

National Institute for Health and Care Excellence

4-year surveillance (2017) – Fever in under 5s: assessment and initial management (2013) NICE guideline CG160

Appendix A: Summary of new evidence from surveillance

Thermometers and the detection of fever

160–01 How accurate are the different types of thermometer in the measurement of body temperature in young children and how do they compare in their ability to detect fever?

Recommendations derived from this question

Oral and rectal temperature measurements

- 1.1.1.1 Do not routinely use the oral and rectal routes to measure the body temperature of children aged 0–5 years. [2007].

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–02 How accurate are the readings of temperature from different sites of the body in young children, and how do these sites compare in the ability to detect fever?

Recommendations derived from this question

Measurement of body temperature at other sites

- 1.1.2.1 In infants under the age of 4 weeks, measure body temperature with an electronic thermometer in the axilla. [2007]
- 1.1.2.2 In children aged 4 weeks to 5 years, measure body temperature by one of the following methods:
- electronic thermometer in the axilla
 - chemical dot thermometer in the axilla
 - infra-red tympanic thermometer. [2007]
- 1.1.2.3 Healthcare professionals who routinely use disposable chemical dot thermometers should consider using an alternative type of thermometer when multiple temperature measurements are required. [2007]
- 1.1.2.4 Forehead chemical thermometers are unreliable and should not be used by healthcare professionals. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–03 How accurate is the subjective detection of fever by parents and carers compared with the detection of fever with a thermometer?

Recommendations derived from this question

Subjective detection of fever by parents and carers

- 1.1.3.1 Reported parental perception of a fever should be considered valid and taken seriously by healthcare professionals. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Clinical assessment of children with fever

160–04 In children with fever, what signs or combination of symptoms and signs are associated with serious illness or mortality?

– Are there any scoring systems that use symptoms and signs in children with fever to predict the risk of serious illness? How accurate are they?

Recommendations derived from this question

Life-threatening features of illness in children

- 1.2.1.1 First, healthcare professionals should identify any immediately life-threatening features, including compromise of the airway, breathing or circulation, and decreased level of consciousness. [2007]

Surveillance decision

This review question should not be updated.

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

One large observational cohort study¹ of 19,524 children aimed to compare two sepsis recognition methods in a paediatric emergency department: an algorithm based on physician

judgment compared against an electronic algorithmic alert. Of 19,524 patients, 88 children were confirmed to have severe sepsis or septic shock. Physician judgement had a sensitivity of 72.7% and a specificity of 99.5% whereas the electronic algorithm had a sensitivity of 92.1% and a specificity of 83.4%. Examination of the areas under receiver operating characteristic curves yielded no significant difference between physician judgement and the electronic algorithm. Combination of both algorithms yielded a sensitivity of 96.6% and a specificity of 83.3%. A sequential approach, in which the electronic algorithm was subsequently confirmed by physician judgment, resulted in a sensitivity of 68.2% and a specificity of 99.6%. The positive predictive value for physician judgement was 40.3% compared to 2.5% for the electronic algorithm. The negative predictive value for physician judgement was 99.88% compared to 99.96% for the electronic algorithm.

Impact statement

The study that topic experts proffered indicated that an electronic algorithmic alert system was

more sensitive but less specific than physician judgment for identifying sepsis or septic shock. The study abstract did not state the age range of participants and did not specify which algorithm (if any) was used by clinicians to identify sepsis. Furthermore, the study did not explore the ability to detect other serious illnesses. Recommendations for identifying sepsis in children under 5, in and out of hospital, are covered in the NICE guideline on [Sepsis: recognition, diagnosis and early management](#) (NG51).

It was considered that the evidence was unlikely to affect recommendations in NICE guideline CG160 as no studies were identified which indicated that clinicians should employ a different criteria to identify life threatening features in children presenting with fever.

New evidence is unlikely to change guideline recommendations.

160–05 What is the value (as shown by likelihood ratios, sensitivity, specificity, positive predictive value and negative predictive value) of the following symptoms and signs, alone or in combination, as initial indications of serious illness:

- **abnormal skin or mucosal colour; appearing ill to a healthcare professional or parent/carer; altered responsiveness or cry; altered breathing (for example nasal flaring, grunting, chest indrawing); abnormal respiratory rate, pulmonary crackles and other sounds; oxygen desaturation; dehydration; prolonged capillary refill time, cold hands and feet; poor feeding; persistent fever (5 days or more); height of fever; limb or joint swelling; unwillingness to bear weight or use a limb; bulging fontanelle; rash (blanching or non-blanching); focal neurological signs; focal seizures; new lumps; neck stiffness; vomiting; status epilepticus (prolonged or continuous fits).**

Recommendations derived from this question

Assessment of risk of serious illness

- 1.2.2.1 Assess 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. [2013]
- 1.2.2.2 When assessing children with learning disabilities, take the individual child's learning disability into account when interpreting the traffic light table. [new 2013]
- 1.2.2.3 Recognise that children with any of the following symptoms or signs are in a high-risk group for serious illness:
 - pale/mottled/ashen/blue skin, lips or tongue

- no response to social cues
 - appearing ill to a healthcare professional
 - does not wake or if roused does not stay awake
 - weak, high-pitched or continuous cry
 - grunting
 - respiratory rate greater than 60 breaths per minute
 - moderate or severe chest indrawing
 - reduced skin turgor
 - bulging fontanelle. **[new 2013]**
- 1.2.2.4 Recognise that children with any of the following symptoms or signs are in at least an intermediate-risk group for serious illness:
- pallor of skin, lips or tongue reported by parent or carer
 - not responding normally to social cues
 - no smile
 - wakes only with prolonged stimulation
 - decreased activity
 - nasal flaring
 - dry mucous membranes
 - poor feeding in infants
 - reduced urine output
 - rigors. **[new 2013]**
- 1.2.2.5 Recognise that children who have all of the following features, and none of the high- or intermediate-risk features, are in a low-risk group for serious illness:
- normal colour of skin, lips and tongue
 - responds normally to social cues[3]
 - content/smiles
 - stays awake or awakens quickly
 - strong normal cry or not crying
 - normal skin and eyes
 - moist mucous membranes. **[new 2013]**
- 1.2.2.7 Recognise that a capillary refill time of 3 seconds or longer is an intermediate-risk group marker for serious illness ('amber' sign). **[2013]**
- 1.2.2.9 In children older than 6 months do not use height of body temperature alone to identify those with serious illness. **[2013]**
- 1.2.2.10 Recognise that children younger than 3 months with a temperature of 38°C or higher are in a high-risk group for serious illness. **[2013]**
- 1.2.2.11 Recognise that children aged 3–6 months with a temperature of 39°C or higher are in at least an intermediate-risk group for serious illness. **[new 2013]**
- 1.2.2.12 Do not use duration of fever to predict the likelihood of serious illness. However, children with a fever lasting more than 5 days should be assessed for Kawasaki disease (see recommendation 1.2.3.10). **[new 2013]**
- 1.2.2.14 Assess children with fever for signs of dehydration. Look for:
- prolonged capillary refill time
 - abnormal skin turgor

- abnormal respiratory pattern
- weak pulse
- cool extremities. [2007]

Table 1: Traffic light system for identifying risk of serious illness [2013]

Risk factor	Green – low risk	Amber– intermediate risk	Red – high risk
Colour (of skin, lips or tongue)	<ul style="list-style-type: none"> • Normal colour 	<ul style="list-style-type: none"> • Pallor reported by parent/carer 	<ul style="list-style-type: none"> • Pale/mottled/ashen/blue
Activity	<ul style="list-style-type: none"> • Responds normally to social cues • Content/smiles • Stays awake or awakens quickly • Strong normal cry/not crying 	<ul style="list-style-type: none"> • Not responding normally to social cues • No smile • Wakes only with prolonged stimulation • Decreased activity 	<ul style="list-style-type: none"> • No response to social cues • Appears ill to a healthcare professional • Does not wake or if roused does not stay awake • Weak, high-pitched or continuous cry
Respiratory		<ul style="list-style-type: none"> • Nasal flaring • Tachypnoea: respiratory rate <ul style="list-style-type: none"> ○ >50 breaths/minute, age 6–12 months; ○ >40 breaths/minute, age >12 months • Oxygen saturation ≤95% in air • Crackles in the chest 	<ul style="list-style-type: none"> • Grunting • Tachypnoea: respiratory rate >60 breaths/minute • Moderate or severe chest indrawing
Circulation and hydration	<ul style="list-style-type: none"> • Normal skin and eyes • Moist mucous membrane 	<ul style="list-style-type: none"> • Tachycardia: <ul style="list-style-type: none"> ○ >160 beats/minute, age <12 months ○ >150 beats/minute, age 12–24 months ○ >140 beats/minute, age 2–5 years • Capillary refill time ≥3 seconds • Dry mucous membranes • Poor feeding in infants • Reduced urine output 	<ul style="list-style-type: none"> • Reduced skin turgor
Other	<ul style="list-style-type: none"> • None of the amber or red symptoms or signs 	<ul style="list-style-type: none"> • Age 3–6 months, temperature ≥39°C • Fever for ≥5 days 	<ul style="list-style-type: none"> • Age <3 months, temperature ≥38°C • Non-blanching rash

		<ul style="list-style-type: none"> • Rigors • Swelling of a limb or joint • Non-weight bearing limb/not using an extremity 	<ul style="list-style-type: none"> • Bulging fontanelle • Neck stiffness • Status epilepticus • Focal neurological signs • Focal seizures
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Table 2: Summary table for symptoms and signs suggestive of specific diseases [2013]

Risk factor	Amber– intermediate risk
Meningococcal disease	<p>Non-blanching rash, particularly with 1 or more of the following:</p> <ul style="list-style-type: none"> ○ an ill-looking child ○ lesions larger than 2 mm in diameter (purpura) ○ capillary refill time of ≥ 3 seconds ○ neck stiffness
Bacterial meningitis	<ul style="list-style-type: none"> • Neck stiffness • Bulging fontanelle • Decreased level of consciousness • Convulsive status epilepticus
Herpes simplex encephalitis	<ul style="list-style-type: none"> • Focal neurological signs • Focal seizures • Decreased level of consciousness
Pneumonia	<ul style="list-style-type: none"> • Tachypnoea (respiratory rate >60 breaths/minute, age 0–5 months; >50 breaths/minute, age 6–12 months; >40 breaths/minute, age >12 months) • Crackles in the chest • Nasal flaring • Chest indrawing • Cyanosis • Oxygen saturation $\leq 95\%$
Urinary tract infection	<ul style="list-style-type: none"> • Vomiting • Poor feeding • Lethargy • Irritability • Abdominal pain or tenderness • Urinary frequency or dysuria
Septic arthritis	<ul style="list-style-type: none"> • Swelling of a limb or joint • Not using an extremity • Non-weight bearing

Kawasaki disease	<p>Fever for more than 5 days and at least 4 of the following:</p> <ul style="list-style-type: none"> o bilateral conjunctival injection o change in mucous membranes o change in the extremities o polymorphous rash o cervical lymphadenopathy
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Surveillance decision

This review question should not be updated. Instead, a footnote should be added to recommendation 1.2.2.10 of the guideline, as well as the traffic light system for identifying risk of serious illness, to highlight that some vaccinations have been found to induce fever in children younger than 3 months.

2-year Evidence Update

One study² was identified which assessed the accuracy of the 2007 version of the NICE traffic light system with and without additional urinalysis, for detection of serious bacterial infection. Data was used from a prospective study of emergency department visits by febrile children under the age of 5. Overall, 15,781 febrile illnesses were assessed, which included 1,120 episodes of serious bacterial infection involving 1,166 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). Authors reported that '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. Authors stated that these serious infections would have been missed if children were assessed solely using the traffic light system. Urinalysis was performed in 23.1% of all episodes of fever and in 44% of episodes of serious bacterial infection, identifying a total of 507 infections: 362 urinary tract infections, 118 cases of pneumonia, and 27 cases of bacteraemia.

When urinalysis was added to the traffic light system, the sensitivity of the combined assessment was 92.1% and specificity was 22.3%.

It was noted that a potential limitation of this study was that data appeared to be reported only at admission to hospital. No details were available about whether children who had 'green' features and were diagnosed with serious bacterial infection developed 'amber' or 'red' features after admission. Additionally, urinalysis was performed in a minority of children. The study was not thought to affect the guideline because NICE CG160 recommends that urine testing is performed in all children.

A case-control study³ analysed data from 9,678 children under the age of 16 who had been diagnosed with sepsis or meningitis to assess the diagnostic value of clinical prediction rules. In all cases, 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 the Yale observation scale. The analysis covered 6 clinical prediction rules: a modified Yale Observation Scale (YOS); Paediatric 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 a sensitivity of 98% and specificity of 2.4%, at a cut-off of 8, and had a sensitivity of 54.0% and specificity of 63.7%, at a cut-off of 10. PAWS had a sensitivity of 58.0% and specificity of 81.3% if any 'red' sign was identified. The APVU scale had a sensitivity of 17.8% and specificity of 100% if the child responded to pain stimulus. The RAIC score had 4% sensitivity and 100% specificity for ruling in serious bacterial infection at a score of 8 or more, and had 76.0% sensitivity of and 6.2% specificity for ruling out serious bacterial infection at a score of 5 or less. The Oxford Vital Signs score had 80% sensitivity and 49.3% specificity if any sign was present. The 2007 NICE traffic light system had a sensitivity of 100% and specificity of 0.12% if any 'amber' or 'red' sign was present, and had a 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.

It was considered that the case-control design may have led to selection bias and bias in the mix of patients. Data seemed to be reported only at presentation. Moreover, 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. Importantly, the sample included children up to age 15 years, whereas the NICE traffic light system was designed for children under 5 years.

Another study⁴ retrospectively assessed the diagnostic accuracy of 4 clinical prediction rules and 2 national evidence-based guidelines using individual patient data from 11,023 individuals. Analysis included data from children aged between 1 month and 18 years with fever, acute illness, acute infection, or signs of meningitis who attended ambulatory care departments in developed countries. The clinical prediction rules assessed were: the 5-stage decision tree, pneumonia, a meningitis rule and the Yale Observation Scale. The 2007 version of CG160 and national guidelines from the Dutch College of General Practitioners were also assessed. Authors reported that 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 another study in a low prevalence setting (n=506), the sensitivity was 100% and specificity was 1%. In a 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, sensitivity was 87.1% and specificity was 28.7% in 1 study (n=700) whereas in the other study (n=593) sensitivity was 98.5% and specificity was 2.1%. The Dutch guideline had broadly similar sensitivity and specificity to the 2007 traffic light system in NICE CG160. A key limitation of this study was heterogeneity between datasets in setting, inclusion criteria, immunisation schedules, and definition of serious infection.

Overall, it was considered in the Evidence Update that the 3 identified studies performed 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 rules assessed, and 2 of the studies used the NICE traffic light system as a stand-alone tool. It was considered that the results were 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 the NICE CG160 traffic light system rather than the current 2013 version, so these findings would not have been reflective of current guidance.

4-year surveillance summary

A systematic review⁵ of 18 studies aimed to assess the diagnostic value of clinical signs and symptoms to identify radiological pneumonia in children younger than 5 years and to review the accuracy of WHO criteria for diagnosis of clinical pneumonia. Fast breathing exhibited a pooled sensitivity of 62% and a specificity of 59% whereas lower chest wall indrawing had a sensitivity of 48% and a specificity of 72%. Authors reported that the pooled positive likelihood ratio of a respiratory rate higher than 50 breaths was 1.90. Positive likelihood ratios for symptoms such as grunting chest indrawing and nasal flaring were 1.78, 1.76, 1.75, respectively. The lowest pooled negative likelihood ratio was observed with

coughing (0-30), followed by a history of fever (0-53), and a respiratory rate higher than 40 breaths per min (0-43).

One systematic review⁶ aimed to determine the diagnostic value of capillary refill time for a range of serious outcomes in children (children were up to 18 years old). Meta-analysis revealed that capillary refill time was able to predict the risk of mortality with a sensitivity of 34.6% and a specificity of 92.3%. The positive likelihood ratio was 4.49 and the negative likelihood ratio was 0.71. In relation to vomiting and diarrhoea, capillary refill time had a sensitivity between 0% and 94% and a specificity between 89 and 94% in included studies.

Topic expert feedback

Topic experts highlighted that there are new algorithms available for identifying meningococcal disease. Experts highlighted a retrospective study⁷ in which investigators compared 2 algorithms for examining children with non-blanching rash (NICE algorithm versus the Newcastle-Birmingham-Liverpool algorithm). The study included 625 children; of whom 145 had confirmed or probable meningococcal disease. The NICE algorithm suggested that 61% (n=382) of children should have received antibiotics. This included 141 of the 145 children with meningococcal disease. As a result the sensitivity of the NICE algorithm was 97% and the specificity was 50%. The Newcastle-Birmingham-Liverpool algorithm identified all children with meningococcal disease and suggested treatment for a further 86 children. The sensitivity of the algorithm was 100% and specificity was 82%.

One prospective observational study⁸ aimed to explore the relationship between peripheral and central capillary refill time and their diagnostic values for detecting serious bacterial infection in febrile children (1 month to 16 years) attending a paediatric emergency department. No significant difference was observed between the two capillary refill times in children between 1 and 5 years. Authors reported that agreement decreases with higher body temperatures with kappa ranging from 0.55 for temperatures less than 37.5°C to 0.21 for temperatures greater than 39.5°C. Abnormal peripheral capillary refill times (greater than 2 seconds) were observed in 12.8% of children whereas abnormal central capillary refill times

were observed in 4.6% of children. The odds ratio of abnormal peripheral capillary refill times for predicting serious bacterial infection was 1.10 (95% CI 0.65 to 1.84) whereas the odds ratio of abnormal central capillary refill times was 0.43 (95% CI 0.13 to 1.39).

Topic experts highlighted RCTs⁹⁻¹¹ which reported that a new protein-based meningococcal B vaccination could induce fever in some children. Intelligence gathering revealed a [Public Health England publication](#) which highlights that fever is an adverse reaction associated with a new protein-based meningococcal B vaccine. Furthermore, an [NHS England publication](#), targeted at parents, highlights that fever is a common side effect after some vaccinations. Experts pointed out that recommendation [1.2.2.10](#), states that clinicians should recognise that children younger than 3 months with a temperature of 38°C or higher are in a high-risk group for serious illness. They expressed some concern that many children under 3 months who develop fever after immunisation will be admitted to hospital and subjected to a full septic screen because the guideline indicates that they are treated this way.

Topic experts suggested that all relevant literature (new and old) should be reappraised, and the risk of serious bacterial infection in febrile children less than 3 months old should be stratified by age; less than 1 month versus 1 to 2 months versus 2 to 3 months. They felt that if the evidence indicates that children between 2 and 3 months old have a lower risk of serious infection compared to those less than 2 months old, then 2 months could be used as a cut-off for high-risk of infection. Since children under 2 months do not routinely receive the meningococcal B vaccine, experts felt that if the evidence permitted an update of guideline recommendations concerns about unnecessary hospital admissions could be addressed.

To justify the proposal of reappraising the evidence base, topic experts highlighted a retrospective cohort study¹² which provided some evidence that the overall risk of serious bacterial infection was highest in neonates compared to children between 1 and 2 months, and 2 and 3 months old. In relation to specific infections, the study indicated that bacteraemia rates and bacterial meningitis rates were highest at 2 weeks and decreased thereafter.

One topic expert suggested that the traffic light table could be amended to highlight that post-vaccination fever could be a green sign, and linked to the absence of the amber and red signs.

Impact statement

The 3 studies identified in the 2-year evidence update performed 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 rules assessed, and 2 of the studies used the NICE traffic light system as a stand-alone tool. The 3 identified studies were considered to have no impact on the 2013 iteration of NICE CG160 because they assessed the utility of the NICE 2007 version of the traffic light system.

The 2 systematic reviews identified via literature searches in this 4-year review highlighted potential signs and symptoms that were indicative of serious illness. However, it was evident that no single clinical feature was sufficient to diagnose serious illness definitively.

Topic experts highlighted a study which compared 2 algorithms devised to help identify which children with non-blanching rash had meningococcal disease. The study revealed that the Birmingham-Liverpool algorithm had a similar sensitivity but higher specificity than the NICE algorithm. Although related to NICE guideline CG160, the usefulness of the Birmingham-Liverpool algorithm in identifying meningococcal disease is more relevant to the clinical guideline on [Meningitis \(bacterial\) and meningococcal septicaemia in under 16s: recognition, diagnosis and management](#) (CG102).

Overall the identified new evidence was considered to be in line with guideline recommendations which list various signs and symptoms that provide initial indications of serious illness.

Topic experts raised concerns that children under 3 months old who develop fever after immunisation with a new protein-based meningococcal B vaccine should be admitted to hospital and subjected to a full septic screen. Intelligence gathering revealed a [Public Health England publication](#) which highlights that fever is an adverse reaction associated with a new protein-based meningococcal B vaccine. Additionally, an [NHS England publication](#), targeted at parents, highlights that fever is a common side effect after some vaccinations.

Topic experts suggested that both old and new evidence could be reviewed to determine whether children less than 1 month, between 1 and 2 months, and between 2 and 3 months old are at greatest risk of serious bacterial infections. They felt that if the evidence indicates that children between 2 and 3 months old have a lower risk of serious infection compared to those less than 2 months old, then 2 months could be used as a cut-off for high-risk of infection. Topic expert feedback and evidence included in the surveillance review and guideline was considered in detail. No evidence was identified including children post vaccine aiming to identify the likelihood of serious bacterial infection in the presence of a post vaccine fever. Therefore, adding a footnote to NICE guideline CG160 to notify clinicians that certain vaccinations can induce fever in children younger than 3 months was considered to be the most appropriate action.

New evidence is unlikely to change guideline recommendations

160–06 What is the predictive value of heart rate, including:

- how heart rate changes with temperature?
- whether heart rate outside the normal range detects serious illness?
- how heart rate changes with temperature?

Recommendations derived from this question

Assessment of risk of serious illness

- 1.2.2.6 Measure and record temperature, heart rate, respiratory rate and capillary refill time as part of the routine assessment of a child with fever. [2007]
- 1.2.2.8 Measure the blood pressure of children with fever if the heart rate or capillary refill time is abnormal and the facilities to measure blood pressure are available. [2007]
- 1.2.2.13 Recognise that children with tachycardia are in at least an intermediate-risk group for serious illness. Use the Advanced Paediatric Life Support (APLS) criteria below to define tachycardia: [new 2013]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–07 In children with fever, what symptoms and signs or combinations of symptoms and signs are predictive of the specific conditions defined as serious illnesses?

Recommendations derived from this question

Symptoms and signs of specific illnesses

- 1.2.3.1 Look for a source of fever and check for the presence of symptoms and signs that are associated with specific diseases. [2007]
- 1.2.3.2 Consider meningococcal disease in any child with fever and a non-blanching rash, particularly if any of the following features are present:
- an ill-looking child
 - lesions larger than 2 mm in diameter (purpura)
 - a capillary refill time of 3 seconds or longer
 - neck stiffness. [2007]
- 1.2.3.3 Consider bacterial meningitis in a child with fever and any of the following features:
- neck stiffness
 - bulging fontanelle
 - decreased level of consciousness
 - convulsive status epilepticus. [2007, amended 2013]
- 1.2.3.4 Be aware that classic signs of meningitis (neck stiffness, bulging fontanelle, high-pitched cry) are often absent in infants with bacterial meningitis. [2007]

1.2.3.5 Consider herpes simplex encephalitis in children with fever and any of the following features:

- focal neurological signs
- focal seizures
- decreased level of consciousness. [2007]

1.2.3.6 Consider pneumonia in children with fever and any of the following signs:

- tachypnoea (respiratory rate greater than 60 breaths per minute, age 0–5 months; greater than 50 breaths per minute, age 6–12 months; greater than 40 breaths per minute, age older than 12 months)
- crackles in the chest
- nasal flaring
- chest indrawing
- cyanosis
- oxygen saturation of 95% or less when breathing air. [2007]

1.2.3.7 Consider urinary tract infection in any child younger than 3 months with fever.

1.2.3.8 Recognise that children with tachycardia are in at least an intermediate-risk group for serious illness. Use the Advanced Paediatric Life Support (APLS)[4] criteria below to define tachycardia: [new 2013]

- vomiting
- poor feeding
- lethargy
- irritability
- abdominal pain or tenderness
- urinary frequency or dysuria. [new 2013]

1.2.3.9 Consider septic arthritis/osteomyelitis in children with fever and any of the following signs:

- swelling of a limb or joint
- not using an extremity
- non-weight bearing. [2007]

1.2.3.10 Consider Kawasaki disease in children with fever that has lasted longer than 5 days and who have 4 of the following 5 features:

- bilateral conjunctival injection
- change in mucous membranes in the upper respiratory tract (for example, injected pharynx, dry cracked lips or strawberry tongue)
- change in the extremities (for example, oedema, erythema or desquamation)
- polymorphous rash
- cervical lymphadenopathy
- Be aware that, in rare cases, incomplete/atypical Kawasaki disease may be diagnosed with fewer features. [2007]

Imported infections

1.2.4.1 When assessing a child with feverish illness, enquire about recent travel abroad and consider the possibility of imported infections according to the region visited. [2007]

Surveillance decision

This review question should not be updated.

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance summary

A systematic review⁵ of 18 studies assessed the diagnostic value of clinical signs and symptoms to identify radiological pneumonia in children younger than 5 years. Age-related fast breathing exhibited a pooled sensitivity of 62% and specificity of 59%. Lower chest indrawing had a sensitivity of 48% and a specificity of 72%. Authors noted that the signs and symptoms with the highest pooled positive likelihood ratios were respiratory rates higher than 50 breathes per min (ratio, 1.90) grunting (1.78), chest indrawing (1.76) and nasal flaring (1.75). Signs and symptoms with the lowest pooled negative likelihood ratio were cough (0.30), history of fever (0.53) and a respiratory rate higher than 40 breaths per minute (0.43).

Topic expert feedback

Topic experts highlighted that there are new algorithms available for identifying meningococcal disease. Experts highlighted a retrospective study⁷ in which investigators compared 2 algorithms for examining children with non-blanching rash (NICE algorithm versus the Newcastle-Birmingham-Liverpool algorithm). The study included 625 children; of whom 145 had confirmed or probable meningococcal disease. The NICE algorithm suggested that 61% (n=382) of children should

have received antibiotics. This included 141 of the 145 children with meningococcal disease. As a result the sensitivity of the NICE algorithm was 97% and the specificity was 50%. The Newcastle-Birmingham-Liverpool algorithm identified all children with meningococcal disease and suggested treatment for a further 86 children. The sensitivity of the algorithm was 100% and specificity was 82%.

Impact statement

The systematic review identified from the literature searches highlighted that fast breathing, lower chest indrawing, grunting and nasal flaring were good indicators of radiological pneumonia. These symptoms are consistent with the symptoms outlined in guideline recommendations.

Topic experts highlighted a study which compared 2 algorithms devised to help identify which children with non-blanching rash had meningococcal disease. It was unclear from the study abstract whether the predictive value of other signs and symptoms of meningococcal disease were explored. Thus, it was considered that this study is unlikely to impact on guideline recommendations which already list non-blanching rash as one of a number of indicators of meningococcal disease.

New evidence is unlikely to change guideline recommendations.

Management by remote assessment

Preamble to the recommendations in this section of the guideline

Remote assessment refers to situations in which a child is assessed by a healthcare professional who is unable to examine the child because the child is geographically remote from the assessor (for example, telephone calls to NHS Direct[7]). Therefore, assessment is largely an interpretation of symptoms rather than physical signs. The guidance in this section may also apply to healthcare professionals whose scope of practice does not include the physical examination of a young child (for example, community pharmacists).

160–08 Management according to risk of serious illness section (No specific question was outlined in the guideline; recommendations were derived from Delphi consensus)

Recommendations derived from this question

Management according to risk of serious illness

- 1.3.1.1 Healthcare professionals performing a remote assessment of a child with fever should seek to identify symptoms and signs of serious illness and specific diseases as described in section 1.2 and summarised in tables 1 and 2. [2007]
- 1.3.1.2 Children whose symptoms or combination of symptoms suggest an immediately life-threatening illness (see recommendation 1.2.1.1) should be referred immediately for emergency medical care by the most appropriate means of transport (usually 999 ambulance). [2007]
- 1.3.1.3 Children with any 'red' features but who are not considered to have an immediately life-threatening illness should be urgently assessed by a healthcare professional in a face-to-face setting within 2 hours. [2007]
- 1.3.1.4 Children with 'amber' but no 'red' features should be assessed by a healthcare professional in a face-to-face setting. The urgency of this assessment should be determined by the clinical judgement of the healthcare professional carrying out the remote assessment. [2007]
- 1.3.1.5 Children with 'green' features and none of the 'amber' or 'red' features can be cared for at home with appropriate advice for parents and carers, including advice on when to seek further attention from the healthcare services (see section 1.7). [2007, amended 2013]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Management by the non-paediatric practitioner

Preamble to the recommendations in this section of the guideline

In this guideline, a non-paediatric practitioner is defined as a healthcare professional who has not had specific training or who does not have expertise in the assessment and treatment of children and their illnesses. This term includes healthcare professionals working in primary care, but it may also apply to many healthcare professionals in general emergency departments.

160–09 Clinical assessment sub-section (No specific question was outlined in the guideline; recommendations were derived from Delphi consensus)

Recommendations derived from this question

Clinical assessment

- 1.4.1.1 Management by a non-paediatric practitioner should start with a clinical assessment as described in section 1.2. Healthcare practitioners should attempt to identify symptoms and signs of serious illness and specific diseases as summarised in tables 1 and 2. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–10 Management according to risk of serious illness sub-section (No specific question was outlined in the guideline; recommendations were derived from Delphi consensus)

Recommendations derived from this question

Management according to risk of serious illness

- 1.4.2.1 Children whose symptoms or combination of symptoms and signs suggest an immediately life-threatening illness (see recommendation 1.2.1.1) should be referred immediately for emergency medical care by the most appropriate means of transport (usually 999 ambulance). [2007]
- 1.4.2.2 Children with any 'red' features but who are not considered to have an immediately life-threatening illness should be referred urgently to the care of a paediatric specialist. [2007]
- 1.4.2.3 If any 'amber' features are present and no diagnosis has been reached, provide parents or carers with a 'safety net' or refer to specialist paediatric care for further assessment. The safety net should be 1 or more of the following:
- providing the parent or carer with verbal and/or written information on warning symptoms and how further healthcare can be accessed (see section 1.7.2)
 - arranging further follow-up at a specified time and place
 - liaising with other healthcare professionals, including out-of-hours providers, to ensure direct access for the child if further assessment is required. [2007]
- 1.4.2.4 Children with 'green' features and none of the 'amber' or 'red' features can be cared for at home with appropriate advice for parents and carers, including advice on when to seek further attention from the healthcare services (see section 1.7). [2007, amended 2013]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–11 In children presenting to primary care with fever and no obvious focus of infection, what is the predictive value of the following investigations in identifying children with a serious illness?

- urinalysis
- chest X-ray
- pulse oximetry
- capillary glucose

Recommendations derived from this question

Tests by the non-paediatric practitioner

- 1.4.3.1 Children with symptoms and signs suggesting pneumonia who are not admitted to hospital should not routinely have a chest X-ray. [2007]
- 1.4.3.2 Test urine in children with fever as recommended in Urinary tract infection in children (NICE clinical guideline 54). [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–12 What are the benefits and risks of giving oral antibiotics to febrile children with no known focus of infection and no symptoms or signs of serious illness?

Recommendations derived from this question

Use of antibiotics by the non-paediatric practitioner

- 1.4.4.1 Do not prescribe oral antibiotics to children with fever without apparent source. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–13 When should children in primary care be treated with empirical parenteral antibiotics in an attempt to decrease mortality or morbidity?

Recommendations derived from this question

Use of antibiotics by the non-paediatric practitioner

- 1.4.4.2 Give parenteral antibiotics to children with suspected meningococcal disease at the earliest opportunity (either benzylpenicillin or a third-generation cephalosporin). [2007]

Surveillance decision

This review question should not be updated.

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance summary.

In an RCT¹³, 60 infants with suspected early onset neonatal sepsis were treated by a 3-day course or 5-day course of empirical antibiotic (Ampicillin + Amikacin) therapy. No treatment failure (reappearance of symptoms of sepsis within two weeks after discontinuation of antibiotics) was reported in infants in the 5-day group whereas 1 infant in the 3-day group had treatment failure. No adverse events were reported in either treatment group.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The identified RCT highlighted the benefits of empirical antibiotics by reporting that a 5-day course of antibiotics reduced the occurrence of sepsis in neonates. The study had a relatively small sample size (n=60) and was focussed on 1 of the serious illnesses covered by NICE guideline CG160. This is unlikely to affect guideline recommendations which advocate parenteral antibiotics for suspected meningococcal disease. No studies were identified which contradicted this recommendation.

New evidence is unlikely to change guideline recommendations.

Management by the paediatric specialist

Preamble to the recommendations in this section of the guideline

In this guideline, the term paediatric specialist refers to a healthcare professional who has had specific training or has recognised expertise in the assessment and treatment of children and their illnesses. Examples include paediatricians, or healthcare professionals working in children's emergency departments.

160–14 In a febrile child what is the predictive value of the following in detecting serious illness?

- WBC
- absolute neutrophil count (ANC)
- CRP
- procalcitonin (PCT)
- erythrocyte sedimentation rate (ESR)
- urinalysis
- lumbar puncture
- chest X-ray
- combination of those above

Recommendations derived from this question

Children younger than 5 years

- 1.5.1.1 Management by the paediatric specialist should start with a clinical assessment as described in section 1.2. The healthcare professional should attempt to identify symptoms and signs of serious illness and specific diseases as summarised in tables 1 and 2. [2007]

Children younger than 3 months

- 1.5.2.1 Infants younger than 3 months with fever should be observed and have the following vital signs measured and recorded:
- temperature
 - heart rate
 - respiratory rate. [2007]
- 1.5.2.2 Perform 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[6]
 - chest X-ray only if respiratory signs are present
 - stool culture, if diarrhoea is present. [2013]
- 1.5.2.3 Perform lumbar puncture in the following children with fever (unless contraindicated):
- infants younger than 1 month
 - all infants aged 1–3 months who appear unwell
 - infants aged 1–3 months with a white blood cell count (WBC) less than $5 \times 10^9/\text{litre}$ or greater than $15 \times 10^9/\text{litre}$. [2007, amended 2013]
- 1.5.2.4 When indicated, perform a lumbar puncture without delay and, whenever possible, before the administration of antibiotics. [2007]
- 1.5.2.5 Give parenteral antibiotics to:
- infants younger than 1 month with fever
 - all infants aged 1–3 months with fever who appear unwell
 - infants aged 1–3 months with WBC less than $5 \times 10^9/\text{litre}$ or greater than $15 \times 10^9/\text{litre}$. [2007, amended 2013]

- 1.5.2.6 When parenteral antibiotics are indicated for infants younger than 3 months of age, a third-generation cephalosporin (for example cefotaxime or ceftriaxone) should be given plus an antibiotic active against listeria (for example, ampicillin or amoxicillin).[2007]

Children aged 3 months or older

- 1.5.3.1 Perform the following investigations in children with fever without apparent source who present to paediatric specialists with 1 or more 'red' features:
- full blood count
 - blood culture
 - C-reactive protein
 - urine testing for urinary tract infection. [2013]
- 1.5.3.2 The following investigations should also be considered in children with 'red' features, as guided by the clinical assessment:
- lumbar puncture in children of all ages (if not contraindicated)
 - chest X-ray irrespective of body temperature and WBC
 - serum electrolytes and blood gas. [2007]
- 1.5.3.3 Children with fever without apparent source presenting to paediatric specialists who have 1 or more 'amber' features, should have the following investigations performed unless deemed unnecessary by an experienced paediatrician.
- urine should be collected and tested for urinary tract infection
 - blood tests: full blood count, C-reactive protein and blood cultures
 - lumbar puncture should be considered for children younger than 1 year
 - chest X-ray in a child with a fever greater than 39°C and WBC greater than $20 \times 10^9/\text{litre}$. [2007]
- 1.5.3.4 Children who have been referred to a paediatric specialist with fever without apparent source and who have no features of serious illness (that is, the 'green' group), should have urine tested for urinary tract infection and be assessed for symptoms and signs of pneumonia (see table 2). [2007]
- 1.5.3.5 Do not routinely perform blood tests and chest X-rays in children with fever who have no features of serious illness (that is, the 'green' group). [2007]

Surveillance decision

This review question should not be updated. Instead, a new recommendation will be added that cross-refers to the NICE guideline on [Sepsis: recognition, diagnosis and early management](#) (NG51) so that appropriate considerations can be made if there is any suspicion of sepsis in febrile children.

2-year Evidence Update

One retrospective case review¹⁴ assessed the diagnostic value of serum procalcitonin (PCT) for detecting invasive bacterial infections in 1,112 'well-appearing' infants younger than 3 months with fever without apparent source. Serious bacterial infections were confirmed in 289 infants (26%), 23 of whom had an invasive bacterial infection (2%). The cut-offs used to assess the diagnostic utility of risk factors for

invasive bacterial infections were: 0.5 ng/ml for PCT; 20 mg/l for C-reactive protein (CRP); 15,000 cells per mm^3 ($15 \times 10^9/\text{litre}$) for White blood cell (WBC), and 10,000 cells per mm^3 for absolute neutrophil count. In multivariate analysis, a PCT measurement of 0.5 ng/ml or higher was the only factor independently associated with a diagnosis of invasive bacterial infection (Odds ratio, 21.69; 95% CI 7.93 to 59.28).

Another study¹⁵ assessed the effectiveness of CRP, serum PCT, WBC and the Acute Infantile Observation Score (AIOS) as indicators of bacterial infection in 46 infants aged between 6 and 26 months with fever. 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. PCT 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 PCT to diagnose serious bacterial infection.

It was considered that both of the identified studies outlined that the investigations assessed would be relevant to children of all ages. However, the evidence indicated that no laboratory test alone appeared to be able to reliably rule-in or rule-out serious bacterial infections. Evidence about the usefulness of PCT testing was deemed inconsistent. Therefore, it was considered that the identified evidence would have no impact on NICE CG160, because the guideline recommends a schedule of tests to be done in children with fever.

4-year surveillance summary

A systematic review¹⁶ of 7 studies, including 2,317 patients, aimed to assess the utility of serum PCT concentrations in detecting serious bacterial infections in febrile infants younger than 91 days. Five out of the 7 studies used a PCT threshold of 0.3ng/mL. The overall relative risk of serious bacterial infection when the threshold was reached was 3.97. Authors reported that the "relative risk clinical prediction rules was 30.6 and 8.75 for infants untreated and treated with antibiotics, respectively."

One systematic review¹⁷ identified 14 studies which reported low-risk criteria to rule out serious bacterial infections in infants less than 3 months old. Authors reported that clinical tools such as the Rochester and Philadelphia criteria support the safe discharge of low-risk infants without empirical antibiotics.

One RCT¹⁸ assessed the accuracy of a Lab-score (a test combining CRP, PCT and urine dipstick results) in detecting serious bacterial infections in children between 7 days and 36 months with fever without source. Patients were randomised to either the Lab-score group (Lab-score plus blinded WBC count) or to the control group (WBC, bands and CRP determined, blinded PCT and Lab-score). No significant difference in antibiotic prescription rates were observed between groups. Authors reported that a lab-score greater than 3 had a sensitivity of 85.1%, specificity of 87.3%, positive predictive value of 68.7% and negative predictive value of 94.1%. The positive and negative likelihood ratios were 6.68 and 0.17, respectively.

Topic expert feedback

Topic experts suggested the following studies:

One prospective observational study¹⁹ assessed the diagnostic value of WBC, Absolute Neutrophil Count (ANC), Interleukin-6 (IL-6) and CRP level to predict serious bacterial infection in 195 febrile infants younger than three months who were hospitalised. The serum IL-6 test (threshold $\geq 20\text{pg/dl}$) had a sensitivity of 79.1%, specificity of 91.6%, a positive predictive value of 75.4% and a negative predictive value of 60.3%. The CRP test (threshold $\geq 10\text{mg/l}$) had a sensitivity of 81.6%, specificity of 89.8%, a positive predictive value of 78.2% and a negative predictive value of 52%. Authors reported that the predictive values of CRP and IL-6 were higher than WBC and ANC.

In a prospective observational study²⁰ including 373 febrile children, the diagnostic performance of CRP tests at different time points from fever onset was compared using a receiver operating characteristic curve. Of the 373 children included 28% (n=103) had a bacterial infection. Results indicated that the optimal cut-off for CRP suggested bacterial infection changed with time from fever onset. Between 12 and 24 hours of fever onset the cut-off was 6mg/dL. Between 24 and 48 hours of onset, the cut-off was 10.7mg/dL. After 48 hours of onset, the cut-off was 12.6 mg/dL. Authors reported that the input of time from fever onset improved the area under the receiver operating characteristic curve. Results indicated that duration of fever mostly affected the ability of CRP tests to correctly rule out bacterial infections. CRP

levels of 2 mg/dL obtained less than 24 hours of fever corresponded with a post-test probability for bacterial infection of 10%, whereas the same value obtained after 24 hours reduced the risk to 2%.

A prospective cohort study²¹ assessed the diagnostic characteristics of PCT tests for detecting serious bacterial infection and invasive bacterial infection in 2,047 febrile infants aged between 7 and 91 days. Overall 6.38% of infants were diagnosed with serious bacterial infections and 1% of infants were diagnosed with invasive bacterial infections. The PCT assay had a similar area under the receiver operating characteristic similar to that for CRP tests for detection of serious bacterial infections. The area under the curve for detection of invasive bacterial infections was significantly higher for PCT tests compared to CRP tests, indicating that the PCT assay had better diagnostic accuracy than CRP measurements for detecting invasive bacterial infections. Similar results were obtained for a subgroup of infants less than 1 month old and for those with fever that lasted for less than 6 hours.

A retrospective study²² reviewed clinical data to determine whether extreme leucocytosis (white blood cell count greater than 25,000/mm) and fever were indicative of serious bacterial infections in children with fever between 3 and 36 months. Serious bacterial infections were reported in 39% of 147 infants: the most common infections were segmental or lobar pneumonia (19%) and urinary tract infections (10.9%). Authors noted that CRP levels were significantly higher in the serious bacterial infection group than in the non-serious bacterial infection group.

One retrospective study²³ assessed the rate of urinary tract infections in febrile infants with respiratory syncytial virus infections who were younger than 3 months and compared them with those between 3 and 12 months old. The rate of urinary tract infections was 6.8% in infants less than 3 months and 6.1% in those older than 3 months (no p values reported). Authors stated that a positive urinalysis result was an independent indicator of urinary tract infection in infants older than 3 months. Demographic (race, sex, and age) and clinical factors (temperature, white blood cell count,

and absolute neutrophil count) were not associated with urinary tract infections.

Another study²⁴ aimed to determine the rate of bacterial infections in children between 3 and 36 months who presented to a paediatric emergency department with fever but otherwise appeared well. Of the 591 children who were assessed 1% (n=6) had a bacterial pathogen isolated from blood tests: of these pathogens, half were *S. pneumoniae*. None of the children with pneumococcal infections had been immunised. Authors noted that a positive band count was most indicative of occult bacteraemia, with a positive likelihood ratio of 10 and a negative likelihood ratio of 0.4.

One study²⁵ conducted a retrospective comparison of 3 different approaches of ascertaining the risk of invasive bacterial infections in 1,123 febrile infants who were less than 3 months old. The 3 approaches were the step by step, Lab-score and Rochester criteria approaches. No further details were provided in the study abstract. Of the 1,123 infants included in the analysis, 4.2% (n=48) had invasive bacterial infections. The percentages of infants classified as low-risk using the step by step, Lab-score and Rochester criteria were 43.4%, 61.7% and 40.7%, respectively. Confirmed invasive bacterial infections were observed in 0.2% of infants classified as low-risk using step by step approach, 0.7% of infants using the Lab-score and 1.1% of infants using the Rochester criteria.

A prospective observational study²⁶ aimed to assess the diagnostic role of CRP and PCT in febrile children (between 1 month and 16 years) at risk of serious bacterial infection. Of the 1,084 children included in the study 170 children (16%) had serious bacterial infections. Authors reported that the areas under receiver operating characteristic curves indicated that CRP (Area, 0.77) and PCT (Area, 0.75) were both strong indicators of serious bacterial infection. It was noted that duration of fever had no added diagnostic value to CRP or PCT. The Lab-score (which combines PCT, CRP and urinalysis) had an area under the receiver operating characteristic curve of 0.79, which was similar to the areas of individual biomarkers. An updated Lab-score improved slightly, with an area of 0.83.

One prospective observational study²⁷ assessed the potential benefits of introducing

CRP bedside testing of febrile children in an emergency department. Note: children were between 1 month and 16 years old. Authors reported that bedside CRP testing significantly reduced hospital length of stay from a mean of 178 minutes to 148 minutes.

Topic experts indicated that multiplex PCR machines can produce results from CSF cultures within 1 hour compared to 18 hours using conventional methods. As a result, one expert suggested that multiplex PCR should be reviewed in relation to cost savings due to reductions in admission as well as antibiotic stewardship. Topic experts highlighted that recommendations about lactate testing are in the [NICE Sepsis guideline](#) (NG51) but are not in NICE guideline CG160. They felt that although lactate testing is used to stratify risk in people who are thought to have sepsis, it is not used for detecting infection. Experts highlighted that children with sepsis comprise a subset of children presenting with fever. Furthermore, they pointed out that most trusts would screen for sepsis first, then fever, unless they are assured that the initial screening process in the fever guideline covers sepsis red flags. As a result, experts felt that it is important that NICE guideline CG160 redirects clinicians to NICE guideline NG51 if they suspect a febrile child has sepsis. They suggested that a recommendation could be added to NICE guideline CG160; cross-referring to NICE guideline NG51 so that clinicians can determine what considerations should be made if they suspect that a febrile child has sepsis. Experts suggested the following recommendation could be added after 1.2.1.1 of NICE guideline CG160:

“Think ‘could this be sepsis?’ and refer to the NICE sepsis guidance if a person presents with signs or symptoms that indicate possible sepsis.”

One expert pointed out that most trusts will screen for sepsis first then fever, unless they are assured that the initial screening process in the fever guideline covers sepsis red flags. The following challenge was raised: currently a child (age, 18 months) with a potentially infective cause who arrives with fever and tachycardia (heart rate greater than 155 beats per minute) would be amber on the NICE CG160 traffic light but would be high risk of severe illness or death via the sepsis guideline.

Impact statement

The studies identified during the 2-year Evidence Update and in this 4-year surveillance review highlighted the usefulness of various clinical tests; notably, WBC, CRP, PCT and lumbar puncture. One RCT, identified from literature searches, and 2 observational studies, highlighted by topic experts, indicated the superior predictive capacity of using approaches which combine laboratory tests; such as, the Lab-score approach which combines PCT, CRP and urinalysis.

Some of the identified studies indicated that PCT testing could be a useful diagnostic test. Currently NICE CG160 does not include PCT in the list of laboratory investigations that could be used to assess children under 5 with suspected serious illness. Furthermore, NICE has published guidance on [Procalcitonin testing for diagnosing and monitoring sepsis](#) (NICE DG18). The diagnostic guideline states that there was not enough evidence to recommend that procalcitonin tests are used in the NHS. The identified new studies were relayed to NICE’s Diagnostics Assessment Programme and it was considered that the new evidence was insufficient to trigger an update of DG18.

One topic expert highlighted that multiplex PCR can produce results from CSF cultures within 1 hour compared to 18 hours, using conventional methods. NICE has published guidance on multiplex PCR: [Tests for rapidly identifying bloodstream bacteria and fungi \(LightCycler SeptiFast Test MGRADE, SepsiTtest and IRIDICA BAC BSI assay\)](#) [NICE DG20]. The diagnostic guideline states that there is currently insufficient evidence to recommend routine adoption in the NHS and further research is needed, particularly to demonstrate the value of using test results in clinical decision-making.

Topic experts highlighted that lactate testing is mentioned in the NICE Sepsis guideline (NG51) but not mentioned in NICE guideline CG160. Experts felt that although lactate testing is used to stratify risk in people who are thought to have sepsis, it is not used for detecting infection. Experts felt that it is important that NICE guideline CG160 redirects clinicians to NICE guideline NG51 if they suspect that a febrile child has sepsis. In light of the topic expert feedback, it is proposed that NICE guideline CG160 could include a

recommendation that cross-refers to NICE guideline NG51 so that clinicians can determine what diagnostic tests should be performed if they suspect that a febrile child has sepsis.

New evidence is unlikely to change guideline recommendations

160–15 What is the predictive value of procalcitonin compared to C-reactive protein for detecting serious illness in fever without apparent source in children under 5?

Recommendations derived from this question

Children aged 3 months or older

- 1.5.3.1 Perform the following investigations in children with fever without apparent source who present to paediatric specialists with 1 or more 'red' features:
- full blood count
 - blood culture
 - C-reactive protein
 - urine testing for urinary tract infection. [2013]
- 1.5.3.2 The following investigations should also be considered in children with 'red' features, as guided by the clinical assessment:
- lumbar puncture in children of all ages (if not contraindicated)
 - chest X-ray irrespective of body temperature and WBC
 - serum electrolytes and blood gas. [2007]
- 1.5.3.3 Children with fever without apparent source presenting to paediatric specialists who have 1 or more 'amber' features, should have the following investigations performed unless deemed unnecessary by an experienced paediatrician.
- urine should be collected and tested for urinary tract infection
 - blood tests: full blood count, C-reactive protein and blood cultures
 - lumbar puncture should be considered for children younger than 1 year
 - chest X-ray in a child with a fever greater than 39°C and WBC greater than $20 \times 10^9/\text{litre}$. [2007]
- 1.5.3.4 Children who have been referred to a paediatric specialist with fever without apparent source and who have no features of serious illness (that is, the 'green' group), should have urine tested for urinary tract infection and be assessed for symptoms and signs of pneumonia (see table 2). [2007]
- 1.5.3.5 Do not routinely perform blood tests and chest X-rays in children with fever who have no features of serious illness (that is, the 'green' group). [2007]

Surveillance decision

This review question should not be updated.

2-year Evidence Update

One study¹⁵ assessed the effectiveness of C-reactive protein (CRP), serum procalcitonin (PCT), white blood cell (WBC) counts and the Acute Infantile Observation Score (AIOS) as indicators of bacterial infection in 46 infants aged between 6 and 26 months with fever. 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. PCT 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 PCT to diagnose serious bacterial infection.

It was considered the study outlined that the investigations assessed would be relevant to children of all ages. However, the evidence also indicated that that no laboratory test alone appeared to be able to reliably rule-in or rule-out serious bacterial infections. Evidence about the usefulness of PCT testing was deemed inconsistent. Therefore, it was considered that the identified evidence would have no impact on NICE CG160, because the guideline recommends a schedule of tests to be done in children with fever.

4-year surveillance summary

One systematic review²⁸ aimed to establish whether PCT testing was a cost-effective adjunct for prodromal meningococcal disease in 881 children presenting with fever without source. Investigators analysed data by comparing 2 diagnostic strategies: standard testing (CRP tests plus white cell counts) compared to standard testing plus PCT tests. Standard testing plus PCT was more accurate (sensitivity, 89%; specificity, 74%) at identifying early meningococcal disease compared to standard testing alone (sensitivity, 47%; specificity, 80%). Authors stated that "analytic model outcomes indicated that the incremental cost effectiveness ratio for the base case was - 8,137.25 (US \$ -13,371.94) per correctly treated patient."

Topic expert feedback

Topic experts highlighted a prospective cohort study²¹ which assessed the diagnostic characteristics of PCT tests for detecting serious bacterial infection and invasive bacterial infection in 2,047 febrile infants aged between 7 and 91 days. Overall 6.38% of infants were diagnosed with serious bacterial infections and 1% of infants were diagnosed with invasive bacterial infections. The PCT assay had a similar area under the receiver operating characteristic similar to that for CRP tests for detection of serious bacterial infections. The area under the curve for detection of invasive bacterial infections was significantly higher for PCT tests compared to CRP tests, indicating that the PCT assay had better diagnostic accuracy than CRP measurements for detecting invasive bacterial infections. Similar results were obtained for a subgroup of infants less than 1 month old and for those with fever that lasted for less than 6 hours.

A prospective observational study²⁶ aimed to assess the diagnostic role of CRP and PCT in febrile children (between 1 month and 16 years) at risk of serious bacterial infection. Of the 1,084 children included in the study 170 children (16%) had serious bacterial infections. Authors reported that the areas under receiver operating characteristic curves indicated that CRP (Area, 0.77) and PCT (Area, 0.75) were both strong indicators of serious bacterial infection. It was noted that duration of fever had no added diagnostic value to CRP or PCT. The Lab-score (which combines PCT, CRP and urinalysis) had an area under the receiver operating characteristic curve of 0.79, which was similar to the areas of individual biomarkers. An updated Lab-score improved slightly, with an area of 0.83.

Topic experts suggested that PCT is superior to CRP in identifying invasive bacterial infections in infants. As a result, they highlighted that it may be useful to use PCT tests in hospital settings.

Impact statement

In the 2-year Evidence Update, evidence about the usefulness of PCT testing was deemed inconsistent. Therefore, it was considered unlikely to affect guideline recommendations.

Topic experts suggested that PCT was superior to CRP in identifying invasive bacterial

infections. One study, highlighted by topic experts, indicated that PCT testing had better diagnostic accuracy than CRP measurements for detecting invasive bacterial infections. A second study, highlighted by experts, suggested that CRP and PCT testing were both strong indicators of serious bacterial infections, with little difference between them. The study also highlighted that combining the results of both tests yielded a higher diagnostic accuracy. These results are supported by 1 study identified from literature searches which highlighted that PCT increases the ability to identify meningococcal disease when combined with CRP and white blood cell counts.

Overall, the identified studies indicate that PCT testing could be a useful diagnostic test which

has a similar, if not better, diagnostic profile to CRP testing.

Currently NICE guideline CG160 does not include PCT in the list of laboratory investigations that could be used to assess children under 5 with suspected serious illness. Furthermore, NICE has published guidance on [Procalcitonin testing for diagnosing and monitoring sepsis](#) (NICE DG18). The diagnostic guideline states that there was not enough evidence to recommend that procalcitonin tests are used in the NHS. The identified new studies were relayed to NICE's Diagnostics Assessment Programme and it was considered that the new evidence was insufficient to trigger an update of DG18.

New evidence is unlikely to change guideline recommendations.

160–16 What is the incidence of co-existing bacterial infection in a child presenting with fever in which a virus (e.g. influenza or RSV) is detected (with a rapid test)?

Recommendations derived from this question

Viral co-infection

- 1.5.4.1 Febrile children with proven respiratory syncytial virus or influenza infection should be assessed for features of serious illness. Consideration should be given to urine testing for urinary tract infection. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–17 In a child with fever what are the benefits, if any, of a period of observation on an assessment facility?

Recommendations derived from this question

Observation in hospital

- 1.5.5.1 In children aged 3 months or older with fever without apparent source, a period of observation in hospital (with or without investigations) should be considered as part of the assessment to help differentiate non-serious from serious illness. [2007]

Surveillance decision

No new information was identified at any surveillance review.
This review question should not be updated.

160–18 What is the predictive value of the clinical response to paracetamol or NSAIDs (non-steroidal anti-inflammatory drugs)?

Recommendations derived from this question

Observation in hospital

- 1.5.5.2 When a child has been given antipyretics, do not rely on a decrease or lack of decrease in temperature at 1–2 hours to differentiate between serious and non-serious illness. Nevertheless, in order to detect possible clinical deterioration, all children in hospital with 'amber' or 'red' features should still be reassessed after 1–2 hours. [new 2013]

Surveillance decision

This review question should not be updated. Instead, a recommendation should be added to the non-paediatric practitioner section highlighting that clinicians should not solely use a response to antipyretic therapy to differentiate between serious and non-serious infection.

2-year evidence update

No relevant evidence was identified.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic expert feedback along with intelligence gathering highlighted an incident in which a child presented at a non-paediatric emergency department with fever. Upon examination, the child was considered to fall within the Amber category of the NICE traffic light system and was given antipyretic medication. After

responding to treatment, the child was considered to fall within the green category and was sent home. They subsequently died 5 days later. Experts highlighted that the guideline provides [advice for paediatric specialists](#) (Section 1.5) on assessment of children who respond, or fail to respond, to antipyretic therapy but no recommendations are provided in the [advice for non-paediatric practitioners section](#) (Section 1.4). Experts suggested that section 1.4 should provide similar advice to section 1.5 [\(advice on management by](#)

[paediatric specialists](#)). Recommendation

1.5.5.2 of NICE CG160 states:

“When a child has been given antipyretics, do not rely on a decrease or lack of decrease in temperature at 1–2 hours to differentiate between serious and non-serious illness. Nevertheless, in order to detect possible clinical deterioration, all children in hospital with ‘amber’ or ‘red’ features should still be reassessed after 1–2 hours.”

Experts suggested that the following recommendation should be added to section 1.4:

“When a child has been given antipyretics, do not rely on a decrease or lack of decrease in temperature to differentiate between serious and non-serious illness”

Impact statement

No published studies were identified at any surveillance time point. Substantive feedback from topic experts indicated that the section on [management by the non-paediatric practitioner](#) (section 1.4) should include a recommendation on how non-paediatric practitioners should consider temperature changes following treatment with antipyretics. As a result, it is proposed that a recommendation will be added stating that clinicians should not rely on a response to antipyretics to differentiate between serious and non-serious illness.

New evidence is unlikely to change guideline recommendations

160–19 For children with symptoms and signs of a serious illness what immediate treatments improve their outcome?

(NB: Evidence of the effect of the following interventions in the treatment of serious illness was looked for: intravenous fluids, steroids, antibiotics, acyclovir, oxygen)

Recommendations derived from this question

Immediate treatment by the paediatric specialist (for children of all ages)

- 1.5.6.1 Children with fever and shock presenting to specialist paediatric care or an emergency department should be:
- given an immediate intravenous fluid bolus of 20 ml/kg; the initial fluid should normally be 0.9% sodium chloride
 - actively monitored and given further fluid boluses as necessary. [2007]
- 1.5.6.2 Give immediate parenteral antibiotics to children with fever presenting to specialist paediatric care or an emergency department if they are:
- shocked
 - unrousable
 - showing signs of meningococcal disease. [2007]
- 1.5.6.3 Immediate parenteral antibiotics should be considered for children with fever and reduced levels of consciousness. In these cases symptoms and signs of meningitis and herpes simplex encephalitis should be sought (see table 2 and Bacterial meningitis and meningococcal septicaemia [NICE clinical guideline 102]). [2007]
- 1.5.6.4 When parenteral antibiotics are indicated, a third-generation cephalosporin (for example, cefotaxime or ceftriaxone) should be given, until culture results are available. For children younger than 3 months, an antibiotic active against listeria (for example, ampicillin or amoxicillin) should also be given. [2007]

- 1.5.6.5 Give intravenous aciclovir to children with fever and symptoms and signs suggestive of herpes simplex encephalitis (see recommendation 1.2.3.5). [2007]
- 1.5.6.6 Oxygen should be given to children with fever who have signs of shock or oxygen saturation (SpO₂) of less than 92% when breathing air. Treatment with oxygen should also be considered for children with an SpO₂ of greater than 92%, as clinically indicated. [2007]

Surveillance decision

This review question should not be updated.

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance summary

Antibiotics

In 1 RCT²⁹, 3,564 new-born infants with clinical signs of severe infection were treated by injectable procaine benzylpenicillin-gentamicin for 7 days (group A), injectable gentamicin and oral amoxicillin for 7 days (group B), injectable procaine benzylpenicillin-gentamicin for 2 days, then oral amoxicillin for 5 days (group C), or injectable gentamicin for 2 days and oral amoxicillin for 7 days (group D). The primary outcome measure was treatment failure; defined as, clinical deterioration, development of a serious adverse event, death, no improvement by day 4, or not cured by day 8. Treatment failure rates were 8% in group A, 6% in group B, 8% in group C, and 5% in group D. Authors report that 'treatment failure rates in groups B, C, and D were within the similarity margin compared with group A'. During the 15 days after randomisation, death was reported in 1% of infants in groups A, B and D whereas, 2% of infants died in group C. One child in group A had a serious adverse event other than death (injection abscess). No serious adverse events were reported in the other study arms.

One RCT³⁰ compared infants between 2 and 59 months with signs of non-severe pneumonia treated by thrice daily or twice daily oral amoxicillin. Treatment failure (development of danger signs, persistence of fever, tachypnoea, development of serious adverse reactions, death and withdrawal from the trial) was reported in 22.8% of children in who received amoxicillin thrice daily and 23% of children who received amoxicillin twice daily (No p values reported). Of the children with confirmed

pneumonia treatment, failure was reported in 18.8% in both treatment arms.

Steroids

An RCT³¹ evaluated the effect of early use of corticosteroids in 53 children with severe mycoplasma pneumoniae pneumonia: note, the age range was not specified. The early treatment group received corticosteroids within 24 hours of admission whereas the control group received corticosteroids 72 hours after admission. Children in the early treatment group had a shorter duration of fever and shorter length of stay compared to children in the control group. Complete radiographic resolution times greater than 4 weeks, was reported in 1.9% of children in the early treatment group and 17.5% of children in the control group (no p value reported).

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The identified new evidence on antibiotic therapy was largely in line with guideline recommendations for the use of parenteral antibiotics in children with signs and symptoms of serious illness. Studies generally reported that treatment with antibiotics reduced the risk of fever persisting, clinical deterioration, development of complications and death. Moreover, early antibiotic treatment was found to reduce length of hospital stay.

In relation to steroid treatment, 1 RCT highlighted that the early use of corticosteroids in children with severe pneumonia resulted in a shorter duration of fever and shorter length of stay. The study was relatively small (n=53) and the age range of participants was not specified. As a result, more evidence is needed to confirm

the role of corticosteroids for the early management of children with suspected serious illness.

New evidence is unlikely to change guideline recommendations.

160–20 What are the most common organisms causing serious illness in young children with fever?

– What is the incidence of serious illness in young children with fever?

Recommendations derived from this question

Causes and incidence of serious bacterial infection

- 1.5.7.1 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. [2007]
- 1.5.7.2 Refer to local treatment guidelines when rates of bacterial antibiotic resistance are significant. [2007]

Surveillance decision

This review question should not be updated.

2-year Evidence Update

One study³² retrospectively assessed hospital admission rates for children with infections caused by *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae* from the 1960s to 2011 (Note: data from children older than 5 years were included). In the 1990s the incidence of *Neisseria meningitidis* 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.

Streptococcus pneumoniae rates were 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.

In relation to *Haemophilus influenzae*, the introduction of a vaccine, in 1992, resulted in a decrease in incidence 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 *Haemophilus 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).

It was considered that the study was potentially limited by the lack of knowledge about the quality and consistency of the data used to performed the analyses (Hospital Episode Statistics data). Moreover, the dataset may have been affected by changes in hospital coding practices over time.

One study³³ assessed the prevalence of invasive bacterial infections in children aged between 1 month and 15 years. Children were categorised as infants (1 to 11 months), preschool (1 to 4 years) or older children (5 to 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. This consisted of 190 episodes in infants (39.6%), and 151 episodes in pre-school children (25.3%) and 163 episodes in older children (36.1%).

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%), *Streptococcus pneumoniae* (33 episodes, 9.8%), *Enterococcus* species. (32 episodes, 9.5%), group B *Streptococcus* (24 episodes, 7.1%), and group A *Streptococcus*. Of Gram negative bacteria, the most common pathogen was *Escherichia coli* (45 episodes, 26.8%), followed by *Klebsiella pneumoniae* (28 episodes, 16.7%), *Enterobacter* species. (15 episodes, 8.9%),

Salmonella species (15 episodes, 8.9%), *Pseudomonas* species (15 episodes, 8.9%), *Neisseria meningitidis* (13 episodes, 7.7%), and *Haemophilus influenzae* (4 episodes, 2.4%). 'Other' pathogens caused 19 (5.7%) gram-positive and 33 (19.6%) gram-negative infections. In children less than 1 year old the incidence of community-acquired invasive infection was 38 episodes per 100,000 population. The incidence of community-onset bacterial meningitis in children under 1 year was 9.3 episodes per 100,000 population.

Possible limitations of this study were that the strict inclusion criteria of a positive blood or CSF culture may have led to an underestimate of the incidence of invasive bacterial infections. The 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. Finally, the fact that the study population was children living in South-West London means that the results may not be generalisable to the rest of the UK.

Overall, it was considered that the identified studies were consistent with the recommendation in NICE CG160 to direct antibiotic treatment against *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus* and *Haemophilus influenzae* type b in children with fever and suspected serious bacterial infection requiring immediate treatment, because these remain clinically important pathogens in the UK

4-year surveillance summary

A systematic review³⁴ included data from 16 studies to assess the prevalence of serious bacterial infection caused by *Listeria*

monocytogenes and *Enterococcus* species in febrile infants less than 90 days old. Pooled assessment of 20,703 blood cultures revealed that the prevalence of *Listeria monocytogenes* and enterococci species were 0.03% and 0.09%, respectively. Pooled analysis of 13,755 cerebrospinal fluid cultures revealed that the prevalence of *Listeria monocytogenes* and *Enterococcus* species were 0.2% and 0.03%, respectively. Of 18,283 urine cultures no cases of *Listeria monocytogenes* were identified;

however, 0.28% of urine samples tested positive for enterococci.

Topic expert feedback

Topic experts highlighted the following studies:

One study used data from a prospective registry³⁵ to analyse the prevalence of bacterial meningitis in 2,362 infants younger than 90 days with fever without source. Lumbar puncture was performed in 27% (n=639) of the infants. Of these patients the odds of lumbar puncture were significantly greater in patients who appeared unwell (Odds ratio, 4.49) and patients who were less than 21 days old (Odds ratio, 9.14). Overall, 11 infants were diagnosed with bacterial meningitis. Bacteria isolated were *Streptococcus agalactiae* (n=3), *Escherichia coli* (n=3), *Listeria monocytogenes* (n=3), *Streptococcus pneumoniae* (n=1) and *Neisseria meningitidis* (n=1). No children who appeared well and were older than 21 days were diagnosed with bacterial meningitis.

One prospective observational study³⁶ reported that, between July 2010 and July 2011, the incidence of bacterial meningitis was 0.38 per 1000 live births in the United Kingdom and Ireland. The incidence of group B streptococcus was 0.16 per 100 live births, and *Escherichia coli* was 0.04 per 100 live births. Authors reported that meningitis due to *Listeria* was only reported within the first month of birth. Furthermore pneumococcal and meningococcal meningitis were rare in the first month. Death was reported in 8% of hospitalised preterm infants diagnosed with bacterial meningitis. The mortality rate due to pneumococcal meningitis was significantly higher than the rate associated with group B streptococcus (19% versus 5%). The preterm mortality rate (17%) was significantly higher than the term mortality rate (4%).

Another study²⁴ aimed to determine the rate of bacterial infections in children between 3 and 36 months who presented to a paediatric emergency department with fever but otherwise appeared well. Of the 591 children who were assessed 1% (n=6) had a bacterial pathogen isolated from blood tests: of these pathogens, half were *Streptococcus pneumoniae*. None of the children with pneumococcal infections had been immunised. Authors noted that a positive band count was most indicative of occult

bacteraemia, with a positive likelihood ratio of 10 and a negative likelihood ratio of 0.4.

One prospective observational study³⁷ explored the aetiology, risk factors, and treatment of children between 1 month and 15 years with community-onset invasive bacterial infections. A total of 119 healthy children had a single invasive bacterial infection while 61 children with non-oncological comorbidities had multiple invasive bacterial infections. Causative pathogens were found to be similar in both sets of children. Authors reported that children with central venous catheters had multiple invasive bacterial infections, often caused by bacteria associated with hospital acquired infection. Notably, gastrointestinal commensals were commonly found to cause invasive bacterial infections in total parenteral nutrition-dependent children with gastrointestinal disease and those with liver disease. Empirical antibiotic treatment was given to 93% of children with additional antibiotics more likely to be prescribed in children with comorbidities or those in intensive care.

Impact statement

It was considered that studies identified in the 2-year Evidence Update were consistent with the recommendations in NICE guideline CG160 to direct antibiotic treatment against *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus* and *Haemophilus influenzae* type B in children with fever and suspected serious bacterial infection requiring immediate treatment, because these remain clinically important pathogens in the UK.

Evidence identified from literature searches and from topic expert feedback in this 4-year surveillance review identified *Listeria*, *Streptococcus* species, *Enterococcus* species, *Neisseria meningitidis*, *Escherichia coli* and *Staphylococcus aureus* as common pathogens that were isolated from blood samples, urine samples and lumbar punctures of febrile children with suspected serious illness. These bacteria remain consistent with the pathogens listed in NICE guideline CG160. As a result, the new evidence is in line with guideline recommendations.

New evidence is unlikely to change guideline recommendations.

160–21 What factors other than the child's clinical condition should be considered when deciding to admit a child with fever to hospital?

Recommendations derived from this question

Admission to and discharge from hospital

- 1.5.8.1 In addition to the child's clinical condition, consider the following factors when deciding whether to admit a child with fever to hospital:
- social and family circumstances
 - other illnesses that affect the child or other family members
 - parental anxiety and instinct (based on their knowledge of their child)
 - contacts with other people who have serious infectious diseases
 - recent travel abroad to tropical/subtropical areas, or areas with a high risk of endemic infectious disease
 - when the parent or carer's concern for their child's current illness has caused them to seek healthcare advice repeatedly
 - where the family has experienced a previous serious illness or death due to feverish illness which has increased their anxiety levels
 - when a feverish illness has no obvious cause, but the child remains ill longer than expected for a self-limiting illness. [2007]
- 1.5.8.2 If it is decided that a child does not need to be admitted to hospital, but no diagnosis has been reached, provide a safety net for parents and carers if any 'red' or 'amber' features are present. The safety net should be 1 or more of the following:
- providing the parent or carer with verbal and/or written information on warning symptoms and how further healthcare can be accessed (see section 1.7.2)
 - arranging further follow-up at a specified time and place
 - liaising with other healthcare professionals, including out-of-hours providers, to ensure direct access for the child if further assessment is required. [2007]
- 1.5.8.3 Children with 'green' features and none of the 'amber' or 'red' features can be cared for at home with appropriate advice for parents and carers, including advice on when to seek further attention from the healthcare services (see section 1.7). [2007, amended 2013]

Referral to paediatric intensive care

- 1.5.9.1 Children with fever who are shocked, unrousable or showing signs of meningococcal disease should be urgently reviewed by an experienced paediatrician and consideration given to referral to paediatric intensive care. [2007]
- 1.5.9.2 Give parenteral antibiotics to children with suspected meningococcal disease at the earliest opportunity (either benzylpenicillin or a third-generation cephalosporin). [2007]
- 1.5.9.3 Children admitted to hospital with meningococcal disease should be under paediatric care, supervised by a consultant and have their need for inotropes assessed. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Antipyretic interventions

160–22 Does the use of antipyretic interventions in children with fever serve a benefit or harm in terms of any of the following:

- time to recovery
- wellbeing
- activity
- eating and drinking
- prevention of febrile convulsions?

Recommendations derived from this question

Effects of body temperature reduction

1.6.1.1 Antipyretic agents do not prevent febrile convulsions and should not be used specifically for this purpose. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–23 Whether reducing fever with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) affects the course of the disease?

Recommendations derived from this question

No recommendation made in the guideline.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–24 What, if any, antipyretic interventions are effective in reducing body temperature in children with fever?

Recommendations derived from this question

Physical interventions to reduce body temperature

1.6.2.1 Tepid sponging is not recommended for the treatment of fever. [2007]

1.6.2.2 Children with fever should not be underdressed or over-wrapped. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–25 What is the effect on fever and associated symptoms of treatment with:

- paracetamol alone or non-steroidal anti-inflammatory drugs (NSAIDs) alone, compared with placebo and with one another.
- alternating paracetamol and NSAIDs, compared with placebo, either drug alone, and taking both at the same time.
- paracetamol and NSAIDs taken at the same time, compared with placebo, and either drug alone and either drug alone.

Recommendations derived from this question

Drug interventions to reduce body temperature

- 1.6.3.1 Consider using either paracetamol or ibuprofen in children with fever who appear distressed. [new 2013]
- 1.6.3.2 Do not use antipyretic agents with the sole aim of reducing body temperature in children with fever. [new 2013]
- 1.6.3.3 When using paracetamol or ibuprofen in children with fever:
- continue only as long as the child appears distressed
 - consider changing to the other agent if the child's distress is not alleviated
 - do not give both agents simultaneously
 - only consider alternating these agents if the distress persists or recurs before the next dose is due. [new 2013]

Surveillance decision

This review question should not be updated.

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic experts highlighted a systematic review³⁸ which assessed the safety and efficacy combining paracetamol and ibuprofen, or alternating them in consecutive treatments,

compared with monotherapy for treating fever in children (age ranges not specified). Data from 2 trials, included 163 patients, indicating that paracetamol plus ibuprofen resulted in significantly lower mean temperatures at 1 hour after treatment compared to single antipyretic alone (Mean difference, -0.27°C). If no additional antipyretics were given, dual antipyretic treatment resulted in significantly lower mean temperatures at 4 hours (Mean

difference, -0.70 °C) and fewer children remaining or becoming febrile for at least 4 hours after treatment (Relative risk, 0.08). In 1 of the included studies which assessed child discomfort, no significant differences were observed between treatment with paracetamol plus ibuprofen and treatment with single antipyretic alone. Authors reported that giving alternating doses of paracetamol and ibuprofen resulted in significantly lower mean temperatures at 1 hour after the second dose (Mean difference, -0.60°C) and resulted in fewer children remaining or becoming febrile for up to 3 hours after treatment (Relative risk, 0.25). In the trial that assessed child discomfort, mean pain scores were lowered with alternating therapy despite fewer doses of antipyretic being given overall. Only 1 trial compared alternating therapy with combined therapy. In this study no significant differences in mean temperatures were observed between groups. Furthermore, no significant differences in the percentages of febrile children were observed between groups at 1, 4 and 6 hours. No serious adverse events directly attributed to the medications used were reported in any of the included studies.

One topic expert highlighted a study³⁹ which investigated risk factors of empyema after acute viral infection. Authors reported that there was an increased risk of empyema associated with exposure to non-steroidal anti-

inflammatory drug exposure (Odd Ratio, 2.79; 95% CI 1.4 to 5.58, p=0.004)

One topic expert stated that there may be some indication that early exposure to paracetamol predisposes towards asthma; however he acknowledged that there is insufficient evidence to warrant changing guidelines on early life paracetamol exposure.

Another topic expert highlighted recently published Italian Paediatric Society guidelines⁴⁰ for management of fever in children. The topic expert pointed out that guidelines state "ibuprofen and paracetamol are not contraindicated in children who are febrile with asthma, with the exception of known cases of paracetamol- or nonsteroidal anti-inflammatory drug-induced asthma."

Impact statement

The systematic review highlighted by topic experts provided some evidence that both dual and alternating antipyretic therapy may be more effective than monotherapy for treating children with fever. However, few studies were included in the meta-analyses and the age range of children participating in these studies was not specified in the abstract. As a result, there was insufficient evidence to deduce whether combined or alternating antipyretic therapy is more beneficial than monotherapy.

New evidence is unlikely to change guideline recommendations.

[Advice for home care](#)

160–26 What advice should be given to parents for further management of a febrile child?

Need to consider: hydration, feeding, frequency of temperature monitoring, methods of cooling, when to attend nursery or school, appearance of non-blanching rash.

Recommendations derived from this question

Care at home

- 1.7.1.1 Advise parents or carers to manage their child's temperature as described in section 1.6. [2007]
- 1.7.1.2 Advise parents or carers looking after a feverish child at home:
- to offer the child regular fluids (where a baby or child is breastfed the most appropriate fluid is breast milk)
 - how to detect signs of dehydration by looking for the following features:
 - sunken fontanelle
 - dry mouth
 - sunken eyes
 - absence of tears
 - poor overall appearance
 - to encourage their child to drink more fluids and consider seeking further advice if they detect signs of dehydration
 - how to identify a non-blanching rash
 - to check their child during the night
 - to keep their child away from nursery or school while the child's fever persists but to notify the school or nursery of the illness. [2007]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

160–27 In children with fever at home following a clinical encounter, what indications should direct the parents or carers to seek further advice?

Recommendations derived from this question

When to seek further help

- 1.7.2.1 Following contact with a healthcare professional, parents and carers who are looking after their feverish child at home should seek further advice if:
- the child has a fit
 - the child develops a non-blanching rash
 - the parent or carer feels that the child is less well than when they previously sought advice
 - the parent or carer is more worried than when they previously sought advice
 - the fever lasts longer than 5 days
 - the parent or carer is distressed, or concerned that they are unable to look after their child. [2007]

Surveillance decision

This review question should not be updated.

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

One topic expert highlighted the potential benefits of delivering educational interventions to parents before their children become ill.

However, they acknowledged that any amendment to the guideline would involve extending the scope to non-febrile children.

One topic expert suggested that telephone advice services do not work for children with fever.

Impact statement

No relevant studies were identified at any surveillance review. Topic expert feedback highlighted that educational interventions could be delivered before children become febrile; however, interventions focussing on healthy children prior to febrile episodes are outside the scope of NICE guideline CG160.

New evidence is unlikely to change guideline recommendations.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the [NICE database for research recommendations](#). The research recommendations will remain in the full versions of the guideline. See NICE's [research recommendations process and methods guide 2015](#) for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision **will** be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
 - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
 - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
 - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
 - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
 - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
 - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
 - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 The GDG recommends a UK-based epidemiological study on the symptoms and signs of serious illness. [new 2013]

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation was made during a recent update of the guideline, therefore the research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 02 The GDG recommends that a UK study is undertaken to determine the validity of symptoms reported on remote assessment for children with fever. [2007]

Topic experts highlighted that this is a relevant and important clinical question. Experts stated that there is little evidence to support recommendations in this area and highlighted that services, such as 111, are widely used but are subject to scrutiny. As a result, the research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 03 The GDG recommends that a UK study of the performance characteristics and cost-effectiveness of procalcitonin versus C-reactive protein in identifying serious bacterial infection in children with fever without apparent source be carried out. [2007]

Although evidence was identified which compared the performance characteristics and cost effectiveness of procalcitonin versus C-reactive protein in identifying serious bacterial infection, it was unclear from the study abstracts whether these studies were based in the UK.

Surveillance decision

Although it was not possible to determine whether the identified studies were applicable to a UK context, the new evidence demonstrates ongoing research in this clinical area. As a result, the research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 04 The GDG recommends that studies are conducted in primary care and secondary care to determine whether examination or re-examination after a dose of antipyretic medication is of benefit in differentiating children with serious illness from those with other conditions.[2007]

Topic experts made comments on considerations made by non-paediatric practitioners when managing children with fever according to their risk of serious illness ([160–18](#)). In light of the comments, the research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 05 The GDG recommends studies on home-based antipyretic use and parental perception of distress caused by fever. [new 2013]

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation was made during a recent update of the guideline, therefore the research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

Other research recommendations

The following research recommendations were not deemed as priority areas for research by the guideline committee.

RR – 06 Measuring temperature in young babies: tympanic versus axilla electronic versus axilla chemical dot versus temporal artery. [2007]

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 07 The GDG recommends that research is carried out on referral patterns between primary and secondary care for children with fever, so the health economic impact of this and future guidelines can be estimated.

2-year Evidence Update

No relevant evidence was identified.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic experts highlighted a prospective observational⁴¹ which explored risk factors for ward and paediatric assessment unit admissions from the emergency department. Tachycardia (Risk ratio [RR], 1.1; 95% CI, 1 to 1.1), ill-appearance (RR, 2.2; 95% CI, 1.2 to 4.2) and abnormal chest findings (RR, 2.1; 95% CI, 1.2 to 4.3) were risk factors associated with paediatric assessment unit admissions. Furthermore, the NICE amber category was also associated with admission to paediatric assessment units (RR, 1.7; 95% CI, 1.2 to 2.5. Authors stated that “there was 30% discordance between NICE categorisation at triage and statistical internal validation”. Systemic (RR, 6.9; 95% CI, 2.4 to 19.8) or gastrointestinal illness (RR, 3.8; 95% CI, 1.4 to 10.4) as well as the NICE red category (RR, 5.9; 95% CI, 2.2 to 15.3) were associated with ward admissions.

Surveillance decision

The identified study highlights what risk factors are associated with referral patterns within secondary care. This is indirectly relevant to the research recommendation which aims to explore referrals between primary and secondary care. This research recommendation will be considered again at the next surveillance point.

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