Journal of Paediatrics and Child Health

doi:10.1111/jpc.14315

ORIGINAL ARTICLE

Fever after meningococcal B immunisation: A case series

Gillian Campbell [1], Ruth M Bland[1,2,3] and Scott J Hendry[1]

[1]Emergency Department, Royal Hospital for Children, [2]Insitute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom and [3]School of Public Health, University of Witwatersrand, Johannesburg, South Africa

Aim: To document the clinical features and management of infants presenting with fever after their first meningococcal B vaccination and develop guidance for clinicians.

Methods: A prospective case series over 12 months was conducted in a tertiary paediatric hospital. Infants ≤3 months of age with fever who had received their first set of immunisations within the preceding 72 h were included.

Results: A total of 92 infants met the inclusion criteria, accounting for 0.78% of the local vaccinated population. The most commonly described associated features were poor feeding, sleepiness and irritability; 66 patients (72%) were admitted to hospital. Median C-reactive protein (CRP) was 12 mg/L, and median white cell count (WCC) was 16 × 10^9/L. Fifteen patients (16%) had a lumbar puncture and were commenced on antibiotics. There was one confirmed bacterial infection in an infant who had presented with fever starting 54 h after immunisation. All other microbiology samples were negative. There were no cases of missed serious bacterial infection (SBI) in those patients who were observed or discharged.

Conclusions: The routine investigation of infants presenting with post-immunisation fever is not warranted if the infant appears otherwise well on examination. Where other common associated features are present or there is clinical concern, a period of observation is a prudent course of action. Paracetamol should be given peri-immunisation as per the national guidance. We suggest selective use of investigations, especially inflammatory markers, which are unlikely to discriminate between SBI and post-immunisation response. We advocate extra caution in infants presenting with fever more than 48 h after immunisation.

Key words: Bexsero; fever; immunisations; infant; meningococcal B.

What is already known on this topic

1 Fever is a common and predictable response to vaccination.
2 Children are more likely to experience post-immunisation fever with the new routine immunisation schedule in the UK that includes *Bexsero*, the vaccine against meningococcal group B, and the routine use of paracetamol after immunisation is recommended.
3 Management of infants presenting with post immunisation fever varies between clinicians.

What this paper adds

1 This is the largest known case series of infants presenting with fever after the meningococcal B immunisation.
2 Leucocytosis is to be expected in the post-immunisation period, and routine investigations in an otherwise well infant with post-immunisation fever are not warranted.
3 Medical attendance rate of <1% of vaccinated population is consistent with previously published data.

Meningococcal meningitis and septicaemia remain the leading infectious causes of death in children younger than 5 years of age in the UK.[1] From September 2015, infants have been offered *Bexsero,*[2] a vaccine against meningococcal serogroup B, as part of the routine UK immunisation schedule at 2, 4 and 12 months. In Australia, from 1 October 2018, the meningococcal B vaccine will be offered as part of an ongoing programme for babies up to 12 months of age in the state of South Australia. However, it is not yet widely available on the National Immunisation Program.

Correspondence: Dr Gillian Campbell, Emergency Department, Royal Hospital for Children, 1345 Govan Road, Glasgow G51 4TF, United Kingdom; email: gillcampbell@nhs.net

Conflict of interest: None declared.

Accepted for publication 29 October 2018.

Fever is a common and predictable response to immunisation. In clinical studies, when *Bexsero* was given alone, the frequency of fever varied between 26 and 41%.[3] This number rose to between 51 and 77% when *Bexsero* was co-administered with other routine immunisations at the same visit.[3–6] The first set of immunisations in the UK schedule at 2 months of age also includes DTaP/IPV/Hib, pneumococcal conjugate and rotavirus vaccines.[2]

Bexsero is the first vaccine in the UK schedule to come with a prophylactic paracetamol recommendation. It is recommended that infants receive paracetamol at the time of immunisation, and parents are advised to administer two further doses at 4–6-hourly intervals.[7] Other very common post-immunisation side effects include loss of appetite, sleepiness and irritability. UK guidelines recommend that parents seek medical advice if their infant appears unwell following immunisation.[7]

For paediatricians, decisions on the appropriate investigation and management of young infants with post-immunisation fever can be challenging. In 2015, we conducted a small pilot study in a tertiary Scottish paediatric hospital of eight infants presenting with fever after meningococcal B immunisation. This demonstrated a wide range of management strategies,[8] with 50% being discharged from the emergency department (ED), 12% being discharged after a brief period of inpatient observation and the remaining 38% being admitted for 48 h of intravenous (IV) antibiotics following a full septic screen including lumbar puncture. In this study, we aimed to document the clinical features and management of a consecutive series of infants presenting to a tertiary paediatric hospital ED with fever after their first meningococcal B vaccination.

Methods

This prospective case series was conducted over a 12-month period, from 1 March 2016 to 28 February 2017, at Royal Hospital for Children, Glasgow, a tertiary paediatric centre where the ED sees in excess of 60 000 attendances per year. Ethics approval was granted by the local Caldicott Guardian.

Inclusion criteria were patients ≤3 months of age who had received their first set of immunisations (including *Bexsero*) within the preceding 72 h and had either a documented fever of ≥38°C or parental concern about fever at home.

Patients were identified using three strategies. First, eligible patients were identified by trained triage staff, and patient details were documented on a 'study clipboard' for collection by the study team on a monthly basis. Second, we conducted an electronic search of all patients aged between 50 and 100 days who presented to the ED over the study period with a relevant discharge code. Included codes were 'other complication following immunizations', 'pyrexia of unknown origin – fever unspecified' and 'drug induced fever'. Finally, an electronic search for all patients aged between 50 and 100 days old presenting to the ED over the study period was carried out to ensure that all relevant infants had been identified and none had been omitted as a result of inaccurate discharge coding.

Patient data were collected from case notes and entered onto a pre-designed data form, which was electronically scanned into a database. The results were collated by the local research and development team. Patient identification and data collection were carried out solely by the primary author to minimise any variation in procedure. Data were analysed using the computer software Excel (Microsoft Office 2010, Redmond, WA, USA).

Results

A total of 92 infants met the study inclusion criteria. Figure 1 demonstrates the yield from each of the three different search strategies.

Monthly variation in the number of presentations was noted, with May to September being the busiest for this particular presenting complaint (Fig. 2). There was a male predominance of 66% (Table 1). Patients were mostly referred from primary care (59%), but many were brought directly to the ED by their parents (40%). Infants presented out of hours more commonly than during the day. Of the 92 patients, 86 (93%) had been given paracetamol prior to ED attendance. Of the 92 infants, 56 (61%) had a fever ≥38°C at triage. The most commonly described associated features were poor feeding, sleepiness and irritability.

Of the 92 patients, 66 (72%) were admitted to either the clinical decision unit (CDU) or a hospital ward. Of these 66 patients, 50 (76%) were discharged within the next 24 h. The median time of admission for this group was 11 h, and they were mostly discharged following the morning ward round. The remaining 16 patients who were admitted for over 24 h had a duration of admission that ranged from 1 to 5 days. Figure 3 demonstrates the discharge destination for each patient. Of those patients discharged, there were two return attendances. One was a developing bronchiolitic illness, and the second required a longer period

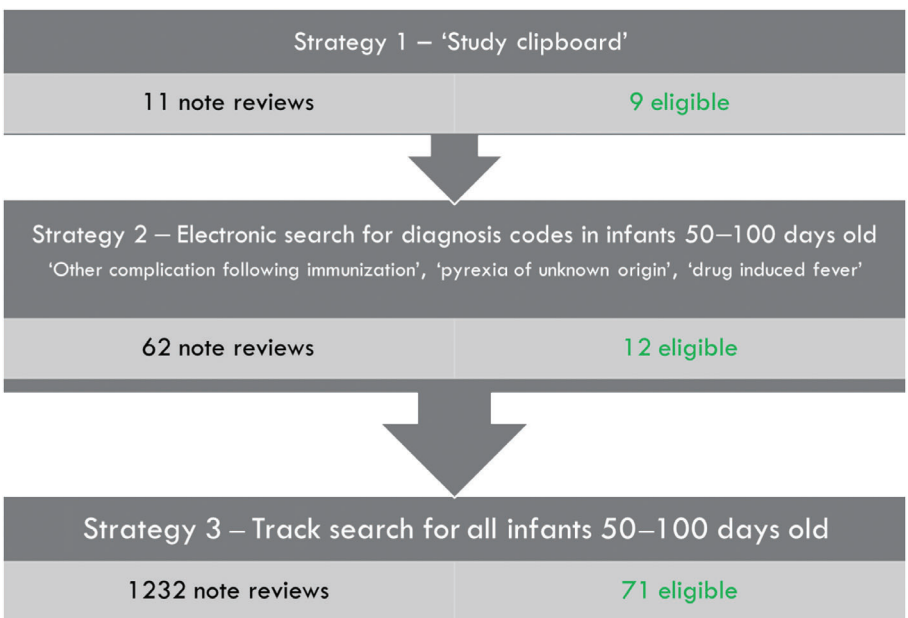

Fig. 1 Summary of search strategy.

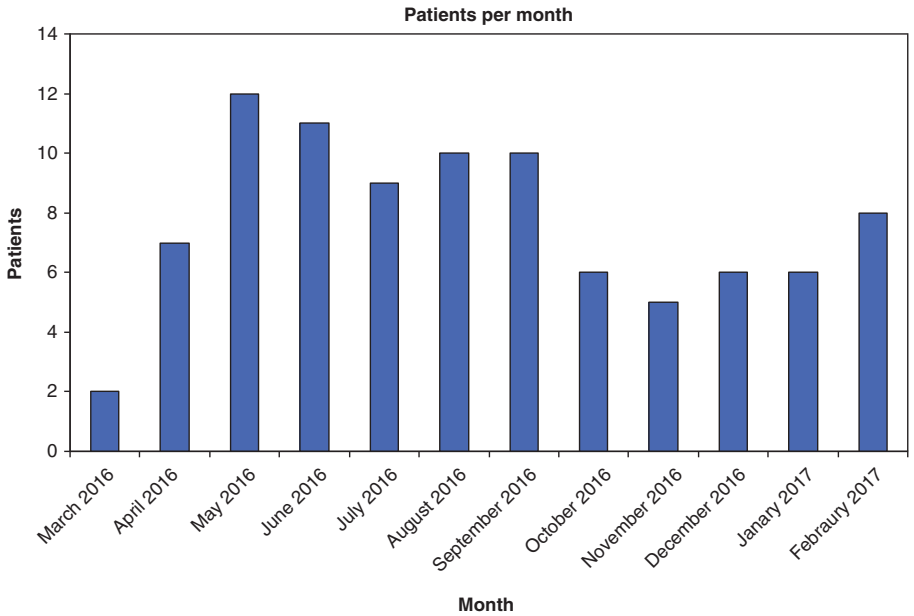

Fig. 2 Month of presentation.

Table 1 Results

Infant characteristic	Results (n = 92), n (%)
Age, weeks	
Range (median)	7–12 (9)
Gender	
Male	61 (66)
Female	31 (34)
Referral source	
Primary care referral	54 (59)
Inter-hospital transfer	1 (1)
Brought by parents	37 (40)
Time of presentation	
9 am–5 pm	14 (15)
5 pm–9 am (out of hours)	78 (85)
Received paracetamol prior to ED attendance	
Yes	86 (93)
No	6 (7)
Triage temperature, °C	
39–39.9	2 (2)
38–38.9	54 (59)
37–37.9	28 (30)
<37	8 (9)
Associated features in the history†	
Poor feeding	60 (65)
Irritability	46 (50)
Sleepiness	30 (33)
Floppy episode	2 (2)
Colour change	3 (3)
Petechial rash	2 (2)
Coryzal symptoms	6 (7)

†Patients could have more than one associated feature. ED, emergency department.

of observation before discharge. Neither of these patients required further investigation.

A total of 61 patients (66%) had at least one investigation; 35 patients (38%) had blood tests, and the values for WCC and CRP are shown in Figure 4. The median CRP was 12 mg/L, and median WCC was 16×10^9/L. Of the patients, 25 (27%) had blood cultures, all of which produced no growth; 26 patients (28%) had a viral throat swab, 12 of which were positive for at least one viral pathogen. There were three positive urine

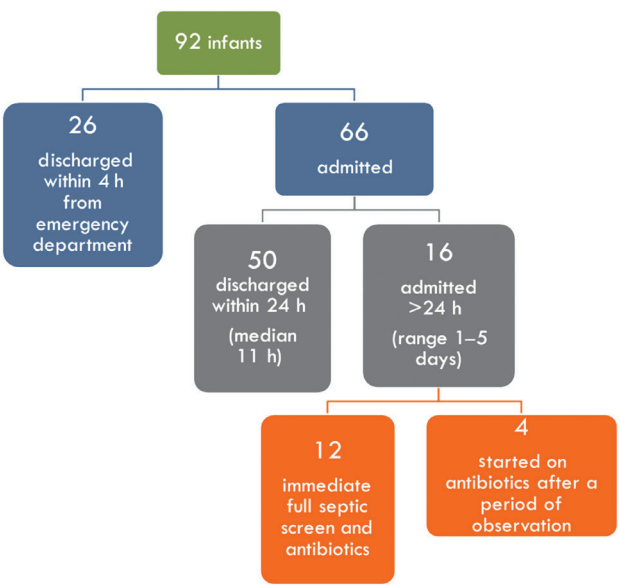

Fig. 3 Discharge destination from the emergency department.

Journal of Paediatrics and Child Health **55** (2019) 932–937

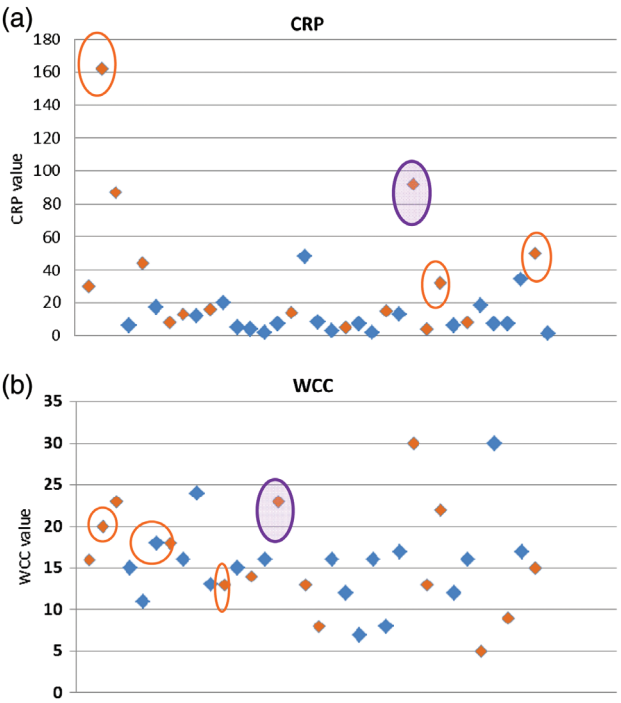

Fig. 4 Orange diamonds: Patients that had a full septic screen and were commenced on intravenous antibiotics. Circled values are those with positive micro (purple circle) and virology (orange circles) results. CRP, C-reactive protein; WCC, white cell count.

cultures, two of which were confirmed contaminants on repeat samples. The remaining sample was positive for *Escherichia coli*. This patient presented with fever starting 54 h after their immunisations, with a CRP of 87 mg/L and a WCC of 23 × 10^9/L.

Fifteen patients (16%) had a lumbar puncture and were started on IV antibiotics immediately after the procedure. The decision to commence antibiotics was not influenced by cerebrospinal fluid (CSF) cell count. Details of this particular subgroup are listed in Table 2. Of note, 100% of these patients had been assessed in primary care and referred to hospital. Associated features were more common in this subgroup. The median CRP was higher in the full septic screen cohort than for the whole group (18 vs. 12 mg/L, range 2–162 mg/L), and the median WCC was 15 × 10^9/L (range 5–30 × 10^9/L). The blood results for this subgroup are identified with orange diamonds in Figure 4. CSF microbiology and virology samples were negative for all 15 patients. Antibiotics were discontinued in all patients once the microbiology results were available, with the exception of one patient with a positive urine culture who had 5 days of IV antibiotic therapy.

Twenty patients (28%) were discharged directly from ED, of whom 70% were afebrile at triage, and none had a temperature > 38.8°C. None of these patients had blood tests prior to discharge. Patients discharged directly from ED were less likely to have documented irritability in the medical notes (36 vs. 60%). Review by, or discussion with, the senior clinician in the department was documented for every patient discharged from ED.

Table 2 Characteristics for patients undergoing full septic screen and commenced on intravenous antibiotics (*n* = 15)

Infant characteristic	*n* (%)
Age, weeks	
Range (median)	7–12 (9)
Gender	
Male	6 (40)
Female	9 (60)
Referral source	
Primary care referral	15 (100)
Inter-hospital transfer	0
Brought by parents	0
Time of presentation	
9 am–5 pm (daytime)	2 (13)
5 pm–9 am (out of hours)	13 (87)
Received paracetamol prior to ED attendance	
Yes	13 (87)
No	2 (13)
Triage temperature, °C	
39–39.9	1 (7)
38–38.9	11 (73)
37–37.9	3 (20)
<37	0
Associated features in the history†	
Poor feeding	11 (73)
Irritability	9 (60)
Sleepiness	8 (53)
Floppy episode	2 (13)
Colour change	0
Petechial rash	2 (13)
Coryzal symptoms	1 (7)
Investigations	
CRP, mg/L	
Range (median)	2–162 (18)
WCC, ×10^9/L	
Range (median)	5–30 (15)
≥1 further spike in temperature ≥38°C during admission	
Yes	12 (80)
No	3 (20)
Blood cultures	
Positive	0
Negative	15 (100)
Throat swabs	
Positive	5 (33)
Negative	10 (67)
Urine culture	
Positive	2 (7) – One contaminant
Negative	14 (93)
CSF culture and virology	
Positive	0
Negative	15 (100)

†Patients may present with more than one associated feature. CRP, C-reactive protein; CSF, cerebrospinal fluid; ED, emergency department; WCC, white cell count.

Discussion

When faced with a febrile child, doctors often refer to the National Institute for Clinical Excellence (NICE) guidelines on 'Feverish Illness in Children' for advice.[9] In infants younger than 3 months of age, the guidance suggests a low threshold for investigations and treatment. Full blood count, CRP and blood cultures are recommended in all infants under 3 months with fever, and lumbar puncture and IV antibiotics should be given if the infant appears unwell or if the WCC is less than 5×10^9/L or greater than 15×10^9/L.[9]

Leucocytosis in response to vaccination has previously been described in the literature.[10] Of the 35 patients who had a WCC measured, 20 had results out with these thresholds that would warrant further investigation and treatment as per the above NICE guidelines. In this cohort, 12 of the 20 infants with leucocytosis did not have further investigation or treatment. We suggest that WCC and CRP are poor discriminatory markers for serious infection in the post-immunisation period.

Differentiating serious bacterial infection (SBI) from minor illness in infants <3 months of age is challenging for clinicians. A large prospective cohort study of 26 EDs found SBI in 9.7% of infants <3 months of age with fever who were perceived, either by their care givers or health-care professionals, as being 'unwell'.[11] Clinical suspicion or clinical scoring systems will not reliably identify all febrile infants <3 months of age with SBI. Usual practice when assessing this patient group is to investigate and treat as recommended by national guidelines. However, the risk of SBI in previously healthy infants who present with fever, having been given a known reactogenic immunisation, is likely to be lower than in those infants presenting with fever who have not. Whilst acknowledging the clear limitation of our small patient cohort, the negative microbiology results and the lack of re-presentations to ED would lend some support to this theory.

At the time of immunisation, parents are told that fever is likely and advised on appropriate management at home.[7] The majority of patients brought to the ED had been given paracetamol at home, suggesting that this advice is well distributed and understood amongst care givers. It does not appear that lack of paracetamol administration influenced clinicians' decision to perform a septic screen and commence IV antibiotics as this subgroup had received appropriate paracetamol prior to ED attendance in 87% of cases.

Patients were more likely to be discharged home from the ED if they were afebrile on arrival. All patients with a temperature > 39°C were admitted for observation, suggesting that height of fever was a significant factor in the decision-making process for clinicians. There was a higher frequency of documented irritability in those patients admitted compared to those discharged, suggesting that this associated feature was a particular concern for clinicians. There was also a higher frequency of associated features noted in patients started on IV antibiotics compared to the group as a whole. Repeated spikes of temperature were cited in the medical notes as a reason for starting antibiotics in four infants who were initially admitted for observation alone.

In safety studies, the attendance rate of infants brought for medical review with fever or other side effects was between 1 and 3%.[3,5] The vaccine uptake rate for meningococcal B vaccine is 95.9% in Scotland.[12] Applying this uptake rate to the live birth rate in Greater Glasgow and Clyde,[13] the medical attendance rate of vaccinated infants in our cohort was 0.78%. This lower value could be explained by infants being reviewed and discharged from primary care and therefore not included in our case series.

There have been two recent studies looking at patients presenting with fever post-immunisation. A case series from Belfast over 5 months included 35 patients aged 30–180 days,[14] and a case series from Edinburgh over 9 months included 43 patients aged 42–252 days.[15] Our data over a 12-month period included 92 patients between 50 and 84 days of age.

The most striking similarity to the already published data was the medical attendance rate of 0.8%[14] compared to 0.78% in our cohort. Other similarities between our study and the earlier published data included the decision to perform lumbar puncture and start treatment in 16–17% of patients.[14,15] Our admission rate of 72%, compared to 33–51% in the other studies, may be due to differences in the definition of 'admission' between different hospitals.[14,15] In the Royal Hospital for Children, Glasgow, transfer to the CDU is recorded as a hospital admission and is the main destination for patients requiring a prolonged (>4 h) period of observation.

The most frequently performed investigation in our patient cohort was urine culture. Urinary sepsis is the most common source of SBI in infants in recent years.[16] Obtaining a clean catch urine sample is non-invasive and can be attempted whilst the patient is undergoing a period of observation. In addition to the patient with a confirmed urinary tract infection, two other patients had initial positive samples that were later confirmed to be contaminants. Medical staff should be aware of the implications of false-positive results when requesting investigations. The single confirmed-positive microbiology sample in this cohort was in a baby that presented with fever which started 54 h after their vaccinations. All other patients had a diagnosis of post-immunisation fever at the time of discharge. There were no missed cases of SBI in those patients who were discharged home. The higher median CRP in the cohort of patients receiving antibiotics may suggest that raised CRP was a contributing factor for deciding to treat. There was no difference in median WCC between the two groups.

Conclusions

Based on our findings, we suggest that routine investigations are not warranted in infants <3 months of age presenting with post-immunisation fever if they appear otherwise well on clinical examination. However, where other associated symptoms are present and/or there is clinical concern, a period of observation is a prudent course of action. We suggest selective use of investigations, especially inflammatory markers, as they are unlikely to be useful in discriminating between SBI and post-immunisation response. We advocate extra caution in infants who present with fever occurring more than 48 h after immunisation. It is reassuring that, in our patient cohort, no cases of SBI were missed in those infants who were observed or discharged.

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Sunset on the green flowers by Evie Corscadden (age 10)