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Differentiating vaccine reactions from invasive bacterial infections in young infants presenting to the emergency department in the 4CMenB era: a retrospective observational comparison

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ABSTRACT

Background Differentiating infants with adverse events following immunisation (AEFIs) or invasive bacterial infection (IBI) is a significant clinical challenge. Young infants post vaccination are therefore often admitted to the hospital for parenteral antibiotics to avoid missing rare cases of IBI.

Methods During a service evaluation project, we conducted a single-centre retrospective observational study of infants with IBI, urinary tract infection (UTI) or AEFI from two previously published cohorts. All patients presented to hospital in Oxfordshire, UK, between 2011 and 2018, spanning the introduction of the capsular group-B meningococcal vaccine (4CMenB) into routine immunisation schedules. Data collection from paper and electronic notes were unblinded. Clinical features, including National Institute for Health and Care Excellence (NICE) 'traffic light' risk of severe illness and laboratory tests performed on presentation, were described, and comparisons made using regression models, adjusting for age and sex. We also compared biochemical results on presentation to those of well infants post vaccination, with and without 4CMenB regimens.

Results The study included 232 infants: 40 with IBI, 97 with probable AEFI, 24 with possible AEFI, 27 with UTI and 44 post vaccination 'well' infants. C-reactive protein (CRP) was the only discriminatory blood marker, with CRP values above 83 mg/L only observed in infants with IBI or UTI. NICE risk stratification was significantly different between groups but still missed cases of IBI, and classification as intermediate risk was non-differential. Fever was more common in probable AEFI cases, while seizures and rashes were equally frequent. Diarrhoea and clinician-reported irritability or rigours were all more common in IBI.

Conclusions Clinical features on presentation may aid risk stratification but cannot reliably differentiate IBI from AEFI in infants presenting to the emergency department. Blood results are generally unhelpful due to post vaccination inflammatory responses, particularly in children receiving 4CMenB vaccination. Improved biomarkers and clinical prediction tools are required to aid management in febrile infants post vaccination.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Discriminating adverse events following immunisation (AEFIs) and invasive bacterial infection (IBI) is challenging, as both present in infants with fever and raised inflammatory markers.
⇒ Since the introduction of the capsular group-B meningococcal vaccine, the incidence of transient vaccine reactions presenting to accident and emergency departments has increased.
⇒ Infants presenting to the hospital with a transient vaccine reaction frequently have blood tests and lumbar punctures due to current low thresholds for these investigations in febrile young infants.

WHAT THIS STUDY ADDS

⇒ Specific symptoms and the National Institute for Health and Care Excellence traffic light system can help risk-stratify patients, but clinical features cannot reliably distinguish AEFI from IBI in young infants.
⇒ Routine blood tests (full blood count and C-reactive protein (CRP)) are largely unhelpful in young infants soon after immunisations, although a very high CRP (>83 mg/L) is rarely found post vaccination.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinical risk assessments for young infants presenting to the hospital should adjust for recent vaccine status.
⇒ Further research is required to determine if specific CRP levels can be used to rule in bacterial infection in unwell young infants presenting to healthcare services post vaccination.

INTRODUCTION

Adverse events following immunisation (AEFIs) are typically mild but common and may lead to parents seeking medical attention. The introduction of the capsular group-B meningococcal vaccine (4CMenB) into the UK immunisation schedule in 2015 has exacerbated this issue, leading to increased

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presentations to both primary care[1] and emergency departments (ED)[2 3] compared with regimens without 4CMenB. The majority present with fever, the risk of which can be reduced but not removed with prophylactic oral paracetamol.[4]

The current routine UK immunisation schedule recommends giving the first three courses at 8, 12 and 16 weeks of age.[5] This coincides with the greatest risk of invasive bacterial infection (IBI)[6] in children, which is highest in infants <3 months of age. Any clinician presented with a young febrile infant must therefore consider the possibility of IBI, as missing this diagnosis can be fatal.

This is reflected in current UK national guidance to perform blood tests for culture, full blood count (FBC) and C-reactive protein (CRP) in all infants <3 months of age with fever, regardless of other symptoms.[7] There is also a low threshold for additional invasive investigations, such as lumbar puncture (LP), and treatment with parenteral antibiotics, necessitating admission to the hospital. These guidelines give no specific advice on management of fever in cases of suspected AEFI. Consequently, infants with AEFI are commonly admitted to the hospital for observation, investigations and antibiotics.[2]

Additionally, the immunological response to vaccination is known to cause a transient rise in inflammatory markers in infants with and without AEFI. In particular CRP, granulocyte colony stimulating factor, interleukin (IL)-1RA and IL-6 have been shown to rise 24 hours post vaccination, with corresponding neutrophil activation,[8] further complicating differentiating AEFI from IBI.

In this descriptive study, our primary objective was to pragmatically describe the presenting clinical and biochemical features of young children with AEFI or IBI in three different data sets. Our secondary objective was to compare features between these cohorts, to determine if certain presenting features could be used by clinicians to differentiate AEFI from IBI.

METHODS

Design and setting

We conducted a retrospective observational study as part of a service evaluation project at Oxford University Hospitals NHS Foundation Trust, which provides emergency paediatric care for Oxfordshire, UK, through two EDs.

Patients were identified from three pre-existing data sets, one of young children with potential AEFI or urinary tract infection (UTI), one of children with IBI and one of infants post vaccination.

Patients and data collection

AEFI and UTI cases were obtained from a cohort of patients identified during a previous observational study from Nainani *et al* examining ED attendances related to immunisations.[2] To identify AEFI cases, the authors reviewed discharge summaries of all infants aged 1–6 months attending ED between 1 September 2013 and 30 October 2017. Patients were classified as either 'probable AEFI' (symptom onset within 48 hours of immunisation, no alternative focus found) or 'possible AEFI' (symptom onset within 48 hours of immunisation, possible alternative focus) or 'not related to immunisation' (symptom onset >48 hours or definite alternative focus found). Records were independently reviewed by a second investigator and classification discrepancies resolved by re-evaluating clinical notes, pathology results and rechecking immunisation histories. Infants with UTIs were similarly identified by reviewing discharge summaries and confirmed by positive urine microscopy or culture.

Infants with invasive bacterial infection (IBI) were identified from a database of patients collected for a previous study by Takata *et al* describing blood and cerebrospinal fluid (CSF) cultures in young children.[9] The authors reviewed all positive blood and CSF cultures in children presenting to our EDs over a 14-year period. Due to electronic data availability, we restricted the data collection period to 1 January 2011 and 31 December 2018. The longer data collection period compared with the AEFI and UTI cases was chosen to augment the IBI group size. To enable comparison with similar ages to vaccinated children, we included only infants with positive cultures and aged between 7 weeks and 6 months. Children were defined as having an IBI if they were unwell with bacteraemia or culture-positive CSF. Commensals were defined using the Centers for Disease Control and Prevention NHSN Common Commensals List 2020, and children with growth of only these were excluded. Patients were also excluded if the culture was taken over 72 hours after hospital admission; there was possible ventriculoperitoneal shunt infection; a planned admission; a transfer from another hospital; or they had a known underlying malignancy or previous bone-marrow transplant.

Additional data were collected, unblinded, for patients from all groups from electronic and paper notes including demographics; symptoms at or before presentation; risk of serious illness (low, intermediate or high, based on described signs and symptoms as defined by National Institute for Health and Care Excellence (NICE) Guidance on fever in under 5's 'traffic light system' (online supplemental table 2)[7]); hospital admission method; length of stay; antibiotic prescribing; inflammatory markers at presentation and highest within first 72 hours; blood cultures; urinalysis and urine culture; and CSF biochemistry, cell count and culture. Where clinical details were unclear or missing from available electronic and paper notes, results were recorded as 'not available'.

To better inform the potential role of routine inflammatory markers in assessing children on presentation to ED post vaccination, we included blood results from a third group of children, recruited into the European Union Childhood Life-threatening Infectious Disease Study (EUCLIDS) into the immunogenicity of the 4CMenB vaccination.[8] In this study, all patients received routine immunisations at 4 months of age according to the UK 2015 immunisation schedule (online supplemental table 1), with half also receiving 4CMenB vaccination. Blood

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samples were taken from these infants at one of four timepoints post vaccination (either 4, 24 and 72 hours or 7 days), regardless of whether or not they exhibited any symptoms or signs of clinical illness. To reflect the time post vaccination infants are likely to present to ED, we included only blood tests taken 24 or 72 hours post vaccination. Full details available in original publications[2 8 9] and inclusion/exclusion criteria for each primary study can be found in online supplemental table 3.

Statistical analysis

We present comparative statistics for clinical features and laboratory results on presentation between infants with IBI and probable AEFI. Sensitivity analyses were conducted repeating each analysis after combining probable and possible AEFIs, separating probable AEFI into pre-4CMenB and post-4CMenB introduction (1 May 2015).

All statistical analyses were undertaken in R (R Foundation) V.4.1.1.[10] Logistic regression was used to compare binary categorical variables, unless there were no positive results in one comparator group, in which case Fisher's exact test was used. We report adjusted p-values and ORs with 95% confidence intervals (CI). Non-binary categorical variables were compared using Fisher's exact test. Variables of age (in days) and sex (binary) were included in regression models to account for potential confounding, except for comparisons with the EUCLIDS cohort, as their age distribution was extremely narrow by design. No corrections were made for missing data or multiple testing.

RESULTS

Study populations

The study included 232 infants after 88 exclusions: 40 with IBI, 97 with probable AEFI, 24 possible AEFI, 27 UTI and 44 postvaccination 'well' infants (figure 1). Infants with IBI were older than probable AEFI (median 117 vs 77 days, online supplemental figure 1) and were more likely to be female (60%) than probable AEFI (37%) (table 1).

Forty-two participants from the EUCLIDS study had one relevant blood test available at 24 or 72 hours. Fifty-nine percent were female and 22/44 received 4CMenB vaccination alongside routine immunisations. None of these children required hospital assessment for symptoms after vaccination.

Clinical features

After adjusting for age and sex, irritability and diarrhoea were significantly more common in infants with IBI than probable AEFI, whereas fever was less common in IBI (tables 1 and 2). Rigours were not reported in any cases of probable or possible AEFI, and reported in 11% of those with IBI. Classification as 'high risk' using the NICE traffic light system was more common in the IBI group compared with probable AEFI (40% vs 13%, adjusted ORs 5.47, 95% CI 1.85 to 16.14). Classification as 'low risk' was less common (10% vs 46%, adjusted OR 0.07, 95% CI 0.02 to 0.2) but still occurred in 4/40 patients who were subsequently diagnosed with IBI. Classification as intermediate risk was similar in both IBI and probable AEFI (25% and 22%, respectively). Seizures reported at or before presentation were uncommon in all groups (5%–12%) and were not statistically different between groups.

Blood results

The percentage of infants who had blood tests (FBC and/or CRP) on presentation was highest in the IBI group (98%), with bloods taken in 28% of probable AEFI, 50% possible AEFI and 44% UTI.

All inflammatory markers (CRP, WCC, neutrophil count) were frequently raised in all groups (figure 2). The widest range for all inflammatory markers was exhibited in the IBI group (CRP 0.1–393, WCC 1.6–34.4, Neutrophil count 0.2–27.4). CRP was the only blood result on presentation that was significantly different between IBI and probable AEFI (table 3). Although CRP values were

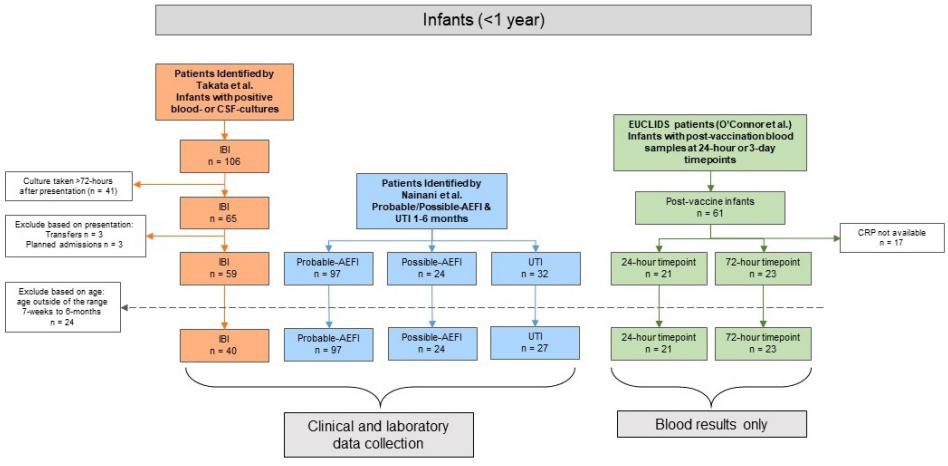


Figure 1 Patient inclusion and exclusion flowchart. AEFI, adverse event following immunisation; CRP, C-reactive protein; CSF, cerebrospinal fluid; IBI, invasive bacterial infection; UTI, urinary tract infection.

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Table 1 Comparison of demographics, admission details and clinical features on presentation

	All	IBI	Probable AEFI	Possible AEFI	UTI	P value (IBI vs probable AEFI)
Number of participants	188 (100)	40 (21)	97 (52)	24 (13)	27 (14)	–
Demographics						
Female sex	80 (43) (0)	24 (60) (0)	36 (37) (0)	10 (42) (0)	10 (37) (0)	**0.015**
Age (days)	94 (62–131) (0)	117 (78–168) (0)	77 (61–115) (0)	84 (60–125) (0)	150 (108–168) (0)	**<0.001**
Clinical outcomes						
Admitted	122 (65) (0)	37 (92) (0)	55 (57) (0)	16 (67) (0)	14 (52) (0)	**<0.001**
Length of stay (days)	0.6 (0.1–2.5) (0)	4.0 (2.3–7.8) (0)	0.5 (0.1–0.7) (0)	1.1 (0.1–2.9) (0)	0.4 (0.1–2.1) (0)	**<0.001**
Antibiotics on presentation	87 (47) (1)	36 (92) (1)	16 (16) (0)	11 (46) (0)	24 (89) (0)	**<0.001**
Method of presentation						
Ambulance	40 (21)	8 (20)	18 (19)	8 (33)	6 (22)	0.6*
GP referral/111	75 (40)	17 (42)	44 (45)	6 (25)	8 (30)	
Self-referral	63 (34)	11 (28)	31 (32)	8 (33)	13 (48)	
Not available	10 (5)	4 (10)	4 (4)	2 (8)	0 (0)	
Clinical features						
Fever on/ prior to presentation	137 (77) (10)	27 (71) (2)	77 (83) (4)	10 (48) (3)	23 (88) (1)	**0.019**
Rash	40 (23) (13)	13 (38) (6)	14 (15) (4)	8 (36) (2)	5 (19) (1)	0.198
Vomiting	45 (26) (13)	16 (47) (6)	17 (18) (4)	4 (18) (2)	8 (31) (1)	0.068
Diarrhoea	27 (16) (14)	14 (42) (7)	7 (8) (4)	3 (14) (2)	3 (12) (1)	**0.003**
Seizures	18 (10) (15)	2 (6) (9)	10 (11) (4)	3 (13) (1)	3 (12) (1)	0.798
Irritability—clinician reported	67 (37) (7)	21 (64) (7)	37 (38) (0)	3 (12) (0)	6 (22) (0)	**0.043**
Rigours—clinician reported	6 (3) (9)	4 (11) (3)	0 (0) (4)	0 (0) (1)	2 (8) (1)	**0.006***
NICE Classification of Risk of Serious Illness (traffic light system)						
High	43 (23)	16 (40)	13 (13)	9 (38)	5 (19)	**0.002**
Intermediate	47 (25)	10 (25)	21 (22)	6 (25)	10 (37)	0.115
Low	66 (35)	4 (10)	45 (46)	8 (33)	9 (33)	**<0.001**
Not determined	32 (17)	10 (25)	18 (19)	1 (4)	3 (11)	–

Categorical variables are reported as number (percentage of total, %) (number of missing results). Continuous variables are reported as median (IQR) (number of missing results). P values are reported for comparison between IBI and probable AEFI groups. P-values for clinical features and NICE classification features are adjusted for age and sex, and those <0.05 are highlighted in bold.
*Indicates comparison using Fisher's exact test, unadjusted for age or sex.
AEFI, adverse event following immunisation; IBI, invasive bacterial infection; NICE, National Institute for Health and Care Excellence; UTI, urinary tract infection.

commonly elevated in probable and possible AEFI cases, the maximal CRP on presentation for these groups were 52.9 mg/L and 82.5 mg/L respectively. 15/40 IBI cases (37.5%) had a CRP higher than this maximum value of 82.5 mg/L on presentation.

In infants from EUCLIDS (ie, those not presenting to ED post vaccination) a similar phenomenon was seen, with substantial inflammatory marker rise 24 hours post vaccination (figure 2, median CRP 25.9 mg/L (IQR 19–43) and WCC 14.9×10^9/L (IQR 13–17)), although the proportion with WCC above laboratory reference range

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Table 2 ORs for IBI versus probable AEFI, adjusted for age and sex

	OR, IBI	95% CI	P values
Fever	0.29	(0.10 to 0.82)	**0.0188**
Rash	1.99	(0.69 to 5.71)	0.1981
Vomiting	2.46	(0.93 to 6.53)	0.0679
Diarrhoea	5.42	(1.75 to 16.77)	**0.0031**
Seizures	0.81	(0.15 to 4.23)	0.7976
Irritability—clinician reported	2.60	(1.02 to 6.59)	**0.0427**
Rigours—clinician reported	Inf†	(1.74 to Inf†)	**0.0060***
NICE Classification of Risk of Serious Illness			
High	5.47	(1.85 to 16.14)	**0.0019**
Intermediate	2.38	(0.80 to 7.08)	0.1147
Low	0.07	(0.02 to 0.27)	**0.0001**

P values <0.05 are highlighted in bold.
*Indicates comparison using Fisher's exact test, unadjusted for age or sex.
†Infinite estimate determined due to zero observations in the probable AEFI group.
AEFI, adverse event following immunisation; IBI, invasive bacterial infection; NICE, National Institute for Health and Care Excellence.

was smaller than for patients presenting to hospital with probable or possible AEFI (25% vs 62% and 58% respectively, table 3). At 72 hours, the postvaccination rise in inflammatory markers was largely resolved (median CRP 5.2 mg/L (IQR 2–8) and WCC 9.1×10^9/L (IQR 8–11)), although one child had a CRP value of 48.1 mg/L 72 hours post vaccination.

CRP, WCC and neutrophil count showed no significant difference between probable AEFI patients before and after the introduction of 4CMenB (figure 2 and online supplemental table 5; p= 0.051, 0.161 and 0.055, respectively). In EUCLIDS infants, at the 24-hour timepoint, CRP was the only inflammatory marker significantly higher in those coadministered 4CMenB compared with those administered routine immunisations without 4CMenB (p=0.007). No inflammatory markers were significantly different between these groups at the 72-hour timepoint.

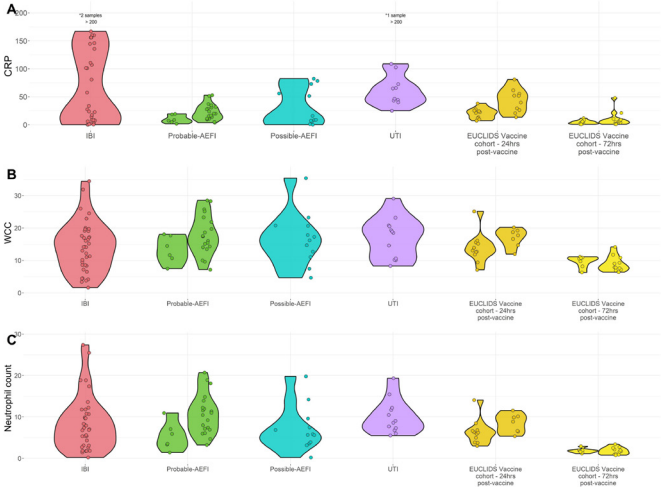


Figure 2 Comparison of inflammatory markers across all groups at presentation. (A) CRP (mg/L), (B) WCC (×10^9/litre), (C) neutrophil count (×10^9/litre). Patients with probable AEFI separated into those before the 4CMenB introduction (violin plot to the left side) and those afterwards (right). Similarly, EUCLIDS participants were separated into those given routine immunisations without (left side) and with (right side) 4CMenB. 4CMenB, capsular group-B meningococcal vaccine; AEFI, adverse event following immunisation; CRP, C-reactive protein; IBI, invasive bacterial infection; UTI, urinary tract infection; WCC, white cell count.

Additional laboratory investigations

Urine dipstick results were not determined or not performed at presentation in the majority of patients with both IBI and probable AEFI (65% and 73%, table 3). Positive leucocytes and nitrites were more common in IBI compared with probable AEFI.

LP was performed in 63% of infants with IBI, 14% with probable AEFI, 38% with possible AEFI and 30% with UTI. Meningitis cases accounted for only 12.5% of all IBI. CSF biochemistry and cell count were not significantly different between all-IBI and probable AEFI (table 3).

Sensitivity analyses

Fever was no longer significantly different between groups after combining probable and possible AEFI groups, but otherwise, this sensitivity analysis did not significantly alter the results (online supplemental table 4). Fever, diarrhoea and CRP on presentation were still significantly different between IBI and probable AEFI when restricting comparisons to the 81 infants with probable AEFI post-4CMenB (online supplemental table 5).

DISCUSSION

Given the high proportion of UK paediatric ED attendances attributable to fever,[11] reliably differentiating AEFI from IBI in unwell infants presenting to ED within 48 hours of immunisation could reduce hospital stays, invasive investigations and improve antimicrobial stewardship. Our pragmatic study identifies important clinical features that may help clinicians evaluating such children. Fever was the the most common presenting feature in probable AEFI cases, and lack of fever was in fact more common in IBI. GI upset (diarrhoea) and the more well-established red-flag feature of clinician-reported irritability were similarly more common in IBI cases, whereas rash and seizures were seen at comparable rates. However, no features were reliable differentiators, highlighting the clinical challenge that remains in separating post vaccination reactions from IBI in young infants.

High-risk and low-risk classifications by NICE was strongly predictive of outcome, but failed to identify

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Table 3 Comparison of laboratory results on presentation

	All	IBI	Probable AEFI	Possible AEFI	UTI	P value (IBI vs probable AEFI)
Number of participants	188 (100)	40 (21)	97 (52)	24 (13)	27 (14)	–
Laboratory results—routine blood tests						
WCC on presentation (10^9/L)	16.1 (10.4–19.7 (101)	14.2 (8.6–19.0 (3)	16.7 (13.6–19.4) (71)	16.7 (12.3–20.7) (12)	18.7 (10.5–20.6) (15)	0.113
Percentage of WCC on presentation above laboratory reference range for age (15×10^9/L) (%)	54	46	62	58	58	–
NC on presentation (10^9//L)	7.4 (5.3–11.6) (101)	7.0 (3.1–10.8) (3)	8.6 (6.0–11.9) (71)	5.7 (3.8–8.0) (12)	8.8 (7.2–11.8) (15)	0.697
Percentage of NC on presentation above laboratory reference range for age (8×10^9//L)	45%	43%	50%	25%	58%	–
LC on presentation (10^9//L)	5.3 (3.0–7.2) (101)	4.7 (2.8–6.0) (3)	5.1 (3.2–7.3) (71)	7.7 (5.7–9.8) (12)	4.9 (2.7–6.4) (15)	0.231
CRP on presentation (mg/L)	26 (9–74) (104)	46 (8–146) (6)	16 (10–28) (70)	12 (7–60) (12)	65 (44–88) (16)	**0.012**
Percentage (%) of CRP on presentation above laboratory reference range for age (5 mg/L)	87	82	89	83	100	–
Highest WCC in first 72 hours (10^9//L)	16.3 (10.6–19.7) (98)	15.0 (9.1–19.1) (2)	17.4 (13.8–19.2) (70)	16.2 (11.1–20.7) (11)	18.7 (10.5–20.6) (15)	0.406
Highest NC in first 72 hours (10^9//L)	7.4 (5.4–11.7) (98)	7.2 (3.4–11.5) (2)	9.2 (6.0–11.8) (70)	5.6 (3.6–7.5) (11)	8.8 (7.2–11.8) (15)	0.732
Highest LC in first 72 hours (10^9//L)	5.8 (3.5–7.6) (98)	5.5 (3.4–7.2) (2)	5.7 (3.3–7.4) (70)	7.9 (5.8–9.7) (11)	5.5 (2.7–6.4) (15)	0.609
Highest CRP in first 72 hours (mg/L)	31 (11–77) (102)	58 (11–151) (5)	19 (10–30) (70)	16 (8–56) (11)	65 (44–88) (16)	**0.007**
Blood cultures						
Pathological growth	37 (20)	37 (92)	0 (0)	0 (0)	0 (0)	–
Negative	51 (27)	3 (8)	26 (27)	12 (50)	10 (37)	
Contaminant	4 (2)	0 (0)	3 (3)	0 (0)	1 (4)	
Not determined/not performed	96 (51)	0 (0)	68 (70)	12 (50)	16 (59)	
Urine dipstick						
Leucocyte positive	36 (51)	10 (71)	3 (12)	3 (38)	20 (91)	**0.004**
Nitrite positive	15 (21)	4 (29)	0 (0)	1 (12)	10 (45)	**0.010***
Not determined/not performed	118 (63)	26 (65)	71 (73)	16 (67)	5 (19)	0.154
Laboratory results—lumbar puncture testing						
Culture						

Continued

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Table 3 Continued

	All	IBI	Probable AEFI	Possible AEFI	UTI	P value (IBI vs probable AEFI)
Positive	6 (11)	5 (21)	0 (0)	0 (0)	1 (12)	–
No growth	48 (89)	19 (79)	13 (100)	9 (100)	7 (88)	
No LP culture	134 (71)	16 (40)	84 (87)	15 (62)	19 (70)	
Biochemistry						
Protein (mg/L)	340 (248–535) (136)	305 (240–514) (17)	334 (276–529) (84)	579 (352–01) (15)	282 (234–364) (20)	0.442
Glucose (mmol/L)	3.2 (2.9–3.6) (135)	3.4 (2.6–3.8) (16)	3.0 (2.9–3.4) (84)	3.1 (2.9–3.2) (15)	3.4 (3.2–3.8) (20)	0.978
Lactate (mmol/L)	1.3 (1.1–1.5) (152)	1.6 (1.0–2.3) (30)	1.3 (1.2–1.5) (86)	1.2 (1.1–1.4) (16)	1.3 (1.1–1.4) (20)	0.152
Cell count						
WCC (10^6/L)	0 (0–2) (137)	0 (0–2) (19)	0 (0–2) (84)	4 (2–6) (15)	0 (0–0) (19)	0.562
PMNs (10^6/L)	0 (0–0) (137)	0 (0–0) (19)	0 (0–0) (84)	2 (0–2) (15)	0 (0–0) (19)	0.696
Lymphocytes (10^6/L)	0 (0–2) (137)	0 (0–2) (19)	0 (0–2) (84)	2 (2–6) (15)	0 (0–0) (19)	0.464

Categorical variables are reported as number (percentage of total, %) (number of missing results). Continuous variables are reported as median (IQR) (number of missing results). P values are reported for comparison between IBI and probable AEFI groups and are adjusted for age and sex. P values <0.05 are highlighted in bold.
*Indicates comparison using Fisher's exact test, unadjusted for age or sex.
AEFI, adverse event following immunisation; CRP, C-reactive protein; IBI, invasive bacterial infection; LC, lymphocyte count; NC, neutrophil count; PMN, polymorphonuclear leucocyte; UTI, urinary tract infection; WCC, white cell count.

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multiple IBI cases. This is in keeping with previous literature, which suggests the traffic light system is a strong predictor of hospitalisation but not diagnosis.[12 13] Our results suggest classification as intermediate risk does not inform diagnosis and leaves many children in the diagnostic middle ground.

More advanced risk-prediction tools for paediatric hospitalisation and IBI have been developed, for example, the Feverkidstool developed through the Management and Outcome of Fever in Children in Europe (MOFICHE) study,[14 15] which incorporate NICE red-flag indicators among other clinical features. Despite showing improved performance compared with NICE guidance alone, both approaches leave a large group of children in an'intermediate' risk group. This is a challenging group of patients, especially when alternative explanations, such as recent immunisation, need to be considered, and are likely to benefit from additional clinical assessment.

Accordingly, clinicians facing this dilemma often resort to laboratory testing to attempt to differentiate AEFI from IBI. Our results clearly demonstrate a rise in inflammatory markers post vaccination, as has previously been reported post immunisation even in children not requiring medical attention.[8] We observed that neither WCC or neutrophils are helpful in predicting IBI in this context. This is consistent with known limitations in their use outside the post immunisation period.[16 17]

While CRP was significantly raised above normal in both IBI and probable AEFI cases, the upper limit of CRP rise appears limited in post vaccination infants when compared with children with IBI. We observed no CRP values above 83 mg/L in any cases of probable or possible AEFI, whereas a substantial proportion of patients with either IBI or UTI had CRP values well above this limit. This suggests that CRP may have some utility as a rule-in test when abnormally raised post vaccination, although a larger sample size is needed to estimate a reliable threshold value.

We also observed a significant difference in inflammatory markers for post vaccination infants after the introduction of 4CMenB, with greater CRP in those receiving 4CMenB. This has potentially important implications when interpreting routine biomarkers in post vaccination infants, as it may be safe to omit antibiotic therapy in children with significantly elevated CRP levels when it is certain the 4CMenB vaccine has been administered in the preceding 24–48 hours.

Given these findings, additional research into clinical decision tools and biomarkers is needed. Solutions such as adding procalcitonin and combining investigation results have been trialled to help detect IBI in young infants, but with marginal gains.[18] Novel transcriptomic signatures for diagnosis of bacterial infection in febrile children are promising.[19] We have recently demonstrated that infants post vaccination can be distinguished from IBI using a minimal six-transcript RNA signature (prepublication).[20 20] However, these tests are still in preclinical development.

This study has several notable limitations. Due to the inherent sampling methodology, groups are not directly comparable. This affects the interpretability of our results as we have not formally assessed risk within 48 hours post vaccine, instead comparing results in distinct observational cohorts. The low numbers and single-centred retrospective nature also limits generalisability, particularly to non-UK settings, and the study is likely only powered to detect larger differences in presentation. There were also much missing clinical data, both in electronic and paper notes. This precluded more advanced multinomial regression modelling due to limited numbers of complete records. In addition, blood results are likely missing not-at-random, which affects the generalisability of our results. This is especially important in the probable AEFI group, where many patients did not have a blood draw during their presentation to ED. To adjust for this ascertainment bias, we included the EUCLIDS cohort of infants who had blood tests taken regardless of any features of clinical illness, demonstrating the rise in inflammatory markers post vaccination is not limited to those with signs/symptoms of clinical illness.

In addition, it was impossible to blind investigators to diagnosis before data collection. An obvious omission is comparison of Paediatric Early Warning Scores (PEWS) between groups. Currently, there is no consensus nationally on PEWS observations and scoring,[21 22] so this analysis was not performed. Finally, due to the descriptive focus of this study, we have not used multiple-testing corrections, so significant comparisons must be interpreted with caution.

Considering these limitations, we suggest that low-risk patients (as defined by NICE traffic light system) without irritability or focal signs/symptoms presenting post vaccination be discharged with appropriate safety netting. The utility of blood tests to guide decisions is limited, except in the context of a very high CRP of >80–85 mg/L, which should not be ignored.

CONCLUSION

Routine clinical features cannot reliably differentiate IBI from benign AEFI in the context of a young child being brought to ED with fever post vaccination. Presence of specific symptoms, existing risk stratification tools and urine dipstick results are helpful in guiding decision making but remain inaccurate. Blood markers are generally unhelpful in this context due to a significant post vaccine inflammatory response, particularly since the introduction of the 4CMenB vaccination. These data show the urgent need to develop improved biomarkers to help identify children with sepsis.

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Contributors SWC-W and MDS were responsible for design of the study. MDS was responsible for obtaining study approval and the relevant permissions. SWC-W, ET and NS were responsible for data collection and analyses. All authors contributed to data interpretation and writing of the manuscript. All authors critically reviewed and approved the final draft version of the revised article as submitted. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SWC-W and MDS are jointly responsible for the overall content as guarantors, and accept full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Permission to conduct this study as a service evaluation was obtained through the OUH NHS trust, thus the inclusion of these patients for this study did not require approval from an NHS ethics committee. The EUCLIDS study was approved by a national research ethics committee (South Central - Oxford A, 14/SC/0077).

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