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Validating clinical practice guidelines for the management of children with non-blanching rashes in the UK (PiC): a prospective, multicentre cohort study

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Summary

Background No previous studies have validated current clinical practice guidelines for the management of non-blanching rashes in children who have received meningococcal B and C vaccinations. The aim of this study was to evaluate the performance of existing clinical practice guidelines in the diagnosis of invasive meningococcal disease in children presenting with a fever and non-blanching rash in the UK.

Methods The Petechiae in Children (PiC) study was a prospective, multicentre cohort study involving children (aged <18 years) presenting to 37 paediatric emergency departments in the UK with a fever (≥38°C) and a new-onset non-blanching rash or features suggestive of meningococcal infection. Children with pre-existing haematological conditions (ie, haematological malignancy, idiopathic thrombocytopenic purpura, or coagulopathy) or an existing diagnosis of Henoch-Schonlein purpura were excluded. Invasive meningococcal disease was confirmed by positive culture or a quantitative PCR test for *Neisseria meningitidis* from either blood or cerebrospinal fluid samples. The primary outcome was the performance of six tailored clinical practice guidelines from participating centres (London, Nottingham, Newcastle–Birmingham–Liverpool, Glasgow, Chester, and Bristol) and two clinical practice guidelines from the National Institutes for Health and Care Excellence (NICE; CG102 and NG51) in identifying children with invasive meningococcal disease, assessed by the sensitivity and specificity of each clinical practice guideline. This study is registered with ClinicalTrials.gov, NCT03378258.

Findings Between Nov 9, 2017, and June 30, 2019, 1513 patients were screened, of whom 1329 were eligible and were included in the analysis. The median age of patients was 24 months (IQR 12–48). 1137 (86%) of 1329 patients had a blood test and 596 (45%) received parenteral antibiotics. 19 (1%) patients had confirmed meningococcal disease. All eight clinical practice guidelines had a sensitivity of 1·00 (95% CI 0·82–1·00) for identifying meningococcal disease. The specificities of NICE guidelines CG102 (0·01 [95% CI 0·01–0·02]) and NG51 (0·00 [0·00–0·00]) for identifying meningococcal disease were significantly lower than that of tailored clinical practice guidelines (p<0·0001). The best performing clinical practice guidelines for identifying meningococcal disease were the London (specificity 0·36 [0·34–0·39]) and Nottingham (0·34 [0·32–0·37]) clinical practice guidelines.

Interpretation Invasive meningococcal disease is a rare cause of non-blanching rashes in children presenting to the emergency department in the UK. Current NICE guidelines perform poorly when compared with tailored clinical practice guidelines. These findings suggest that UK national guidance could be improved by shifting towards a tailored approach.

Funding Public Health Agency.

Introduction

Despite the successful implementation of vaccination programmes, meningococcal disease remains one of the leading infectious causes of childhood sepsis and death in the UK.[1–4] Early diagnosis of sepsis can reduce morbidity and mortality,[1,2] but can be challenging when clinical assessments and currently available tests are relied on.[1,4] Meningococcal disease has several phenotypic presentations; the most typically described sign is non-blanching rash with a fever.[1–4] However these clinical features are common in children who present to hospital emergency departments, and most of these children actually have a self-limiting viral illness.[5–11] Differentiating children with these signs who have meningococcal disease from those with a benign cause is difficult.[1,2] The resultant diagnostic dilemma for clinicians predisposes to a cautious approach, with many children undergoing painful procedures and receiving unnecessary broad-spectrum parenteral antibiotics. Despite taking this early cautious approach, meningococcal disease could still be missed, and children might be discharged from hospital with adverse sequelae.[11] Current clinical practice guidelines are

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Research in context

Evidence before this study

It has been reported that between 10% and 20% of children with a fever and non-blanching rash will have an underlying meningococcal infection. Because of this high reported risk of meningococcal disease, many clinical practice guidelines advocate a cautious approach to the investigation and treatment of any child with a history of fever and a non-blanching rash. This approach leads to many children undergoing painful procedures and receiving parenteral antibiotics unnecessarily. Unfortunately, the studies on which these guidelines are based were poorly conducted (ie, they involved single centres, convenience sampling, and retrospective data collection), were done before the introduction of meningococcal vaccinations, and included small populations of inpatient children. Most clinical practice guidelines currently in use in the UK have never been validated, and none have been validated in a vaccinated population.

We searched PubMed on Oct 23, 2020, using the search terms "meningococcal", "rash", "meningitis", "sepsis", "petechiae", and "purpura". We searched for primary research and reviews published in English between Jan 1, 1980, and Oct 23, 2020. We found one study that aimed to validate UK clinical practice guidelines for meningococcal infection that used retrospective data collected from 1998 to 2001. Most children in the study had not received the meningococcal C vaccine, which became available in the UK in 1999.

Added value of this study

To our knowledge, this study is the largest study of meningococcal disease in children with fever and non-blanching rash done to date and the first to involve a vaccinated population; most children in this study had received the meningococcal B and meningococcal C vaccinations. The results showed that, at present, meningococcal disease is a rare cause of fever and non-blanching rash in the UK, accounting for just 19 (1%) of 1329 such presentations in our study. We found that a tailored approach was superior to National Institute for Health and Care Excellence (NICE) guidelines CG102 and NG51, as there were no missed cases of meningococcal disease, fewer investigations, fewer parenteral antibiotics used, and the financial cost per patient was lower.

Implications of all the available evidence

This study supports a change from current NICE guidance to a more tailored approach in the UK. Changing to a tailored approach, such as the London clinical practice guideline, would have resulted in 332 fewer children requiring blood tests, 475 fewer children requiring parenteral antibiotics, and a cost saving of £170 per patient when compared with NICE NG51 guidelines.

based on evidence that predates the introduction of meningococcal B and C vaccines. The quality of this supporting evidence is also largely limited because of the single-centre or retrospective design of previous studies, and the use of convenience sampling with small patient numbers.[7–11] These previous studies reported meningococcal disease as the causal illness in 10–20% of children with a fever and non-blanching rash.[7–11] This high reported prevalence of meningococcal disease has led to the use of reasonable but aggressive investigation and treatment strategies, as recommended by some clinical practice guidelines. Since 1999, vaccination programmes have reduced the prevalence of meningococcal disease in many countries, including the UK,[12,13] thus potentially affecting the performance of current clinical practice guidelines and creating a need for a well powered validation study.

The Petechiae in Children (PiC) study aimed to prospectively assess the management of children presenting to paediatric emergency departments in the UK with a fever and non-blanching rash.[14] The study protocol was designed to observe current practice, validate existing clinical practice guidelines, and report the accuracy of a range of diagnostic tests. The primary aim of this validation study was to evaluate the performance accuracy of current UK clinical practice guidelines for the diagnosis of meningococcal disease in febrile children with a non-blanching rash.

See Online for appendix

Methods

Study design and participants

The PiC study was a prospective, multicentre cohort study involving children (aged <18 years) who presented to 37 paediatric emergency departments in the UK (appendix p 2) with a fever (≥38°C) and a new-onset non-blanching rash or features suggestive of meningococcal infection.[15] Participating centres were distributed across the UK, with one centre in Northern Ireland, three centres in Scotland, and 33 centres in England, and included a range of tertiary paediatric specialist hospitals and district general hospitals. Children with pre-existing haematological conditions (ie, haematological malignancy, idiopathic thrombocytopenic purpura, or coagulopathy) or an existing diagnosis of Henoch-Schönlein purpura were excluded.

The PiC study protocol has been published previously and adheres to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement for prediction model validation (appendix p 25).[13]

Due to the potentially life-threatening nature of invasive meningococcal disease, we used research without prior consent (ie, deferred consent), which is described in full in the study protocol.[13,14,16,17] Patients were enrolled to ensure contemporaneous data collection and their guardians or next of kin were thereafter invited to provide written informed consent at the

earliest appropriate opportunity (typically within 24 h of presentation to the emergency department), once the clinical condition had stabilised. The PiC study had patient involvement from the onset, including parents of children with a history of either meningococcal infection or a non-blanching rash in the study design, oversight, authorship, and promotion.

The Northern Ireland Research Ethics Committee (17/NI/0169) and the Belfast Health and Social Care Trust Research Governance (16201MS-SW) approved the PiC protocol, including the embedded qualitative research.

Procedures

Study data were collected and managed by use of Research Electronic Data Capture tools.[18] Children were screened for eligibility and for clinical risk factors for meningococcal disease by clinical staff at the first medical assessment, and study data were recorded prospectively by use of an electronic case report form (case report form 1; appendix pp 9, 10). These data about the appearance of the patient were recorded contemporaneously by clinical staff before discussions about consent and before laboratory test results were available. All patients in the PiC study received clinical care without delay as per local guidance. The second case report form (appendix pp 11, 12) was completed 7 days after the patient was discharged from hospital, and recorded laboratory results, length of stay, and other aspects of care not susceptible to recall bias.

Potential clinical risk factors for meningococcal disease were identified by reviewing clinical practice guidelines from all participating sites. The following eight clinical practice guidelines were submitted before study commencement: Barts and London Health National Health Service (NHS) Trust (London guideline); Countess of Chester Hospital (Chester guideline); National Institute for Health and Care Excellence (NICE) meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102); NICE sepsis: recognition, diagnosis and early management (NG51); Newcastle–Birmingham–Liverpool (Newcastle–Birmingham–Liverpool guideline); Nottingham Children's Hospital (Nottingham guideline); Royal Hospital for Children Glasgow (Glasgow guideline); and the Bristol Royal Hospital for Children (Bristol guideline). The clinical practice guidelines are available in the appendix (pp 3–8). The risk factors identified included background information (age and vaccination status), a description of the rash and its progression, the duration of illness, an unwell appearance (ie, from an overall assessment of their appearence), the presence of signs of shock (ie, clinician-diagnosed shock, a long capillary refill time of 4 s or more, or hypotension), and meningism (ie, a positive Brudzinski's and Kernig's sign, a bulging fontanelle, irritability, photophobia, neck stiffness, and headache), gastrointestinal symptoms (ie, abdominal pain, abdominal distension, diarrhoea, and nausea or vomiting), other symptoms (ie, reduced consciousness, respiratory symptoms, or limb pain), and blood results (ie, full blood count, and concentrations of C-reactive protein and coagulation factors).

The reference standard for the identification of meningococcal disease or other invasive bacterial infection, against which the performance of existing clinical practice guidelines were assessed, was defined as a positive culture or PCR test for *Neisseria meningitidis* or other bacterial pathogen from a sterile body site (eg, blood or cerebral spinal fluid). These tests were done at accredited NHS hospital laboratories (appendix p 2) by technicians who were masked to the clinical information of patients. Hospital records were checked for the re-attendance of any patients who did not undergo culture or PCR testing, and these children were assumed not to have meningococcal disease provided the following criteria were met: (1) they were not subsequently diagnosed with meningococcal disease within 7 days of hospital discharge; and (2) the Public Health Agency had no record of the participant having been diagnosed with meningococcal disease.

At the end of the study, participating sites identified all patients who had had confirmed meningococcal disease from positive culture or PCR tests by checking notifications to the Public Health Agency. Meningococcal disease is a notifiable disease in the UK, thus providing a reliable method for such an identification strategy. This list was cross-referenced with the list of enrolled patients, and the reasons why any patients who had a positive meningococcal disease test result were not enrolled to the study were recorded. Research teams were also required to check for any unplanned hospital re-attendances within 7 days of hospital discharge, as a further method to identify any patients with meningococcal disease who might have been initially discharged from hospital without treatment.

Before statistical analyses were done, three authors (TW, LM, and HM) checked the database for completeness of data using SPSS version 23. Any enrolled patients with incomplete data were excluded from the analysis. Two authors (TW and MDS) applied the eight clinical practice guidelines to the data set. As standard of care was followed, not all patients had a blood test. For these patients, single imputation with data assumed to within the normal range (ie, C-reactive protein <6 mg/L; white blood cell counts of between 5×10^9 and 15×10^9 cells per L; and neutrophil counts of $<10\times10^9$ cells per L) was done. We chose this approach because none of the patients who did not have a blood test received parenteral antibiotics, nor were subsequently diagnosed with meningococcal disease. The group of patients who did not have a blood test were those at the lowest risk of meningococcal disease. To minimise potential bias from this approach, the analysis was repeated by use of two additional techniques. First, with missing data (C-reactive protein and white blood cell count) imputed via multiple imputations with chained equations to

create five imputed datasets, and second, by excluding patients with incomplete test data (C-reactive protein and white blood cell count) excluded.

Outcomes

The primary outcome measure was the performance accuracy of the eight clinical practice guidelines in identifying children with invasive meningococcal disease. Secondary outcome measures included the performance accuracy of clinical practice guidelines in identifying children with other invasive bacterial infections, and a cost comparison of the different clinical practice guidelines.

Statistical analysis

The demographic characteristics, vaccination status, risk factors, parenteral antibiotic use, admission to hospital, admission to intensive care units, and survival of the PiC study population are presented as descriptive statistics. The performance of the eight clinical practice guidelines was compared by calculating the sensitivity, specificity, negative predictive values, and positive predictive values (with 95% CIs). The McNemar's test was used to assess differences in sensitivity and specificity between the eight clinical practice guidelines. We used a stepwise approach to assess clinical risk factors. Initially, all possible predictors were assessed by univariate analysis with χ^2 testing of categorical data and with the Mann-Whitney *U* test for continuous data (continuous data were skewed). Age-dependent predictors, such as heart rate, respiratory rate, and blood pressure were converted to categorical data and classified as within or outside published normal ranges.[18] All predictors showing a significant association with meningococcal disease (ie, with a p value of <0·20) were included in a binary multivariate logistic regression model. A liberal level of significance (p<0·20) was chosen to avoid falsely excluding a significant variable on the basis of univariate analysis alone. The predictors identified from the univariate analysis were then included in logistic regression modelling. Empirical binary multivariate forward and backward logistic regression modelling was used to identify a best-fit model to distinguish children at the highest risk of meningococcal disease.

A decision analytic model was constructed to compare the costs of following each of the eight clinical practice guidelines and individual clinican decision making (appendix pp 13–15). The cost comparison analysis was done by use of a case-mix group approach from the perspective of the NHS and included costs associated with hospital resource use for the diagnosis and inpatient care of study participants. Clinical pathways based on patient data identified and recorded 7 days after hospital discharge were detailed for three groups of patients: (1) those assessed in the emergency department and discharged from hospital; (2) those assessed in the emergency department and admitted to hospital; and (3) and those assessed in the emergency department and admitted to hospital for the treatment of meningococcal disease. Resource use for each group was assessed and costed in UK sterling (£) according to unit costs from the National Schedule of Reference Costs 2017–18 of NHS Trusts and Primary Care Trusts combined.[19] Average costs to the NHS per patient were estimated. A Monte-Carlo simulation method with bootstrapping was used to replicate the sample with 10 000 iterations to estimate 95% CIs around the mean cost per patient.

We did statistical analyses using SPSS version 23, and R version 3.6.1.

This study is registered with ClinicalTrials.gov, NCT03378258.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 9, 2017, and June 30, 2019, 1513 consecutive children who presented to paediatric emergency departments were screened, of whom 179 were excluded (figure). The remaining 1334 children were enrolled to the study, and 1329 were included in the analysis (figure). Five (<1%) of these children were excluded because of missing data in the case report forms (figure). Patient recruitment by site is noted in the appendix (p 2). The median age of patients was 24 months (IQR 12–48), and 781 (59%) of 1329 patients were male. Most patients were up to date with age-appropriate vaccinations, with 938 (73%) of 1289 participants having received at least one dose of meningococcal B vaccine and 987 (77%) of 1289 having received at least one dose of meningococcal C vaccine (table 1). 1137 (86%) of 1329 patients had a blood test and 596 (45%) received parenteral antibiotics. The median length of stay of patients admitted to hospital was one night (IQR 0–2). 11 (1%) of 1329 patients were admitted to paediatric intensive care units (PICU) and two (<1%) died. There were 19 (1%) confirmed cases of meningococcal disease in the study population (17 had *N meningitidis* serogroup B, one had serogroup C, and one had serogroup W), and a further two children with confirmed meningococcal disease were not enrolled; one child was missed, and the other child was not enrolled because local staff felt that inclusion would have been inappropriate. *N meningitidis* was the invasive pathogen identified in eight (73%) of 11 patients admitted to the PICU, and in the two (<1%) patients who died. A further seven (1%) of 1329 patients had an invasive bacterial infection, including five pneumococcal infections, one *Escherichia coli* infection, and one group A streptococcal infection. In total, 26 (2%) of 1329 patients had an invasive bacterial infection (including meningococcal disease); a breakdown of these

infections is provided in the appendix (p 23).

There were 45 (5%) of 983 patients who had blood culture results with suspected contamination (appendix p 24). None of these patients were admitted to the PICU or required inotrope treatment, and all survived to hospital discharge. 346 (26%) of 1329 patients did not undergo reference standard testing. Two (1%) of these patients received parenteral antibiotics; one was subsequently diagnosed with a haematological malignancy, and the other patient was given a single dose of ceftriaxone in the emergency department before they were discharged from hospital with a diagnosis of viral illness. In this cohort, 19 (5%) of the 346 patients had a single unplanned hospital re-attendance within 7 days of being discharged, although none were subsequently admitted to hospital, given parenteral antibiotics, or diagnosed with meningococcal disease or invasive bacterial infection.

Univariate analysis of individual clinical features is shown in table 1. Clinical predictors that were deemed significant (p<0·20) were included in the multivariate analysis. Following multivariate analysis, four independent risk factors for meningococcal disease were identified: purpuric rash (p=0·0010), shock (p<0·0001), reduced consciousness (p<0·0001), and limb pain (p=0·0030).

All eight clinical practice guidelines correctly identified all 19 cases of meningococcal disease, with identical sensitivities of 1·00 (95% CI 0·82–1·00; table 2). In addition, all eight guidelines correctly identified all 26 cases of invasive bacterial infection, with identical sensitivities of 1·00 (0·87–1·00; table 3). The specificities varied more widely, with the NICE NG51 guideline showing the lowest specificity (0·00 [0·00–0·00]) for the identification of meningococcal disease and invasive bacterial infection compared with the other clinical practice guidelines. The NICE CG102 guideline showed the second lowest specificity (0·01 [0·01–0·02]) for the identification of meningococcal disease and invasive bacterial infection. The remaining six guidelines showed significantly higher specificities (p<0·0001). Of all clinical practice guidelines analysed, those with the highest specificities were the London guideline (0·36 [0·34–0·39]) for the identification of meningococcal disease and invasive bacterial infection, and the Nottingham guideline for the identification of meningococcal disease (0·34 [0·32–0·37]) and invasive bacterial infection (0·35 [0·32–0·37]). The observed differences in specificity between the London and the Nottingham guidelines were not significant (p=1·00). Validation of clinical practice guidelines by use of multiple imputation or exclusion of incomplete datasets had a negligible effect on the results (appendix pp 16–19). Irrespective of the approach to imputation, all clinical practice guidelines correctly identified all meningococcal disease and invasive bacterial infections in this cohort of patients, with the London and Nottingham guidelines consistently showing the highest specificities and the NICE NG51 and CG102 guidelines consistently showing the lowest specificities (p<0·0001).

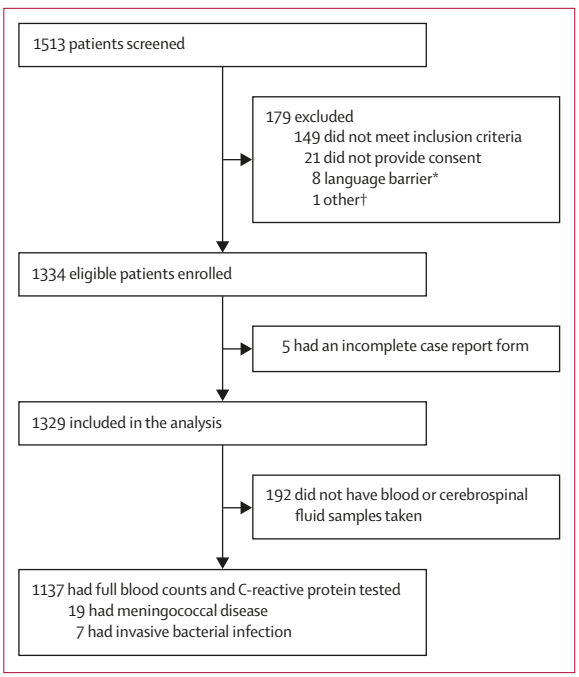

Figure: **Study profile**
*The family did not speak English, and a suitable translator was not available at the time. †Parental responsibility could not be ascertained.

The most widely used clinical practice guideline was the NICE CG102 guideline (29 [78%] of 37 sites) followed by the Newcastle–Birmingham–Liverpool guideline (two [5%] sites). Clinicians adhered to their departmental guidance (ie, local or national guidelines) for 607 (46%) of 1329 patients. This degree of adherence was similar if they followed the NICE NG51 and CG102 guidelines (437 [46%] of 944 patients) or one of the six tailored guidelines (170 [44%] of 385 patients). Deviation from clinical practice guidelines resulted in fewer patients receiving parenteral antibiotics (596 [45%] of 1329 patients) compared with when any of the eight clinical practice guidelines were followed exactly. These deviations from the clinical practice guidelines also resulted in two (<1%) of 1329 patients being incorrectly discharged from the hospital with early meningococcal disease, both of whom subsequently re-attended the emergency department and were admitted to hospital. These patients survived and were not admitted to the PICU.

Individual clinician decision making showed a significantly greater specificity (0·56 [95% CI 0·53–0·59]) for the diagnosis of meningococcal disease or invasive bacterial infection than any of the eight clinical practice guidelines (p<0·0001; tables 2, 3). However, clinician practice was less sensitive for the detection of meningococcal disease (0·89 [0·67–0·98]) and invasive bacterial infection (0·92 [0·75–0·99]) compared with all

	Patients without meningococcal disease (n=1310)	Patients with meningococcal disease (n=19)	p value
Age in month (median and IQR)*	24 (12–48)	37 (9–58)	0·090
Sex	..	..	
Male	765 (58%)	16 (84%)	0·18
Female	545 (42%)	3 (16%)	0·0034
Vaccines up to date for age	1220/1271 (96%)	19 (100%)	0·38
Received the meningococcal B vaccine	926/1268 (73%)	12 (63%)	0·40
Received the meningococcal C vaccine	973/1268 (77%)	14 (74%)	0·85
Duration of illness (<24 h)	430/1303 (33%)	10 (53%)	0·076
Duration of rash (<4 h)	753/1214 (62%)	12 (63%)	0·90
Highest temperature, °C	39·0 (38·4–39·6)	39·0 (38·4–39·6)	0·87
Petechiae	1245 (95%)	6 (32%)	<0·0001
Purpura	65 (5%)	13 (68%)	<0·0001
Superior vena cava distribution of rash	482 (37%)	6 (32%)	0·64
Spreading rash	308 (24%)	12 (63%)	<0·0001
Unwell appearance	362 (28%)	16 (84%)	<0·0001
Signs of shock	67 (5%)	13 (68%)	<0·0001
Tachycardia	592/1315 (45%)	15 (79%)	0·0030
Tachypnoea	431/1294 (33%)	12 (63%)	0·0060
Gastrointestinal symptoms	557 (43%)	8 (42%)	0·97
Shivers or chills	106 (8%)	6 (32%)	<0·0001
Pallor	95 (7%)	8 (42%)	<0·0001
Unusual skin colour	108 (8%)	9 (47%)	<0·0001
Cold hands or feet	129 (10%)	9 (47%)	<0·0001
Respiratory symptoms	400 (31%)	8 (42%)	0·28
Sore throat or coryza	673 (51%)	5 (26%)	0·030
Lethargy	307 (23%)	13 (68%)	<0·0001
Refusal of food and drink	403 (31%)	8 (42%)	0·29
Limb pain	66 (5%)	6 (32%)	<0·0001
Signs or symptoms of meningism	273 (21%)	7 (37%)	0·089
Reduced consciousness	13 (1%)	10 (53%)	<0·0001
Received antibiotics before hospital admission	69 (5%)	6 (32%)	<0·0001

Data are median (IQR), n (%), or n/N (%).

Table 1: **Univariate analysis of individual clinical features**

eight guidelines (tables 2, 3).

Of all clinical practice guidelines, the two guidelines with the highest average costs to the NHS per patient were the NICE NG51 (£660 per patient [bootstrapped 95% CI 620–706]) and NICE CG102 (£655 per patient [615–701]; table 2). The clinician practice approach had the lowest cost per patient (£426 [382–475]), followed by the London guideline (£490 [448–538]), and then the Nottingham guideline (£499 [457–546]; table 2).

Discussion

To our knowledge, this is the largest study of meningococcal infection in febrile children with non-blanching rashes done to date. We enrolled patients from a range of hospital types and geographic regions over two winters to provide a true reflection of the epidemiology of the disease, clinician practices, and performance accuracy of clinical practice guidelines in the UK. The proportion of patients who had an invasive bacterial infection was low, although most of these infections were due to invasive meningococcal disease, typically *N meningitidis* serogroup B. Invasive meningococcal disease accounted for the most severe outcomes, including in most patients who were admitted to the PICU, and in both children who died. All eight clinical practice guidelines currently in use correctly identified all cases of meningococcal disease and invasive bacterial infection, although specificity varied widely across the different guidelines, with NICE guidelines performing significantly less favourably than the tailored guidelines. We identified the optimally performing current guidelines that provide a reasonable compromise between sensitivity and specificity in assisting clinician decision making.

The PiC study showed that the risk of meningococcal disease among febrile children presenting to the emergency department with non-blanching rashes in the UK is much lower than previously reported. Previous estimates suggested that between 10% and 20% of children with a fever and non-blanching rash have underlying meningococcal disease.[7,9,11] However, the data informing these findings were mostly collected from inpatient populations before the introduction of the meningococcal C vaccine (in 1999) and the meningococcal B vaccine (in 2015) to the UK vaccination schedule.[7,9,11–13] Successful vaccination programmes in the UK have led to a reduction in the number of cases of meningococcal disease, with the recent meningococcal B vaccination programme accounting for a 75% reduction in meningococcal B infections in vaccinated children.[12] This observation was reflected in the PiC study, with 73% of patients having received the meningococcal B vaccine and 77% having received the meningococcal C vaccine, and only 1% had meningococcal disease.

The eight clinical practice guidelines included in the PiC study can be broadly divided into three distinct strategies. The first and most cautious strategy is that all children with fever and non-blanching rash undergo investigation and treatment for meningococcal disease, and are immediately administered parenteral antibiotics (ie, as recommended by the NICE NG51 guideline). The second strategy involves blood testing in all children with a fever and non-blanching rash, and tailoring treatment on the basis of a combination of clinical features and blood test results (ie, as recommended by the NICE CG120 guideline). The final and least cautious strategy involves tailored investigation and treatment of children, in which some are identified as suitable for hospital discharge without blood testing or parenteral antibiotics (ie, as recommended by the London, Nottingham, Newcastle–Birmingham–Liverpool, Chester, Glasgow, and Bristol guidelines). Our analysis showed that the

	Number of children requiring blood tests (n=1329)	Positive for meningococcal disease (n=19)		Negative for meningococcal disease (n=1310)		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Mean cost per patient (bootstrapped 95% CI)
		Treat	Do not treat	Treat	Do not treat					
Clinician practice	1137 (86%)	17 (89%)	2 (11%)	579 (44%)	731 (56%)	0·89 (0·67–0·99)	0·56 (0·53–0·59)	0·03 (0·02–0·05)	1·00 (0·99–1·00)	£425·95 (382·06–474·65)
London	997 (75%)	19	0	835 (64%)	475 (36%)	1·00 (0·82–1·00)	0·36 (0·34–0·39)	0·02 (0·01–0·03)	1·00 (0·99–1·00)	£490·29 (447·60–537·98)
Nottingham	1030 (78%)	19	0	859 (66%)	451 (34%)	1·00 (0·82–1·00)	0·34 (0·32–0·37)	0·02 (0·01–0·03)	1·00 (0·99–1·00)	£498·88 (456·56–546·21)
Newcastle–Birmingham–Liverpool	1019 (77%)	19	0	893 (68%)	417 (32%)	1·00 (0·82–1·00)	0·32 (0·29–0·34)	0·02 (0·01–0·03)	1·00 (0·99–1·00)	£511·06 (468·38–558·76)
Glasgow	1030 (78%)	19	0	897 (68%)	413 (32%)	1·00 (0·82–1·00)	0·32 (0·29–0·34)	0·02 (0·01–0·03)	1·00 (0·99–1·00)	£512·49 (469·79–558·76)
Chester	1087 (82%)	19	0	965 (74%)	345 (26%)	1·00 (0·82–1·00)	0·26 (0·24–0·29)	0·02 (0·01–0·03)	1·00 (0·99–1·00)	£536·85 (494·17–582·76)
Bristol	1169 (88%)	19	0	1092 (83%)	218 (17%)	1·00 (0·82–1·00)	0·17 (0·15–0·19)	0·02 (0·01–0·03)	1·00 (0·98–1·00)	£582·33 (540·01–629·00)
NICE CG102	1329 (100%)	19	0	1295 (99%)	15 (1%)	1·00 (0·82–1·00)	0·01 (0·01–0·02)	0·01 (0·01–0·02)	1·00 (0·78–1·00)	£655·04 (614·87–700·60)
NICE NG51	1329 (100%)	19	0	1310 (100%)	0	1·00 (0·82–1·00)	0 (0·00–0·00)	0·01 (0·01–0·02)	NA	£660·41 (620·24–705·61)

CG102=National Institute for Health and Care Excellence meningitis (bacterial) and meningococcal septicaemia in under 16s. NICE NG51=National Institute for Health and Care Excellence sepsis: recognition, diagnosis and early management. NA=not applicable.

Table 2: **Diagnostic performance of clinical practice guidelines at identifying meningococcal disease and the estimated costs per patient (single imputation)**

	Positive for invasive bacterial infection (n=26)*		Negative for invasive bacterial infection (n=1303)		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)
	Treat	Do not treat	Treat	Do not treat				
Clinician practice	24 (92%)	2 (8%)	572 (44%)	731 (56%)	0·92 (0·75–0·99)	0·56 (0·53–0·59)	0·04 (0·03–0·06)	1·00 (0·99–1·00)
London	26 (100%)	0	828 (64%)	475 (36%)	1·00 (0·87–1·00)	0·36 (0·34–0·39)	0·03 (0·02–0·04)	1·00 (0·99–1·00)
Nottingham	26 (100%)	0	852 (65%)	451 (35%)	1·00 (0·87–1·00)	0·35 (0·32–0·37)	0·03 (0·02–0·04)	1·00 (0·99–1·00)
Newcastle–Birmingham–Liverpool	26 (100%)	0	886 (68%)	417 (32%)	1·00 (0·87–1·00)	0·32 (0·29–0·35)	0·03 (0·02–0·04)	1·00 (0·99–1·00)
Glasgow	26 (100%)	0	890 (68%)	413 (32%)	1·00 (0·87–1·00)	0·32 (0·29–0·34)	0·03 (0·02–0·04)	1·00 (0·99–1·00)
Chester	26 (100%)	0	958 (74%)	345 (26%)	1·00 (0·87–1·00)	0·26 (0·24–0·29)	0·03 (0·02–0·04)	1·00 (0·99–1·00)
Bristol	26 (100%)	0	1085 (83%)	218 (17%)	1·00 (0·87–1·00)	0·17 (0·15–0·19)	0·02 (0·02–0·03)	1·00 (0·98–1·00)
NICE CG102	26 (100%)	0	1288 (99%)	15 (1%)	1·00 (0·87–1·00)	0·01 (0·01–0·02)	0·02 (0·01–0·03)	1·00 (0·78–1·00)
NICE NG51	26 (100%)	0	1303 (100%)	0	1·00 (0·87–1·00)	0 (0·00–0·00)	0·02 (0·01–0·03)	NA

NICE CG102=National Institute for Health and Care Excellence meningitis (bacterial) and meningococcal septicaemia in under 16s. NICE NG51=National Institute for Health and Care Excellence sepsis: recognition, diagnosis and early management. NA=not applicable. *Includes meningococcal disease.

Table 3: **Diagnostic performance of clinical practice guidelines at identifying all invasive bacterial infection (single imputation)**

tailored strategy had the best overall performance in terms of sensitivity and specificity. The best performing clinical practice guidelines in the PiC study were the London and Nottingham guidelines, with very similar specificities for the identification of invasive bacterial infection and overall performance. The London and Nottingham clinical practice guidelines had significantly higher specificities than either of the NICE clinical practice guidelines.

Although the tailored strategy, advocated by six of the clinical practice guidelines, performed more favourably than the two other strategies recommended by NICE, the specificities of the tailored guidelines varied significantly. The poorer performing guidelines (eg, the Chester and Bristol guidelines) listed the greatest number of concerning features indicating that treatment was required, whereas the best performing guidelines (the London and Nottingham guidelines) listed the lowest number of concerning features. It appears that a greater number of concerning features is associated with a lower specificity of the guidance. All of the tailored guidelines included the presence of purpura and signs of shock as concerning features. None of these guidelines included limb pain or reduced consciousness as concerning, and

the results of our study suggest that they should be considered as high-risk clinical features. All of the tailored clinical practice guidelines allowed for children with a healthy appearance and a mechanical cause for a petechial rash (ie, not a purpuric rash) to be discharged from hospital.

Based on our findings, individual hospital departments should now consider their own practices. Applying NICE clinical practice guidelines (CG102 and NG51) is likely to be safe; however, this approach involves the greatest use of parenteral antibiotics, the greatest number of painful procedures, and the highest mean cost per patient (between £655 and £660) compared with a tailored approach. A tailored approach, as exemplified by the London and Nottingham guidelines, appears to be safe, with reduced parenteral antibiotic use, a reduced number of invasive procedures, and a lower mean cost per patient (between £490 and £499) compared with the approach recommended by the NICE guidelines. Finally, departments could allow for individual clinician decision making. This approach would further reduce parenteral antibiotic use, but would not alter the number of phlebotomy tests done, and carries an increased risk of missing early meningococcal disease compared with all other approaches. In 2017–18, failures or delays in the diagnosis of meningococcal disease cost the NHS an average of £227 667 per case of litigation.[20] Individual clinician decision making could lead to higher mean costs per patient than either NICE or tailored clinical practice guidelines because of the increased risk of missing early meningococcal disease and subsequent litigation costs.

The PiC study has several strengths. The study provides the best available evidence for estimating the risk of meningococcal disease in children who present to the emergency department with a fever and non-blanching rash. The PiC study also accurately reports the performance of a range of current clinical practice guidelines. The main limitation to the PiC study was that there were only few cases of meningococcal disease in the study population. As such, the 95% CIs for the sensitivity of each clinical practice guideline were wide. The findings from PiC should therefore be interpreted with extreme caution in regions where the prevalence of meningococcal disease is significantly higher than it is in the UK, and where vaccines are not offered or uptake is low. An additional limitation is that, even with a robust study design and prospective data collection, some children with a fever and non-blanching rash were not included in the study. It is therefore possible that the reported proportion of children with meningococcal disease in this cohort is an over-estimation.

Because of successful vaccination programmes, invasive meningococcal disease is now a rare cause of fever and non-blanching rashes in children who present to the emergency department. Current UK NICE guidelines performed poorly when compared with local, tailored clinical practice guidelines, with NICE guidance recommending a greater number of invasive procedures and greater use of parenteral antibiotics, and resulting in a greater financial cost per patient, without any demonstrable benefit to patients.

Contributors

TW, MDL, DR, J-AM, DF, JPM, and MDS conceived and designed the study. TW coordinated the running of the study, including data management and on-site training. MC and BP were involved with the conduct of the study including data collection. TW provided study design expertise and designed the approach to consent. FL provided health economics expertise and supervised the cost assessment. LM and HM provided statistical expertise and statistically analysed the data. All authors contributed to the writing of the manuscript.

Declaration of interests

DF is non-executive director, advisory board member, and shareholder in HiberGene Diagnostics (Sandyford, Dublin, Ireland). JPM has a patent named, Detection of *Neisseria Meningitidis* by Loop Mediated Isothermal Amplification Assay, licensed to HiberGene Diagnostics, and share options in HiberGene Diagnostics Ireland. All other authors declare no competing interests.

Data sharing

All of the individual patient data collected during this study (including data dictionaries) will be available on the Queen's University Belfast data repository. The full study protocol is available as an open access publication.

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