test in 23% of cases and even when done it was ≥ 4weeks in 40%. National guidelines emphasize the need for early diagnosis of deafness to allow early interventions such as cochlear implantation [16]. Follow-up of infants with bacterial meningitis is also believed to be important as it should allow early identification of those with neurodevelopmental impairment (likely to be around 50% of survivors)[4, 25] and timely intervention and support[16].

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Summary

The impact of bacterial meningitis on young infants and their families is significant. Case fatality rates and severe complications among survivors remains unacceptably high, at least partly due to delayed recognition and management. Unlike children with meningococcal disease, for example, we were unable to identify any distinctive features at disease onset or of symptom progression that might aid earlier recognition or trigger earlier healthcare presentation. We propose a targeted campaign for education of new parents, primary care health workers (including telephone advice providers) and hospital doctors regarding the non-specific features, the lack of progression of clinical features at least in the first 24 hours and the lack of fever in young infants with bacterial meningitis. There is also need to explore ways of harmonising clinical practice with evidence-based management algorithms, including timely investigation and administration of appropriate antibiotics and adequate follow up of infants with bacterial meningitis.

Ethical Approval

Ethical approval was given by Cambridgeshire 2 REC (Ref: 10/H0308/64). Paediatricians were approached by email asking if there would be willing to take part in the study. If in agreement, a National Institute for Health Research Coordinated System for gaining NHS Permission (NIHR CSP**)** application was made and the hospital listed once approval was granted.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; PTH is a consultant to Novartis and Pfizer on group B streptococcus vaccines but receives no payment for this. NN is a consultant to Pfizer on Meningococcal

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Group B vaccines, has received honoraria to teaching on meningitis from Novartis. All other

authors declare no conflicts of interests. The ICMJE Form for Disclosure of Potential

conflicts of Interest has been submitted.

Contributorship statement:

Ifeanyichukwu O Okike completed the ethics application form, finalised the data collection

tool, coordinated the study, entered all data into an Access database, data interpretation,

performed the analysis and wrote the initial manuscript, reviewed and revised the manuscript

and submitted the final manuscript.

Shamez N Ladhani helped with case ascertainment from the Public Health England,

supported the data analysis and data interpretation, reviewed and revised the manuscript and

approved the final manuscript.

Mark Anthony co-conceived and designed the study including the grant application, was a

member of the expert panel who reviewed the management of cases, took part in data

interpretation, reviewed and revised the manuscript and approved the final manuscript.

Nelly Ninis co-conceived and designed the study including the grant application, was a

member of the expert panel who reviewed the management of cases, took part in data

interpretation, reviewed and revised the manuscript and approved the final manuscript.

Paul T Heath was the Chief Investigator, co-conceived and designed the study including the

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grant and ethics application, was a member of the expert panel who reviewed the

management of cases, contributed to the data analysis and data interpretation, reviewed and

revised the manuscript and approved the final manuscript.

Transparency declaration:

 The lead author affirms that the manuscript is an honest, accurate, and transparent account of

the study being reported; that no important aspects of the study have been omitted; and that

any discrepancies from the study as planned (and, if relevant, registered) have been explained

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the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Data sharing: We are happy to share our anonymised raw data which is not included in the manuscript. All requests should be made to the corresponding author.

What this paper adds

Section 1: What is already known on this subject

- The incidence of bacteria meningitis is higher in young infants than in any other age group and is often associated with a poor outcome - this has not changed over the last three decades

- The early clinical presentation of meningitis in young infants can be subtle and non-specific

Section 2: What this study adds

- The majority of symptoms and signs in young infants with bacterial meningitis are present at the onset of the illness, with little progression over time.

- Inadequate pre-hospital management, delayed antibiotic administration in hospital and post discharge management were found in a significant proportion of cases.

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FIGURE LEGENDS

Figure 1: Recruitment algorithm. (*: died (8), moved away (5), foster care (2), language barrier (2)).
Recruited cases were from 2010 (n=25), 2011 (n=39), 2012 (n=22) and 2013 (n=11)

Figure 2A: Time (hours) at which parents first noticed a specific clinical feature. Figure 2B: Number of features present at each hour as reported by parents Figure 2C: Clinical features present at onset and time of admission
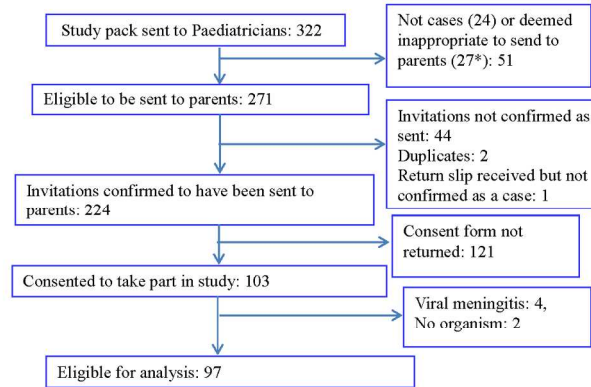
Figure 3A: Time (hours) at which parents first noticed a specific clinical feature (in-patient cases). Figure 3B: Number of features present at each hour as reported by parents (in-patient cases) Figure 3C: Clinical features present at onset and time of admission (in-patient cases)

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Study pack sent to Paediatricians: 322	Not cases (24) or deemed inappropriate to send to parents (27*): 51
Eligible to be sent to parents: 271	Invitations not confirmed as sent: 44 Duplicates: 2 Return slip received but not confirmed as a case: 1
Invitations confirmed to have been sent to parents: 224	Consent form not returned: 121
Consented to take part in study: 103	Viral meningitis: 4, No organism: 2
Eligible for analysis: 97	

Figure 1: Recruitment algorithm. (*: died (8), moved away (5), foster care (2), language barrier (2)).
Recruited cases were from 2010 (n=25), 2011 (n=39), 2012 (n=22) and 2013 (n=11)
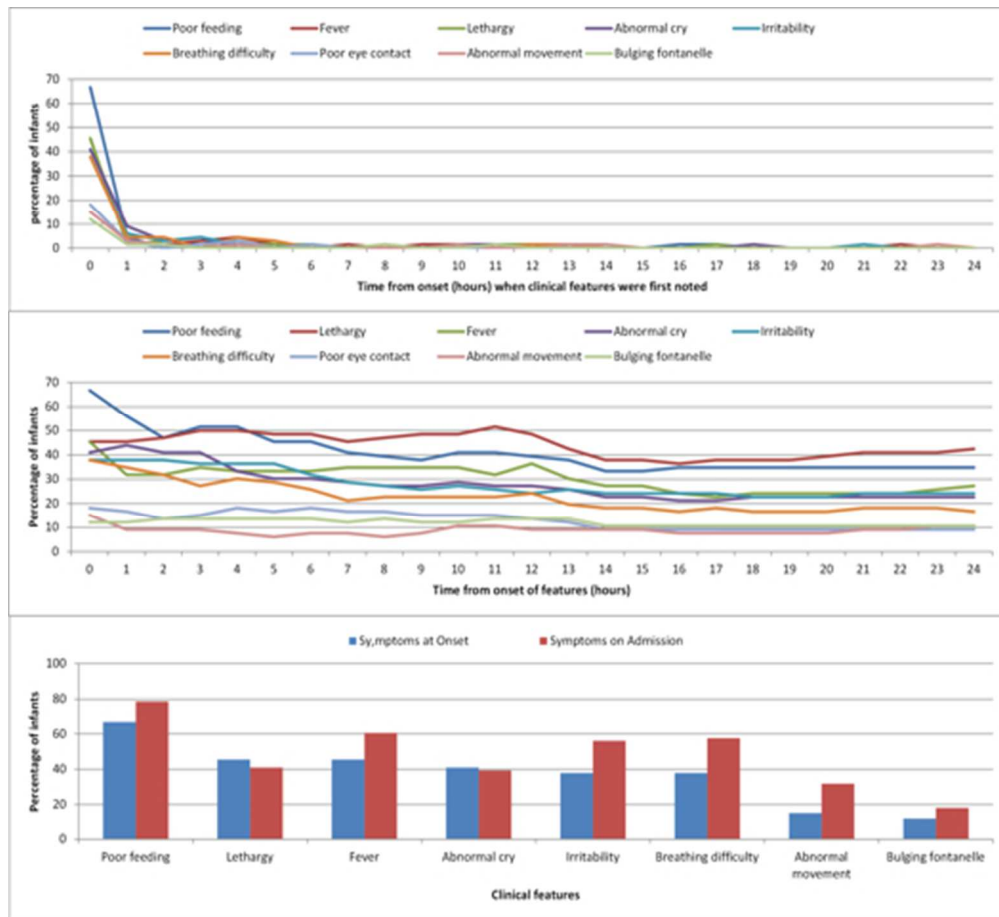
210x297mm (200 x 200 DPI)

Figure 2A: Time (hours) at which parents first noticed a specific clinical feature. Figure 2B: Number of features present at each hour as reported by parents Figure 2C: Clinical features present at onset and time of admission
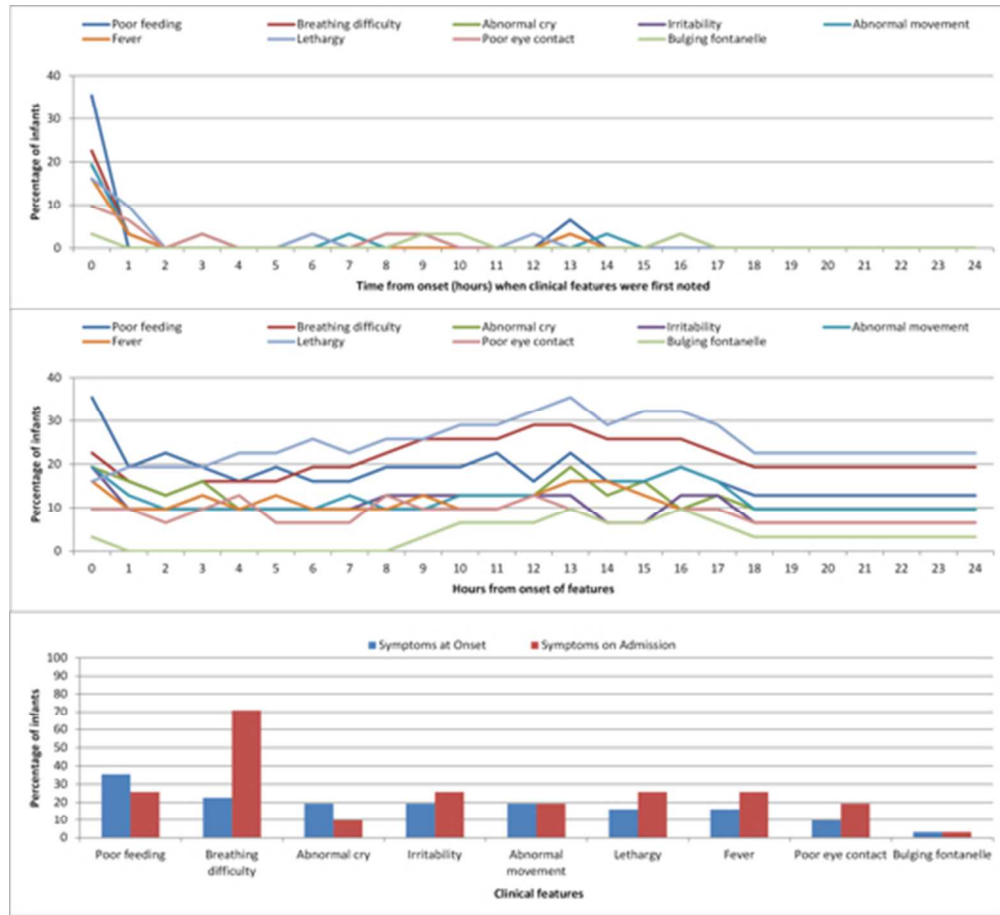
185x169mm (72 x 72 DPI)

Figure 3A: Time (hours) at which parents first noticed a specific clinical feature (in-patient cases). Figure 3B: Number of features present at each hour as reported by parents (in-patient cases) Figure 3C: Clinical features present at onset and time of admission (in-patient cases)

185x169mm (72 x 72 DPI)

SUPPLEMENTARY TABLE

Parameter	All cases			Home (n=66)			In-patient (n=31)		
	No complications	Complications	P-value	No complications (n=40)	Complications (n=26)	P-value	No complications (n=17)	Complications (n=14)	P value
Median age at presentation	14 (3-31)	12 (3-23)	0.4	19 (13-37)	16 (9-25)	0.3	1 (0-3)	2 (1-8)	0.3
Early onset	16/57 (28)	14/40 (35)	0.5	3/40 (8)	5/26 (19)	0.2	13/17 (76)	9/14 (64)	0.7
Male	29 (51)	23/ 40 (58)	0.5	20/40 (50)	14/26 (54)	0.8	9/17 (53)	9/14 (64)	0.7
Prematurity	11/57 (19)	12/40 (30)	0.2	4/40 (10)	4/26 (15)	0.7	7/17 (41)	8/14 (57)	0.4
Median maternal age	30 (26-35)	29 (24-32)	0.2	29 (26-34)	29 (24-32)	0.8	31(27-40)	27(23-33)	**0.07**
OOH presentation	31/57 (54)	16/40 (40)	0.2	21/40 (53)	9/26 (35)	0.2	10/17 (59)	7/14 (50)	0.6
Inappropriate advice	NA	NA	NA	16/40 (40)	14/26 (54)	0.3	NA	NA	NA
Fever or seizure	39/57 (68)	32/40 (80)	0.2	30/40 (75)	24/26 (92)	0.1	9/17 (53)	8/14 (57)	0.8
Fever	30/ 57 (53)	18/40 (45)	0.5	25/40 (63)	15/26 (58)	0.7	5/17 (29)	3/14 (21)	0.7
Seizure	13/57 (23)	20/ 40 (50)	**0.005**	7/40 (18)	14/26 (54)	**0.002**	6/17 (35)	6/14 (43)	0.7
Fluid bolus	30/57 (53)	24/40 (60)	0.5	22/40 (55)	15/26 (58)	0.8	8/17 (47)	9/14 (64)	0.5
Bacteria in CSF	41/57 (72)	23/40 (58)	0.1	31/40 (78)	17/26 (65)	0.3	10/17 (59)	6/14 (43)	0.6
Non-conformity antibiotics	31/57 (54)	21/40 (53)	0.9	21/40 (53)	14/26 (54)	0.8	10/17 (59)	7/14 (50)	0.6
Antibiotics delay >6h	7/57 (12)	5/40 (13)	0.8	2/40 (5)	2/26 (8)	0.6	5/17 (29)	3/14 (21)	1.0
Onset to help ≥12h	NA	NA	NA	7/40 (18)	10/26(38)	**0.06**	NA	NA	NA

Supplementary Table 1: Univariate analysis of death (1 case) and serious complications. OOH= out of hours, h=hours, CSF= cerebrospinal fluid

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Pathogen	HOME	IN-PATIENT
GBS : Home (24) in-patient (10)	Cefotaxime/ ceftriaxone alone 9 Benzyl penicillin and gentamicin 7 Amoxicillin and gentamicin 3 Cefuroxime and metronidazole 1 Cefotaxime and flucloxacillin 1 Cefotaxime and gentamicin 1 Benzyl penicillin 1 and Co-amoxiclav 1	Cefotaxime/ ceftriaxone alone 4 Benzyl penicillin and gentamicin 2 flucloxacillin and gentamicin 2 Amoxicillin and gentamicin 1 Vancomycin and gentamicin 1
E. coli (5)	Benzyl penicillin and gentamicin 4 Benzyl penicillin and cefotaxime 1	Cefotaxime/ ceftriaxone 1 Tazocin and Vancomycin 1
N. meningitidis (3)	Cefotaxime/ ceftriaxone 3	
L. monocytogenes (2)	Cefotaxime 1	Cefotaxime 1
Pasteurella spp (1)	Benzyl penicillin and gentamicin 1	
Salmonella agama (1)	Flucloxacillin and gentamicin 1	
Klebsiella spp. (1)		Teicoplanin 1
S. bovis (1)		Cefotaxime 1
H. influenzae (1)		Cefotaxime and gentamicin 1

Supplementary Table 2: Isolated bacteria in cases where empiric antibiotics was not in conformity with existing guidelines and antibiotics started empirically