Evaluation of temperature–pulse centile charts in identifying serious bacterial illness: observational cohort study

Andrew J Brent,[1,2] Monica Lakhanpaul,[1,3] Nelly Ninis,[1,2] Michael Levin,[1,2] Roddy MacFaul,[1,4] Matthew Thompson[1,5,6]

[1]Royal College of Paediatrics & Child Health (RCPCH) Working Group on Recognising Acute Illness in Children, London, UK
[2]Department of Paediatrics, Imperial College London, London, UK
[3]Division of Paediatrics, Department of Medical Education and Social Care, University of Leicester
[4]Paediatric Department, Pinderfields Hospital, Wakefield, UK
[5]Oxford University Department of Primary Health Care, Institute of Health Sciences, Oxford, UK
[6]Oregon Health & Science University, Portland, Oregon, USA

Correspondence to
Dr Andrew J Brent, KEMRI-Wellcome Trust Research Programme, PO Box 230, 80108 Kilifi, Kenya; dr.a.brent@gmail.com

Accepted 21 November 2010
Published Online First 12 January 2011

ABSTRACT

Background Distinguishing serious bacterial infection (SBI) from milder/self-limiting infections is often difficult. Interpretation of vital signs is confounded by the effect of temperature on pulse and respiratory rate. Temperature–pulse centile charts have been proposed to improve the predictive value of pulse rate in the clinical assessment of children with suspected SBI.

Objectives To assess the utility of proposed temperature–pulse centile charts in the clinical assessment of children with suspected SBI.

Study design and participants The predictive value for SBI of temperature–pulse centile categories, pulse centile categories and Advanced Paediatric Life Support (APLS) defined tachycardia were compared among 1360 children aged 3 months to 10 years presenting with suspected infection to a hospital emergency department (ED) in England; and among 325 children who presented to hospitals in the UK with meningococcal disease.

Main outcome measure SBI.

Results Among children presenting to the ED, 55 (4.0%) had SBI. Pulse centile category, but not temperature–pulse centile category, was strongly associated with risk of SBI (p=0.0005 and 0.288, respectively). APLS defined tachycardia was also strongly associated with SBI (OR 2.90 (95% CI 1.60 to 5.26), p=0.0002). Among children with meningococcal disease, higher pulse and temperature–pulse centile categories were both associated with more severe disease (p=0.004 and 0.041, respectively).

Conclusions Increased pulse rate is an important predictor of SBI, supporting National Institute for Health and Clinical Excellence recommendations that pulse rate be routinely measured in the assessment of febrile children. Temperature–pulse centile charts performed more poorly than pulse alone in this study. Further studies are required to evaluate their utility in monitoring the clinical progress of sick children over time.

What is already known on this topic

- Distinguishing serious bacterial infection (SBI) from milder/self-limiting infections is often difficult but is important to avoid serious illness and death.
- Debate exists regarding the utility of pulse rate in the assessment of children with suspected infection, since fever itself causes tachycardia.

What this study adds

- There was strong evidence for an association between increased pulse rate/tachycardia and risk of SBI.
- Temperature–pulse centile charts performed more poorly than pulse alone in identifying children with SBI in this study.
- These data support National Institute of Health and Clinical Excellence.

INTRODUCTION

Despite great progress in the prevention of childhood infections, particularly through immunisation, infection remains a leading cause of illness and death among children in industrialised as well as developing countries.[1] In the UK, a recent confidential enquiry into child deaths found that infection was the single largest natural cause of death in children.[2] Although early recognition of sepsis is associated with better treatment outcomes,[3 4] this and other reports have highlighted the difficulty often faced by clinicians in recognising serious illness in children, partly because many of the early clinical features of serious bacterial infection (SBI) also occur in milder, self-limiting febrile illnesses.[2 5 6]

The need for simple tools to help guide clinical decision-making is most acute in the settings of primary care and hospital emergency departments (EDs), where only a small proportion of the large presenting case load has a serious acute medical condition,[7] but where failure to identify these children may be life-threatening. Given limited time and diagnostic resources to perform detailed investigations on all children, assessment relies in most cases on history and clinical examination. Vital signs have an important role in indicating a child's current physiological state.[6 8] However, interpretation is often difficult in febrile children, since fever itself elevates both pulse and respiratory rates. Perhaps reflecting this, a recent study of general practitioners in the UK revealed that many doubt the utility of measuring the pulse rate in febrile children.[9]

In an attempt to control for the confounding effect of temperature on the relationship between pulse rate and serious (usually bacterial) infections, age-specific temperature–pulse centile charts derived from children with self-limiting febrile illnesses have been proposed.[10] These centile charts represent a novel and potentially very useful tool to aid clinicians working in front

line health services. In order to determine the clinical utility of these centile charts in identifying children with SBIs, we tested their performance in two separate paediatric populations presenting to hospital in the UK.

METHODS

Participants and clinical definitions

Data for analysis were derived from two studies. The first was a study of paediatric presentations to a hospital ED; the second a large national case control study of factors associated with death and survival from meningococcal disease. Data-collection methods and clinical definitions for both studies have been described in detail elsewhere (A J Brent, M Lakhanpaul, M Thompson, *et al* (published online *Arch Dis Child* 2011.183111), unpublished observations).[11]

For the ED study, data on presenting clinical symptoms and signs, laboratory indices, treatment and final diagnosis were collected prospectively on all children presenting to a large ED in Nottingham, with the exception of children requiring emergency resuscitation directly at presentation (A J Brent, M Lakhanpaul, M Thompson, *et al* (published online *Arch Dis Child* 2011.183111), unpublished observation). Each child's outcome was classified as SBI or not SBI after a detailed review of clinical and laboratory data. SBI was defined as admission to hospital plus any of the following (in the absence of an alternative non-infective or non-bacterial diagnosis to explain the clinical and laboratory findings): positive bacterial cultures from blood or another normally sterile site in the appropriate clinical context; radiological signs of pneumonia; clinical meningitis plus a cerebrospinal fluid polymorphonuclear leucocytosis; acute febrile purpura; deep collection(s) requiring intravenous antibiotics±surgical drainage; a white blood cell count ≥20×10^9/l; a C reactive protein ≥120 mg/l; or a final diagnosis of septic arthritis, osteomyelitis, empyema or mastoiditis. Children who reattended hospital within 1 week of discharge from either the ED or the ward were identified from the electronic patient register, their notes reviewed, and final diagnoses and SBI classification amended in the light of their second presentation (A J Brent, M Lakhanpaul, M Thompson, *et al* (published online *Arch Dis Child* 2011.183111), unpublished observation).

For the meningococcal study, regional notification data and data from the Office for National Statistics were used to identify incident cases of paediatric meningococcal disease between December 1997 and February 1999 (A J Brent, M Lakhanpaul, M Thompson, *et al* (published online *Arch Dis Child* 2011.183111), unpublished observation).[5] Each case was classified according to accepted definitions as possible, probable or confirmed meningococcal disease,[12] and any unconfirmed cases were excluded following expert panel review. For each fatal case, three age- and region-matched survivors were selected, and clinical data at hospital presentation were extracted retrospectively from the case notes of children. Severe meningococcal disease was defined a priori as a Glasgow Meningococcal Septicaemia Prognostic Score >8.[13 14]

For each dataset, we confined this analysis to children aged between 3 months and 10 years, since these are the age groups for which centile charts have been proposed,[10] and to those for whom a contemporaneous temperature and pulse were documented at presentation. We also confined analysis of the meningococcal dataset to children with meningococcal septicaemia, and excluded children with meningitis and signs of raised intracranial pressure to avoid possible confounding due to bradycardia caused by raised intracranial pressure. Tachycardia was defined according to UK Advanced Paediatric Life Support (APLS) guidelines as a heart rate >160 beats/min in children <1 year old; >150 beats/min in children 1–2 years old; >140 beats/min in children 3–4 years old; and >120 beats/min in children 5–12 years old.[15]

Statistical methods

For each dataset, we summarised demographic and outcome data for children included in this analysis. Temperature–pulse centile categories were defined according to the published age-specific temperature–pulse centile charts.[10] For comparison, corresponding age group-specific centile categories for pulse rate alone (irrespective of temperature) were derived among all children in the ED dataset.

To investigate the performance of the centile charts in the clinical assessment of children presenting to the ED with possible SBI, we plotted each child's admission temperature and pulse on the appropriate age-specific centile chart. We calculated the OR for SBI in each centile range, and performed a χ^2 test for trend in the proportion of children with SBI across temperature–pulse centile categories. For comparison, we also calculated the OR for SBI in each pulse centile range and performed a χ^2 test for trend across pulse centile ranges. We then calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and positive likelihood ratio (LR+) and negative likelihood ratio (LR–) of cut-offs defined by temperature–pulse centiles, pulse centiles and tachycardia alone for identifying children with SBI.

To investigate the utility of the temperature–pulse centile charts in identifying children with meningococcal septicaemia, we plotted these children's temperature and pulse, and performed χ^2 tests for trend in the proportion of children who had severe meningococcal disease (GSMP score >8) across centile categories. The sensitivity for SBI of cut-offs defined by temperature–pulse centiles, pulse centiles and tachycardia alone was calculated overall and for those with severe disease at presentation.

All analyses were performed using Stata version 10 (Stata).

Research ethics approval

Research ethics approval for the ED and meningococcal studies was granted by the Nottingham Research Ethics Committee and the South Thames Multi-Research Ethics Committee, respectively. The current analysis was also approved by the research ethics committee of the London School of Hygiene and Tropical Medicine.

RESULTS

The final ED dataset comprised 1360 children with a median age of 21 months (IQR 9–47 months), of whom 786 (57.9%) were boys, and 55 (4.0%) had SBI. Final diagnoses of children with SBI included pneumonia (41), sepsis without a clear focus (10), urinary sepsis (2) and soft-tissue infection (2). One hundred and thirty-three (9.8%) children could not be assigned a temperature–pulse category, since their temperature lay outside the range for which age-specific centiles have been defined. The proportion of children with SBI in this group (four children, 3.0%) was not significantly different from those whose temperature lay within the ranges of the centile charts (p=0.523).

Scatter graphs of temperature and pulse for children presenting to the ED with and without SBI are shown superimposed on the age-specific temperature–pulse centile charts in

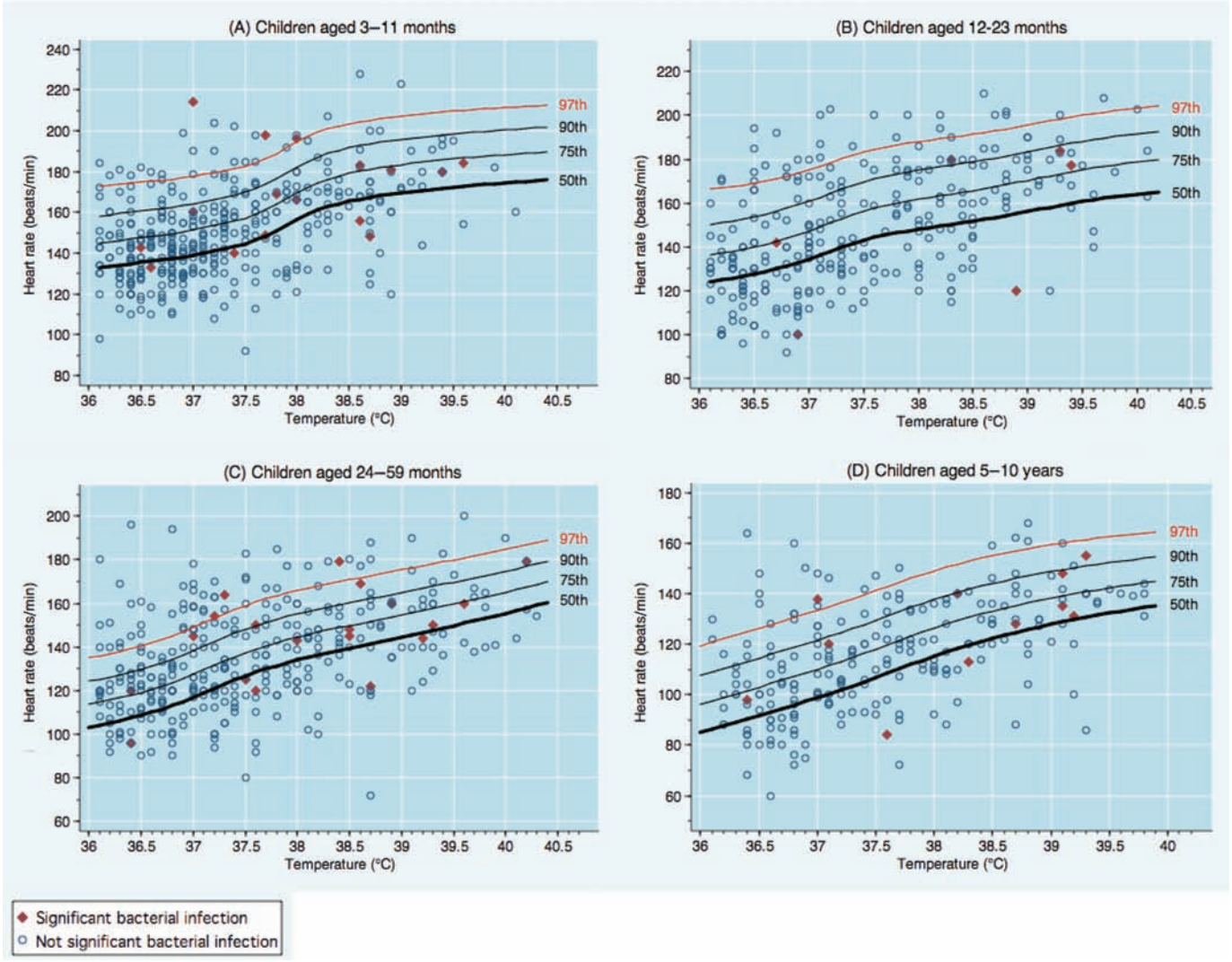

Figure 1 Temperature and pulse of children presenting to the emergency department with and without significant bacterial infection, superimposed on age-specific temperature–pulse centile charts.

Table 1 Distribution of temperature–pulse data by centile group for children presenting to the emergency department with suspected serious bacterial infection

Nomogram centile category	N	Children with serious bacterial infection (n)	OR	95% CI	p Value
Age specific temperature–pulse centiles					
>97th centile	132	7	1.84	0.72 to 4.71	0.288
>90th–97th centile	114	4	1.19	0.38 to 3.73	
>75th–90th centile	227	11	1.67	0.73 to 3.79	
>50th–75th centile	316	16	1.75	0.83 to 3.69	
≤50th centile	439	13	1.00	–	
Age specific pulse centiles					
>97th centile	28	1	1.51	0.19 to 12.0	0.0005
90th–97th centile	91	10	5.04	2.14 to 11.9	
75th–90th centile	199	12	2.62	1.19 to 5.79	
50th–75th centile	324	14	1.85	0.87 to 3.93	
<50th centile	586	14	1.00	–	
Tachycardia	514	34	2.90	1.60 to 5.26	0.0002

figure 1. The distribution of children with and without SBI and ORs for SBI by temperature–pulse centile ranges, pulse centile ranges and tachycardia are shown in table 1. There was no significant trend across temperature–pulse centile categories in the proportion of children with SBI (p=0.288); however the risk of SBI increased significantly with higher pulse centile ranges (p=0.0005; table 1). This is reflected in the poorer diagnostic performance for SBI of cut-offs defined by temperature–pulse centiles compared with pulse centiles and tachycardia (table 2). As expected, specificity increased for higher

Table 2 Sensitivity, specificity, PPVs* and NPVs† for significant bacterial infection of cut-offs defined by temperature–pulse and pulse centiles and by tachycardia

	Percentage sensitivity (95% CI)	Percentage specificity (95% CI)	Percentage PPV* (95% CI)	Percentage NPV† (95% CI)	Percentage LR+‡ (95% CI)	Percentage LR–§ (95% CI)
Age-specific temperature–pulse centiles						
Above 97th centile	13.7 (5.7 to 26.3)	89.4 (87.5 to 91.1)	5.3 (2.2 to 10.6)	96.0 (94.6 to 97.1)	1.4 (0.69 to 2.7)	0.96 (0.48 to 1.9)
Above 90th centile	21.6 (11.3 to 35.3)	80.0 (77.6 to 82.3)	4.5 (2.3 to 7.9)	95.9 (94.5 to 97.1)	1.2 (0.76 to 1.8)	0.96 (0.63 to 1.5)
Above 75th centile	43.1 (29.3 to 57.8)	61.7 (58.8 to 64.5)	4.7 (2.9 to 7.0)	96.2 (94.5 to 97.4)	1.2 (0.58 to 2.3)	0.90 (0.45 to 1.8)
Above 50th centile	74.5 (60.4 to 85.7)	36.2 (33.4 to 39.0)	4.8 (3.4 to 6.6)	97.0 (95.0 to 98.4)	1.1 (0.50 to 2.6)	0.75 (0.33 to 1.7)
Age-specific pulse centiles						
Above 97th centile	2.0 (0.04 to 10.4)	97.7 (96.7 to 98.5)	3.6 (0.1 to 18.3)	95.8 (94.5 to 96.9)	2.7 (2.2 to 3.4)	0.96 (0.76 to 1.2)
Above 90th centile	21.6 (11.3 to 35.3)	90.8 (89.0 to 92.4)	9.2 (4.7 to 15.9)	96.4 (95.1 to 97.4)	2.4 (1.6 to 3.7)	0.86 (0.57 to 1.3)
Above 75th centile	45.1 (31.1 to 59.7)	75.7 (73.1 to 78.1)	7.2 (4.6 to 10.7)	96.9 (95.6 to 97.9)	1.7 (0.84 to 3.3)	0.78 (0.40 to 1.5)
Above 50th centile	72.5 (58.3 to 84.1)	48.6 (45.7 to 51.5)	5.8 (4.1 to 7.9)	97.6 (96.0 to 98.7)	1.3 (0.58 to 3.1)	0.64 (0.28 to 1.5)
Tachycardia	66.7 (52.1 to 79.2)	59.2 (56.3 to 62.0)	6.6 (4.6 to 9.1)	97.6 (96.2 to 98.6)	1.5 (0.67 to 3.4)	0.65 (0.29 to 1.46)

*PPV, positive predictive value (predictive value of a positive test).
†NPV, negative predictive value (predictive value of a negative test).
‡LR+, likelihood ratio of a positive test.
§LR–, likelihood ratio of a negative test.

temperature–pulse and pulse centiles, but at the expense of very poor sensitivity. There was strong evidence of an association between tachycardia and SBI (OR 2.90 (95% CI 1.60 to 5.26), p=0.0002).

In the meningococcal dataset, admission temperature and pulse data were available for 325 children with a median age of 23 months (IQR 9–50 months), of whom 86 (31.3%) had severe disease on admission. The admission temperature of 19 (5.8%) children lay outside the range for which age-specific centiles have been defined; there was no difference in the proportion with severe disease between these children and those whose temperature lay within the centile chart ranges (p=0.115). Scatter graphs of admission temperature and pulse for children with and without severe disease are shown superimposed on temperature–pulse centile charts in figure 2. Higher temperature–pulse centile categories and higher pulse centile categories were both associated with a higher proportion of children with severe disease (p=0.041 and p=0.004, respectively). The sensitivity of cut-offs defined by temperature–pulse centiles, pulse centiles and tachycardia alone are shown in table 3.

DISCUSSION

Distinguishing children with serious infections from those with milder, self-limiting febrile illnesses remains a daily challenge in primary care and hospital EDs, where clinicians rely on a limited number of clinical symptoms and signs to risk-stratify children for further observation, investigation and/or referral.[6] Measurement of vital signs is recommended as part of this assessment, but evidence for the predictive value of individual or combinations of vital signs in these settings is limited.[6] Centile charts such as those published by Thompson *et al*[10] might make an important contribution to the assessment of febrile children if they could be shown to improve the predictive value of heart rate as one component of this assessment.

The performance of the temperature–pulse centile charts in this study was disappointing. There was no strong evidence of an association between temperature–pulse centile category and risk of SBI, reflected in the poor sensitivity, specificity, PPVs, NPVs, LR+ and LR– of individual centile cut-offs. Importantly, although imperfect, the corresponding age group-specific centile ranges for pulse alone was more strongly associated with SBI, and the simpler APLS definition of tachycardia was a better predictor of SBI. This is perhaps not surprising, since bacterial infection causes fever, which in turn increases the pulse rate, so that increased temperature positively confounds (is at least part of the explanation for) the observed association between increased pulse rate and SBI. One would therefore expect any adjustment for the effect of temperature (eg, using the temperature–pulse centiles) to reduce the strength of this association.

Owing to the relatively small proportion of children with SBI in the ED dataset we also examined the performance of the centile charts in identifying children with meningococcal septicaemia in a large, independent dataset. The sensitivity for meningococcal septicaemia of cut-offs defined by each temperature–pulse centile was nevertheless disappointing. Since meningococcal disease represents a broad clinical spectrum, and children may present at different stages of their illness, we further explored the value of the centile charts in identifying those children with severe disease at presentation. However, the sensitivity of temperature–pulse centile cut-offs for identifying this group remained poor, and in both groups tachycardia alone was a more sensitive predictor of meningococcal septicaemia.

The strengths of the ED dataset include the large number of children for whom detailed clinical and laboratory data were collected prospectively, and the non-selective nature of the group of children included, which suggests our findings might be generalisable to other paediatric ED settings. One potential limitation is the lack of a clear, gold-standard definition of severe bacterial illness. Definitions confined to microbiologically confirmed invasive bacterial disease (such as a positive blood culture) are highly specific but lack sensitivity, since a microbiological diagnosis is achieved in only a minority of cases.[16–18] Adopting such a definition would not only reduce the power of any analysis of potential clinical predictors, but also limit the generalisability of the findings, since clinical features of children with microbiologically confirmed bacterial disease may differ from those in whom microbiological confirmation is not possible. We therefore adopted a pragmatic but nevertheless rigorous definition of SBI that sought to capture the full range of children requiring admission and/or treatment for proven or presumed severe bacterial infections.

The main limitation of the meningococcal dataset is the inclusion of only children with meningococcal disease, so we were unable to assess the specificity, NPV or PPV of centile cut-offs in indentifying children presenting with meningococcal

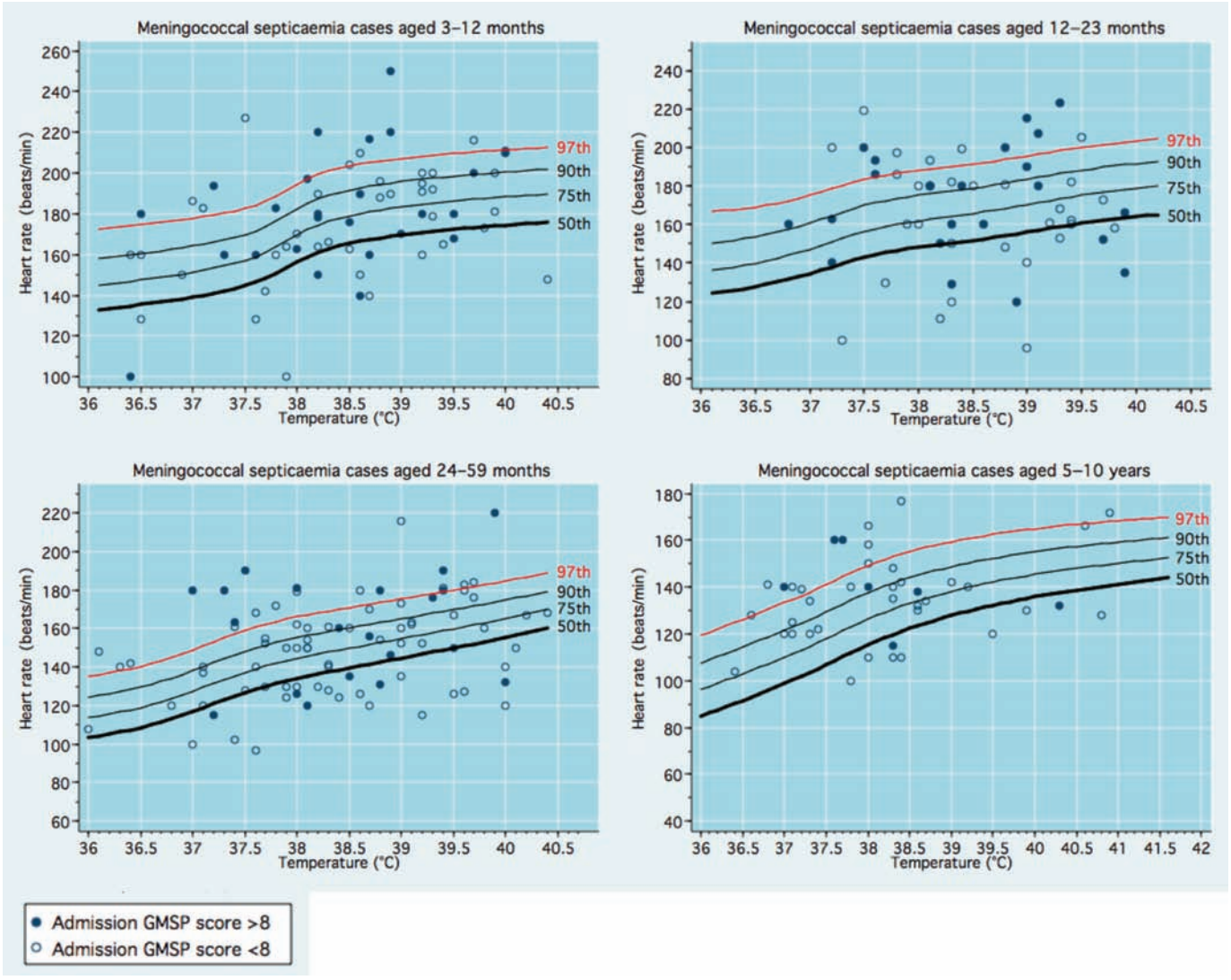

Figure 2 Admission temperature and pulse of children with meningococcal septicaemia, superimposed on proposed age-specific temperature–pulse centile charts. GMSP, Glasgow Meningococcal Septicaemia Prognostic score.

Table 3 Sensitivity of cut-offs defined by temperature–pulse centiles, pulse centile and tachycardia for detecting children with meningococcal septicaemia of various degrees of severity

	Percentage sensitivity of centile ranges for identifying all children with meningococcal septicaemia and those with severe disease (95% CI)	
	All children with meningococcal septicaemia	Children with severe disease on admission
Age-specific temperature–pulse centiles		
Above 97th centile	23.6 (18.5 to 29.3)	33.3 (22.9 to 45.2)
Above 90th centile	37.8 (31.8 to 44.1)	50.7 (38.9 to 62.4)
Above 75th centile	55.5 (49.2 to 61.7)	62.7 (50.7 to 73.6)
Above 50th centile	70.1 (64.0 to 75.6)	74.7 (63.3 to 84.0)
Below 50th centile	29.9 (24.4 to 36.0)	25.3 (16.0 to 36.7)
Age-specific pulse centiles		
Above 97th centile	11.0 (7.7 to 15.1)	17.9 (10.2 to 28.3)
Above 90th centile	27.8 (22.8 to 33.2)	38.5 (27.7 to 50.2)
Above 75th centile	49.2 (43.4 to 55.0)	61.5 (49.8 to 72.3)
Above 50th centile	73.9 (68.5 to 78.8)	84.6 (74.7 to 91.8)
Below 50th centile	26.1 (21.2 to 31.5)	15.4 (8.2 to 25.3)
Tachycardia	68.9 (63.3 to 74.1)	78.2 (67.4 to 86.8)

disease. The case–control design of the original meningococcal study also results in over-representation of fatal cases.[11] Given the observed association between higher pulse rate and severe disease, this is likely to have resulted in a slight overestimate of the sensitivity for SBI of all three methods of pulse assessment (temperature–pulse centiles, pulse centiles and APLS definition of tachycardia).

Measurement error is also possible in both datasets, since temperature and pulse rate were measured in the routine clinical setting. This is likely to be minimal in the ED dataset, since temperature and pulse rate were measured using an electronic tympanic thermometer and pulse oximeter. However, methods of vital sign measurement are not documented for children in the meningococcal dataset (who presented to many different hospitals), and there was no standardised mechanism for calibration of the instruments in either study. Nevertheless, this pragmatism may be a strength of our study, increasing its generalisability to other routine clinical settings.

Although the findings of this study do not appear to support a role for the temperature–pulse centile charts in identifying children with SBI at presentation, it is important to assess their utility in a variety of clinical settings. A recent study in a paediatric ED did show an association between

higher temperature–pulse centiles and serious infection.[19] The higher PPV of a pulse above the 90th temperature–pulse centile observed in this study (23%) may reflect a broader definition of serious infection. No comparison was made with pulse centiles alone. To date, no study has assessed the performance of the centile charts in a primary care setting where the prevalence of serious infection is lower.

Importantly, despite the disappointing performance of the temperature–pulse centile charts, these data do confirm a significant association between pulse rate alone and SBI among children presenting to the ED, supporting recommendations from the UK National Institute for Health and Clinical Excellence that vital signs including the pulse rate be measured in the assessment of all febrile children.[6] Formal demonstration of a direct clinical benefit arising from routine measurement of the pulse is challenging, owing to multiple potential biases and confounders, perhaps explaining why data addressing this question are scarce.[6] Nevertheless, given these methodological challenges, and pending evidence to the contrary, we believe that pulse rate should remain a routine part of the assessment of a febrile child, since it is quick and easy to elicit, helps to provide a more complete picture of the child's physiological state and facilitates monitoring of their clinical course. Clinical guidelines stress the importance of reviewing a child's clinical progression, particularly if symptoms do not resolve,[2 6 8] and changes in a child's physiological state may be at least as informative as their condition at a single time point.[8] The role of the temperature–pulse centile charts may be in controlling for the confounding effects of temperature on pulse in assessing the clinical progression of an individual child, rather than at a single presentation. This hypothesis requires further investigation in longitudinal studies.

Acknowledgements The study was carried out on behalf of the Royal College of Paediatrics & Child Health (RCPCH) working group on Recognising Acute Illness in Children (RAIC). MT is a member of University of Oxford Department of Primary Health Care that is part of the NIHR National School of Primary Care Research. ML is member of the Leicester Collaboration for Leadership in Applied Health Research and Care (CLARCH) team and Director of the Health Education Research and Development Unit (HERADU). The authors would like to thank S Ray, J Collier and T Stephenson for their contributions to the initial data collection and analysis; and staff and patients at the Nottingham Queens Medical Centre emergency department for their help and participation in the study.

Funding AJB is supported by a Wellcome Trust research training fellowship (081697). The authors wish to thank the Meningitis Research Foundation for their support for the meningococcal study, and the Well Child Medical Charity for their funding of the studies in Nottingham and for this study. Funding for the University of Oxford Department of Primary Health Care work on vital signs is provided by the NIHR programme grant 'Development and implementation of new diagnostic processes and technologies in primary care.'

Competing interests None.

Ethics approval Ethics approval was provided by the emergency department and meningococcal studies—granted by the Nottingham Research Ethics Committee and the South Thames Multi-Research Ethics Committee, respectively. The current analysis was also approved by the ethics committee of the London School of Hygiene and Tropical Medicine.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Bryce J,** Boschi-Pinto C, Shibuya K, *et al.* WHO estimates of the causes of death in children. *Lancet* 2005;**365**:1147–52.
2. **Pearson GA.** *Why Children Die: A Pilot Study 2006, England (South West, North East and West Midlands), Wales and Northern Ireland*. London: Confidential Enquiry into Maternal and Child Health 2008.
3. **Dellinger RP,** Levy MM, Carlet JM, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;**36**:296–327.
4. **Kumar A,** Roberts D, Wood KE, *et al.* Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;**34**:1589–96.
5. **Thompson MJ,** Ninis N, Perera R, *et al.* Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006;**367**:397–403.
6. NICE. *Feverish Illness in Children: Assessment and Initial Management in Children Younger Than 5 Years*. London: National Institute of Clinical Excellence, 2007.
7. **MacFaul R.** *The Health of Children and Young People: Provision and Use of Services*. Newport: Office for National Statistics, 2004.
8. **Duncan H,** Hutchison J, Parshuram CS. The Pediatric Early Warning System score: a severity of illness score to predict urgent medical need in hospitalized children. *J Crit Care* 2006;**21**:271–8.
9. **Thompson M,** Mayon-White R, Harnden A, *et al.* Using vital signs to assess children with acute infections: a survey of current practice. *Br J Gen Pract* 2008;**58**:236–41.
10. **Thompson M,** Harnden A, Perera R, *et al.* Deriving temperature and age appropriate heart rate centiles for children with acute infections. *Arch Dis Child* 2009;**94**:361–5.
11. **Ninis N,** Phillips C, Bailey L, *et al.* The role of healthcare delivery in the outcome of meningococcal disease in children: case–control study of fatal and non-fatal cases. *BMJ* 2005;**330**:1475.
12. **Ramsay M,** Kaczmarski E, Rush M, *et al.* Changing patterns of case ascertainment and trends in meningococcal disease in England and Wales. *Commun Dis Rep CDR Rev* 1997;**7**:R49–54.
13. **Sinclair JF,** Skeoch CH, Hallworth D. Prognosis of meningococcal septicaemia. *Lancet* 1987;**2**:38.
14. **Thomson AP,** Sills JA, Hart CA. Validation of the Glasgow Meningococcal Septicemia Prognostic Score: a 10-year retrospective survey. *Crit Care Med* 1991;**19**:26–30.
15. Advanced Life Support Group. *Advanced Paediatric Life Support: The Practical Approach*. 4th edn. Wiley-Blackwell, Oxford, UK. 2004.
16. **Cutts FT,** Zaman SM, Enwere G, *et al.* Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005;**365**:1139–46.
17. **Luck S,** Torny M, d'Agapeyeff K, *et al.* Estimated early-onset group B streptococcal neonatal disease. *Lancet* 2003;**361**:1953–4.
18. **Sáez-Llorens X,** Vargas S, Guerra F, *et al.* Application of new sepsis definitions to evaluate outcome of pediatric patients with severe systemic infections. *Pediatr Infect Dis J* 1995;**14**:557–61.
19. **Thompson M,** Coad N, Harnden A, *et al.* How well do vital signs identify children with serious infections in paediatric emergency care? *Arch Dis Child* 2009;**94**:888–93.