NICE National Institute for
Health and Care Excellence

Feverish illness in children

Evidence Update February 2015

A summary of selected new evidence relevant to NICE
clinical guideline 160 'Feverish illness in children: assessment and
initial management in children younger than 5 years' (2013)

Evidence Update 73

Contents

Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

[1] **Feverish illness in children.** NICE clinical guideline 160 (2013)

A search was conducted for new evidence from 1 October 2012 to 21 August 2014. A total of 1192 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 23 references underwent a rapid critical appraisal process and then were reviewed by an Evidence Update Advisory Group, which advised on the final list of 7 items selected for the Evidence Update. See Appendix A for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 160 (NICE CG160). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal. See the NICE clinical guidelines development methods guides for further information about updating clinical guidelines.

NICE Pathways

NICE pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathway covers advice and recommendations related to this Evidence Update:

- Feverish illness in children. NICE Pathway

Quality standards

- Feverish illness in children under 5 years. NICE quality standard 64

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk

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[1] NICE-accredited guidance

Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on NICE CG160. Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from NICE CG160.

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

Key point	Potential impact on guidance	
	Yes	**No**
Assessment of risk of serious illness • The NICE traffic light system appears to have high sensitivity for detecting serious bacterial infection. The sensitivity is further improved when urinalysis is performed as recommended in the guideline. The traffic light system appears to have moderate specificity for detecting serious bacterial infection.		✓
Diagnostic value of laboratory tests • No laboratory test alone appears to be able to reliably rule-in or rule-out serious bacterial infections. Evidence about the usefulness of procalcitonin testing is inconsistent.		✓
Causes and incidence of serious bacterial infection • Vaccination programmes have resulted in reductions in the incidence of serious bacterial infections in England, and the overall incidence of invasive bacterial infections in children seems to be low. However, children under 1 year, and those with comorbidities, appear to be at higher risk of invasive bacterial infections.		✓

1   Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from NICE CG160.

1.1   Thermometers and the detection of fever

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.2   Clinical assessment of children with fever

Assessment of risk of serious illness

NICE CG160 recommends assessing children with feverish illness for the presence or absence of symptoms and signs that can be used to predict the risk of serious illness using the traffic light system. The traffic light system consists of signs and symptoms of serious illness, categorised as: 'green' for low risk of serious illness; 'amber' for intermediate risk of serious illness; and 'red' for high risk of serious illness. The traffic light system should be used in conjunction with the recommendations on investigations and initial management in children with fever. The traffic light system was introduced in a previous version of this guideline in 2007, and was revised when the guideline was updated in 2013.

De et al. (2013) assessed the accuracy of the 2007 version of the NICE traffic light system, with and without urinalysis, for detection of serious bacterial infection. Data collected prospectively for the Febrile Evaluation of Children in the Emergency Room (FEVER) study during 2004–6 were used for the analysis. The FEVER study included 19,889 emergency department visits by feverish children aged under 5 years at an Australian paediatric hospital.

At presentation, children were triaged, and then the examining physician used a mandatory electronic reporting system to record clinical information, including 40 signs and symptoms, and relevant background medical information for each child at each episode of illness. Tests were ordered at the discretion of the treating clinician, and urine analysis was done according to local protocol. All eligible children were followed up until they met the case definition of serious bacterial infection or resolution of fever for more than 24 hours.

Items from the NICE traffic light system were retrospectively matched to records from the FEVER trial. Each episode of fever was categorised as low, intermediate or high probability of serious bacterial infection, based on whether clinical features matched the 'green', 'amber' or 'red' sections of the traffic light system respectively. Of the 43 items in the 2007 NICE traffic light system, 13 had an exact match in the reporting system used in the FEVER study and 19 were captured by similar wording. The 11 items that had no data captured in FEVER were thought not to affect the detection of urinary tract infection, bacteraemia or pneumonia. The probability of serious bacterial infection according to the traffic light system was then compared with the final diagnosis determined by standard tests and follow-up.

The outcomes of interest were urinary tract infection, pneumonia and bacteraemia, because other serious bacterial infections occurred in too few children for robust assessment of the traffic light system. However, an additional category of 'any serious bacterial infection' included all infections. Multiple infections in one child were included separately for all relevant outcomes. If children had multiple presentations with the same illness, only data from the first episode were used. Children were designated as having the same illness if they presented within 24 hours of a previous visit or if fever persisted between visits without a fever-free period of at least 24 hours.

Overall, 15,781 febrile illnesses were assessed, which included 1120 episodes of serious bacterial infection involving 1166 infections. The serious bacterial infections diagnosed were urinary tract infection (n=543), pneumonia (n=533), bacteraemia (n=64), osteomyelitis (n=12), meningitis (n=8), and septic arthritis (n=6).This study included more girls (56%) than boys (44%).

'Red' features, or those indicating a high probability of serious bacterial infection, had sensitivity of 47.9% and specificity of 75.9% for detection of any serious bacterial infection. For 'red' and 'amber' features combined, the sensitivity was 85.8% and specificity was 28.5%. 'Green' features only were seen in 40 of 533 (7.5%) cases of pneumonia, 108 of 543 (19.9%) cases of urinary tract infection and 9 of 64 (14.1%) cases of bacteraemia. These serious infections would have been missed if children were assessed solely using the traffic light system.

Overall, urine analysis was done in 23.1% of all episodes of fever and in 44% of episodes of serious bacterial infection, giving a sample of 507 infections: 362 urinary tract infections, 118 cases of pneumonia, and 27 cases of bacteraemia. When urine analysis was added to the traffic light system, the sensitivity of this combined assessment was 92.1% and specificity was 22.3%. However, the authors acknowledged that urine testing is recommended for all children in NICE CG160, but is not part of the traffic light system.

A potential limitation of this study is that data seemed to be reported only at admission to hospital. No details were reported about whether children who had 'green' features and were diagnosed with serious bacterial infection developed 'amber' or 'red' features after admission. Moreover, urinalysis was performed only on a minority of the children enrolled in the study, which is not in line with the recommendations in NICE CG160.

A retrospective case–control study by **Verbakel et al. (2014)** assessed the diagnostic value of clinical prediction rules for identifying sepsis and meningitis. Data for 9678 children aged up to 16 years presenting to a UK emergency department between 2000 and 2005 were used for this study. The admitting paediatrician had conducted a structured clinical assessment of vital signs, overall assessment of the appearance of the child, responsiveness, and clinical assessment using a modified version of YOS. Most children had additional tests according to a standardised protocol including: full blood count; C-reactive protein; blood and urine culture; lumbar puncture; and chest X-ray.

All children with a discharge diagnosis of meningitis, bacteraemia or sepsis and with positive culture of pathogenic bacteria from blood or cerebrospinal fluid (CSF) were included in this analysis (n=50). The control group was a random sample of half of the children whose final diagnosis was of self-limiting or mild infection, with negative blood or CSF cultures (n=807). More boys than girls were included in both the case (54% boys) and control (56% boys) groups.

The analysis covered 6 clinical prediction rules: a modified Yale Observation Scale (YOS); Pediatric Advanced Warning Score (PAWS); Alert, Voice, Pain, Unresponsive (AVPU) scale; Recognising Acute Illness in Children (RAIC) score; Oxford Vital Signs score; and the 2007 version of NICE CG160 traffic light system.

The modified YOS had sensitivity of 98% and specificity of 2.4% at a cut-off of 8, and had sensitivity of 54.0% and specificity of 63.7% at a cut-off of 10. PAWS had sensitivity of 58.0% and specificity of 81.3% if any 'red' sign was present. The APVU scale had sensitivity of 17.8% and specificity of 100% if the child responds to pain stimulus. The RAIC score had sensitivity of 4% and specificity of 100% for ruling in serious bacterial infection at a score of 8 or more, and had sensitivity of 76.0% and specificity of 6.2% for ruling out serious bacterial infection at a score of 5 or less. The Oxford Vital Signs score had a sensitivity of 80.0% and specificity of 49.3% if any sign was present. The 2007 NICE traffic light system had sensitivity

of 100% and specificity on 0.12% if any 'amber' or 'red' sign was present, and had sensitivity of 62% and specificity of 74.5% if any 'red' sign was present. However, the data available for validation covered only 9 of the 17 'amber' features and 11 of the 18 'red' features of the NICE traffic light system.

Limitations of this study include possible selection bias and bias in the mix of patients (spectrum bias) due to its case–control design. Data seemed to be reported only at presentation. No details were reported about whether children who had 'green' features and were diagnosed with serious bacterial infection developed 'amber' or 'red' features after admission. The sample included children up to age 15 years, whereas the NICE traffic light system was designed for children under 5 years. Similarly, other prediction rules tested were designed for specific age groups.

Verbakel et al. (2013) retrospectively assessed the diagnostic accuracy of 4 clinical prediction rules and 2 national evidence-based guidelines using individual patient data (n=11,023) from the UK, Belgium and the Netherlands. Individual patient data were obtained from 7 studies identified in a previously published systematic review (Van den Bruel et al. 2010) on the diagnostic value of assessing clinical features at presentation in children with suspected serious infection.

The current analysis included studies published from 2003 that enrolled at least 500 children aged between 1 month and 18 years attending ambulatory care departments in developed countries. Ambulatory care was defined as: general or family practice; paediatric outpatient clinics; paediatric assessment units; or emergency departments. Children were included in the analysis if they had fever, acute illness, acute infection, or signs of meningitis. Children with congenital or acquired immunodeficiency were excluded. Serious infection was defined as: sepsis including bacteraemia; meningitis; osteomyelitis; pneumonia; cellulitis; or complicated urinary tract infection. Care settings were stratified by prevalence as having low (0–5%), intermediate (5–20%) or high (>20%) rates of serious infections.

The clinical prediction rules assessed were: the 5-stage decision tree (validated in 5 datasets), a pneumonia rule (5 datasets), a meningitis rule (3 datasets) and the YOS (3 datasets). Also assessed were the 2007 version of NICE CG160 (4 datasets) and national guidelines from the Dutch college of General Practitioners (5 datasets). Data used to create an assessed clinical prediction rule were not used to validate the same rule. For clinical features that were not identical across studies, similar terms were used as proxies. A minimum number of clinical features needed to be recorded in each study, depending on the rule or guideline being validated. Missing data were not imputed.

Clinical prediction rules had variable sensitivity and specificity across data sets and depending on the prevalence of infection in the setting studied. For example, in settings with low prevalence, the meningitis rule had a sensitivity of 100% in 1 study (n=700) but only 33% in another study (n=3981). This variability was also evident in the results for the 2007 version of NICE CG160. In 1 study in a low prevalence setting (n=506), the sensitivity was 100% and specificity was 1%. In 1 study in an intermediate prevalence setting (n=2777), the sensitivity was 97.3% and specificity was 26.7%. Of 2 studies in high prevalence settings, in 1 study (n=700) sensitivity was 87.1% and specificity was 28.7% and the other study (n=593) sensitivity was 98.5% and specificity was 2.1%. The Dutch guideline had broadly similar sensitivity and specificity to NICE CG160.

The authors noted that all prediction rules had lower performance than in their original derivation studies, which might have been caused by the proxy terms used to cover variables measured and recorded in differing ways in different languages. Meta-analysis of pooled validation results was not done because of heterogeneity between datasets in setting, inclusion criteria, immunisation schedules, and definition of serious infection.

Limitations of all 3 studies included that they were retrospective analyses of data not collected for the purpose of validating clinical decision rules or national guidelines. The clinical features recorded did not always fully match the decision rule assessed, and 2 of the studies used the NICE traffic light system as a stand-alone tool. Furthermore, NICE CG160 covers all potential causes of serious illness in children with fever, including herpes simplex encephalitis and Kawasaki disease, whereas these studies covered serious bacterial infections only.

These studies suggest that the 2007 NICE traffic light system appears to have high sensitivity for detecting serious bacterial infection, especially when urinalysis is done. The specificity of the traffic light system is reported as being variable. The specificity appears to be moderate for detecting serious bacterial infection. However, the specificity seems to be lower in settings with a low incidence of serious illness. The NICE traffic light system is intended to be used in conjunction with appropriate investigations and treatments; it is not a stand-alone tool for clinical decision-making. These results are unlikely to impact NICE CG160 because the guideline aims to detect all cases of serious illness with fever rather than bacterial infections only. Additionally, all 3 studies used the 2007 version of NICE CG160 traffic light system rather than the current 2013 version, so these findings may not be reflective of current guidance. For instance, the updated version of the traffic light table includes symptoms and signs, such as tachycardia, that have recently been found to be significant predictors of serious illness.

Key references
De S, Williams GJ, Hayen A et al. (2013) Accuracy of the "traffic light" clinical decision rule for serious bacterial infections in young children with fever: a retrospective cohort study. BMJ 346: f866

Verbakel JY, MacFaul R, Aertgeerts B et al. (2014) Sepsis and meningitis in hospitalised children: performance of clinical signs and their prediction rules in a case-control study. Pediatric Emergency Care 30: 373–80

Verbakel JY, Van den Bruel A, Thompson M et al. (2013) How well do clinical prediction rules perform in identifying serious infections in acutely ill children across an international network of ambulatory care datasets. BMC Medicine 11: 10

Supporting references
Van den Bruel A, Haj-Hassan T, Thompson M et al. (2010) Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. Lancet 375: 834–45

1.3 Management by remote assessment

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.4 Management by the non-paediatric practitioner

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.5 Management by the paediatric specialist

Diagnostic value of laboratory tests

Investigations in children younger than 3 months
NICE CG160 recommends performing the following investigations in infants younger than 3 months with fever:

- full blood count
- blood culture
- C-reactive protein
- urine testing for urinary tract infection

- chest X-ray, only if respiratory signs are present
- stool culture, if diarrhoea is present.

Lumbar puncture is recommended in: infants younger than 1 month; infants aged 1–3 months with fever who appear unwell; and infants aged 1–3 months with a white blood cell count (WBC) less than 5×10^9/litre or greater than 15×10^9/litre.

Gomez et al. (2012) conducted a retrospective assessment of the diagnostic value of serum procalcitonin for detecting invasive bacterial infections in 'well-appearing' infants younger than 3 months with fever without apparent source.

Anonymised data were obtained from 5 Spanish and 2 Italian paediatric emergency departments that had similar protocols for management of infants with fever without apparent source. Infants had urine dipstick, C-reactive protein, WBC and procalcitonin testing, and blood and urine cultures. For each emergency department, records were assessed from December 2010 backwards for a maximum of 3 years, depending on when procalcitonin testing was added to the local protocol. Additionally, data were included only as full years to avoid potential bias from seasonal variations in infections. Therefore, 1 hospital provided data for 3 years, 3 provided data for 2 years, and 3 contributed data for 1 year.

Fever without apparent cause was defined as a temperature of 38°C or more with no respiratory signs or symptoms or diarrhoea. 'Well appearing' was defined as a 'normal' paediatric assessment triangle or, if this coding was not used, descriptions from the record such as 'poor general appearance', 'irritable' or 'cyanosis' were used to exclude infants from the analysis. Infants were excluded from analysis if at admission: origin of infection was determined; they did not appear well; fever was not confirmed and fever had been suspected at home but no thermometer was used; or they did not have procalcitonin testing or blood culture. Invasive bacterial infection was defined as positive blood, or CSF, urine or stool culture. Serious bacterial infections included all invasive bacterial infections plus urinary tract infections.

Over the study period, 533,133 children were admitted to the paediatric emergency departments, including 1112 infants aged less than 3 months with fever without apparent source who met all inclusion criteria. This sample included more boys (60%) than girls (40%). Serious bacterial infection was confirmed in 289 infants (26%), 23 of whom had an invasive bacterial infection (2%). The invasive bacterial infections were: 12 cases of urinary tract infection with bacteraemia, 10 cases of occult bacteraemia, and 1 case of bacterial meningitis.

The cut-offs used to assess the diagnostic utility of risk factors for invasive bacterial infections were: 0.5 ng/ml for procalcitonin; 20 mg/l for C-reactive protein; 15,000 cells per mm³ (15×10^9/litre) for WBC, and 10,000 cells per mm³ for absolute neutrophil count. In multivariate analysis, procalcitonin of 0.5 ng/ml or higher was the only test independently associated with a diagnosis of invasive bacterial infection (odds ratio=21.69, 95% CI 7.93 to 59.28).

Limitations included that the retrospective nature of the study may have limited the number of cases identified for inclusion in the analysis. Additionally, clinical practice did not completely adhere to protocols, resulting in exclusion of infants who did not have a blood culture taken or procalcitonin measurement despite otherwise meeting inclusion criteria. The Spanish hospitals tested for urinary tract infection mainly by bladder catheterisation, whereas the Italian hospitals used urine collection bags but needed 2 positive consecutive urine samples for a diagnosis of urinary tract infection. However, the prevalence of urinary tract infection was higher in the Italian hospitals (30.6%) compared with the Spanish hospitals (22.5%, p=0.03). This disparity could have led to an overestimate of serious bacterial infections, but would not have affected the results for invasive bacterial infections.

Investigations in children aged 3 months or older
NICE CG160 recommends laboratory investigations depending on the presence of 'red', 'amber' or 'green' features in children aged older than 3 months. Children with fever without apparent source who present to paediatric specialists with 1 or more 'red' features should have the following tests performed: full blood count; blood culture; C-reactive protein; urine testing for urinary tract infection. Children with fever without apparent source presenting to paediatric specialists who have 1 or more 'amber' features, should also have these investigations performed unless deemed unnecessary by an experienced paediatrician.

Freyne et al. (2013) assessed the effectiveness of C-reactive protein, serum procalcitonin, WBC and the Acute Infantile Observation Score (AIOS) as indicators of bacterial infection in 46 infants aged 6–36 months with fever. The analysis included infants with confirmed axillary temperature of more than 38.1°C presenting to the emergency department of 1 hospital in Ireland between 8 am and midnight. Exclusion criteria were: underlying chronic illness; vaccination in the previous 2 days; and antipyretic use in the previous 2 hours.

The need for laboratory investigation was assessed by the paediatrician on call. Standard laboratory investigations were blood culture, urinalysis, WBC, and measurement of urea, electrolytes and C-reactive protein. In enrolled infants, measurement of procalcitonin was added to the laboratory tests. Diagnostic utility of tests was assessed at pre-defined cut-offs, including AIOS greater than 10 and serum procalcitonin of more than 1.0 ng/ml.

The mean age of infants enrolled in the study was 19 months, and there was an equal split of boys and girls. Bacterial illness was confirmed with positive culture in 11 infants, with 7 of those cases meeting criteria for serious bacterial infection. The remaining 35 infants were diagnosed with viral infections.

C-reactive protein had sensitivity of 83.5% and specificity of 84.3% for detecting serious bacterial infections. Procalcitonin had sensitivity of 16.0% and specificity of 63.3%. WBC had sensitivity of 83.3% and specificity of 56.6%. The AIOS had sensitivity of 66.6% and specificity of 52.5%. The authors concluded that testing for C-reactive protein was clinically relevant and testing for WBC or the AIOS would not aid clinical decision-making. The results did not support testing for procalcitonin to diagnose serious bacterial infection.

Limitations of this study included the small sample size and lack of information on duration of symptoms before admission to hospital. Although steps were taken to exclude viral pneumonia from the analysis, the absolute number of cases of bacterial pneumonia could not be confirmed. Additionally, the prevalence of serious bacterial infection in this sample was 15.2%, which was higher than the local population prevalence. This was noted to be due to the population being a secondary sample, that is, children who were already known to be ill.

Although the studies by Freyne et al (2013) and Gomez et al. (2012) assessed children of different age groups, the investigations assessed would be relevant to children of all ages. Together, these studies suggest that no laboratory test alone appears to be able to reliably rule-in or rule-out serious bacterial infections. Evidence about the usefulness of procalcitonin testing is inconsistent. Therefore, no impact on NICE CG160 is expected, because the guideline recommends a schedule of tests to be done in children with fever, and the benefit of adding procalcitonin to this schedule is not clear.

Key references

Freyne B, Divilley R, Kissoon-Harrison G et al. (2013) Field testing the utility of procalcitonin and the acute infantile observation score in infants 6 to 36 months old presenting to the pediatric emergency department with no obvious focus of infection. Clinical Pediatrics 52: 503–6

Gomez B, Bresssan S, Mintegri S et al. (2012) Diagnostic value of procalcitonin in well-appearing young febrile infants. Pediatrics 130: 815–22

Causes and incidence of serious bacterial infection

NICE CG160 recommends that in a child presenting to hospital with a fever and suspected serious bacterial infection, requiring immediate treatment, antibiotics should be directed against *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus* and *Haemophilus influenzae* type b. A third-generation cephalosporin (for example, cefotaxime or ceftriaxone) is appropriate, until culture results are available. For infants younger than 3 months, an antibiotic active against listeria (for example, ampicillin or amoxicillin) should be added.

Martin et al. (2014) retrospectively assessed hospital admission rates for children with infections caused by *H influenzae*, *N meningitidis* and *S pneumoniae* from the 1960s to 2011. In the UK, vaccination against *H influenzae* type b started in 1992; in 1999, a serogroup C meningococcal vaccine was introduced; and pneumococcal vaccination began in 2006.

Data on children younger than 15 years were obtained for 1968–85 from the Hospital In-Patient Enquiry (HIPE), which was a 10% sample of NHS hospital admissions in England. Data for this period were multiplied by 10 to represent the whole population. From 1989, Hospital Episodes Statistics (HES) recorded 100% of hospital admissions in England. Most data were recorded as episodes of care. From 1999, data on both number of episodes and number of people were available. No national hospital statistics were obtained between HIPE stopping in 1985 and HES starting in 1989.

N meningitidis was responsible for about 5 admission episodes per 100,000 children per year for meningococcal disease from 1963 to 1985, with a short-term increase to about 10 episodes per 100,000 children per year in the 1970s. However, in the 1990s the incidence increased to a peak of 34.54 episodes per 100,000 children per year in 1999. After introduction of vaccination in 1999, admission episodes for meningococcal disease decreased to 12.40 per 100,000 children in 2011. The corresponding number of children admitted was 26.68 per 100,000 per year at peak incidence in 1999 and 9.10 per 100,000 per year in 2011. The annual person-based rates of admission for meningococcal disease were 19–27% lower than the episode-based rates of admission over the period studied.

S pneumoniae was associated with 1.13–2.29 admission episodes per 100,000 children per year for pneumococcal meningitis from 1968 to 1985. Yearly rates increased through the 1990s and early 2000s to a peak of 4.45 episodes per 100,000 children year in 2006. After introduction of vaccination, the incidence dropped to 2.03 episodes per 100,000 children per year in 2011. The person-based admission rates were 2.67 per 100,000 children per year for the 2006 peak and 1.19 per 100,000 children per year in 2011.

H influenzae caused 2.86–6.72 admission episodes per 100,000 children per year for meningitis from 1968 to 1992, with the highest number of episodes in 1992. After introduction of the vaccine in 1992, the incidence dropped by 94% in 2 years to 0.39 episodes per 100,000 children per year. A small increase in incidence was seen in the early 2000s, but by 2008 the rate had dropped to 0.28 episodes of meningitis per 100,000 children per year.

The incidence of disease was consistently higher in boys than in girls for all diseases: 55% of cases of *H influenzae* meningitis, 56% of meningococcal disease and 62% of pneumococcal meningitis. The admission rates for all types of meningitis studied were largest in children under 1 year. The admission episode rates per 100,000 children per year from 2007 to 2011 in this age group were:

• 70.34 for meningococcal disease (compared with 12.40 episodes in all children)

• 19.66 for pneumococcal meningitis (compared with 2.03 episodes in all children)

• 2.19 for haemophilus meningitis (compared with 0.28 episodes in all children).

The study also measured pneumococcal bacteraemia and haemophilus bacteraemia. Both types of bacteraemia had substantially lower incidence than meningitis caused by the same organism but trends before and after the introduction of vaccination schedules were similar.

The study was potentially limited by the lack of knowledge about the quality and consistency of HES data, and the dataset would have been affected by changes in hospital coding practices. Additionally, improved microbiological diagnostic techniques in recent years could have led to an increase in reporting; however, all pathogens studied showed reductions in incidence over the study period.

Le Doare et al. (2014) reported a prospective surveillance programme for monitoring invasive bacterial infections in 5 NHS hospitals in south-west London. The Childhood Acute Bacterial Infection Network (CABIN) recorded infection in children aged from 1 month to 15 years who had microbiological confirmation of disease from blood or CSF samples.

Anonymised data were collected for each hospital episode, covering: demographics; clinical information; laboratory parameters; microbiological data; management; final diagnosis; and outcome. The participating hospitals used standardised microbiological techniques, and taking 1–2 ml blood before starting antibiotics was standard clinical practice for suspected infection.

A positive blood or CSF sample was considered clinically significant if the clinical presentation was consistent with the pathogen and the child had antibiotic treatment for that pathogen. A hospital-acquired infection was defined as a positive sample more than 48 hours after admission to hospital. Multiple positive cultures in a patient within 7 days were considered to be part of the same episode. Children were categorised as infants (1–11 months), preschool (1–4 years) or older children (5–15 years).

In 2009–11, 44,118 children were admitted to hospital in a total of 46,039 admissions, 20,578 (44.7%) of which were suspected to be related to infection. These figures represent an overall incidence of 2575 per 100,000 admissions and 1151 suspected infection-related admissions per 100,000 population. Overall, 504 episodes of invasive infection were confirmed in 375 children over the 3-year period assessed. This consisted of 190 episodes in infants (39.6%), 151 episodes in preschool children (25.3%) and 163 episodes in older children (36.1%). Slightly more than half of invasive infections (55.3%) occurred in boys.

Of Gram-positive pathogens identified in blood or CSF samples, coagulase-negative staphylococci were the most common (171 episodes, 50.9%), followed by *S aureus* (42 episodes, 12.5%), *S pneumoniae* (33 episodes, 9.8%), *Enterococcus* spp. (32 episodes, 9.5%), group B streptococcus (24 episodes, 7.1%), and group A streptococcus. Of Gram-negative bacteria, the most common pathogen was *E coli* (45 episodes, 26.8%), followed by *Klebsiella pneumoniae* (28 episodes, 16.7%), *Enterobacter* spp. (15 episodes, 8.9%), *Salmonella* spp. (15 episodes, 8.9%), *Pseudomonas* spp. (15 episodes, 8.9%), *N meningitidis* (13 episodes, 7.7%), and *H influenzae* (4 episodes, 2.4%). 'Other' pathogens caused 19 (5.7%) Gram-positive and 33 (19.6%) Gram-negative infections.

Children with pre-existing comorbidities accounted for 57.5% of all community-acquired invasive infections and 96.9% of hospital-acquired infections. Previously-healthy children accounted for only 22.28% of episodes. Although coagulase-negative staphylococci were the most common pathogens isolated, all cases were in children with comorbidities or were hospital-acquired infections. No previously healthy children presented with this infection from the community. The overall incidence of community-acquired invasive infection in healthy children aged up to 15 years was 6 episodes per 100,000 population; however, in children aged under 1 year the incidence was 38 episodes per 100,000 population. The incidence of community-onset bacterial meningitis in children aged up to 15 years was 1.1 episodes per

100,000 population overall and 9.3 episodes per 100,000 population for children aged under 1 year.

Possible limitations of this study were that the strict inclusion criteria of a positive blood or CSF culture could have led to an underestimate of the incidence of invasive bacterial infections. This study also excluded severe infections that had not spread to the blood, such as pneumonia, urinary tract infections or osteomyelitis. Rates of invasive bacterial infection in healthy children could not be compared with rates in those with comorbidities because the study did not include data on the background prevalence of comorbidity in children in the region. Additionally, all *Salmonella* spp. infections occurred in September and October in children returning from travel to India or Pakistan. Therefore, these results may not be generalisable to the rest of the UK.

The studies by Martin et al. (2014) and Le Doare et al. (2014) together suggest that vaccination programmes have resulted in reductions in the incidence of serious bacterial infections in England, and the overall incidence of invasive bacterial infections in children seems to be low. However, children under 1 year, and those with comorbidities, appear to be at higher risk of invasive bacterial infections.

These findings are consistent with the recommendation in NICE CG160 to direct antibiotic treatment against *N meningitidis*, *S pneumoniae*, *E coli*, *S aureus* and *H influenzae* type b in children with fever and suspected serious bacterial infection requiring immediate treatment, because these remain clinically important pathogens in the UK.

Children with comorbidities may be more susceptible to infection with other organisms, such as coagulase-negative staphylococci but further studies are needed to establish whether this finding applies only locally to the study population or to the UK as a whole.

Key references

Le Doare K, Nichols AL, Payne H et al. (2014) Very low rates of confirmed invasive bacterial infections in a prospective population-based surveillance in Southwest London. Archives of Disease in Childhood 99: 526–31

Martin NG, Sadarangani M, Pollard AJ et al. (2014) Hospital admission rates for meningitis and septicaemia caused by *Haemophilus influenzae, Neisseria meningitidis*, and *Streptococcus pneumoniae* in children in England over five decades: a population-based observational study. The Lancet Infectious Diseases 14: 397–405

1.6 Antipyretic interventions

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.7 Advice for home care

No new key evidence for this section was selected for inclusion in this Evidence Update.

2 New evidence uncertainties

No new evidence uncertainties were identified during the Evidence Update process, however current uncertainties for feverish illness in children can be found in the UK Database of Uncertainties about the Effects of Treatments (DUETs) at and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Feverish illness in children. NICE clinical guideline 160 (2013)

NICE CG160 was a partial update of NICE CG47 (originally published in 2007) and had an amended scope; however, this Evidence Update included the full scope of NICE CG47 to identify new evidence for sections of the guidance that were not updated in 2013.

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 October 2012 (the end of the search period of NICE clinical guideline 160) to 21 August 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)

The Evidence Update search strategy replicates the strategy used by NICE CG160 (for key words, index terms and combining concepts) as far as possible. Where necessary, the strategy is adapted to take account of changes in search platforms and updated indexing language.

In developing the guideline, searches for each review question included a different search strategy for the population and condition for each intervention. The Evidence Update has used the cumulative search terms for the population and condition from all review questions in a single search strategy.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network (SIGN) search filters for RCTs, systematic reviews, observational studies and diagnostic accuracy studies. The Cochrane definition of a diagnostic accuracy study was used in sifting because the SIGN filter is very sensitive and retrieves a high volume of results.
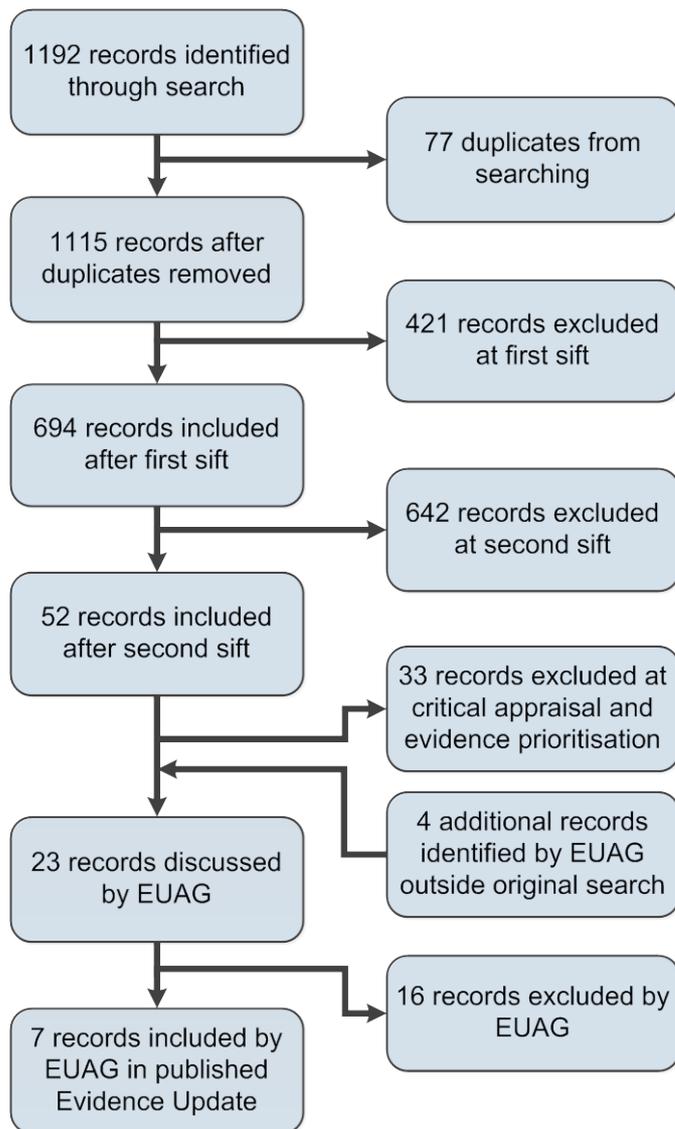
Additionally, 1 study (Martin et al. 2014) was identified outside of the literature search. Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the NICE Evidence Services website for more information about how NICE Evidence Updates are developed.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp INFANT/	28	exp ARTHRITIS, INFECTIOUS/
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab.	29	(arthrit$ adj3 (bacteri$ or septic$ or infect$ or suppurat$ or purulen$ or pyogen$)).ti,ab.
3	exp CHILD/	30	py?arth$.ti,ab.
4	(child$ or toddler$).ti,ab.	31	or/28-30
5	or/1-4	32	OSTEOMYELITIS/
6	exp FEVER/ or exp BODY TEMPERATURE/	33	osteomyelit$.ti,ab.
7	(fever$ or febri$ or hyper therm$ or hyper?therm$ or pyrex$ or hyper?pyrex$ or temperature?).ti,ab.	34	or/32-33
		35	exp URINARY TRACT INFECTIONS/
8	or/6-7	36	((urin$ or bladder$ or genito?urin$ or kidney$ or pyelo$ or renal$ or ureter$ or ureth$ or urolog$ or uro gen$ or uro?gen$) adj5 infect$).ti,ab.
9	exp BACTERIAL INFECTIONS/		
10	CRITICAL ILLNESS/ or ACUTE DISEASE/	37	((upper or lower) adj5 urin$).ti,ab.
11	((bacteri$ or streptococc$ or staphylococc$ or serious$ or severe$ or critical$ or acute$) adj (infect$ or ill$ or disease?)).ti,ab.	38	UTI.ti,ab.
		39	exp CYSTITIS/
		40	(cystit$ or pyocystit$ or pyelocystit$ or cystopyelit$).ti,ab.
12	or/9-11	41	exp PYELONEPHRITIS/
13	exp MENINGITIS, BACTERIAL/	42	(pyelonephr$ or pyonephr$).ti,ab.
14	MENINGOENCEPHALITIS/	43	or/35-42
15	mening$.ti,ab.	44	MUCOCUTANEOUS LYMPH NODE SYNDROME/
16	or/13-15		
17	SEPSIS/	45	(mucocutaneous adj3 lymph$).ti,ab.
18	exp BACTEREMIA/	46	MCLS.ti,ab.
19	(sepsis or septic?emi$).ti,ab.	47	(kawasaki$ adj (disease? or syndrome?)).ti,ab.
20	bacter?emi$.ti,ab.		
21	or/17-20	48	or/44-47
22	exp PNEUMONIA/	49	exp PYROGENS/
23	pneumon$.ti,ab.	50	pyrogen$.ti,ab.
24	or/22-23	51	or/49-50
25	ENCEPHALITIS, HERPES SIMPLEX/	52	or/12,16,21,24,27,31,34,43,48,51
26	(encephalit$ adj5 (herpe$ or HSV)).ti,ab.	53	and/5,8,52
27	or/25-26		

Figure 1 Flow chart of the evidence selection process

1192 records identified through search

77 duplicates from searching

1115 records after duplicates removed

421 records excluded at first sift

694 records included after first sift

642 records excluded at second sift

52 records included after second sift

33 records excluded at critical appraisal and evidence prioritisation

4 additional records identified by EUAG outside original search

23 records discussed by EUAG

16 records excluded by EUAG

7 records included by EUAG in published Evidence Update

EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

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